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Fluid Management in Adult and Pediatric Trauma Patients

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Fluid therapy is an integral aspect of trauma resuscitation. With advances in resuscitation research, controversies abound regarding approaches to the initial fluid management. Advanced Trauma Life Support (ATLS) guidelines recommend an initial rapid infusion of fluid (1–2 liters) in trauma and hemorrhage victims as a diagnostic procedure to aid treatment decisions.[1] To determine therapeutic strategies, patients' response to the initial fluid challenge is very important. However, the appropriate rate of infusion and the choice of fluid have not been clearly defined.[1] The ATLS program by the American College of Surgeons provides a chart that allows monitoring of patients' response to the initial fluid resuscitation.[2] (See Table 1.)

Controversies also abound about pre-hospital fluid therapy in patients with blunt and penetrating injuries, as well as pediatric and head injury patients. It is often difficult to draw conclusions from the available body of literature because of the significant variation in study designs, target hemodynamic parameters, the type of population utilized, and the end point of resuscitation. Furthermore, consensus studies that utilize meta analysis are hard to interpret because of the extreme variation in the collected data and the inclusion of very old data. This article will not propagate the controversies, but rather extensively review pertinent literature from the last decade (1998–2008), with the goal of providing some clarification to these controversies.

— The Editor

Choice of Fluid

A discussion of fluid management would be incomplete without a detailed review of the fluids available for resuscitation. The ideal resuscitation fluid should be capable of carrying oxygen, have little or no effect on coagulation, be inexpensive and non-allergic or antigenic, and possess a relatively long shelf life at room temperature. At present, none of the available fluids have all

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these qualities. Currently available fluids for resuscitation include crystalloids, colloids, and blood products.

Crystalloids. Crystalloids are water solutions of inorganic ions and small organic molecules. They have increased volume of distribution that encompasses the entire interstitial and intercellular compartment. Owing to capillary permeability, they have limited half-life because they easily escape from the intravascular space into the tissues.[3,4] When crystalloids are infused, about 75% extravasate into the interstitial space, while only 25% remain in the intravascular space.[4]

Based on pharmacokinetics, the general rule is that three volumes of crystalloids replace one volume of lost blood. This rule originated from the study done by Shires and colleagues in the 1960s that demonstrated that about three times the volume of blood loss of isotonic crystalloid is required to restore extra-cellular deficit during hemorrhagic shock.[5] Crystalloid-based resuscitation has mainly dosage-related side effects, which include fluid overload, albumin dilution, reduction of plasma oncotic pressure, and tissue edema. Commonly utilized crystalloids are isotonic (normal saline and lactated Ringer's [LR]), hypertonic (3%, 6%, and 7.5% NaCl) saline (HTS), and hypotonic (D5 water) solution.

Normal saline solution is a mildly hypertonic crystalloid with increased sodium and chloride concentration when compared to plasma. The solution is a suitable blood dilutent, since it does not contain calcium that could potentially interact with the citrate component in blood. In resuscitation, large volumes of normal saline are often required to obtain similar hemodynamic effects when compared to HTS. This increased volume potentially increases transvascular filtration of fluids and protein, increased interstitial fluid, increased capillary permeability, and increased pulmonary artery pressure, with subsequent development of pulmonary edema. The utilization of normal saline in the large volumes required in hemorrhaging patients could lead to hyperchloremic metabolic acidosis. This non-anion gap acidosis could potentially interfere with acid–base interpretation. Base deficit is one of the parameters utilized in guiding adequacy of resuscitation; the hyperchloremia produced by large volumes of normal saline may lead to persistent base deficit. A study by Skellet and colleagues concluded that "normal saline (0.9% saline) and other chloride-rich fluids may not be ideal resuscitation fluids; if used, clinicians must be aware of their potential to cause persistent base deficit." Normal saline is not currently the initially recommended resuscitation fluid, according to ATLS guidelines.[6]

ATLS guidelines recommend LR solution as the recommended initial resuscitation fluid. However, several recent studies have shown deleterious effects of this solution. The complication seen in trauma resuscitation has been attributed to the activation of the inflammatory system cascade and the type of fluid utilized. LR, in particular, has being implicated in this hyper-inflammatory state.[4,7,8] Rhee and colleagues demonstrated that neutrophil activation increased significantly after hemorrhage, but the rise was greatest with LR resuscitation.[9] They also inferred that neutrophil activation may be caused by LR and not reperfusion. Other studies demonstrated significant neutrophil activation with LR solution, and have also shown that resuscitation with LR solution leads to greater hypercoagulability when compared to normal saline.[10,11]

The currently utilized LR solution is a racemic mixture of the L and D isomers. The deleterious effect seen with LR resuscitation has been shown to be attributed to the D-isomer. Kaustova and colleagues studied the effects of LR solution on human leukocytes.[12] Using donated blood from human volunteers, they were able to show that when compared with the L-LR isomer, the D-LR isomer causes an increased expression in genes responsible for inflammation, neutrophil activation, and cell migration.

