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Traumatic Hemorrhagic Shock: Advances In Fluid Management

November 2011
Volume 13, Number 11

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Abstract

A number of concerns have been raised regarding the advisability of the classic principles of aggressive crystalloid resuscitation in traumatic hemorrhagic shock. This issue reviews the advances that have led to a shift in the emergency department (ED) protocols in resuscitation from shock state, including recent literature regarding the new paradigm for the treatment of traumatic hemorrhagic shock, which is most generally known as damage control resuscitation (DCR). Goals and endpoints for resuscitation and a review of initial fluid choice are discussed, along with the coagulopathy of trauma and its management, how to address hemorrhagic shock in traumatic brain injury (TBI), and new pharmacologic treatment for hemorrhagic shock. The primary conclusions include the administration of tranexamic acid (TXA) for all patients with uncontrolled hemorrhage (Class I), the implementation of a massive transfusion protocol (MTP) with fixed blood product ratios (Class II), avoidance of large-volume crystalloid resuscitation (Class III), and appropriate usage of permissive hypotension (Class III). The choice of fluid for initial resuscitation has not been shown to affect outcomes in trauma (Class I).

CME Objectives

Upon completion of this article, you should be able to:

1. Discuss hypotensive resuscitation.
2. Identify the coagulopathy of trauma.
3. Describe the advances in pharmacologic management of hemorrhage.
4. Initiate critical interventions for patients in hemorrhagic shock.

Date of original release: November 1, 2011
Date of most recent review: October 10, 2011
Termination date: November 1, 2014
Medium: Print and Online
Method of participation: Print or online answer form and evaluation
Prior to beginning this activity, see "Physician CME Information" on the back page.

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Case Presentations

In the middle of your Saturday overnight shift, you are called to see a patient who drove himself to the hospital with a stab wound to the left upper back. This 19-year-old male states that he was on the way to church when he was accosted by "2 dudes" who stabbed him "out of the blue." He said he may have run into something with his car while trying to get away from them. You find the patient awake, but sluggish. He is speaking and his airway appears patent. Breath sounds are equal bilaterally. The patient's initial vital signs are: heart rate of 140 beats per minute, blood pressure of 80/50 mm Hg, respiratory rate of 20 breaths per minute, temperature of 97°F (36.1°C), and SpO_2 of 100% on room air. He reports only the single injury and when he is fully undressed, no other signs of trauma are found. Peripheral pulses are palpable, and on close inspection, the wound appears to be bleeding only minimally. The trauma surgeon is notified and is en route to assist. Initial FAST examination is negative. Two 18-gauge IVs are placed, lab work is drawn, and 2 L of lactated Ringer solution are administered. The blood pressure rapidly rises to 110/75 mm Hg, and the patient starts to complain of shortness of breath. Chest x-ray reveals a large hemothorax, and the patient's blood pressure drops to 75/55 mm Hg. You begin to wonder if your initial resuscitation is really helping this patient.

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EM Practice Guidelines Update: "Management Of Massive And Submassive Pulmonary Embolism In The ED," www.ebmedicine.net/PulmonaryEmbolism

About 50 minutes later, EMS arrives with a pedestrian struck by a car. EMS states that this 24-year-old male was the victim of a hit-and-run accident in which the driver apparently backed over him after first clipping him with the car and knocking him to the ground. When you walk into the patient's room, you find him awake and angry, complaining of pain in his right upper quadrant. He is on a backboard, wearing a cervical collar, and has obvious bruising to the right chest and abdomen. His airway is patent and his breath sounds are equal bilaterally. The patient's initial vital signs are: heart rate of 125 beats per minute, blood pressure of 120/80 mm Hg, respiratory rate of 20 breaths per minute, temperature of 98°F (36.6°C), and SpO_2 of 94% on room air. Per EMS, the patient was hypotensive on their arrival, with initial blood pressure of 80/40 mm Hg, but it rapidly improved with 2 L of crystalloid given in the field. A second large-bore IV is placed and labs are drawn. The FAST examination reveals significant hemoperitoneum. He then becomes diaphoretic, and repeat blood pressure is now 75/40 mm Hg. The nurse asks if you want 2 more liters of crystalloid…

Introduction

Resuscitation from shock state is a central part of emergency medicine practice. For many years, the gold standard of treatment was the rapid restoration of circulating volume with crystalloid solutions to normal, or even supraphysiologic, levels. Research over the past 30 years has yielded significant improvements in the treatment of various etiologies of shock, including the treatment of septic shock, using variations on early goal-directed therapy first described by Rivers et al.[1] However, all types of shock are not the same, and different etiologies require different approaches. Intravascular losses that result from third spacing, as in sepsis or pancreatitis, are primarily water and electrolytes. Aggressively replacing these losses with crystalloid before irreversible damage occurs makes perfect sense. In contrast, losses from hemorrhage include water, electrolytes, colloids, clotting factors, platelets, and blood cells. Additionally, there are inflammatory and immune responses to hemorrhage and tissue injury that result in third spacing, causing further losses. The complexity inherent in the management of these losses is just now beginning to be understood.

This issue of *Emergency Medicine Practice* focuses on advances in knowledge that should fundamentally change how we treat trauma patients in hemorrhagic shock. The best available evidence from the literature suggests that we must shift away from the paradigms that have guided emergency clinicians in the past. The following questions provide a guide to the changing landscape:

- What is resuscitation injury?

- What fluid is best for resuscitation?
- When should fluid resuscitation start, and once initiated, what should the endpoints be?
- How should the coagulopathy of trauma be managed?
- What is the most appropriate role of pharmacologic management?

Current standard resuscitation methods are probably appropriate for more than 90% of trauma patients.[2] This review is primarily intended to address the needs of the most critically injured patients who are in hemorrhagic shock. Even in the largest civilian academic trauma centers, these patients are uncommon, constituting only 1% to 2% of all trauma presentations.[2] Nonetheless, since hemorrhagic shock is a leading preventable cause of death, implementation of effective treatment strategies for this small population can improve overall trauma survival.

Critical Appraisal Of The Literature

A search of PubMed was carried out using the following combinations of key words: *hemorrhagic shock, fluid management, shock, resuscitation, hypertonic saline, trauma-hemorrhage, damage control resuscitation, trauma,* and *coagulopathy*. More than 300 articles were reviewed, which provided the background for further literature review. The Cochrane Database of Systematic Reviews was also consulted, and the combination of these resources served as the foundation of this evidence-based review. Until recently, research in the treatment of hemorrhagic shock was of questionable quality, limited to animal data, or driven by expert opinion. Particularly in the United States (US), there are significant difficulties in conducting randomized controlled trials with trauma patients where consent is not readily available and who may be part of a vulnerable population. As a result, the only Level I evidence reviewed in this article is from abroad.

Epidemiology

The imperative to control and treat hemorrhage has been a challenge since William Harvey first described the process of blood circulation in the early 1600s. Trauma is the leading cause of death for young people in the US, and while central nervous system injury is the leading cause of trauma-related death, exsanguination accounted for 39% of all trauma-related deaths in one study and remains the leading preventable cause of trauma-related death.[3] Physiologic saline was first produced in the late 1800s, and soon after, crystalloid resuscitation with either normal saline (NS) or lactated Ringer (LR) became the mainstay of therapy for the treatment of hemorrhage. Major blood types were discovered in 1900 and transfusion was added to the armamentarium soon after.

