Prehospital Emergency Trauma Care and Management

Jeffrey D. Kerby, MD, PhD[a,b,*], Marianne V. Cusick, MD, MSPH[c]

KEYWORDS

• Trauma • Emergency care • Prehospital

KEY POINTS

- Use of endotracheal intubation in the prehospital care environment remains controversial. Well-designed randomized trials are necessary to assess the efficacy and risks associated with prehospital endotracheal intubation. Alternatives to endotracheal intubation for airway management are available and becoming more commonly used.
- Tourniquets should be considered, even in the civilian setting, when direct pressure fails to control bleeding from extremity wounds. Emergency medical service (EMS) systems should train medics in proper use and placement of tourniquets.
- Current trends are for limited crystalloid resuscitation and early use of blood and blood products before hemorrhage control. Randomized trials are currently under way to test limited crystalloid resuscitation in the prehospital environment for both blunt and penetrating injury. Several resuscitation adjuncts are currently being investigated for prehospital use.
- Traditional vital signs are limited in their ability to accurately identify patients in shock. Identification of patients in occult shock is an active area of investigation using point-of-care devices, assessment of heart-rate variability, and measurement of tissue oxygenation.
- Prehospital research infrastructure is being established and continuing to expand, which will allow for further growth of research activities to evaluate new products and resuscitative strategies.

This work was supported by Grant No. 5UO1H077881 from the National Heart, Lung, and Blood Institute.

Jeffrey D. Kerby, MD, PhD, is a principal investigator and director of the Alabama Regional Clinical Center for the National Heart, Lung, and Blood–sponsored Resuscitation Outcomes Consortium.

[a] Section of Trauma, Burns, and Surgical Critical Care, Department of Surgery, University of Alabama at Birmingham, 701 19th Street South, LHRB 112, Birmingham, AL 35294-0007, USA; [b] Alabama Resuscitation Center, University of Alabama at Birmingham, 619 19th Street South, Room 251, Birmingham, AL 35249, USA; [c] Department of Surgery, University of Alabama at Birmingham, 1922 7th Avenue South, KB 217, Birmingham, AL 35294-0007, USA

* Corresponding author. Section of Trauma, Burns, and Surgical Critical Care, Department of Surgery, University of Alabama at Birmingham, 701 19th Street South, LHRB 112, Birmingham, AL 35294-0007.

E-mail address: jeffrey.kerby@ccc.uab.edu

Surg Clin N Am 92 (2012) 823–841
doi:10.1016/j.suc.2012.04.009 **surgical.theclinics.com**
0039-6109/12/$ – see front matter Published by Elsevier Inc.

INTRODUCTION

Approximately 50% of injury-related deaths occur in the first 12 hours, and both mortality and late complications have been linked to the efficacy of early interventions. Consequently, improvements in prehospital treatment algorithms and resuscitation strategies have the potential to improve survival and reduce morbidity.[1–3] The indications and type of airway control maneuvers in the prehospital setting continue to evolve. Devices used to control exsanguinating hemorrhage and further innovation in the field of topical hemostatic agents are further refining prehospital and combat casualty care paradigms. Early detection of occult shock along with the use of resuscitation adjuncts and refinements of delayed resuscitation strategies are being investigated actively. With advancements in federal regulations governing informed consent procedures and development of the necessary infrastructure to perform randomized trials in the prehospital environment, research in the field of prehospital resuscitation of trauma patients has increased significantly. This article provides an overview of the current status of prehospital care and also highlights some of the recent advancements and future research in each of the following critical areas:

- Airway control
- Hemorrhage control
- Prehospital resuscitation and resuscitation adjuncts
- Identification of occult shock
- Prehospital research infrastructure.

AIRWAY CONTROL

Prehospital endotracheal intubation remains one of the more controversial interventions in the emergency medical service repertoire. Some investigators call into question the safety and efficacy of performing endotracheal intubation in the prehospital care setting whereas proponents of endotracheal intubation by EMS personnel report that first responders are capable of endotracheal intubation with low complication rates.[4–9] EMS systems with the highest reported endotracheal success rate are stringently trained with some systems requiring more than 20 live intubations before certification and a minimum of 12 field or prehospital intubations annually to remain certified and maintain adequate clinical experience.

More recent studies have reported successful prehospital intubation rates as high as 97% in regions where paralytics agents are routinely used.[4] Proponents of the use of paralytic agents suggest that allowing neuromuscular blockade allows for the expansion of the indications for intubation to a larger population from merely those that are comatose to those that are critically injured who may benefit from airway protection and controlled oxygenation and ventilation. The current use of neuromuscular blocking agents, however, is limited to all but a few ground EMS systems currently, whereas the practice is more common among aeromedical agencies under direct medical control.

The opponents of prehospital intubation have raised concerns regarding the safety and efficacy of prehospital intubation.[8,10–14] The leading arguments against the procedure are related to the level of complexity of the intervention, the lack of proved benefit, and the potential delay to definite care. Wang and colleagues[12] noted that more than 50 cognitive and psychomotor tasks are required for successful endotracheal intubation. Further opponents suggest that the national requirements for certification are inadequate and EMS responders are not prepared to perform endotracheal intubation in the chaotic environment of the prehospital resuscitation scene.[8] A main

concern regarding prehospital intubation is the associated increased morbidity and mortality found in several retrospective and observational studies.

Only one randomized trial of prehospital intubation has been performed to date. The trial enrolled 830 pediatric patients and randomized patients to either endotracheal intubation or bag-valve mask ventilation.[15] Although the study did have significant limitations, it observed no difference in survival to hospital discharge and no difference in the rate of good neurologic outcome between groups. Other smaller and nonrandomized studies have also concluded that in an urban EMS system endotracheal intubation offered no benefit versus bag-valve mask ventilation.[16,17]

The role of prehospital intubation in the brain injury population is a particular point of interest because brain-injured patients often have compromised mental status and concerns for maintaining an adequate airway. Only one study published to date has shown a survival advantage for head-injured patients undergoing intubation,[9] whereas several publications have shown the association between out-of-hospital intubation and higher morbidity and mortality.[7,13,14,17–20] All of these studies have limitations, including the retrospective or nonrandomized design, small populations with limited survivors to hospital discharge, and patients identified in the field by Glasgow Coma Scale score or retrospectively with head or head and neck Abbreviated Injury Severity Score. These factors are known to be poor identifiers of traumatic brain injury in the prehospital setting and, therefore, may have included a large number of patients without true head injury, therefore biasing the sample. In the only study to date that used CT data to identify head injury, the investigators concluded that nearly 90% of patients with prehospital Glasgow Coma Scale score less than or equal to 8 and CT-verified head injury required intubation either in the field or in the emergency department and that prehospital intubation resulted in no increased risk of mortality.[6]

At the current time, there is inconclusive evidence regarding the impact of prehospital intubation in trauma patients. Because endotracheal intubation is a skill that will remain in use by emergency medical providers, they should be adequately trained and maintain sufficient numbers of clinical intubations to remain certified. A large multicentered study is needed to accurately assess the efficacy and risks associated with prehospital endotracheal intubation.

Multiple alternatives to endotracheal intubation are available, including:

- Bag-valve mask
- Laryngeal mask
- Combitube
- King airway.

The alternatives listed previously are being used more commonly in the prehospital setting and not only require less training and skill for insertion but also have been shown to result in less delay to definitive care.[17,21] In addition, adjuncts to endotracheal intubation, such as video-assisted laryngoscopy, are being developed and tested for use in the prehospital setting.[22]

When a patient arrives at the authors' medical center with one of these alternative airways, if they are hemodynamically stable, the time is taken to secure a definitive airway with an endotracheal tube if possible or place a surgical airway if there is significant facial trauma. If a patient needs immediate surgery, the patient is transported to the operating room before manipulating these alternative airways.