The initial changes the endothelium undergoes to modulate inflammation in response to trauma and hemorrhagic shock could also be exacerbated by the choice of resuscitation fluid. Savage and colleagues performed a study to evaluate the effect of LR solution on endothelial function during resuscitation for hemorrhagic shock.[13] The study showed that resuscitation with LR requires larger volume, and also causes a decrease in endothelial dependent relaxation (EDR), leading to endothelial dysfunction.

Jaskille and colleagues performed a study to determine if the elimination of D-Lactate isomer will attenuate liver apoptosis.[14] Rats in a controlled hemorrhage model were stratified to receive different resuscitation fluid, including racemic (D and L) mixture and solution containing only the L-lactate isomer. The result shows that racemic LR solution induces liver apoptosis, which is decreased if the D-isomer was eliminated. A study using a swine model also demonstrated that clearance of lactic acid was impeded following resuscitation with the DL racemic mixture.[15] However, this was not seen in the L-isomer solution. Hence, elimination

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Table 1. Responses to Initial Fluid Resuscitation

	RAPID RESPONSE	TRANSIENT RESPONSE	NO RESPONSE
Vital signs	Return to normal	Transient improvement, recurrence of lowered BP, and increased HR	Remain abnormal
Estimated blood loss	Minimal (10-20%)	Moderate and ongoing (20-40%)	Severe (>40%)
Need for more crystalloid	Low	High	High
Need for blood	Low	Moderate to high	Immediate
Blood preparation	Type and cross-match	Type-specific	Emergency blood release
Need for operative intervention	Possibly	Likely	Highly likely
Early presence of surgeon	Yes	Yes	Yes

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of the D-isomer from the conventional racemic mixture will eliminate the deleterious effect attributed to LR resuscitation.

HTS has been used successfully in both animals and human models of hemorrhagic shock. The typical 7.5% HTS has osmolality of 2400 Mosml/L. It requires a smaller volume of about 4–5 mL/kg to effectively restore cardiovascular function.[4,5,8] Several characteristics of HTS make the solution promising for resuscitation. It has a direct vasodilatory effect in the systemic and pulmonary circulation, thus reducing venous capacitance. These effects result in the increase in mean arterial pressure (MAP), cardiac output (CO), and renal, mesenteric, total splanchnic, and coronary blood flow.[7]

Furthermore, HTS has been shown both in vivo and in vitro to display some immune modulating effects such as inflammatory mediation, neutrophil down-regulation, and macrophage activation.[4,8] Studies have shown that HTS resuscitation after hemorrhagic shock prevents the development of lung injury when compared to LR, which shows significant lung derangement.[16] This finding was attributed to the ability of HTS to reduce neutrophil oxidative burst and lung neutrophil influx. These inherent characteristics of HTS are transient. However, this could be extended by mixing HTS with colloids. A currently utilized mixed solution is HTS-Dextran (typically NaCl 7.5% + Dextran-70, 6%).[17]

Several studies have shown that low-dose HTS dextran reduces the risk of lethal rebleeding in uncontrolled hemorrhage, and demonstrated that HTS results in rapid restoration of hemodynamics with laboratory evidence of improved microcirculatory hemodynamics.[17,18] Another study, which utilized the small volume concept of HTS/hydroxyethyl starch (HES) solutions, showed reduced blood loss and less impairment of hemostasis in pigs after resuscitation from hemorrhagic shock.[19]

In combat casualties, HTS is routinely utilized with great results. According to the recommendation for the initial fluid resuscitation in combat casualties, if vital signs and mental status are normal, intravenous access should be established but fluid withheld. However, if vital signs and mental status are abnormal, intravenous access should be established and 7.5% HTS given, up to 500 mL. If more fluid is needed, the recommendation was to switch to colloids or isotonic saline.[20]

Colloids are heterogeneous resuscitation fluids with increased molecular size and weight. They have similar volume of distribution as the crystalloids, which are limited to the intravascular space. They are often referred to as volume expanders because of their inherent characteristic variable molecular size and water-retaining capability. Agents in this category also have side effect profiles that are dose-related, and potential anaphylactic reactions.[3,4,8] Commonly available colloids include albumin, dextran, gelatin, and HES.

Albumin, which is synthesized in the liver, is the prototype colloid. Its molecular weight (69 kd) determines plasma oncotic pressure. An extensive review performed by the Cochrane group in 1998 on 37 randomized controlled trials comparing albumin with crystalloids concluded that the odds ratio of mortality was significantly increased in patients given albumin.[21] However, these results have not been reproducible.[22,23] The SAFE study, which was an attempt to challenge the validity of the Cochrane report, enrolled 7,000 patients from 2000 to 2002, with end point of 28 days all-cause mortality in critically ill patients receiving 4% albumin or saline. Their findings did not support the Cochrane report, and they concluded that "albumin is SAFE." Presently, albumin is not frequently utilized as a volume expander in resuscitation because of cost and other options.