By World War I, surgeons began to worry about the potential negative effects of fluid resuscitation. In a frequently cited 1918 article, Cannon et al state, "If the pressure is raised before the surgeon is ready to check any bleeding that may take place, blood that is sorely needed may be lost."[4] This thinking was also prevalent during World War II, and articles from that time discuss the pitfalls of fluid resuscitation prior to definitive control of bleeding.[5]

Beginning in the 1960s, work pioneered by Fogelman and Wilson[6] and consolidated by Shires[7] and others showed that trauma and hemorrhage led to extracellular volume losses beyond the blood lost and that the addition of crystalloid to blood replacement could lead to improved survival. As a result, by the mid-1960s, the approach of large-volume crystalloid resuscitation had become popular. Despite earlier concerns, the centerpiece of resuscitation from hemorrhage became early intravenous (IV) access and aggressive crystalloid resuscitation. The ubiquitous American Trauma Life Support® (ATLS®) course recommends 2 liters of crystalloid be infused, and this maxim has been extrapolated so that it is "…now common that all trauma patients (not just patients in shock) are infused with 2 or more liters of LR solution."[8,9]

By the early 1980s, new concerns developed about the side effects of large-volume crystalloid infusion. Some were related to the immunologic effects of hemorrhage and of the fluids chosen for resuscitation. Others were based on complications associated with the timing and volume of fluid resuscitation.[10-12] In a landmark study by Bickell et al in 1994, 598 hypotensive patients with penetrating torso injuries were randomized to either standard or delayed fluid resuscitation. The results of the study showed that survival was 62% for those who received immediate fluid resuscitation and 70% in the delayed resuscitation group ($P = 0.04$). Moreover, only 23% of the delayed fluid resuscitation group had postoperative complications, whereas 30% of the standard group had complications ($P = 0.08$), and mean duration of hospitalization was shorter in the delayed resuscitation group.[13] The results of this study were hotly debated, both because of its conclusions and because of methodological problems. These developing clinical controversies prompted the Office of Naval Research to request in 1988 that the Institute of Medicine (IOM) conduct a review of fluid resuscitation strategies.[14] Recommendations made in the IOM report have driven research over the past decade and have yielded advances in the understanding of both hemorrhage and its treatment. Current US military trauma care guidelines suggest fluid resuscitation be restricted only to those

patients in shock, be very limited in volume, and have specific endpoints.[15]

Because the vast majority of knowledge about hemorrhage is trauma-related or trauma-inspired, researchers have long looked at military combat casualty statistics to evaluate the quality of resuscitation measures. Although drawing conclusions about resuscitation techniques across different decades and types of conflicts is extremely challenging, the historical data remain some of our most valuable windows into the evolution of the treatment of hemorrhage. It is generally accepted that the rate of individuals killed in action (KIA) is an indicator of the lethality of weapons used and the effectiveness of countermeasures (for example, body armor). Died of wounds (DOW) has generally been thought to measure the effectiveness of combat casualty medical care, and case fatality rate (CFR) is used to measure the overall lethality of the battlefield environment. Some authors noted that the percentage KIA and the percentage DOW changed little between World War II and the Vietnam War and used this as evidence that the prevailing approach of aggressive fluid resuscitation in Vietnam was not effective.[9] Others have looked at the improvement in CFR in recent conflicts and suggested that significant improvements in the trauma care system are responsible.[16]

Evaluation of the data in **Table 1** suggests that there is likely reciprocity between KIA and DOW rates in the most recent conflict. The best explanation for this is probably that the most severely injured casualties who, in the past, would have died before reaching definitive medical treatment (KIA) are now being resuscitated more effectively in the field and transported more rapidly to field hospitals where their injuries are deemed too great for salvage, changing their classification to DOW. It is likely that the increase in DOW rates would be even greater if not for improvements in initial resuscitation, surgical care, and critical care since the Vietnam War.[17] It is these improvements in initial resuscitation that are most relevant for emergency clinicians. Unfortunately, this evolution in quality of care has been implemented in limited or fragmentary ways in civilian trauma care and even less so in the treatment of hemorrhage from nontraumatic sources.

Table 1. Comparison, By Conflict, Of Killed In Action, Died Of Wounds, And Case Fatality Rates (As Of 2006)

	World War II	Vietnam War	Total Iraq/Afghanistan Wars
Killed in action, %	20.0	20.0	13.8
Died of wounds, %	3.5	3.2	4.8
Case fatality rate	19.1	15.8	9.4

Etiology And Pathophysiology

Many of the modern approaches discussed in this review are based on the idea of damage control resuscitation (DCR). This is a treatment strategy pioneered in the military and now used in civilian trauma care, which targets the conditions that exacerbate hemorrhage. The most commonly conceived elements of this philosophy are permissive hypotension, minimization of crystalloid resuscitation, control of hypothermia, prevention of acidosis, and the use of TXA and fixed-ratio blood product transfusion to minimize coagulopathy. The rationale and evidence regarding each of these therapies, and others, is the subject of this review.

Resuscitation Injury

In the setting of trauma, capillary permeability increases, leading to a loss of intravascular fluid into the interstitial space. Moreover, the acidosis that results from significant trauma impairs cardiac function. Treating these patients with large volumes of crystalloids can lead to cellular swelling and resulting dysfunction.[18] Animal studies suggest that the administration of crystalloid is associated with increased neutrophil activation and increased inflammatory markers.[19,20] This inflammatory response may create a vicious cycle where "…fluid overload and edema beget further fluid replacement and worsening edema."[10] This cycle was initially thought to be a reperfusion injury, but it has now come to be understood as resuscitation injury.[21] **(See Figure 1.)**

In the Vietnam War, the clinical entity of acute lung injury characterized by increased pulmonary capillary permeability and inflammation was first described.[22] Sometimes called "Da Nang Lung," after the Navy field hospital in Vietnam where it was frequently seen, this later became known as adult respiratory distress syndrome (ARDS). Although it has never been definitively proven that large-volume crystalloid resuscitation causes ARDS, the link is very concerning.

Large-volume crystalloid resuscitation has other harmful effects, including gastrointestinal and cardiac complications,[10] increased extremity compartment pressures,[23] and coagulation disturbances. Abdominal compartment syndrome is the only complication clearly proven to be a result of large-volume crystalloid resuscitation. Primary abdominal compartment syndrome, which results from severe, direct abdominal injury, has been understood for years. Secondary abdominal compartment syndrome occurs in patients without any underlying abdominal injury, has mortality greater than 50%, and is clearly linked to overaggressive fluid resuscitation strategies.[24]

Differential Diagnosis

Evaluation of the patient in shock requires rapid assessment of the etiology. Although hypotension in trauma patients is assumed to be caused by hemorrhage (until proven otherwise), it is critically important to evaluate and treat the patient for other potential causes of hypotension, including tension pneumothorax, pericardial tamponade, myocardial contusion, and neurogenic shock. The patient's injuries must also be viewed in light of his underlying physiologic condition. The possibility that the patient may be affected by poor baseline cardiac function, alcohol, drugs, medications, bleeding diathesis, or other significant conditions must be considered. **(See Table 2.)**

Prehospital Care

There are 3 critical goals of prehospital care for the trauma patient in hemorrhagic shock. The first goal is to stanch bleeding and minimize further blood loss (ie, by wrapping an unstable pelvis or applying direct pressure to a bleeding wound instead of ineffectively layering a bulky dressing). The second goal is to rapidly transport the patient to a trauma center where he can receive definitive treatment. The third goal is to initiate resuscitative measures needed to maintain mental status and peripheral pulses without delaying transportation. The 2005 World Health Organization expert consensus on prehospital care for the trauma patient found little evidence that advanced prehospital interventions were superior to basic interventions.[25]

Two recent trials support minimizing prehospital time by limiting time-consuming interventions. A prospective multicenter Canadian study involving 9405 patients showed increased mortality with ATLS® interventions in the field when compared to "scoop and run."[26] In a retrospective study, Seamon et al studied 180 penetrating trauma victims who underwent ED thoracotomy and reported that the sole independent predictor of mortality was the number of prehospital procedures.[27] For each procedure, the risk of death increased 2.63 times (odds ratio [OR] 0.38, 95% confidence interval [CI], 0.18-0.79, $P < 0.0096$). These findings are not likely to be applicable in austere, remote, or military settings, however.