An example of a prehospital airway management algorithm is provided in **Fig. 1**. Within this simple algorithm, prehospital personnel are encouraged to rapidly progress to the next step rather than repetitively attempting a given approach after initial failure. This algorithm also incorporates the alternative or rescue airways (discussed previously).

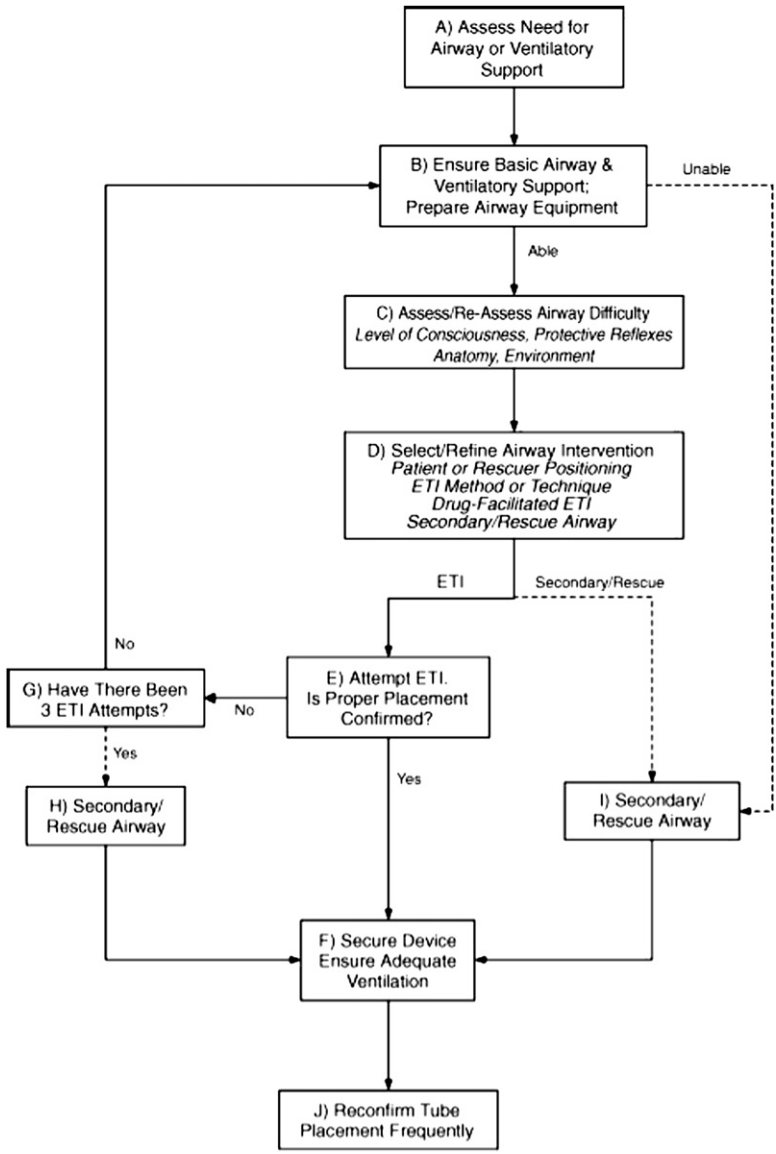

Fig. 1. Prehospital airway management algorithm. ETI, endotracheal intubation. (*From* Wang HE, Kupas DF, Greenwood MJ, et al. An algorithmic approach to prehospital airway management. Prehosp Emerg Care 2005;9(2):145–55; with permission.)

Some EMS groups may use a variation of this algorithm wherein alternative airway management strategies are the first-line approach.

HEMORRHAGE CONTROL

Uncontrolled hemorrhage is the leading cause of mortality among combat casualties and the second leading cause of death for civilian trauma.[1,23,24] Control of compressible hemorrhage is one of the first priorities for prehospital personnel when caring for an

injured patient and takes precedence in Tactical Combat Casualty Care (TCCC). When hemorrhage cannot be stopped with direct pressure or simple maneuvers, then advanced maneuvers need to be used. Recently, there have been major advances in understanding of how to appropriately use tourniquets and also the development of deployable hemostatic agents that can be used as adjuncts for hemorrhage control.

Tourniquet Use

Hemorrhage from extremity wounds is common especially in wartime and with increasing numbers of penetrating trauma. There has been a long and ongoing debate over the use of tourniquets in the prehospital setting, specifically in the battlefield. Although tourniquets were commonly used in the US Civil War, Spanish Civil War, and World War I, they lost favor given the concerns of increased morbidity with their use.[25] With advancements in technology and more precise indications for its use, the tourniquet has once again come into favor and all military personnel in the active combat theater are provided tourniquets. Recent reports suggest that tourniquets used appropriately have a low morbidity risk and improved outcomes are seen when tourniquets are applied early, before the onset of shock.[25,26] Kragh and colleagues[27] performed a prospective review of tourniquet use during Operation Iraqi Freedom. Of 2838 patients admitted to a combat support hospital in Baghdad during 2006, 232 injured combatants had 429 tourniquets applied on 309 injured extremities. Tourniquet use in the prehospital care environment and before the development of shock was strongly associated with survival. No amputations resulted solely from tourniquet use. In the current TCCC guidelines, combat medics are encouraged to consider early application of the tourniquet for control of bleeding. The current recommendation is for placement of a Combat Application Tourniquet-1 (Composite Resources, Rock Hill, South Carolina) directly to the skin 2 inches to 3 inches above the wound. Preferably, placement occurs above the knee or the elbow of the injured extremity to insure adequate compression of inflow to the injured extremity.

Although commonly used in the military setting, tourniquet use in civilian prehospital trauma care currently is not common. This is primarily related to the differences in wounding mechanisms and patterns as well as short transport times, particularly in more urban locations. Current recommendations are to use a tourniquet if hemorrhage cannot be controlled with direct pressure, a pressure dressing, or selective clamping of bleeding vessels.[28] A recent review of experience with isolated exsanguinating extremity hemorrhage from penetrating injury in one community noted that although infrequent, more than half of the patients that succumbed to their injury had bleeding from a site that anatomically would have been amenable to tourniquet control.[29]

Based on the military experience and improvements in tourniquet technology, some emergency medical personnel are being trained in tourniquet application. The 6th edition of *PHTLS: Prehospital Trauma Life Support* endorses the use of tourniquets before extrication and transport if direct pressure or a pressure dressing fail to control hemorrhage.[30] Widespread familiarity with indications for tourniquet use and proper application technique could also have benefits in disaster or mass casualty situations in the future where extremity injuries amenable to tourniquet application.

Approaches to Noncompressible Hemorrhage

The issue of noncompressible torso hemorrhage is discussed in detail by Morrison and Rasmussen elsewhere in this issue. A brief review, however, of the prehospital management of this problem is also warranted.

A new variety of tourniquet has recently been developed to compress the abdominal aorta in instances of exsanguinating lower-extremity junctional hemorrhage, massive blood loss from areas proximal to the inguinal ligaments, buttocks, perineum, gluteal, and pelvic areas. The tourniquet is designed to wrap around the abdomen and has a wedge shaped anterior portion inflated by a hand pump to compress the aorta near the umbilicus.[31] The device has recently been given premarket clearance by the US Food and Drug Administration (FDA) and has started production for orders received by the US military and other law enforcement agencies.[32] The concept for this device is supported in part by research by Blaivas and colleagues,[33] who evaluated cessation of blood flow in the common femoral arteries during external compression and showed that a weight of 140 pounds to the distal abdominal aorta or 120 pounds to the proximal iliac artery was adequate to stop blood through the common femoral artery.