Dextran is a glucose polymer available in two different molecular weights (70 kd and 40 kd) and has been extensively used as a volume expander. Its utility has been limited due to harmful side effects, which include severe hypersensitivity reactions and coagulation abnormalities.[24,25]

Gelatins are derived from bovine collagen, and have very low molecular weight (35–40 kd). Owing to molecular size and relatively short half-life, they are not an effective volume expander, though they have less hypersensitivity reaction when compared to dextrans.[24,25]

HES are the most commonly used colloids. They are derived from amylopectin extracted from maize and conjugated with eth-

Table 2. Summary of Recent Polyheme Studies

Study	Number of patients	Indication for Polyheme	Results
Gould et al, 1997	39	Received up to 6 units of Polyheme in lieu of RBC	Polyheme maintained total Hb in lieu of RBC in acute blood loss
Gould et al, 1998	44	Randomized to receive RBC or up to 6 units Polyheme as initial resuscitation	Amount of RBC given on day 1 was significantly less for Polyheme group
Johnson et al, 1998	13	Randomized to receive RBC or up to 6 units Polyheme as initial resuscitation	Polyhemes lack the vasoconstrictive effects associated with other HB-based substitutes
Gould et al, 2002	171	Compared patients who were given up to 20 units of Polyheme with historical patient who refused blood	Polyheme increased survival at life-threatening HB levels by maintaining total HB without RBC transfusion
Johnson et al, 2003	25	Compared rates of multiple organ failure in patients receiving Polyheme and those receiving RBC	Relative increase in post-inflammatory cytokines as well as counter-regulatory cytokines was less with Polyheme

Source: Polyheme, Northfield Laboratories Inc., Evanston, IL.

ylene oxide. Amongst all HES, pentastarch has the most anti-inflammatory effect and efficiently retains more fluid in the intravascular space. All HES have side effect profiles similar to dextrans (anaphylaxis and coagulation abnormalities).[3] A study that evaluated the beneficial effects of HES in a near-fatal model of hemorrhagic shock demonstrated that early colloid infusion with modern HES solution resulted in prompt recovery of tissue perfusion when compared with the infusion of equal volume of LR solution.[26]

Hemoglobin-based oxygen carriers (HBOC) are hemoglobin-based products referred to as oxygen therapeutics. These are compounds derived from outdated human packed red blood cells or bovine red blood cells through a process of lysis and filtration.[18] Owing to their characteristic high oxygen-carrying capacity at ambient partial pressure, they can either augment or replace the oxygen-carrying capacity of red blood cells (RBCs).

The HBOCs have been tested in multiple settings to temporarily augment oxygen-carrying capacity without utilizing RBC transfusion in situations such as trauma resuscitation, resuscitation during surgery involving large blood loss, and intraoperative autologous blood donation during cardiac surgery.[27] Available data have shown that when used during active hemorrhage, HBOCs can temporarily maintain adequate oxygen-carrying capacity and intravascular volume until hemorrhage is controlled. When utilized in this fashion, HBOCs minimize exposure to banked blood, and therefore decrease potential for exposure to infectious agents and the negative immunologic effects associated with banked blood.

A study by Moore and colleagues shows that transfusion of more than six units of packed RBC during the initial resuscitation of trauma patients is an independent predictor of multiple organ failure.[28] This effect was theorized to be due to the pro-inflammatory effect of substances present in banked blood. It could be extrapolated from this study that reducing exposure to banked blood during trauma resuscitation should improve outcome.

Another study evaluated the utility of HBOC solution in the resuscitation of patients with severe chest trauma.[29] Using an anesthetized swine model and four different types of HBOC solutions, the authors found that all HBOCs were pressors and all reduced the supplemental fluid required to maintain systemic hemodynamics during resuscitation. However, the pressor characteristics also increased right and left ventricular afterload that further compromised marginal cardiac performance.

As a new therapeutic modality, concerns about HBOC's potential side effects abound. Some of the concerns are nephrotoxicity, vasoconstriction, methemoglobinemia, and neurotoxic effect on the brain. Although nephrotoxicity has been almost completely eliminated with the polymerization of the components, the vasoconstriction still persists. The methemoglobinemia is, however, dose-dependent.

Overall, HBOC may be the future of RBC-free resuscitation. The currently available HBOC preparations in the United States are Polyheme (Northfield Labs), Hemopure (Biopure Inc.), and Hemolinks (Hemosol Inc.). All these products are currently in phase III trials. Polyheme is so far the only HBOC with trials in human trauma subjects, and it's showing significant promise.[30-35] *(See Table 2.)*

After review of the available resuscitation fluids, and knowing the components and the adverse effect profiles, crystalloids should be the initial fluid of choice in trauma patients in the absence of contraindication, since they lack the adverse effects seen in other resuscitation fluids. However, studies are showing the benefits of HTS in low-volume resuscitation for traumatic brain injury (TBI), hemorrhagic shock, and also as the initial fluid

for resuscitation of hypotensive trauma patients. Presently, utilization of HTS is not approved by the U.S. Food and Drug Administration (FDA), though it is currently utilized in Europe and in the military.