Current guidelines offer several Level II recommendations that are primarily applicable to areas with relatively short transport times. The first significant recommendation is that vascular access not be obtained in the field, as it delays arrival to definitive care. The second major recommendation is that while access may be obtained en route, fluid administration should be limited to "keep vein open."[28]

Emergency Department Evaluation

When the trauma patient arrives at triage, he must be rapidly assessed for either being in shock or at risk of shock. Classic teaching from ATLS® divides hemorrhagic shock into categories based on the percentage of blood volume lost and expected accompanying vital signs and physiologic features. **(See Table 3, page 6.)**

Figure 1. The Vicious Cycle Of Fluid Administration

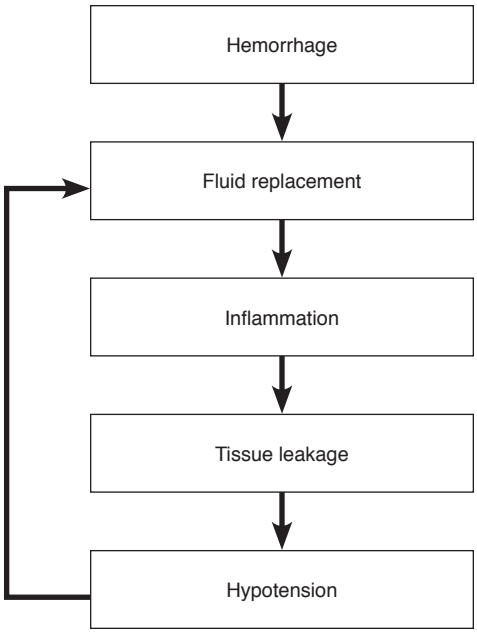


Table 2. Differential Diagnosis For Shock In Trauma

Etiologies of Shock in Trauma	Associated Physical Examination Clues
Hemorrhage/volume loss	Narrow pulse pressure, slowing of external bleeding without intervention
Tension pneumothorax	Deviated trachea, absent unilateral breath sounds, distended neck veins, narrow pulse pressure, pulsus paradoxus
Pericardial tamponade	Distended neck veins, muffled heart sounds, narrow pulse pressure, pulsus paradoxus
Myocardial contusion	Tachycardia out of proportion to other injuries, abnormal electrocardiogram or cardiac enzymes
Neurogenic shock	Spinal injury above T6, bradycardia, warm extremities

A recent large observational study attempted to evaluate this dogma, and found it quite far off the mark.[29] For patients with estimated blood loss greater than 40% (Class 4 shock), the median heart rate was 95 (interquartile range 80-114), and the median systolic blood pressure (SBP) was 120 (interquartile range 98-140). In another recent study, mortality for elderly blunt trauma patients with initial SBP of 120 was more than 12%.[30] Thus, while vital sign abnormalities may indicate that a patient is in shock, normal vital signs are not sufficient to exclude this possibility. Factors such as the mechanism of injury, (with particular attention to prevailing local injury patterns), concomitant head injury, and patient age must all be considered in the initial triage calculus.

Trauma patients should have their airway, breathing, and circulation (ABCs) addressed immediately, with the primary evaluation geared towards identifying the etiology of shock. In most trauma centers, identification of a patient in hemorrhagic shock will lead to trauma team activation and the marshaling of resources, including blood products, surgeons, and the operating room. In centers that are not equipped to regularly manage patients in traumatic hemorrhagic shock, a rapid assessment of resources versus needs must be made. If sufficient assets will not be available in a timely manner, early provision for transfer to definitive care must be made. Sources of bleeding should be controlled, when possible (eg, direct pressure to a bleeding vessel), minimized when practical (eg, wrapping an unstable pelvis), and rapidly localized (eg, via focused assessment and sonography in trauma [FAST] examination or chest x-ray), so that when definitive care is available it can be directed appropriately.

Diagnostic Studies

Laboratory Testing

A detailed discussion of laboratory testing in trauma is beyond the scope of this article. In general, trauma patients in or at risk of hemorrhagic shock require the following:

- Complete blood count
- Blood type and crossmatch
- Coagulation profile, including prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR)
- Basic metabolic panel (Chem 7)
- Toxicology studies, including alcohol level and drug screen, as appropriate
- Pregnancy test, as appropriate
- Lactate level and base deficit (usually, both can be ascertained from a blood gas syringe)

Bedside Ultrasound

The FAST examination is appropriate for all trauma patients in hemorrhagic shock; extended FAST (eFAST), which also evaluates for pneumothorax and hemothorax, may be preferred. This modality has essentially replaced diagnostic peritoneal lavage (DPL) in most centers. See the March 2011 issue of *Emergency Medicine Practice*, "An Evidence-Based Approach To Emergency Ultrasound" for more information on the FAST examination.

Diagnostic Radiography And Computed Tomography Scans

Chest radiography is fundamental in the evaluation of trauma patients and may rapidly identify hemothorax, pneumothorax, pulmonary contusions, mediastinal injury, or significant bony abnormality. Pelvis and cervical spine x-rays should also be obtained in appropriate patients. Cervical x-rays in hemorrhagic shock patients have little value.

In general, computed tomography (CT) scans have no role in the initial evaluation or resuscitation of trauma patients in hemorrhagic shock.

Treatment

Which Fluid Is Best For Resuscitation?

Tremblay et al stated that "…the optimal fluid for resuscitation would combine the volume expansion and oxygen-carrying capacity of blood, without the need for crossmatching or the risk of disease transmission. In addition, it would restore and maintain the normal composition and distribution of body fluid compartments."[31] Taking this one step further, the ideal fluid would combine all of those things

Table 3. Classes Of Shock By ATLS® Designation*

	Class 1	Class 2	Class 3	Class 4
Blood loss, %	< 15%	15%-30%	30%-40%	> 40%
Heart rate, beats per minute	< 100	> 100	> 120	> 140
Blood pressure, mm Hg	Normal	Normal	Decreased	Decreased
Pulse pressure	Normal or increased	Decreased	Decreased	Decreased
Respiratory rate, breaths per minute	14-20	20-30	30-40	> 35
Mental status	Slightly anxious	Mildly anxious	Anxious, confused	Confused, lethargic

*See the text, page 6, for a discussion of the utility of these criteria.

with positive immunologic and coagulation effects, and be durable, portable, and cheap. None of the fluid options currently available comes close to this ideal. Standard trauma resuscitation as defined by the ATLS® course includes infusion of LR solution.[8] Lactated Ringer was created in the 1930s by Hartmann in an attempt to make Ringer solution produce a beneficial effect on acidosis. Lactate is metabolized in the liver, producing either pyruvate or CO_2 and H_2O. In either case, there is release of hydroxide, which is rapidly converted to bicarbonate, thus offering a physiologic buffer against acidosis.[32,33] Given that this represents standard therapy, essentially all of the trials over the past 20 years involving fluid choice have compared alternatives to LR.

Conventional LR is a racemic mixture containing 2 stereo-isomers of lactate: D-lactate and L-lactate. L-lactate is a product of normal cellular function, and small concentrations are found in serum. D-lactate is produced either by microorganisms or from ketone bodies, and if administered alone, it is known to produce neurologic disturbances.[34] Importantly, several authors have shown that removal of the D-isomer from conventional LR results in significant decreases in inflammatory mediators and reductions in apoptotic cell death.[35,36] These concepts were central to the 1999 recommendation by the IOM that D-lactate be eliminated from resuscitative fluids.[14]

Approximately 7% of traumatic death is caused by organ failure, typically multiorgan failure or ARDS.[3] Therefore, hemorrhage mortality can be directly related to both exsanguination and resulting inflammatory and immunologic processes. In other words, trauma is an immune disease.[37] Early research by Rhee et al showed that fluid choice significantly impacted immune function and that LR, in particular, increased neutrophil activation.[19] More interestingly, administration of LR – even in the absence of hemorrhage – increased neutrophil activation. Numerous researchers have shown that standard LR is associated with increased expression of E- and P-selectin and ICAM-1, which have been associated with neutrophil-related reperfusion injury.[38,39] Similarly, hemorrhage-induced apoptosis and cellular damage appear to be affected by fluid choice, with LR being associated with increases in cellular damage.[35]

Significant research has been directed at identifying and then either altering or modulating the immune response to hemorrhage by varying the types of fluid used in resuscitation. In particular, hypertonic saline (HTS) and hypertonic saline-dextran (HSD) have been extensively studied. In addition, NS, albumin, and other synthetic colloids have also been advanced as alternatives to LR.

Normal Saline

Normal saline continues to be used frequently (and in many institutions, interchangeably), with LR for resuscitation from hemorrhagic shock. It has long been known to cause hyperchloremic acidosis, particularly when given in large volumes.[39] Recently, a study by Todd et al compared resuscitation with LR to NS in a swine model of uncontrolled hemorrhage. Animals resuscitated with NS had a significantly higher volume requirement ($P = 0.04$), were more acidotic ($P < 0.01$), and had lower fibrinogen levels ($P = 0.02$), suggesting increased dilutional coagulopathy.[40] There are no significant studies that directly compare NS with LR for resuscitation from hemorrhagic shock. At facilities that continue to use NS as the primary crystalloid in trauma, strategies that promote the early transition of NS to LR in the resuscitation may avert potential acidosis, coagulopathy, and hypothermia, long-considered the lethal triad of trauma.