Aortic occlusion to increase or preserve central perfusion can also be attained via an endovascular technique.[34–36] Although not yet adopted in resuscitative practices, the technique for endovascular occlusion of the aorta has been well described.[34] When comparing the two techniques to no aortic occlusion in a large animal hemorrhagic shock model, endovascular occlusion animals had more normal pH, had lower serum lactate, and required less fluid and vasopressor resuscitation than the aortic clamping group while maintaining similar aortic pressure, carotid blood flow, and brain oximetry.[36] Although neither technique is currently used in the prehospital setting, as the technology and expertise with femoral access techniques improve along with the capabilities of providers in the prehospital environment, it is interesting to speculate whether or not this maneuver could find its way into the prehospital environment as a means of providing control for noncompressible hemorrhage.

The role of topical hemostatic agents in controlling hemorrhage had been limited to primarily combat resuscitation; however, more recently, their use has become more commonplace in civilian prehospital practice. In general, the compounds are useful in curtailing massive hemorrhage from deep, penetrating wounds, particularly in junctional zones, such as the groin, axilla, and base of the neck. The ideal topical hemostatic agent has been described as having the ability to stop both arterial and venous hemorrhage, working quickly, packaged ready-to-use, simple to apply, lightweight, durable, risk-free, and inexpensive.[37,38] Although an agent that meets these exact specifications has not yet been developed, the three most common classes of topical hemostatic compounds are:

- Mucoadhesive agents (eg, WoundStat, HemCon, and Celox)
- Procoagulant supplementors (eg, QuikClot Combat Gauze)
- Clotting factor concentrators (eg, QuikClot Zeolite granular and QuikClot ACS+).

Mucoadhesive agents work by creating a seal over bleeding wounds, specifically the positively charged complex binds to the negatively charged red blood cells and forms a clot that hardens. Procoagulant supplementors deliver additional clotting factors or active existing clotting factors directly at the point of hemorrhage. Lastly, the clotting factor concentrators work through the rapid hemoconcentration at the bleeding site, resulting in concentration of platelets and clotting factor proteins.

All agents have shown benefit over traditional field dressing gauze application in animal models of hemorrhage.[37,39–41] In a recent comparison of hemostatic agents, Clay and colleagues[39] investigated the effectiveness of several topical hemostatic agents compared with traditional gauze in a swine extremity hemorrhage model and found all topical hemostatic agents resulted in less blood loss and improved survival versus standard gauze field dressing. Specifically, WoundStat achieved 100% survival

whereas Celox, HemCon, and QuikClot ACS+ attained 85% survival. Traditional field gauze application resulted in 100% mortality. Furthermore, in a recent comprehensive review of hemostatic dressings, Granville-Chapman and colleagues reviewed 60 articles comparing hemostatic agents in venous, arterial, mixed venous-arterial hemorrhage. They report that although the early topical hemostatics (HemCon and QuikClot) improved hemostasis in animal hemorrhage models versus traditional gauze application; the newer agents (WoundStat, QuikClot Combat Gauze, and Celox) delivered more superior hemorrhage control, with WoundStat 100% effective in controlling hemorrhage.[37]

Although they show efficacy, there are safety concerns that have been outlined related to these agents. The initial formulation of QuikClot, made from Zeolite granules, created a significant exothermic reaction related to the rapid dehydration effect of the product that could lead to thermal injury and necrosis of tissues.[42] This reaction was confirmed in case reports documenting significant burns to the skin and surrounding tissues. In earlier experiments with WoundStat, granular particles were identified in the tissues by histology, raising the possibility of thrombogenic potential. On further investigation by Kheirabadi and colleagues,[43] they noted WoundStat caused occlusive thrombus in injured vessels and significant irreparable damage to the endothelium precluding surgical repair. WoundStat granules were also seen in systemic circulation as emboli in the lungs. An additional concern is ease of removal of the product as the powder-based and granule-based products require multiple surgical washouts to remove compared with the gauze type products. Due to these concerns, the first-generation formulation of QuikClot has been replaced with second-generation and third-generation products and WoundStat has been removed from the market. Currently, QuikClot Combat Gauze is the hemostatic agent of choice for military use and is incorporated in TCCC guidelines. Similar to tourniquet application, the use of hemostatic agents in the civilian prehospital care setting is currently limited in scope and application compared with military use.

PREHOSPITAL RESUSCITATION

In conjunction with airway control and controlling external hemorrhage, a primary goal of emergency medical service providers is to restore perfusion. Prompt and appropriate access to the intravascular space is crucial for resuscitation with administration of fluids and medications. The placement of large-bore peripheral intravenous catheters is still the standard of care. Vascular access, however, is not always feasible and an alternative approach must be used. The use of intraosseous (IO) devices has steadily increased over time and become more commonplace. The concept of accessing the bone marrow, which can act as a noncollapsible conduit to the central circulation, was first described in 1922.[44] Although IO devices were often used in the 1930s and 1940s, their use dissipated with the advent of plastic catheters and better techniques for intravascular access. In recent years, however, there has been a resurgence of interest in the IO route for resuscitation and the FDA has approved several IO catheters and insertion systems, including automatic and spring-loaded systems for insertion into the tibia, sternum, and humerus.[45–47] Use of the IO devices, with focus on sternal placement, has been incorporated in TCCC guidelines and training and are commonly deployed in EMS systems for use in the both pediatric and adult civilian trauma.

The traditional treatment regimen for trauma patients is aggressive fluid resuscitation to restore circulating volume and systolic blood pressure (SBP) to a minimum of 90 mm Hg. The current guideline endorsed by the American College of Surgeons Committee on Trauma and the Advanced Trauma Life Support (ATLS) course is to

resuscitate all trauma patients with 2 L or more of crystalloid after injury.[28,48] Since the 1960s, both crystalloid and colloid solutions have been used to correct hypotension during the resuscitation of injured patients. The principle of aggressive fluid resuscitation is based on the belief that the administration of fluids results in greater likelihood of survival after severe hemorrhage compared with no treatment. These original experiments were fraught with limitations because the studies were animal trials designed to control hemorrhage before the initiation of fluid resuscitation. In these trials there was improved survival with early administration of intravenous fluids. Although external control of compressible hemorrhage is a tenet of prehospital resuscitation, patients with life-threatening surgical bleeding not amenable to compression do not achieve hemostasis before fluid administration in the field. Aggressive resuscitation in this scenario could in theory lead to more blood loss than a strategy of limited volume resuscitation.

Although there is a growing body of evidence regarding the issue of prehospital fluid administration, there is no consensus and little has changed with the approach in the prehospital arena. For example, conventional civilian prehospital practice uses either normal saline (NS) or lactated Ringer (LR) solution for resuscitation, but there is ongoing debate regarding which solution is better, which patients require fluid administration, and how much fluid to give. Currently there are several options under consideration and investigation.

- No fluids
- Crystalloid (isotonic or hypertonic)
- Colloids
- Oxygen-carrying solutions
- Blood products.