Pre-Hospital Resuscitation

The importance of the emergency response teams to trauma victims cannot be overstated. Fluid administration in the pre-hospital setting is a challenging and controversial area. Despite advances in research, there is no unequivocal view that can be supported by well documented and reliable evidence. However, several consensus data that culminate the review of available body of evidence over the past decade are beginning to streamline parameters to guide pre-hospital personnel regarding approach to a trauma victim.

Table 3. Classes of Shock

	CLASS I	CLASS II	CLASS III	CLASS IV
Blood loss (mL)	Up to 750	750–1,500	1,500–2,000	>2,000
Blood loss (% blood volume)	Up to 15%	15%–30%	30%–40%	>40%
Pulse rate (bpm)	<100	>100	>120	>140
Blood pressure	Normal or increased	Decreased	Decreased	Decreased
Respiratory rate	14–20	20–30	30–40	>40
Urine output (mL/hr)	>30	20–30	5–15	Negligible
CNS/mental status	Slightly anxious	Mildly anxious	Anxious, confused	Confused, lethargic
Fluid replacement (3:1 rule)	Crystalloid	Crystalloid	Crystalloid and blood	Crystalloid and blood

Used with permission from: American College of Surgeons Committee on Trauma. Advanced Trauma Life Support for Doctors: Student Course Manual, 8th edition. Chicago,IL: American College of Surgeons; 2008:61.

The principle of advanced life support for paramedics traditionally involves early, rapid intravenous fluid replacement to increase circulating volume and blood pressure with the belief that this will maintain vital organ perfusion, thereby improving outcome and survival.[2] Currently, the available data may demonstrate that many longstanding practices for pre-hospital fluid resuscitation may be detrimental. The prevailing question now is how do pre-hospital personnel perform fluid resuscitation? The debate between under-resuscitation versus over-resuscitation has been raging over several decades. A study by Riddez and colleagues attempted to answer this question.[36] Standardized aortotomy was performed in dogs stratified into four resuscitation groups — no fluid, 1:1 LR, 2:1 LR, and 3:1 LR volume ratio. The study showed that the rate of bleeding and aortic blood flow increased with amount of fluid used. Also, the highest mortality was seen in the no-fluid and the 3:1 LR resuscitation groups. These findings were attributed to shock in the no-fluid group and re-bleeding in the aggressively resuscitated group.

To streamline pre-hospital personnel's approach to fluid resuscitation, there have to be set diagnostic parameters that rapidly identify hypoperfusing , hypotensive, or potentially unstable trauma patients. Currently available parameters utilized, such as heart rate, blood pressure, and cyanosis, are often influenced by the effects of drugs and alcohol, pain, pneumothorax, and spinal cord injury. Such multifactoral influences render these markers potentially unreliable as guides to therapeutic goals.[37,38]

The approach to trauma patients in the pre-hospital setting should involve a strategy that employs immediate stratification by mechanism of injury (blunt vs. penetrating), anatomic involvement (truncal vs. isolated head or extremity injuries), and condition staging (hemodynamically stable vs. unstable or moribund), and also an understanding of the different classes of shocks as described in ATLS guidelines.[39] *(See Table 3.)*

Using this approach, most of the controversies that surround pre-hospital fluid resuscitation could be resolved. Based on available data, liberal use of fluid in presumed uncontrolled bleeding in a penetrating trauma patient is no longer advised.[40-42] The priority of paramedics in this situation is localized control of obvious hemorrhage, rapid evacuation, and intravenous cannulation en route to definitive surgical intervention.[42,43]

Extensive review shows that when it comes to fluid resuscitation in the pre-hospital setting, most consensus data seem to arrive at the same conclusion. The current recommendations for fluid resuscitation in the United Kingdom, the Joint Royal Colleges Ambulance Liaison Committee (JRCALC) guidelines (2004), state that "intravenous infusion should be commenced en route to the hospital, and only sufficient fluid given to maintain systolic blood pressure of 80–90 mmHg."[42] They recommend that "500 mL IV of crystalloid solution should be given, and the effects on the circulatory system be assessed before further fluid is given."[42]

Berlot and colleagues reported in 2006 that "in the presence of a disturbance of consciousness, it is safer to obtain a relatively elevated systolic arterial pressure of 120–130 mmHg to prevent the occurrence of secondary brain injury, whereas lower values of systolic arterial pressure of 90 mmHg are tolerated in trauma patients without any neurologic injury provided arrival at the hospital does not exceed 30–40 minutes."[44]

In blunt trauma patients, the resuscitation modality is the same. In a paired case-control study on a blunt trauma patient with scene systolic blood pressure less than or equal to 90 mmHg, one arm received more than 500 mL of fluid and the other arm

received no fluid. The study concluded that pre-hospital fluid resuscitation of blunt-injured trauma patients with systolic blood pressure less than or equal to 90 mmHg increases systolic blood pressure but has no effect on survival or length of hospital stay.[43] Another group summarized that the goal in blunt injury is to secure safe perfusion of the injured brain through adequate cerebral perfusion pressure (SBP > 100 mmHg); patients without brain injury tolerate lower blood pressure.[45] They also recommended that the ideal pre-hospital fluid regimen may be a combination of an initial hypertonic solution given as an infusion over 10–20 minutes, followed by crystalloids.[45]