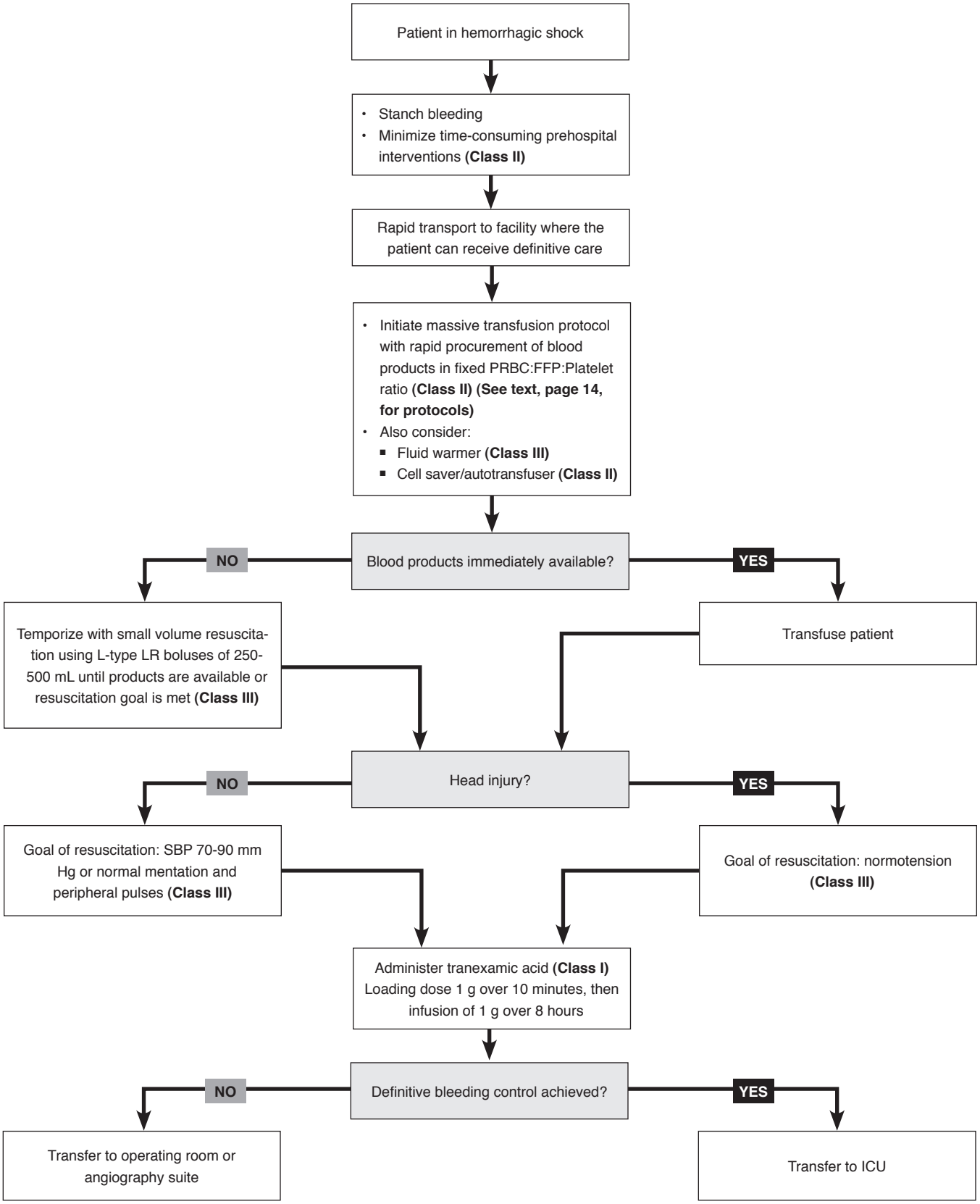
Albumin And Other Colloids

The controversy regarding the use of crystalloids versus colloids for resuscitation has been debated for more than 60 years. One theoretical benefit of colloids in resuscitation from hemorrhage is the decreased volume required in comparison to LR. Estimates vary, but some researchers assert that it would take 3 times as much LR to achieve the same plasma volume expansion as 5% albumin.[41] The second main benefit of colloids is the durability of plasma volume expansion. Lastly, it has been shown that albumin does not cause neutrophil activation when compared with LR.[20]

Large systematic reviews performed in the late 1990s comparing colloid and crystalloid fluid resuscitation reported different outcomes. Schierhout et al reported an increased absolute risk of mortality of 4% (95% CI, 0%-8%) in the group treated with colloids.[42] On the other hand, Choi et al found no difference in mortality for all patients, but subgroup analysis of trauma patients showed significantly worse mortality in the colloid group (relative risk [RR] 0.39, 95% CI, 0.17-0.89).[43] Both authors and subsequent commentary noted that the underlying studies were of relatively poor quality.

Published in 2004, the Saline Versus Albumin Fluid Evaluation (SAFE) Study compared 4% albumin to NS. In this study, 6997 patients were randomized and no significant differences were reported in risk of death (RR 0.99, 95% CI, 0.91-1.09). Incidence of organ failure, intensive care unit (ICU) days, hospital days, ventilator days, and days of renal-replacement therapy were also all similar. The authors concluded that albumin and saline should be considered "equivalent" in a heterogeneous population of patients in the ICU.[44] Another important conclusion from the SAFE study was that the ratio of intravascular volume required with albumin in comparison to NS was only 1.4:1. At the time, commentators stated that although albumin

Clinical Pathway For Resuscitation In Hemorrhagic Shock



Abbreviations: FFP, fresh frozen plasma; ICU, intensive care unit; LR, lactated Ringer solution; PRBC, packed red blood cell; SBP, systolic blood pressure.

is likely equally safe when compared to saline, it offers little benefit.[45] A Cochrane review published in 2007, which included data from the SAFE trial, concluded that in patients with trauma, burns, or following surgery, colloids are not associated with reductions in death when compared to crystalloids and further stated that their use cannot be justified as they are more expensive.[46]

A subgroup analysis of the SAFE trial published in 2007 found an increased mortality for patients with TBI who were resuscitated with 4% albumin (RR 1.63, 95% CI, 1.17-2.26; $P = 0.003$).[47] One possible explanation is that dilutional coagulopathy resulted in higher rates of transfusion of packed red blood cells (PRBCs) in the first 2 days postrandomization.[48] Given that this increased mortality comes from a subgroup analysis, it should be treated as somewhat suspect. Nevertheless, it seems sensible to avoid albumin administration in patients with TBI.

A recent Cochrane review compared colloid solutions for fluid resuscitation including dextran 70, hydroxyethyl starches, modified gelatins, albumin, and plasma protein fraction. In reviewing 70 trials, no significant mortality differences were found, and the reviewers were unable to reach any clear conclusions about the effectiveness of different colloids. The quality of the underlying data was sufficiently poor, however, that the reviewers were unable to either rule out or detect any clinically significant differences between different colloids.[49]

Hypertonic Saline

Hypertonic saline was first used for resuscitation from hemorrhage in 1980.[50] In addition to volume expansion, it has been shown to have immunologic effects. In one animal study, HTS restored T-cell function that had been suppressed by hemorrhage and was found to be protective from subsequent sepsis.[51] The hypertonic environment appears to have a direct effect on the cytotoxic response of polymorphonuclear neutrophils, particularly when given early posthemorrhage.[52,53] In 2004, a Cochrane review failed to show mortality difference between hypertonic, isotonic, and near-isotonic crystalloid but reported that confidence intervals were too wide to exclude significant differences.[54] Despite the potential benefits of HTS, concerns regarding hypernatremia and hyperchloremia persisted. These concerns led investigators to develop and test HSD combinations.[37] The largest recent study of hemorrhagic shock patients included an arm of HTS along with HSD and is discussed below.