The concept of withholding resuscitation and allowing for permissive hypotension in patients with ongoing hemorrhage dates back to World War I.[49] This concept has been adopted into the management of several medical conditions, including major gastrointestinal hemorrhage and aortic aneurysm rupture, and has been shown to increase survival in select groups of injured patients.[50,51] The theory of worsening hemorrhage associated with intravenous fluid administration is based on the concept that excess fluid dilutes clotting factors and increased hydraulic pressure leads to "popping the clot."[49,52] Permissive hypotensive resuscitation or delayed resuscitation may result in early reintroduction of clotting factors and minimize tissue edema with improved oxygen exchange.[53,54] In a systematic review of the literature, it was observed that in all animal trials investigating hypotensive resuscitation, restriction of fluid was associated with reduced risk of death.[54] In the most well-known and described clinical study to date evaluating delayed resuscitation in a human clinical trial, standard resuscitation in the field was compared with delayed resuscitation initiated only after the patient reached the operating room in 598 hypotensive patients with penetrating injury to the torso. Mean SBP on hospital arrival was 79 $\pm$ 46 mm Hg in the immediate group and 72 $\pm$ 43 mm Hg in the delayed group ($P = .02$). Blood pressure on arrival to the operating room was similar. Mortality was 62% in the delayed resuscitation group versus 70% in the standard resuscitation group, a statistically significant difference.[50] Although these results are compelling, this study was a single institution study in an urban setting that enrolled only those with penetrating torso injury. Despite the evidence showing benefit, these limitations have kept this approach from becoming more widely adopted. A multicenter trial evaluating limited crystalloid resuscitation in both blunt and penetrating trauma patients in mixed urban and rural settings organized by the Resuscitation Outcomes Consortium (ROC)[55] is currently under way. This

study will limit the use of crystalloid infusion for hypotensive patients in both the prehospital setting and for up to 2 hours in hospital or until surgical control of hemorrhage has been achieved. In contrast to the civilian setting, permissive hypotension with administration of limited amounts of fluids (maximum of two 500-mL boluses of Hextend a minimum of 30 minutes apart) is the current standard of care in the field for treatment of combat casualties and has been adopted in TCCC guidelines. Although the basis for this decision is in part related to judicious use of a limited resource in the far forward military environment, the cumulative literature regarding limited resuscitation provides additional rationale for this approach.

Regarding the NS versus LR debate, several studies, both human and animal, have evaluated the difference between the two, with NS resuscitation resulting in significantly higher sodium and chloride values with lower bicarbonate and pH levels.[56–58] Additionally, in a porcine animal study where resuscitation was initiated after animals sustained a grade V liver injury, the animals resuscitated with NS after 30 minutes of uncontrolled hemorrhage lost twice as much blood as those resuscitated with LR, required more fluid to maintain adequate blood pressure, and were more coagulopathic.[58] Currently, ATLS guidelines recommend LR as the initial resuscitative fluid and NS as an alternative.[28] Despite this recommendation, however, a majority of EMS agencies continue to use NS exclusively in the prehospital arena, mostly because of the compatibility of NS with medication administration in medical emergencies and the logistic and cost issues associated with deploying two different types of crystalloids. Further research and clinical trials need to be performed to evaluate the relative safety and efficacy of both fluids as well as other newer generation isotonic alternatives in prehospital trauma care.

Several studies, including a large multicenter, randomized controlled trial have investigated the potential benefits of hypertonic saline (HS) resuscitation after injury.[5,59–62] HS has been shown to decrease inflammation, improve organ perfusion, and limit organ injury in many animal studies; however, the clinical trials of HS resuscitation compared with isotonic fluids have not shown improvements in survival. In the largest and most recent randomized placebo-controlled trial investigating the effectiveness of HS solutions to date, 7.5% HS with and without 6% dextran-70 was compared with NS in patients with hemorrhagic shock or traumatic brain injury. A total of 853 patients were enrolled in the hemorrhagic shock arm and 1282 patients in the traumatic brain injury arm. Both studies were stopped early, however, on the basis of futility, because there was no observed benefit in survival or neurologic outcome.[60,63]

There are some promising data suggesting select colloid solutions may provide survival benefit. Hextend, 6% hetastarch in lactated electrolyte buffer, is a colloid solution approved for use in hypovolemic patients undergoing elective surgery. In the first report discussing the safety and efficacy of hetastarch during the initial resuscitation of trauma patients, Ogilvie and colleagues[64,65] determined hetastarch was safe and resulted in reduced deaths and overall mortality compared with standard crystalloid resuscitation. Despite its potential benefit, there are concerns related to the use of colloid solutions, including the potential for anaphylaxis and coagulopathy.[66] As discussed previously, Hextend is currently the initial fluid used in limited quantities for combat casualty resuscitation in the field under TCCC guidelines. It is currently not commonly used in civilian prehospital practice.

All the fluids discussed previously can provide some volume expansion capabilities and improve blood pressure; however, none of these agents possesses any oxygen carrying capability. Third-generation hemoglobin-based oxygen carriers, acellular hemoglobin solutions derived from either outdated human blood stores (PolyHeme) or from bovine blood (Hemopure), held great promise as candidate resuscitative

agents for prehospital use.[67–70] In addition to their oxygen-carrying capacity, they had the additional benefit of being heat stable with long shelf lives and the ability to adequately resuscitate after hemorrhage in low volumes.[71] All of these characteristics made them ideal for use in the prehospital civilian and combat casualty care situations. A randomized clinical trial using PolyHeme, however, failed to show a mortality benefit[72] and the FDA did not approve the planned Navy-sponsored RESUS prehospital trauma study using Hemopure.[73] The primary concern with these products is the nitric oxide scavenging effect associated with the cell-free hemoglobin with the end result of increased blood pressure and concerns for increased bleeding, stroke, and myocardial infarction in at risk populations. The potential for use of oxygen-carrying solutions in prehospital resuscitation is at the current time limited and will rely on the development of newer products capable of oxygen-carrying capacity with limited nitric oxide scavenging potential.

The deployment of blood components in the prehospital setting is becoming more frequent, particularly in rotary wing transport. Currently, there are multiple air services that carry packed red blood cells with a few also carrying plasma. Although contemporary data on experience with the use of prehospital blood products are currently limited, more information about the utility of this approach should become available as these sites gain clinical expertise and ultimately publish their experience. Additionally, the Department of Defense has recently funded research grants to evaluate the prehospital use of plasma for traumatic hemorrhage.[74] The development of lyophilized formulations of fresh frozen plasma will also make prehospital plasma use logistically more appealing.[75,76]

In addition to the primary resuscitation agents discussed previously, there are several potential resuscitative adjuncts that could be used prehospital to improve outcomes for trauma patients, with some undergoing active investigation. The prehospital administration of arginine vasopressin in injured patients who do not respond to standard resuscitation fluids may be beneficial through enhancing and prolonging the compensatory mechanisms that respond to shock and by shunting blood centrally to maintain blood flow to the heart, brain, and kidneys.[77–80] Arginine vasopressin is an endogenous hormone that is known to be beneficial in septic shock and cardiopulmonary arrest.[81] In a small, randomized, double-blinded study, hypotensive trauma patients who were given a low-dose arginine vasopressin infusion compared with saline alone required less fluid for resuscitation and trended toward early survival advantage, although no statistical difference was observed.[80] A large international multicenter, randomized controlled trial (Vasopressin in Refractory Traumatic Hemorrhagic Shock [VITRIS]) has been designed to investigate the effects of prehospital arginine vasopressin in injured hemorrhagic shock patients and is currently enrolling patients.[82]

Tranexamic acid (TXA), an antifibrinolytic agent that has been used since the 1960s to control bleeding from blood dyscrasias, gastrointestinal sources, and surgical sites, is also being evaluated as an adjunct to trauma resuscitation of trauma patients.[83] TXA inhibits both plasminogen activation and plasmin activity, thus preventing the breakdown of formed clot. In a recent large, multicenter, randomized, double-blind, placebo-controlled trial (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage 2 [CRASH 2]), more than 20,000 adult trauma patients were enrolled and randomized. The population who received TXA had a significant reduction in all-cause mortality and an overall reduction in death secondary to hemorrhage. There was no observed difference in amount of blood transfusions administered between groups. Further analysis suggested greater benefit was observed if TXA was administered within 3 hours of injury.[83,84] A recent retrospective military-based study

comparing outcomes in patients who had received TXA with those who did not receive TXA showed improved mortality in the group that received the drug, particularly for those who received a massive transfusion.[85] Although studies to date have focused primarily on in hospital administration of the drug, prehospital trials have been discussed to evaluate if early administration of TXA would extend the reported benefits of in hospital treatment.