According to a consensus view by Revell and colleagues, fluid should not be administered to trauma patients in the pre-hospital setting before hemorrhage control if a radial pulse can be palpated.[46] Judicious fluid of 250 mL should be titrated for other patients. If the radial pulse returns, fluid resuscitation can be suspended and the situation monitored. *(See Table 4.)*

ED-based Resuscitation

The arrival of a trauma patient in the hospital begins the phase of definitive care. The goal of this phase is to control hemorrhage, ensure adequate end organ perfusion, increase oxygen delivery to tissues, normalize base deficit, obtain a perfusing blood pressure, and prevent reperfusion injury.The mantra that has been propagated over the years is to obtain two large-bore vascular accesses and infuse 1–2 liters of saline to return blood pressure to pre-injury level. Several recent experimental studies have discouraged this approach.

Presently, the trend in the field of resuscitation is to restrict the amount of fluid utilized. This is based on the theory that aggressive intravenous fluid resuscitation in a hemorrhaging patient may actually promote increased bleeding. The increase in blood pressure to near normal in a hypotensive trauma patient may dislodge hemostatic clots, alter blood viscosities, and cause hemodilution of platelets and clotting factors.[47]

Restrictive or low-volume resuscitation is not a new phenomenon. In 1918, Cannon pointed out the disadvantages of fluid resuscitation and emphasized that an increase in blood pressure before surgical hemostasis would "pop the clot" and increase bleeding with potential exsanguination.[48] Cannon also warned that "injection of a fluid that will increase blood pressure has danger in itself. Hemorrhage in case of shock may not have occurred to a marked degree because pressure has been too low to overcome the obstacle offered by a clot. If pressure is raised before checking the bleeding, blood that is sorely needed may be lost."

The term "permissive hypotension" is the current trend in trauma resuscitation. Despite favorable evidence and increasing proponents of this modality, opponents still contend with the idea of hypotensive resuscitation. Opponents raise the concerns of the consequences of avoidance of fluid in the early phases of hypotensive trauma patient resuscitation. The contention was that hypotensive resuscitation leads to hypoperfusion, organ failure, death prior to bleeding control, and deleterious effect on patients with concomitant head injury. Despite these contentions, there are overwhelming data to support restrictive fluid resuscitation or permissive hypotension in the treatment of a patient with uncontrolled hemorrhaging until definitive surgical intervention is available. However, there are special considerations for head-injured patients.

A randomized control study on human subjects presenting in hemorrhagic shock and stratified into two fluid treatment arms concluded that titration of initial fluid therapy to a lower-than-normal systolic blood pressure during active hemorrhage did not affect mortality.[49] Another study performed on sheep that underwent left anterior thoracotomy with transection of the left internal mammary artery suggested that early, aggressive fluid resuscitation in penetrating thoracic trauma exacerbated total hemorrhage volume.[50]

Krausz and colleagues, using the standard massive spleen injury (MSI) model of uncontrolled hemorrhage, studied the effect of vigorous crystalloid or colloid fluid resuscitation on hemodynamic response and survival in rats.[51] The study revealed that vigorous large-volume infusion of LR solution or HES following MSI resulted in a significant increase in intra-abdominal bleeding and shortened survival time when compared with those untreated and those treated with small-volume HTS and HES-7.5% solutions.

A group using the standardized MSI model of uncontrolled hemorrhagic shock evaluated the effects of continuous fluid resuscitation and splenectomy on the hemodynamic response and survival in rats. Their study showed that continuous infusion of large-volume LR with splenectomy after MSI resulted in significant increases in intra-abdominal bleeding and shortened survival time compared with small-volume LR infusion.[52]

In a study evaluating the general and pathophysiologic effects of controlled fluid resuscitation in the treatment of severe and uncontrolled hemorrhagic shock, rat models were stratified into no fluid, controlled fluid, and aggressive fluid resuscitation arms.[51] The study concluded that "among the three resuscitation arms, controlled fluid resuscitation can effectively decrease additional blood loss, minimize hemodilution and coagulopathy, improve early survival rate, and reduce apoptosis of visceral organs in rats with severe and uncontrolled hemorrhagic shock."[53]

With strong evidence to support small-volume resuscitation, this modality should be embraced as the standard of care when resuscitating hypotensive, hemorrhaging trauma patients. However, this standard should exclude patients with TBI, since hypotension has been shown to promote secondary brain injury. The discussion that follows will elaborate on the care of patients with TBI.

Traumatic Brain Injury Considerations

TBI is the leading cause of trauma-related mortality. Despite advances in current treatment strategies, the overall mortality still ranges from 31% to 49%.[54] Among the survivors, large proportions have persistent severe neurologic disability, with the estimated lifetime cost for each individual exceeding $2 million.[55]

Preventable morbidity and mortality following the initial head trauma is a consequence of the secondary brain injury that occurs due to hypoxia, hypotension, and elevated intracranial pressure (ICP).