Hypertonic saline has also long been used as a treatment for increased intracranial pressure, and in the last decade there has been increasing interest in hypertonic solutions as early treatment for TBI. In 2004, Cooper et al reported the results of a double-blind randomized controlled trial of 229 patients with severe TBI (Glasgow Coma Scale [GCS] score < 9) who were also hypotensive. Patients were randomized to a rapid bolus of 250 mL of either 7.5% saline or LR. No restrictions were placed on subsequent fluid administration. There was no significant difference in either neurologic outcome, based on the Glasgow Outcome Scale Extended (GOSE), ($P = 0.45$) or mortality (RR 0.99, 95% CI, 0.76-1.30; $P = 0.96$). Interestingly, despite the increased hemodynamic effects that would be expected in the HTS group, both groups ended up receiving the same total volume of prehospital fluid, median 1.25 L.[55]

Hypertonic Saline-Dextran

The combination of hypertonic saline with dextran to initiate fluid resuscitation was first described by Kramer et al[56] and Maningas et al[57] in 1986 and showed promise as a fluid for resuscitation. The currently accepted formulation of HSD is 7.5% NaCl and 6% dextran 70. Since 1986, there have been

Class Of Evidence Definitions

Each action in the clinical pathways section of *Emergency Medicine Practice* receives a score based on the following definitions.

Class I
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II
- Safe, acceptable
- Probably useful

Level of Evidence:
- Generally higher levels of evidence
- Non-randomized or retrospective studies: historic, cohort, or case control studies
- Less robust RCTs
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate
- Continuing area of research
- No recommendations until further research

Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

Significantly modified from: The Emergency Cardiovascular Care Committees of the American Heart Association and representatives from the resuscitation councils of ILCOR: How to Develop Evidence-Based Guidelines for Emergency Cardiac Care: Quality of Evidence and Classes of Recommendations; also: Anonymous. Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part IX. Ensuring effectiveness of community-wide emergency cardiac care. *JAMA*. 1992;268(16):2289-2295.

a very large number of clinical and experimental studies looking at resuscitation using HSD. An early meta-analysis comparing HSD with isotonic crystalloid showed a trend towards improved survival with HSD but did not reach significance (RR 1.20 favoring HSD, 95% CI, 0.94-1.57).[58] More recently, a randomized controlled double-blind trial of HSD compared to placebo (NS) showed that HSD blunted neutrophil activation and reduced the production of inflammatory mediators.[59] The authors suggest that the use of HSD could attenuate post-trauma multiorgan dysfunction. An animal model raised concern about increased bleeding risk with HSD, but this appears to be dose-dependent.[60] More recently, Bruttig et al showed that the rate of infusion was the critical element in limiting bleeding.[61]

The Resuscitation Outcome Consortium (ROC) attempted to definitively determine whether early resuscitation with HTS or HSD could lead to a reduction in mortality. In a randomized controlled double-blind 3-arm clinical trial, a 250 mL bolus of 7.5% saline (HTS) was compared against 7.5% saline with 6% dextran 70 (HSD) and placebo as the initial fluid given to patients with hemorrhagic shock in the out-of-hospital setting. Primary outcome was 28-day survival. Secondary outcomes included fluid and blood requirements in the initial 24 hours, incidence of ARDS, multiorgan dysfunction, and nosocomial infections. The study was initially expected to enroll more than 3700 patients, but it was stopped early for futility in the setting of a trend towards increased early mortality in the HTS and HSD arms. The 28-day mortality (74.5% HSD, 73% HTS, and 74.4% NS) and all of the secondary outcomes were the same in all 3 arms of the study. The authors postulated that because there was no fluid restriction after administration of the study fluid, early mortality may have been related to over-resuscitation. This is an entirely likely conclusion because patients given hypertonic solutions received similar total volumes as patients who were given isotonic solution, and total prehospital volume averages were more than 1 L in all 3 arms.[62]

Hypertonic saline-dextran has also been evaluated as a potential early treatment for TBI. Recent work suggests that in patients with severe TBI, early administration of HSD can lead to improved serum biomarkers of brain injury.[63] The ROC conducted a large study of TBI patients simultaneous with the trial for hypovolemic shock and with the same treatment arms. These included a prehospital 250 mL bolus of NS, HTS, or HSD. Primary outcomes were GOSE and mortality. The study was terminated early for futility. Data analysis for the 1331 patients who were randomized showed no difference in GOSE ($P = 0.55$) or 28-day mortality (74.3% HSD, 75.5% HTS, and 75.1% NS). Again, despite the greater anticipated hemodynamic effects of HTS and HSD, there was no difference in total volume of fluid given between the 3 groups.[64] At this time, there is no evidence to suggest that either HTS or HSD provides a significant benefit in the early treatment of patients with TBI.

In summary, the current data have failed to show that any crystalloid or colloid is superior to LR for the resuscitation of patients in hemorrhagic shock. The largest studies, to date, have been hampered by the current standard treatment, where patients are routinely given large volumes of crystalloid in addition to the study fluid. Nevertheless, it seems appropriate to continue the use of LR as the initial fluid choice for patients in hemorrhagic shock. Given that L-isomer LR has fewer inflammatory and immune consequences and is equally available and similarly priced to racemic LR, it is probably the most appropriate fluid choice for patients in hemorrhagic shock. Further, because HSD was shown to be nearly equivalent, it is also reasonable to consider its use in specific settings, particularly where portability is paramount. The bottom line is that the choice of initial fluid for resuscitation from hemorrhagic shock probably has little impact on morbidity or mortality.

Timing And Goals Of Resuscitation From Hemorrhagic Shock

It has been recognized since World War I that resuscitation in the absence of bleeding control can be harmful.[4] Standard practice changed, however, after seminal studies done in the 1950s by Wiggers and others showed that aggressive fluid resuscitation could improve survival in animal models.[65] These were largely studies performed on animals that had been bled to a fixed volume or blood pressure. Bleeding was then stopped and the animal was resuscitated. This model is commonly referred to as *controlled hemorrhage*, and it is similar to what might be seen, postoperatively, in trauma patients. The primary problem with this model is that the majority of patients in hemorrhagic shock present to the ED with uncontrolled hemorrhage. *Uncontrolled hemorrhage* means that bleeding is either ongoing or may restart if coagulopathy worsens or blood pressure is raised.

Advocates of aggressive crystalloid resuscitation suggest that the theoretical benefits of normalizing – or even supranormalizing – blood pressure and oxygen delivery are clear. These benefits include repayment of oxygen debt, clearance of acidosis, and correction of extracellular fluid deficit.[7,66] However, more-recent evidence (primarily in models of uncontrolled hemorrhage) suggests that premature or aggressive resuscitation may lead to the dislodging of soft clots and dilutional coagulopathy, with the result of increased hemorrhage and mortality. The bulk of the literature on fluid rate and timing comes from animal data.

One recent study reported that overly aggressive

fluid treatment accelerated hepatocellular injury, while another suggested that slower rates of fluid resuscitation led to improvements in cell-mediated immunity.[11,12] Numerous studies have shown that immediate fluid resuscitation caused increases in the rate, volume, and duration of hemorrhage.[67,68] Still more studies have shown improvements in mortality with resuscitation regimens that slow, delay, or limit fluid administration.[69-71] A 2003 systematic review of animal trials found that excessive fluid resuscitation could be harmful in some situations and that hypotensive resuscitation reduced the risk of death in all trials in which it was investigated.[72]

Before discussing human data on restrictive resuscitation strategies, it must be noted that all strategies that permit hypotension are absolutely contraindicated in patients with TBI. It has been shown that even a single episode of hypotension causes a doubling of mortality in this patient population.[73] Although there remains some debate on the subject, at this time, any treatment that results in hypotension for a TBI patient is contraindicated.

Two slightly different strategies have been advanced to prevent clot disruption and dilutional coagulopathy. The first is *delayed resuscitation*, where fluid is withheld until bleeding is definitively controlled. The second is *permissive hypotension*, where fluid is given, but the resuscitative endpoint is something less than normotension.[74] The largest human study of delayed resuscitation was done in 1994 by Bickell et al. This randomized controlled trial of 598 hypotensive patients (prehospital SBP < 90) demonstrated an improvement in mortality from 70% to 62% with delayed resuscitation ($P = 0.04$) compared to traditional resuscitation.[13] This strategy also has 1 nontrauma trial supporting it. In 1986, Blair et al reported that incidence of rebleeding was decreased in patients with gastrointestinal hemorrhage for whom early transfusion was withheld ($P < 0.01$).[75] With a relative paucity of human data, a Cochrane review came to the conclusion that there was no evidence for or against early volume resuscitation in uncontrolled hemorrhage.[76]

Controversy over the delayed resuscitation strategy continues. The current data suggest that patients with penetrating trauma who arrive rapidly at a center with immediate access to definitive care may benefit from a delayed resuscitation strategy. Outside of this small subgroup, the delayed resuscitation strategy does not have enough evidence to support its implementation.