Basic scientific studies have long espoused the beneficial effect of administration of estrogen after trauma regardless of gender or age.[86,87] Of particular interest to prehospital care is the ability of a single dose of 17β-estradiol to improve survival in male animals after trauma hemorrhage even in the absence of fluid administration.[88] There are currently 2 pilot studies being performed in ROC, 1 in patients with hemorrhagic shock and another in patients with traumatic brain injury (Resuscitative Endocrinology: Single-dose Clinical Uses for Estrogen [RESCUE]). The purpose of these initial studies is to assess the feasibility and safety of a single dose of intravenous Premarin prior to moving forward with larger, multicenter prehospital trials.

IDENTIFICATION OF OCCULT SHOCK

Since the mid-twentieth century, hypotension and shock were defined as an SBP less than or equal to 90 mm Hg. Little scientific evidence is available, however, to support the belief that actual tissue hypoperfusion or ischemia is first observed or limited to patients with SBP less than or equal to 90 mm Hg. More recent reports suggest that SBP less than or equal to 110 mm Hg more accurately reflects the first clinical evidence of hypoperfusion.[89–92] Furthermore, some investigators suggest the use of SBP alone is unreliable and cannot accurately assess tissue hypoperfusion or shock.[93,94]

Adjuncts to traditional vital signs are commercially available for prehospital use and are being tested in the prehospital setting. Simple point-of-care devices (similar to glucometers) along with specific monitors to analyze heart rate variability and tissue oxygenation saturations are promising and will undoubtedly provide additional benefit in recognizing hypoperfusion and shock, even in the chaotic prehospital setting. Adjuncts, specifically point-of-care blood lactate, have been studied by several investigators and found a reliable predictor of postinjury hemorrhage. Lactate elevations are associated with the need for hospital admission, ICU admission, emergent intervention, and death.[95,96] In a study of more than 2000 patients with borderline hypotension, defined as SBP between 90 mm Hg and 110 mm Hg, serum lactate obtained immediately on arrival to the emergency department was more predictive than blood pressure, obtained either prehospital or on arrival to the emergency department, in predicting the need for greater than 6 units of red blood cell transfusion within 24 hours of arrival and mortality.[95] Furthermore, Guyette and colleagues[96] measured prehospital point-of-care blood lactate in more than 1000 patients and found that higher values are predictive and that addition of blood lactate levels to initial vital signs and Glasgow Coma Scale score significantly increased the predictability of need for urgent operation, multiple organ dysfunction syndrome, and mortality. This study has now been extended to a multicenter prehospital trial (Biomarker Lactate Assessment of Shock in Trauma [BLAST]). The primary aim of the study is to evaluate prehospital lactate in comparison to SBP for the ability to predict the need for resuscitative care (the administration of packed red blood cells or emergent intervention for hemorrhage control using thoracotomy, laparotomy, pelvic fixation, or interventional radiologic control) or death within 6 hours of emergency department arrival.

The noninvasive prehospital adjuncts have been useful in identifying patients with increased mortality or need for massive transfusion. The shock index (SI), a calculation

of heart rate divided SBP, is a simple method that has been shown to be more predictive of mortality within 48 hours than heart rate or SBP alone. In a study of more than 8000 normotensive patients with SBP greater than 90 mm Hg, prehospital vital signs were used to calculate SI, and SI greater than 0.9 was associated with significant increase likelihood of needed massive transfusion, longer length of stay, and not surviving the injuries sustained. From this analysis, the investigators concluded the SI was able to identify patients at high risk for needing massive transfusion although they were reported to be hemodynamically stable en route.[97] Zarzaur and colleagues[98] further investigated the utility of the SI in the older populations greater than 54 years old and found that age $\times$ SI was the best predictor of mortality and need for at least 4 units of blood transfusion. Although these studies suggest a that SI may be a useful adjunct in predicting sicker patients, further prospective studies will need to be performed to determine the practical utility of this measure with regard to field trauma triage.

In a study by Sagraves and colleagues,[99] use of the InSpectra StO_2 (Hutchinson Technology) tissue oxygen monitor was evaluated in the prehospital environment for feasibility and predictive ability. They concluded that the monitors were easy to use without interference from other monitoring systems or avionics. The device was able to distinguish between survivors and nonsurvivors with a 3-fold increase in mortality for every 10% drop in StO_2 reading.

The ability of an injured patient to compensate and maintain blood pressure during hemorrhagic blood loss is secondary to the inherent autonomic responses of the patient. Heart rate variability, as determined by ECG analysis, may be able to characterize the autonomic compensation of a patient to loss of blood volume and, therefore, be used in field triage of trauma victims. Cooke and colleagues[100] have investigated heart rate variability in the prehospital environment. In their study, ECG tracings from on-board monitors obtained during transport from the scene of injury to the emergency department were analyzed using commercially available software. Heart rate variability of patients who died was compared with the tracings of those who survived and differences in R-R intervals were reported in the patients who died from hemorrhagic shock. This study was limited by its retrospective nature and the need for clean ECG data that excluded a large number of patients from the analysis. Although these results are intriguing, it is unknown at this time whether these measures will add any additional real-time information and triage accuracy to the field provider.

PREHOSPITAL RESEARCH INFRASTRUCTURE

In the care of severely injured trauma patients, timely intervention and transport to an appropriate level of care are paramount to improve the chance of survival. Although prehospital care has greatly improved with the development of trauma systems of care, the infrastructure to evaluate new interventions in the field and to translate promising scientific and clinical advances into improved outcomes has only been recently developed. The ROC is a clinical trial network focusing on research in the area of prehospital cardiopulmonary arrest and severe traumatic injury. The National Heart, Lung, and Blood Institute primarily funds the network with additional support from the American Heart Association, the United States Army Medical Research and Materiel Command, the Canadian Institutes of Health Research, the Heart and Stroke Foundation of Canada, and Defence Research and Development Canada. The network consists of 10 primary regional clinical centers along with many satellite centers and is tasked with performing both prehospital trauma and cardiac arrest trials. The network has allowed the clinical sites involved in the research to actively engage their

prehospital care providers in the design and implementation of studies aimed at prehospital care. Along with interventional clinical trials, the network has an ongoing observational data collection and evaluation component. The end result of these collaborations is establishment of a sustainable research infrastructure able to rapidly design and implement needed studies as well as the fostering of a prehospital research culture that will stimulate further ideas and organized approaches to systematically evaluate prehospital care. The cumulative effect has great potential to rapidly transform prehospital care in the coming years.