The deleterious effect of hypotension in TBI has been well documented. Studies have shown that patients with hypotension after severe TBI have twice the mortality of normotensive patients.[56] Consequently, aggressive resuscitation with intravenous fluid is recommended in the current guidelines for management of severe TBI.[57] The question that arises now is, How aggressively should we resuscitate in the era of permissive hypotension?

The primary therapeutic goal in a non-operative TBI patient should be to maintain adequate mean arterial pressure (MAP), control ICP, and provide adequate cerebral perfusion pressure (CPP) to prevent cerebral ischemia or massive cerebral edema. Permissive hypotension is not recommended in TBI.

Recent emphasis in the study of resuscitation of TBI patients involves the utilization of HTS. Although not FDA approved, several animal and human models have demonstrated its benefit. HTS has been shown to decrease cerebral edema while maintaining adequate MAP and CPP. The mechanism by which HTS solution accomplishes these beneficial cerebral effects is most likely multifactorial.

The authors of "Guidelines for the Field Management of Combat-Related Head Trauma" made the following recommendations:

• Inadequate outcome clinical data exists to prefer one resuscitation fluid over another; however, HTS and colloids offer clear logistical advantage over isotonic crystalloids in a combat environment;[58]

• There is Class 1 evidence that the use of HTS is a safe alternative method of treating hypotensive TBI patients without worsening outcome;[58] and

• The authors recommended two boluses of 250 mL 5% HTS or 500 mL 3% HTS.[58]

Ware and colleagues assessed the safety and efficacy of small-volume injections of 23.4% sodium chloride solution for the treatment of intracranial hypertension in patient with TBI who became tolerant to mannitol.[59] From the study, the mean reductions in ICP after treatment were significant for both mannitol and HTS. However, the mean duration of ICP reduction was much longer for HTS (96 minutes) when compared to mannitol (59 minutes). The study suggested that 23.4% HTS is a safe and effective treatment for elevated ICP in patients after TBI.

A group that evaluated the neuronal and behavioral outcome after TBI plus hemorrhage when resuscitated with hypertonic solution of HTS, or HTS plus I-arginine, arrived at the premise that hypertonic solutions will acutely improve cerebral blood flow after TBI followed by hypotension.[60] The study stratified rats into six arms receiving different resuscitation fluids, with subsequent assessments of vestibulomotor and spatial memory functions. The study concluded that both HTS and HTS plus I-arginine were effective at promoting long-term neuronal survival and behavioral recovery.

Although existing evidence supports HTS, controversy still persists. Baker and colleagues looked at the effect of resuscitation fluid on neurologic physiology after cerebral trauma and hemorrhage.[61] Using the rat model, various resuscitation strategies (blood, normal saline, HTS, and albumin) were evaluated. MAP and cerebral oximetry were assessed in the hemorrhage group.

Table 4. Consensus View of Pre-hospital Fluid Resuscitation in Trauma Patients

1. Cannulation should take place en route to the hospital
2. Only two attempts at cannulation should be made
3. Transfer should not be delayed in an attempt to obtain intravenous access
4. Entrapped patients require cannulation at the scene
5. Normal saline is recommended as a suitable fluid for administration to trauma patients
6. Boluses of 250 mL of fluid may be titrated against the presence or absence of a radial pulse

Source: Revell M, Porter K, Greaves I. Fluid resuscitation in pre-hospital trauma care: A consensus view. *Emerg Med J* 2002;19:494-498.

The study found that regional tissue oxygen tension level in hemorrhaged animals reached significantly higher levels in the albumin-treated group compared with the normal saline and HTS groups. They concluded that albumin demonstrated the greatest beneficial effects on neurophysiology end points over crystalloid alternatives.

A recently published human study sought to answer questions regarding HTS in hypotensive head-injured patients.[62] The study demonstrated that mean ICP level dropped by 45%, and this drop persisted for 6 hours, while CPP level increased by 20%. $PbtO_2$ levels remained persistently elevated for all time points after HTS infusion. Although this study provides strong support for HTS utilization in TBI, there were no control data, and the sample size was too small to adequately power.

The use of HTS in TBI has evolved, and evidence now supports its utilization. Presently, there is a paucity of well-controlled clinical trials to determine the evidence for the best concentration, administration approach, and length of therapy.[63] Although there is no currently available randomized, controlled trial with a large enough sample size to be adequately powered, a current phase III, multi-center, randomized, controlled trial titled "Hypertonic Saline Following Traumatic Brain Injury," expected to be completed in 2010 at the University of Washington, may shed more light on the beneficial effects of HTS in TBI.

The role of HBOC in TBI continues to be evaluated despite the fact that HBOC utilization in TBI remains an exclusionary criterion in nearly every HBOC trial because of its vasoactive properties. Several studies are beginning to show its benefit in low-volume resuscitation.