The discussion of hypotensive resuscitation is more complicated than that of delayed resuscitation. In order to describe a strategy of limited resuscitation, it is necessary to define the endpoints for that strategy. Perfusion status is typically assessed by whole-body parameters such as mental status, heart rate, blood pressure, and palpable pulses. Some data suggest that these measures correlate poorly with tissue perfusion.[77] Other parameters, such as base deficit and lactate, are recommended to guide resuscitation for patients who have received definitive bleeding control.[78]

In the only randomized controlled trial in humans, Dutton et al chose to target a SBP of 70 mm Hg. They chose blood pressure as their resuscitation endpoint because it is readily available and is already typically used to drive fluid therapy in standard practice. They used a technique of 250- to 500-mL boluses to treat hypotensive values. Unfortunately, they found that blood pressure tended to fluctuate with the boluses, making it hard to accurately maintain the desired value. As a result, for the 110 patients they randomized, the average SBP was 100 mm Hg in the restricted protocol and 114 mm Hg in the standard cohort ($P < 0.001$). Survival was equal at 92.7%, with 4 deaths in each group.[79]

In the only study of its type, Sondeen et al investigated the blood pressure that was necessary to induce rebleeding in pigs with a vascular injury. They found a reliable rebleeding point at a SBP of 94 mm Hg and a MAP of 64 mm Hg.[80] Given these results, it is not surprising that there was little difference found in the study by Dutton et al. Putting this all together, it is probably reasonable to attempt to target a SBP between 70 and 90 or a MAP near 65.

Recent human studies address outcomes other than mortality in the setting of decreased crystalloid use. In a trial of restrictive versus liberal perioperative fluid use, the restricted fluid group had significantly lower pulmonary complications and a trend towards lower mortality.[81] Incidence of ARDS was noted to significantly decline in a 5-year observational study of 1913 major trauma patients. The authors do not assert causation, but they postulate that implementation of lung-protective strategies and a significant decline in early fluid administration from 3.9 L to 3.2 L ($P < 0.001$) may be factors in this improvement.[82]

Current US military guidelines suggest that the best indicators of hemorrhagic shock are abnormal mentation (in the absence of TBI) and weak or absent peripheral pulse.[15] Essentially, this is designed to identify patients who are profoundly hypotensive and require immediate intervention. Moreover, fluids are not recommended in patients who do not meet those criteria. For patients who do meet criteria for shock, the military recommends a single bolus of Hextend™, which may be repeated once after 30 minutes if there is no response or response is transient. Hextend™ is a balanced crystalloid/colloid solution that does not have a large body of literature supporting it. It was chosen for tactical reasons over crystalloid with the understanding that HSD is not currently available.[83]

The Israeli military frequently operates in en-

vironments with transport times and resources that may closely resemble current American civilian EDs. Their guidelines prohibit aggressive fluid resuscitation in uncontrolled hemorrhagic shock. They further recommend a "scoop and run" approach for patients with less than 1 hour of transport time.[84]

In summary, for the vast majority of patients with uncontrolled hemorrhage, there is no Level I evidence for guidance; however, the best available evidence supports the following:

- It is critical to recognize that fluid resuscitation for the patient in hemorrhagic shock must be individualized.
- Resuscitate patients with TBI to normotension as rapidly as practical.
- When bleeding control has been achieved in the ED, the goal of resuscitation is to normalize physiologic parameters such as blood pressure and heart rate but should also be directed at clearing lactate and normalizing base deficit.
- Patients with penetrating trauma to the chest or abdomen for whom definitive care is immediately available may benefit from delayed resuscitation.
- The best current recommendations are to resuscitate trauma patients only to the point where they have adequate mentation and peripheral pulses that correspond to a SBP of about 80 mm Hg. This approach represents one part of what has been termed DCR. **(For more information, see the "Etiology And Pathophysiology" section on page 4).**

Managing Coagulopathy Of Trauma

For the most severely injured patients, the lethal triad of hypothermia, acidosis, and coagulopathy has long been recognized. Damage control surgery, which gained widespread acceptance in the

Risk Management Pitfalls For Traumatic Hemorrhagic Shock

1. **"The patient said she couldn't be pregnant."**
   All women of childbearing age who are hypotensive should have a pregnancy test done to exclude ruptured ectopic pregnancy.

2. **"The patient might be bleeding, but he is rock-stable as long as he is getting fluids."**
   Resuscitation is not a substitute for definitive bleeding control.

3. **"This trauma victim is paralyzed, so he must be in neurogenic shock."**
   Hypotensive victims of trauma must have hemorrhagic shock ruled out definitively.

4. **"She was bleeding out. I had to address that first."**
   Trauma care goes ABC for a reason. There is nothing wrong with addressing circulation early, but airway and breathing come first.

5. **"I read this awesome thing about permissive hypotension. I thought it was the way to go for everyone."**
   Permissive hypotension is contraindicated in patients with TBI.

6. **"I know I can get this patient's blood pressure back to normal if I attach him to the rapid infuser."**
   Normalizing blood pressure is contraindicated in patients who have ongoing bleeding.

7. **"Trauma management is a cookbook. You just do the same thing for everyone and wait for the cavalry."**
   This is an abdication of responsibility and means we are not maximizing the patient's chance for survival.

8. **"Blood products are dangerous and this guy is only mildly hypotensive. I'm just going to give him 2 L of crystalloid and see what happens. I know all bleeding stops eventually."**
   Failing to recognize hemorrhagic shock and initiate treatment will leave your patient far behind the 8-ball.

9. **"I read about early goal-directed therapy for sepsis and I saw the Surviving Sepsis guidelines. Clearly the right treatment for shock is 6 L of crystalloid empirically."**
   Treatment of shock must be tailored to the etiology of shock and to the specific patient. Large-volume crystalloid resuscitation is discouraged in hemorrhagic shock.

10. **"This old guy syncopized and it's not clear why. I suspect his low blood pressure is just his baseline."**
    Consider gastrointestinal bleeding and aneurysmal rupture as etiologies of hypotension and syncope. Early appropriate treatment and endoscopic or surgical bleeding control will help this patient.

late 1990s, grew out of the need to minimize these factors and has been successful in lowering mortality in severely injured patients.[85] In 2002, MacLeod et al reported that 28% of trauma patients were coagulopathic on arrival to the trauma bay and that abnormal PT and PTT were independent predictors of mortality, with an adjusted odds ratio of 1.35 for PT (95% CI, 1.11-1.68; $P < 0.001$) and 4.26 for PTT (95% CI, 3.23-5.63; $P < 0.001$).[86] **(See Figure 2.)**