Much of the difficulty in performance of prehospital research lies in the ability to obtain informed consent. Although informed consent is a fundamental of human research subjects, there are instances when it is not possible. Inherently, research in the prehospital or emergency setting is difficult because the critical nature of the patient population and limited amount of time to enroll patients. Research on emergency patients was traditionally performed using deferred consent; however, the ability to perform emergency research using this mechanism was halted in 1993. With the passage of the Final Rule in 1996 by the FDA, which has oversight authority for medical research, emergency and prehospital research was allowed under what has become known as exception from informed consent.

The FDA Final Rule (21 CFR 50.24) has several conditions that all must be met and justified to perform emergency research under this mechanism:

1. The human subjects are in a life-threatening condition and valid scientific evidence is available that indicates the safety and effectiveness of the intervention.
2. Obtaining informed consent from patients or their legally authorized representative is not feasible because of a patient's condition; the intervention must be administered before obtaining consent is possible; or there is no way to prospectively identify the individuals likely to become eligible for the research.
3. Participation in the research holds the prospect of direct benefit based on the life-threatening condition of the patient, appropriate preclinical and clinical evidence of benefit, and an appropriate risk-to-benefit ratio.
4. The research could not practically be performed without the waiver.
5. The research protocol defines the therapeutic window and the investigator is committed to the obtaining the legally authorized representative consent during the window.
6. The local institutional review board has approved informed consent documents that could be used during the therapeutic window.
7. Additional protections of a patient's rights and welfare will be provided to include community consultation, public disclosure, and a commitment from the research team to contact family members if the patient cannot consent or the legally authorized representative is not available.

In the years after passage of the Final Rule, an increasing number of research trials have been conducted in all areas of emergency care, but there are limitations. In addition to the expanded cost, time, and administration to supply community consultation, there is a concern of introducing bias in study results if patients or their legally authorized representative does not consent to allow review of records after initial enrollment under the waiver of consent. Nichol and colleagues[101] state the importance of further review of the medical records as endpoints, such as survival to discharge. Furthermore, they suggest the exception of consent should extend to allow review of the medical record, because the benefit would include a more thorough assessment of outcomes and adverse effects; this would allow a reduction in bias at the expense of minimal risk related to confidentiality.[101] The regulations allowing waiver of informed

consent included specific clauses to protect enrollment of racial and ethnic minorities in emergency research. In a recent study, Sugarman and colleagues[102] retrospectively compared registry enrollment with trial enrollment from sites participating in the ROC HS trial. After comparison of the patients enrolled in the observational trial registry, there were no racial or ethnical differences observed among those enrolled in the interventional trials.

Performance of research in the prehospital setting is an evolving process. As more studies are performed, more will be learned about the effectiveness of the community consultation and public disclosure practices and the acceptance of the public regarding these studies and consent procedures.[103,104]

REFERENCES

1. Stewart RM, Myers JG, Dent DL, et al. Seven hundred fifty-three consecutive deaths in a level I trauma center: the argument for injury prevention. J Trauma 2003;54(1):66–70 [discussion: 70–1].
2. MacLeod JB, Cohn SM, Johnson EW, et al. Trauma deaths in the first hour: are they all unsalvageable injuries? Am J Surg 2007;193(2):195–9.
3. Trunkey DD. Trauma. Accidental and intentional injuries account for more years of life lost in the U.S. than cancer and heart disease. Among the prescribed remedies are improved preventive efforts, speedier surgery and further research. Sci Am 1983;249(2):28–35.
4. Bulger EM, Copass MK, Maier RV, et al. An analysis of advanced prehospital airway management. J Emerg Med 2002;23(2):183–9.
5. Bulger EM, Nathens AB, Rivara FP, et al. National variability in out-of-hospital treatment after traumatic injury. Ann Emerg Med 2007;49(3):293–301.
6. Vandromme MJ, Melton SM, Griffin R, et al. Intubation patterns and outcomes in patients with computed tomography-verified traumatic brain injury. J Trauma 2011;71(6):1615–9.
7. Davis DP, Koprowicz KM, Newgard CD, et al. The relationship between out-of-hospital airway management and outcome among trauma patients with Glasgow Coma Scale Scores of 8 or less. Prehosp Emerg Care 2011;15(2):184–92.
8. Strote J, Roth R, Cone DC, et al. Prehospital endotracheal intubation: the controversy continues (conference proceedings). Am J Emerg Med 2009;27(9):1142–7.
9. Winchell RJ, Hoyt DB. Endotracheal intubation in the field improves survival in patients with severe head injury. Trauma Research and Education Foundation of San Diego. Arch Surg 1997;132(6):592–7.
10. Davis DP, Fakhry SM, Wang HE, et al. Paramedic rapid sequence intubation for severe traumatic brain injury: perspectives from an expert panel. Prehosp Emerg Care 2007;11(1):1–8.
11. Wang HE, Kupas DF, Paris PM, et al. Multivariate predictors of failed prehospital endotracheal intubation. Acad Emerg Med 2003;10(7):717–24.
12. Wang HE, Kupas DF, Greenwood MJ, et al. An algorithmic approach to prehospital airway management. Prehosp Emerg Care 2005;9(2):145–55.
13. Bochicchio GV, Ilahi O, Joshi M, et al. Endotracheal intubation in the field does not improve outcome in trauma patients who present without an acutely lethal traumatic brain injury. J Trauma 2003;54(2):307–11.
14. Wang HE, Peitzman AB, Cassidy LD, et al. Out-of-hospital endotracheal intubation and outcome after traumatic brain injury. Ann Emerg Med 2004;44(5):439–50.

15. Gausche M, Lewis RJ, Stratton SJ, et al. Effect of out-of-hospital pediatric endotracheal intubation on survival and neurological outcome: a controlled clinical trial. JAMA 2000;283(6):783–90.
16. Cobas MA, De la Peña MA, Manning R, et al. Prehospital intubations and mortality: a level 1 trauma center perspective. Anesth Analg 2009;109(2):489–93.
17. Stockinger ZT, McSwain NE. Prehospital endotracheal intubation for trauma does not improve survival over bag-valve-mask ventilation. J Trauma 2004; 56(3):531–6.
18. Davis DP, Hoyt DB, Ochs M, et al. The effect of paramedic rapid sequence intubation on outcome in patients with severe traumatic brain injury. J Trauma 2003; 54(3):444–53.
19. Davis DP, Peay J, Sise MJ, et al. The impact of prehospital endotracheal intubation on outcome in moderate to severe traumatic brain injury. J Trauma 2005; 58(5):933–9.
20. Sloane C, Vilke GM, Chan TC, et al. Rapid sequence intubation in the field versus hospital in trauma patients. J Emerg Med 2000;19(3):259–64.
21. Langeron O, Birenbaum A, Amour J. Airway management in trauma. Minerva Anestesiol 2009;75(5):307–11.
22. Bjoernsen LP, Lindsay B. Video laryngoscopy in the prehospital setting. Prehosp Disaster Med 2009;24(3):265–70.
23. Bellamy RF. The causes of death in conventional land warfare: implications for combat casualty care research. Mil Med 1984;149(2):55–62.
24. Acosta JA, Yang JC, Winchell RJ, et al. Lethal injuries and time to death in a level I trauma center. J Am Coll Surg 1998;186(5):528–33.
25. Welling DR, McKay PL, Rasmussen TE, et al. A brief history of the tourniquet. J Vasc Surg 2012;55(1):286–90.
26. Kragh JF, Walters TJ, Baer DG, et al. Practical use of emergency tourniquets to stop bleeding in major limb trauma. J Trauma 2008;64(Suppl 2):S38–49 [discussion: S49–50].
27. Kragh JF Jr, Walters TJ, Baer DG, et al. Survival with emergency tourniquet use to stop bleeding in major limb trauma. Ann Surg 2009;249(1):1–7.
28. Surgeons ACo. Advanced trauma life support for doctors—student course manual. 8th edition. Chicago: American College of Surgeons; 2010.
29. Dorlac WC, DeBakey ME, Holcomb JB, et al. Mortality from isolated civilian penetrating extremity injury. J Trauma 2005;59(1):217–22.
30. NAEMT's PHTLS: Prehospital Trauma Life Support. 6th edition. Mosby; 2007.
31. Greenfield EM, Schwartz RB, Croushorn JM, et al. Efficacy and safety of a novel abdominal tourniquet device for the control of pelvic and lower extremity hemorrhage. Paper presented at: 16th World Congress for Disaster and Emergency Medicine. Victoria, BC, Canada, May 12–15, 2009.
32. Baker T. Emergency medicine physicians develop device to stop lethal bleeding in soldiers. 2012. Available at: http://news.georgiahealth.edu/archives/5001. Accessed January 25, 2012.
33. Blaivas M, Shiver S, Lyon M, et al. Control of hemorrhage in critical femoral or inguinal penetrating wounds–an ultrasound evaluation. Prehosp Disaster Med 2006;21(6):379–82.
34. Stannard A, Eliason JL, Rasmussen TE. Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) as an Adjunct for Hemorrhagic Shock. J Trauma 2011;71(6):1869–72.
35. White JM, Cannon JW, Stannard A, et al. A porcine model for evaluating the management of noncompressible torso hemorrhage. J Trauma 2011;71(Suppl 1):S131–8.