King and colleagues hypothesized that low-volume resuscitation with vasoactive hemoglobin-based oxygen carrier (hemoglobin glutamer-201, HBOC-301) will improve outcome after severe TBI with hemorrhagic shock.[64] Using the swine model, they stratified anesthetized animals to receive HBOC alone, LR + HBOC, or LR + mannitol + packed RBC. They demonstrated that HBOC alone and HBOC + LR had superior outcomes. Also, lactate level and base excess corrected faster with the HBOC + LR combination despite a 40% decrease in cardiac index. Furthermore, with HBOC alone and HBOC + LR, MAP and heart rate rapidly corrected and remained normal. HBOC alone also allowed all ani-

Table 5. Pediatric Patient Systemic Responses to Blood Loss

System	Mild blood volume loss (<30%)	Moderate blood volume loss (30-45%)
Cardiovascular	Increased HR, weak, thready peripheral pulses	Markedly increased heart rate; low-normal blood pressure; narrowed pulse pressure; absent peripheral pulses, with weak, thready central pulses
Central nervous system	Anxious, irritable, confused	Lethargic, dulled response to pain
Skin	Cool, mottled; prolonged capillary refill	Cyanotic; markedly prolonged capillary refill
Urinary output	Minimal	Minimal

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mals to wean and extubate when compared to LR + mannitol + RBC. After 72 hours, the study also revealed that no HBOC-resuscitated animal had a detectable neurologic deficit.

This is a very promising animal model study. Several other recent studies have shown similar results.[65,66] However, until a controlled human study trial is performed, the utility of HBOC in TBI currently is not recommended.

Pediatric Consideration

Trauma is the leading cause of death in children age 1–14 years in the developed world. It is also the major cause of disability.[67] Thirty percent of early death in severe trauma is due to inadequate evaluation and inappropriate treatment.[67] Reduction in morbidity and mortality is dependent on early transport and appropriate resuscitation.

Skill in resuscitating the injured child includes understanding the physiologic variances. Children have excellent physiological adaptations; hence, shock may not be recognized in the early stages. Hypotension is oftentimes a late critical sign. In the pediatric circulatory system, shock may exist with a normal blood pressure. Normal systolic blood pressure could be estimated by adding 80 to age in years times two (80 + [age in years × 2]), while the diastolic blood pressure is roughly two thirds the systolic pressure. The total pediatric blood volume is estimated at 80 mL/kg; for a child to display hypotension resulting from hypovolemia, at least 25% of blood volume must have been lost.[67-69]

In a child, the decrease in cardiac output is proportional to the rate of blood volume decrease, although blood pressure may remain unchanged. Also, the stroke volume is fixed and, in the event of hypovolemia, cardiac output is maintained by increased heart rate and peripheral vascular resistance. In the presence of exhausted cardiac reserves, bradycardia indicates significantly decreased blood volume.

Fluid resuscitation in the pediatric trauma population has not changed much over the past decade. An extensive literature search revealed a paucity of articles in pediatric trauma fluid resuscitation. The goal of resuscitation in a hypovolemic injured child is restoration of normovolemia. Intravenous access in the pediatric population is often difficult and time-consuming in a volume-depleted state due to compensatory vasoconstriction. If intravenous cannulation is unsuccessful after two attempts, an intraosseous line should be established. The goal for peripheral access insertion should be 60–90 seconds. If this fails, intraosseous access should be obtained. A flow rate of about 40 mL/min can be achieved through an intraosseous line using a pressure bag.[70] The intraosseous access allows resuscitation until a definitive central vascular access can be established.

Owing to epidemiology of injury pattern in children, field fluid resuscitation may not be critical.[71] The mantra for the pre-hospital personnel should be scoop-and-run while assessing for vascular access en route to the hospital. Since children have smaller blood volume, they cannot afford to lose large volumes of blood. Scalp, neck region, penetrating truncal, and extremity injuries can produce significant amounts of blood loss, resulting in hemodynamic instability. Priority should be aggressive control of obvious bleeding. **Table 5** depicts the systematic response of pediatric patients to blood loss.

Since all pediatric trauma patients do not necessarily need resuscitation, what are the predictors of fluid resuscitation in pediatric trauma patients? ATLS guidelines are currently the standard of care for pediatric trauma care. However, ATLS applicability to pediatric patients has come under some question, since it is designed for the adult population.

Vella and colleagues performed a study to evaluate and establish the predictors of fluid resuscitation, and to determine whether all pediatric level 1 trauma victims require two intravenous accesses as per the ATLS guidelines.[71] They retrospectively reviewed charts of children younger than 18 years of age who met the criteria for level 1 trauma. Their review revealed that 70% of the patients received no fluid bolus, 20% received a single bolus, 7% received two boluses, and 3% received more than two boluses. They show that there are no statistically significant differences in fluid resuscitation or second intravenous access placement based on mechanism of injury. Age was the only predictor of second IV access placement and the injury severity score (ISS) was the only predictor of need for fluid resuscitation (not likely to be helpful in the clinical setting) They concluded that ATLS guidelines for IV access may not be appropriate for management of pediatric trauma.