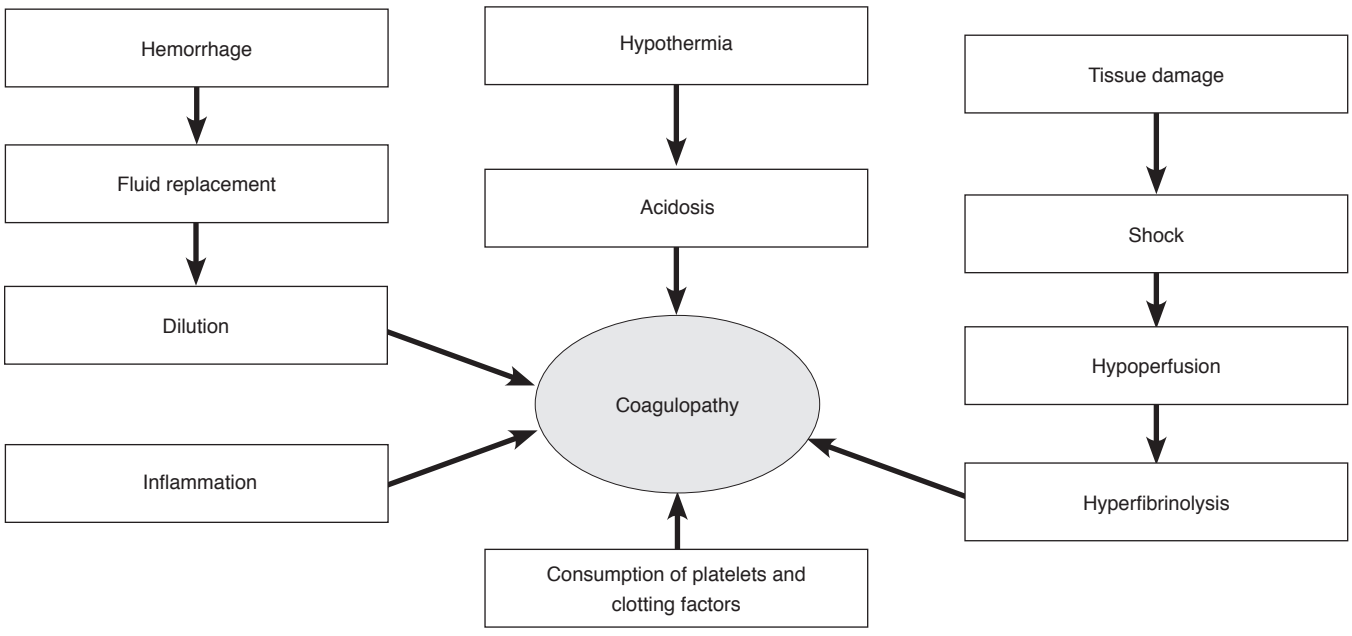
Several mechanisms explain how patients can arrive in the ED already coagulopathic. The first is that tissue injury plays a direct role in the development of coagulopathy. Tissue damage initiates both coagulation and fibrinolytic pathways and may result in a consumption of platelets and clotting factors. Coagulopathy has been shown to be closely related to injury severity and appears to be caused by hypoperfusion and resulting hyperfibrinolysis.[87-89] Hemodilution, which may be a product of physiologic vascular refill, crystalloid administration, and even transfusion of PRBCs, is also a major cause of coagulopathy in victims of hemorrhagic shock.[90] Hypothermia is common in trauma patients, and even mild hypothermia can have significant deleterious effects on platelet function and clotting factor activity.[91] A simple intervention to help prevent or treat hypothermia is to use a fluid warmer. Acidemia is nearly universal in hemorrhagic shock and further impairs the function of plasma proteases. In animal models, simply reversing acidosis with bicarbonate does not appear to be sufficient to reverse the coagulopathy caused by acidosis.[92]

Understanding that the coagulopathy of trauma is already present for many patients on their arrival to the ED impacts management in that the treatment of coagulopathy in hemorrhagic shock is no longer the responsibility of just the surgeon and the intensivist, but initiating treatment is also within the emergency clinician's purview. This treatment is an essential part of what has come to be known as DCR.

Standard treatment of acute hemorrhagic shock as defined by ATLS® follows crystalloid infusion with PRBCs, but it discourages the routine use of plasma, platelets, and cryoprecipitate.[8] Blood product administration is not a benign intervention. Adverse effects include infection, depressed cellular immunity, hyperkalemia, hypocalcemia, citrate toxicity, and mistransfusion.[93] It has also been shown that liberal transfusion strategies can result in increased mortality in some critically ill patients.[94,95] In 2003, Hirshberg et al analyzed massive transfusion guidelines using a computer simulation and found that existing protocols underestimated the dilution of clotting factors in severely bleeding patients. They recommended ratios of 1:1.5 for plasma and 1:1.25 for platelets.[96] Theoretically, if implementation of this ratio were successful, it would decrease bleeding and perhaps lessen the need for transfusion and would improve mortality.

A number of studies have reported significant improvements in survival of patients who were resuscitated with a fresh frozen plasma (FFP)-to-PRBC ratio of 1:1.[97-99] Snyder et al challenged these findings, however, noting that most of the mortality improvement was within the first 24 hours and represented a survival bias.[100] Another study similarly

Figure 2. Coagulopathy Chart



found no specific benefit to the 1:1 ratio in patients who survived to ICU admission.[101] The extent to which blood product ratio is responsible for the improvements in survival remains unclear, but most current protocols appear to have ratios close to those recommended by Hirshberg.

Several recent studies have suggested that the implementation of an MTP with fixed ratio transfusion can improve mortality at rates that were previously ascribed to increased plasma use.[102] There have been 3 recent natural case-control trials where patients treated with a newly implemented MTP were followed prospectively and compared to matched historical controls. Cotton et al found a significant reduction in mortality of patients whose resuscitation was done according to the MTP (RR 0.26; 95% CI, 0.12-0.56; $P = 0.001$).[103] Further, while there were increases in blood products used prior to admission to the ICU, total PRBC ($P = 0.695$) and FFP (0.595) use was similar and crystalloid use was significantly decreased ($P = 0.002$). Dente et al reported significant improvements in mortality from 36% to 17% ($P = 0.008$) and decreased mean use of crystalloid from 9.2 L to 6.9 L ($P = 0.006$).[104] Riskin et al similarly reported decreased mortality from 45% to 19% ($P = 0.02$). This study also reported significantly faster times to first crossmatched RBCs, FFP, and platelets.[102] Given this evidence, implementation of an MTP at every institution that treats patients in hemorrhagic shock is recommended. For a summary of MTPs, **see Table 4.**

Duchesne et al reported the first study of DCR in the civilian literature in 2010. This retrospective study of 196 patients found a significant improvement in 30-day mortality from 73.6% to 54.8% ($P < 0.009$), and, after adjustment for confounders, found an odds ratio of death of 0.19 (95% CI, 0.05-0.33; $P = 0.005$) favoring DCR over conventional resuscitation. Not surprisingly, the DCR patients received significantly more FFP and platelets and significantly less crystalloid. In fact, mean crystalloid volume given in the ED declined from 4.7 L to 1.1 L ($P = 0.0001$).[105]

A number of other therapies have been advanced to address coagulopathy and minimize transfusion requirements. A recent Cochrane review of recombinant factor VIIa for treatment of bleeding found no improvement in mortality and did not recommend its use.[106] On the other hand, a Cochrane review on cell salvage, or autotransfusion, concluded that there was sufficient evidence to support its use in some circumstances.[107] Although there are relatively few potential indications for patients in hemorrhagic shock, one clear opportunity to consider this approach is for patients with large hemothorax.

There are 3 main recommendations regarding the management of coagulopathy in trauma:

- Begin treatment of trauma-associated coagulopathy as soon as the patient arrives in the ED.
- Implement an MTP that minimizes delays in the administration of blood products that should be given in a fixed ratio.
- While DCR requires more study, the early literature is very promising.

The Role Of Tranexamic Acid In Hemorrhagic Shock

In 2010, the high-quality prospective randomized placebo-controlled double-blind CRASH-2 trial was done to evaluate TXA for the treatment of significant hemorrhage. Tranexamic acid is an antifibrinolytic that inhibits both plasminogen activation and plasmin activity and had previously been shown to reduce bleeding in patients undergoing elective surgery. In this study, 20,211 patients from 40 countries were randomized to receive either standard care or TXA, 1 gram over 10 minutes followed by a 1-g infusion over 8 hours. Mortality in the treatment group was reduced from 16.0% to 14.5% (RR 0.91; 95% CI, 0.85-0.97; $P = 0.0035$), and the risk of death from bleeding was reduced from 5.7% to 4.9% (RR 0.85; 95% CI, 0.76-0.96; $P = 0.0077$). Moreover, there was no difference in episodes of vascular occlusion.[108] Tranexamic acid is inexpensive, and a recent review

Table 4. Examples Of Massive Transfusion Protocols

Protocol	Salient Features
Riskin et al[102]	• Definition of massive transfusion: anticipation that > 10 units PRBCs will be required in resuscitation • Who can activate the protocol: anyone • FFP:PRBC ratio: 1:1.5 • Given in packages of 6 units PRBCs, 4 units FFP, and 1 unit apheresis platelets
Cotton et al[103]	• Definition of massive transfusion: attending surgeon thinks patient will need > 10 units of blood • Who can activate the protocol: attending surgeon • FFP:PRBC ratio: initially ~1:2.5; subsequently, 1:1.5 • Given in packages. Initial package: 10 units PRBCs, 4 units FFP, and 2 units single-donor platelets. All subsequent packages: 6 units PRBCs, 4 units FFP, and 2 units single-donor platelets
Dente et al[104]	• Definition of massive transfusion: > 10 units of PRBCs anticipated in 24 hours • Who can activate the protocol: ED, surgery, anesthesia, ICU • FFP:PRBC ratio: 1:1 • Given in packages of 6 units PRBCs, 6 units FFP; 1 unit apheresis platelets given with every other package delivery

Abbreviations: ED, emergency department; FFP, fresh frozen plasma; ICU, intensive care unit; PRBCs, packed red blood cells.

calculated a cost of $6300 per life saved based on administering it to all military casualties who received blood products.[109] Based on this evidence, the use of TXA in bleeding patients is recommended. A reasonable strategy is to give TXA to all patients with uncontrolled bleeding who require transfusion.