36. White JM, Cannon JW, Stannard A, et al. Endovascular balloon occlusion of the aorta is superior to resuscitative thoracotomy with aortic clamping in a porcine model of hemorrhagic shock. Surgery 2011;150(3):400–9.
37. Granville-Chapman J, Jacobs N, Midwinter MJ. Pre-hospital haemostatic dressings: a systematic review. Injury 2011;42(5):447–59.
38. Pusateri AE, McCarthy SJ, Gregory KW, et al. Effect of a chitosan-based hemostatic dressing on blood loss and survival in a model of severe venous hemorrhage and hepatic injury in swine. J Trauma 2003;54(1):177–82.
39. Clay JG, Grayson JK, Zierold D. Comparative testing of new hemostatic agents in a swine model of extremity arterial and venous hemorrhage. Mil Med 2010; 175(4):280–4.
40. Ward KR, Tiba MH, Holbert WH, et al. Comparison of a new hemostatic agent to current combat hemostatic agents in a Swine model of lethal extremity arterial hemorrhage. J Trauma 2007;63(2):276–83 [discussion: 283–4].
41. Alam HB, Uy GB, Miller D, et al. Comparative analysis of hemostatic agents in a swine model of lethal groin injury. J Trauma 2003;54(6):1077–82.
42. Wright JK, Kalns J, Wolf EA, et al. Thermal injury resulting from application of a granular mineral hemostatic agent. J Trauma 2004;57(2):224–30.
43. Kheirabadi BS, Mace JE, Terrazas IB, et al. Safety evaluation of new hemostatic agents, smectite granules, and kaolin-coated gauze in a vascular injury wound model in swine. J Trauma 2010;68(2):269–78.
44. Drinker CK, Drinker KR, Lund CC. The circulation in the mammalian bone marrow. Am J Physiol 1922;62:92.
45. Byars DV, Tsuchitani SN, Erwin E, et al. Evaluation of success rate and access time for an adult sternal intraosseous device deployed in the prehospital setting. Prehosp Disaster Med 2011;26(2):127–9.
46. Paxton JH, Knuth TE, Klausner HA. Proximal humerus intraosseous infusion: a preferred emergency venous access. J Trauma 2009;67(3):606–11.
47. Hulse EJ, Thomas GO. Vascular access on the 21st century military battlefield. J R Army Med Corps 2010;156(4 Suppl 1):385–90.
48. Kortbeek JB, Al Turki SA, Ali J, et al. Advanced trauma life support, 8th edition, the evidence for change. J Trauma 2008;64(6):1638–50.
49. Cannon WB, Fraser J, Cowell EM. The preventive treatment of wound shock. J Am Med Assoc 1918;70:618–21.
50. Bickell WH, Wall MJ, Pepe PE, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. N Engl J Med 1994; 331(17):1105–9.
51. Dutton RP, Mackenzie CF, Scalea TM. Hypotensive resuscitation during active hemorrhage: impact on in-hospital mortality. J Trauma 2002;52(6): 1141–6.
52. Sondeen JL, Coppes VG, Holcomb JB. Blood pressure at which rebleeding occurs after resuscitation in swine with aortic injury. J Trauma 2003;54(Suppl 5): S110–7.
53. Stern SA, Wang X, Mertz M, et al. Under-resuscitation of near-lethal uncontrolled hemorrhage: effects on mortality and end-organ function at 72 hours. Shock 2001;15(1):16–23.
54. Mapstone J, Roberts I, Evans P. Fluid resuscitation strategies: a systematic review of animal trials. J Trauma 2003;55(3):571–89.
55. Resuscitation outcomes consortium. Available at: https://roc.uwctc.org. Accessed January 16, 2012.

56. Reid F, Lobo DN, Williams RN, et al. (Ab)normal saline and physiological Hartmann's solution: a randomized double-blind crossover study. Clin Sci (Lond) 2003;104(1):17–24.
57. Scheingraber S, Rehm M, Sehmisch C, et al. Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. Anesthesiology 1999;90(5):1265–70.
58. Kiraly LN, Differding JA, Enomoto TM, et al. Resuscitation with normal saline (NS) vs. lactated ringers (LR) modulates hypercoagulability and leads to increased blood loss in an uncontrolled hemorrhagic shock swine model. J Trauma 2006;61(1):57–64 [discussion: 64–5].
59. Brasel KJ, Bulger E, Cook AJ, et al. Hypertonic resuscitation: design and implementation of a prehospital intervention trial. J Am Coll Surg 2008;206(2): 220–32.
60. Bulger EM, May S, Brasel KJ, et al. Out-of-hospital hypertonic resuscitation following severe traumatic brain injury: a randomized controlled trial. JAMA 2010;304(13):1455–64.
61. Vassar MJ, Perry CA, Holcroft JW. Analysis of potential risks associated with 7.5% sodium chloride resuscitation of traumatic shock. Arch Surg 1990; 125(10):1309–15.
62. Vassar MJ, Perry CA, Holcroft JW. Prehospital resuscitation of hypotensive trauma patients with 7.5% NaCl versus 7.5% NaCl with added dextran: a controlled trial. J Trauma 1993;34(5):622–32 [discussion: 632–3].
63. Bulger EM, May S, Kerby JD, et al. Out-of-hospital hypertonic resuscitation after traumatic hypovolemic shock: a randomized, placebo controlled trial. Ann Surg 2011;253(3):431–41.
64. Ogilvie MP, Pereira BM, McKenney MG, et al. First report on safety and efficacy of hetastarch solution for initial fluid resuscitation at a level 1 trauma center. J Am Coll Surg 2010;210(5):870–80, 880–72.
65. Ogilvie MP, Ryan ML, Proctor KG. Hetastarch during initial resuscitation from trauma. J Trauma 2011;70(Suppl 5):S19–21.
66. Bunn F, Trivedi D, Ashraf S. Colloid solutions for fluid resuscitation. Cochrane Database Syst Rev 2011;3:CD001319.
67. Manning JE, Katz LM, Brownstein MR, et al. Bovine hemoglobin-based oxygen carrier (HBOC-201) for resuscitation of uncontrolled, exsanguinating liver injury in swine. Carolina Resuscitation Research Group. Shock 2000;13(2):152–9.
68. York GB, Eggers JS, Smith DL, et al. Low-volume resuscitation with a polymerized bovine hemoglobin-based oxygen-carrying solution (HBOC-201) provides adequate tissue oxygenation for survival in a porcine model of controlled hemorrhage. J Trauma 2003;55(5):873–85.
69. Gould SA, Moore EE, Hoyt DB, et al. The first randomized trial of human polymerized hemoglobin as a blood substitute in acute trauma and emergent surgery. J Am Coll Surg 1998;187(2):113–20 [discussion: 120–2].
70. Rice J, Philbin N, Handrigan M, et al. Vasoactivity of bovine polymerized hemoglobin (HBOC-201) in swine with traumatic hemorrhagic shock with and without brain injury. J Trauma 2006;61(5):1085–99.
71. Fitzpatrick CM, Biggs KL, Atkins BZ, et al. Prolonged low-volume resuscitation with HBOC-201 in a large-animal survival model of controlled hemorrhage. J Trauma 2005;59(2):273–81 [discussion: 281–3].
72. Moore EE, Moore FA, Fabian TC, et al. Human polymerized hemoglobin for the treatment of hemorrhagic shock when blood is unavailable: the USA multicenter trial. J Am Coll Surg 2009;208(1):1–13.