Special Circumstances

As previously noted, hypotensive resuscitation is not indicated in patients with TBI. Also, if definitive bleeding control is possible in the ED (eg, extremity stab wound), patients should be resuscitated to normotension with a goal of normalizing lactate and/or base deficit. Careful consideration must be given to patients with abnormal platelet function or coagulopathy. While these issues must be addressed in trauma patients who are in hemorrhagic shock, to date, no ideal approach has been elucidated.

Controversies And Cutting Edge

One critical logistical problem with DCR in most centers is that it takes a significant amount of time to thaw type-specific FFP. While waiting, resuscitation continues, worsening coagulopathy.[90] The US military has addressed this issue in several ways. In many situations, they are using fresh whole blood provided by "walking donors." For obvious reasons (including fear of infection and logistical issues), this approach is not feasible in civilian centers. Busy military centers also frequently maintain a stock of thawed universal donor-type AB plasma.[2] Given that thawed plasma has only a 5-day shelf life, risking scarce AB-type blood is probably only plausible in the busiest centers.[110]

It has been observed that women are more tolerant of major trauma and less prone to sepsis and multiorgan failure after trauma.[111] Sex hormones are generally thought to be the primary contributor to this difference.[112] Estrogen has been shown to have a salutary effect on the cardiovascular, hepatic, and immune systems as well as improving survival after prolonged hypotension in animal models.[113,114] Based on this evidence, the Resuscitation Outcomes Consortium is currently conducting pilot trials to assess if estrogen improves mortality in hemorrhage.

The "holy grail" of resuscitation from hemorrhagic shock is the development of a blood substitute. To date, none of the attempts has been successful.[115] A number of other therapies for hemorrhagic shock have been proposed and demonstrate at least some potential benefits in animal models, including low-dose vasopressin, valproic acid, and androstenediol.[116-118] These therapies are not only unproven, but they are largely untested.

Disposition

All patients in hemorrhagic shock must be transferred to the operating room, admitted to the ICU, or transferred to a facility with appropriate capabilities.

Summary

Hemorrhagic shock continues to be a leading cause of death worldwide. Advances in management provide the potential to decrease morbidity and mortality. There are few well-designed studies that provide Level I evidence upon which to base recommendations; however, there is a growing body of literature that supports the following practices. **(For Level of Evidence definitions, see page 9.)**

- Prehospital care for patients in hemorrhagic shock is directed at rapid transport to definitive care. It is recommended that emergency medical services avoid time-consuming procedures in the field (Level of Evidence II[27]).
- Fluid choice has not been shown to affect outcomes in trauma (Level of Evidence I[62]). Theoretical advantages support the use of L-type LR solution (Level of Evidence III[37]).
- Avoid large-volume crystalloid resuscitation (Level of Evidence III[72]).
- For uncontrolled hemorrhage in the absence of TBI, target resuscitation to a SBP between 70 and 90 mm Hg or normal mentation and palpable peripheral pulses (Level of Evidence III[15]).
- It is recommended that all hospitals that anticipate caring for patients with hemorrhagic shock institute an MTP with fixed ratios (Level of Evidence II[102-104]).
- Give TXA to all patients with uncontrolled hemorrhage who require transfusion (Level of Evidence I[108]).

Case Conclusions

The patient who was stabbed in the upper back was in hemorrhagic shock exacerbated by resuscitation to normal blood pressure, and possibly hemodilution, with crystalloid. You activated the MTP and inserted a chest tube, which drained 1500 mL of blood immediately. You would have considered an autotransfuser, had one been available. The patient was given a dose of TXA and, on re-evaluation, was still awake, with palpable peripheral pulses. Further crystalloid administration was avoided, the patient's blood pressure trended down, and peripheral pulses became thready. The first installments of PRBCs and FFP were given to the patient through a fluid warmer, with improvement of blood pressure to 90/60 mm Hg. The surgeon arrived and agreed to take the patient to the operating room. Because the patient was warm and his coagulopathy had been addressed, he breezed through the surgery and was released from the hospital on postinjury day 4.

The second patient, who was the victim of blunt trauma, was also in hemorrhagic shock with hemoperitoneum. You again activated the MTP and gave the patient a dose of TXA. Surgical consultation was delayed by the prior patient. Blood products were brought to the bedside, and crystalloid administration was strictly limited. The patient's blood pressure remained steady around 80/50 mm Hg, and he continued to be alert, with good peripheral pulses. Initial labs came back and showed a normal hemoglobin, but elevated PT. You decided to gently transfuse him with 2 units of PRBCs and 2 units of FFP through a fluid warmer. These brought the patient's blood pressure up to 100/60 mm Hg and heart rate down to 100 beats per minute. The patient remained stable until surgical consultation arrived. Because of his demonstrated stability, he underwent a CT scan, which showed a grade 3 liver injury with a blush. He was taken to the angiography suite and his liver injury was embolized. The patient was monitored in the ICU and did well, never requiring an operation. He was discharged home after 1 week in the hospital.

At the end of your busy shift, you reflected on the outstanding care you were able to provide these 2 critically ill patients. In contrast to the "cookbook" you were given to take care of trauma patients as a resident, you were able to manage the complexity of their problems with panache. In less-capable hands, these patients might have not have done so well. You also resolved to call your local EMS director to discuss an update to their protocols.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study, will be included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the author, will be noted by an asterisk (*) next to the number of the reference.

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1. Intravascular losses from third spacing in sepsis are largely fluids and electrolytes. All of the following are also lost in hemorrhage EXCEPT:
a. Clotting factors
b. Blood cells
c. Colloids
d. Platelets
e. Vascular tone

2. Major tenets of DCR include all of the following EXCEPT:
a. Permissive hypotension
b. Aggressive crystalloid resuscitation
c. Fixed ratio transfusion
d. Control of hypothermia
e. Prevention of acidosis

3. In the study by Seamon et al, which of the following was an independent predictor of mortality for patients who underwent an ED thoracotomy?
a. Number of prehospital procedures
b. Injury severity score
c. Age
d. Sex
e. Mechanism of injury

4. The IOM recommended removing the D-isomer from LR solution because it is associated with all of the following EXCEPT:
a. Increased inflammatory mediators
b. Apoptotic cell death
c. Neurologic disturbances when given alone
d. Potential to cause edema

5. Large trials by the ROC that hoped to determine the best fluid for initial resuscitation were stopped early for:
a. Futility
b. Lack of funding
c. Methodologic problems
d. Worse neurologic outcomes

6. **Hypotensive or delayed resuscitation strategies are contraindicated in which of the following patients?**
   a. Penetrating thoracic injuries
   b. Blunt trauma
   c. TBI
   d. Young adults

7. **Approximately what percentage of trauma patients arrive in the ED with coagulopathy (abnormal PT or PTT)?**
   a. 2%
   b. 12%
   c. 28%
   d. 40%
   e. 55%

8. **The coagulopathy of trauma is caused by all of the following EXCEPT:**
   a. Acidosis
   b. Dilution
   c. Direct tissue injury
   d. Hypothermia
   e. Early administration of FFP

9. **Implementation of a massive transfusion protocol with fixed transfusion ratio has been shown to improve mortality and also:**
   a. Significantly decrease crystalloid use
   b. Decrease use of FFP
   c. Decrease use of platelets
   d. Increase crystalloid use

10. **Which of the following has been shown to improve mortality in bleeding patients?**
    a. HSD
    b. TXA
    c. LR
    d. Vasopressin
    e. Valproic acid

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Emergency Medicine Practice (ISSN Print: 1524-1971, ISSN Online: 1559-3908) is published monthly (12 times per year) by EB Medicine (5550 Triangle Parkway, Suite 150, Norcross, GA 30092).