73. Quick summary—blood products advisory committee 88th Meeting. 2006. Available at: http://www.fda.gov/ohrms/dockets/ac/06/minutes/2006-4270M.htm. Accessed January 22, 2012.
74. Prehospital use of plasma for traumatic hemorrhage (PUPTH); 2011. Funding Opportunity Number: W81XWH-11-PUPTH-IAA.
75. Spoerke N, Zink K, Cho SD, et al. Lyophilized plasma for resuscitation in a swine model of severe injury. Arch Surg 2009;144(9):829–34.
76. Shuja F, Shults C, Duggan M, et al. Development and testing of freeze-dried plasma for the treatment of trauma-associated coagulopathy. J Trauma 2008; 65(5):975–85.
77. Krismer AC, Wenzel V, Voelckel WG, et al. Employing vasopressin as an adjunct vasopressor in uncontrolled traumatic hemorrhagic shock. Three cases and a brief analysis of the literature. Anaesthesist 2005;54(3):220–4.
78. Voelckel WG, Convertino VA, Lurie KG, et al. Vasopressin for hemorrhagic shock management: revisiting the potential value in civilian and combat casualty care. J Trauma 2010;69(Suppl 1):S69–74.
79. Raab H, Lindner KH, Wenzel V. Preventing cardiac arrest during hemorrhagic shock with vasopressin. Crit Care Med 2008;36(Suppl 11):S474–80.
80. Cohn SM, McCarthy J, Stewart RM, et al. Impact of low-dose vasopressin on trauma outcome: prospective randomized study. World J Surg 2011;35(2): 430–9.
81. Dünser MW, Hasibeder WR, Wenzel V. Vasopressin in septic shock. N Engl J Med 2008;358(25):2736 [author reply: 2737–8].
82. Lienhart HG, Lindner KH, Wenzel V. Developing alternative strategies for the treatment of traumatic haemorrhagic shock. Curr Opin Crit Care 2008;14(3): 247–53.
83. Cap AP, Baer DG, Orman JA, et al. Tranexamic acid for trauma patients: a critical review of the literature. J Trauma 2011;71(Suppl 1):S9–14.
84. Shakur H, Roberts I, Bautista R, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet 2010;376(9734):23–32.
85. Morrison JJ, Dubose JJ, Rasmussen TE, et al. Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study. Arch Surg 2012; 147(2):113–9 [Epub 2011 Oct 17].
86. Angele MK, Schwacha MG, Ayala A, et al. Effect of gender and sex hormones on immune responses following shock. Shock 2000;14(2):81–90.
87. Knoferl MW, Angele MK, Diodato MD, et al. Female sex hormones regulate macrophage function after trauma-hemorrhage and prevent increased death rate from subsequent sepsis. Ann Surg 2002;235(1):105–12.
88. Chen JG, Not L, Ng T, et al. 17 b-estradiol (E2) administration after major blood loss improves liver ATP, 3-hour survival and also long-term survival following prolonged hypotension (3 hour) and fluid resuscitation. Shock 2006;25(Suppl 1):11.
89. Eastridge BJ, Salinas J, McManus JG, et al. Hypotension begins at 110 mm Hg: redefining "hypotension" with data. J Trauma 2007;63(2):291–7 [discussion: 297–9].
90. Eastridge BJ, Salinas J, Wade CE, et al. Hypotension is 100 mm Hg on the battlefield. Am J Surg 2011;202(4):404–8.
91. Edelman DA, White MT, Tyburski JG, et al. Post-traumatic hypotension: should systolic blood pressure of 90-109 mmHg be included? Shock 2007;27(2):134–8.

92. Bruns B, Gentilello L, Elliott A, et al. Prehospital hypotension redefined. J Trauma 2008;65(6):1217–21.
93. Hick JL, Rodgerson JD, Heegaard WG, et al. Vital signs fail to correlate with hemoperitoneum from ruptured ectopic pregnancy. Am J Emerg Med 2001; 19(6):488–91.
94. McGee S, Abernethy WB, Simel DL. The rational clinical examination. Is this patient hypovolemic? JAMA 1999;281(11):1022–9.
95. Vandromme MJ, Griffin RL, Weinberg JA, et al. Lactate is a better predictor than systolic blood pressure for determining blood requirement and mortality: could prehospital measures improve trauma triage? J Am Coll Surg 2010;210(5): 861–7, 867–9.
96. Guyette F, Suffoletto B, Castillo JL, et al. Prehospital serum lactate as a predictor of outcomes in trauma patients: a retrospective observational study. J Trauma 2011;70(4):782–6.
97. Vandromme MJ, Griffin RL, Kerby JD, et al. Identifying risk for massive transfusion in the relatively normotensive patient: utility of the prehospital shock index. J Trauma 2011;70(2):384–8 [discussion: 388–90].
98. Zarzaur BL, Croce MA, Fischer PE, et al. New vitals after injury: shock index for the young and age x shock index for the old. J Surg Res 2008;147(2):229–36.
99. Sagraves SG, Newell MA, Bard MR, et al. Tissue oxygenation monitoring in the field: a new EMS vital sign. J Trauma 2009;67(3):441–3 [discussion: 443–4].
100. Cooke WH, Salinas J, Convertino VA, et al. Heart rate variability and its association with mortality in prehospital trauma patients. J Trauma 2006;60(2):363–70 [discussion: 370].
101. Nichol G, Powell J, van Ottingham L, et al. Consent in resuscitation trials: benefit or harm for patients and society? Resuscitation 2006;70(3):360–8.
102. Sugarman J, Sitlani C, Andrusiek D, et al. Is the enrollment of racial and ethnic minorities in research in the emergency setting equitable? Resuscitation 2009; 80(6):644–9.
103. Holcomb JB, Weiskopf R, Champion H, et al. Challenges to effective research in acute trauma resuscitation: consent and endpoints. Shock 2011;35(2):107–13.
104. Bulger EM, Schmidt TA, Cook AJ, et al. The random dialing survey as a tool for community consultation for research involving the emergency medicine exception from informed consent. Ann Emerg Med 2009;53(3):341–50, e341–2.