The choice of fluid for pediatric resuscitation has not been

well studied except in cases of TBI. According to the excerpts from the spring 2003 International Trauma Anesthesia and Critical Care Symposium (ITACCS), crystalloids 20 mL/kg bolus in two doses should be given to the hemodynamically unstable child.[67] If there is no improvement, blood products at 10 mL/kg should be administered. Colloid should only be given as a temporizing measure while awaiting blood products. However, in burn patients, the Parkland formula using LR at 4 mL/kg/% of burn in the first day is still the most commonly utilized resuscitation modality.[72]

Although there is a paucity of research in pediatric fluid resuscitation, we can extrapolate the theory of hypotensive or small-volume resuscitation to the injured child to minimize fluid overload until control of active hemorrhage is achieved. Because of deleterious effect of hypotension to the neurologic outcome in TBI, hypotensive resuscitation is not recommended in this subset.

Complications from aggressive fluid resuscitation in children have been reported. One group reported a case of secondary abdominal compartment syndrome in a case of pediatric trauma shock resuscitation.[73] The case was that of a 17-year-old trauma patient with ongoing blood loss from a lacerated superficial temporal artery who received aggressive crystalloid resuscitation before arrival at a designated trauma hospital.

In pediatric head injury, the goal of resuscitation is to prevent secondary brain injury that could result from hypotension, hypoxia, anemia, and hyperglycemia. To accomplish this goal, CPP should be optimized, accounting for age-related differences in optimal CPP goal.[74] According to ITACCS excerpts, CPP ought to be maintained at greater than 40 mmHg in younger children, and greater than 50 mmHg in older children and adolescents.[75]

The use of HTS in pediatric TBI has also gained favor. A prospective, randomized, controlled study of fluid management in children with severe head injury comparing LR solution to hypertonic saline, performed at a level III pediatric intensive care unit, concluded that treatment with hypertonic saline is superior to that of LR solution.[76] An increase in serum sodium concentration correlates well with lower ICP and higher CPP. The study also shows that the children with HTS require fewer interventions, have fewer complications, and have shorter stays in the intensive care unit.

Khanna and colleagues evaluated the effect of prolonged infusion of 3% HTS and sustained hypernatremia on refractory intracranial hypertension in pediatric TBI.[77] In the study, they treated 10 pediatric TBI patients with increased ICP refractory to conventional treatment with titrated infusion of 3% normal saline to achieve a sodium level that would maintain ICP less than 20 mmHg. They demonstrated a statistically significant decrease in ICP and increase in CPP.[77] Based on these results, they concluded that increase in serum sodium concentration significantly decreased ICP and increased CPP, and that hypernatremia and hyperosmolarity are safely tolerated in pediatric patients with TBI.[77]

Conclusion

The review of the current body of literature is beginning to shed light on the future direction of resuscitation. Presently, the general consensus based on the available data from the last 10 years is to avoid under-resuscitation or over-resuscitation. The premise behind this is that under-resuscitation promotes end organ ischemia, while over-resuscitation may lead to re-bleeding, hemodilution, and coagulation abnormalities.[30] The goal of resuscitation should be to accomplish a perfusing blood pressure. The ideal blood pressure end point for non-head-injured patients should be guided by the radial pulse, the presence of which suggests systolic blood pressure of approximately 80–90 mmHg. Based on this parameter, if radial pulse cannot be palpated, fluid should be given until it is palpated. With this parameter, we can resuscitate to perfuse while minimizing the consequences of under- or over-resuscitation.

Regarding resuscitation fluids, clarity is emerging while the search for the ideal resuscitative fluid continues. From available data, initial resuscitation with large-volume isomeric LR solution could promote reperfusion injury. This is due to the effect of the D-isomer on neutrophil oxidative burst, endothelial damage, and the clearance of lactic acids. However, these adverse effects were not seen with the L-isomer solution. Based on this information, it could be concluded that the L-isomer LR solution should be utilized in place of the racemic mixture. However, until adequately powered, randomized, controlled trials are performed in human subjects, it will be difficult to propose changes to the ATLS guideline that recommends racemic LR as the initial resuscitation fluid of choice.

HTS has also shown significant promise, and it's slowly becoming the fluid of choice in Europe and in the military. In the era of low-volume resuscitation, its ability to act as a volume expander by rapidly mobilizing endogenous fluid, its immunomodulatory and hemodynamic effects, and the requirement of only a small volume to effectively restore cardiovascular function makes it an ideal choice for resuscitation. Although not FDA-approved yet, its ability to increase CPP while decreasing ICP in TBI patient has been well documented. It should be the fluid of choice in TBI, and this utility can be extrapolated to include non-head-injured trauma patients.

The search for the elusive ideal fluid for resuscitation is more promising than ever before. The ideal resuscitation fluid should have the following characteristics: capable of carrying oxygen, little or no effect on coagulation, inexpensive, non-allergic or antigenic, and a relatively long shelf-life at room temperature. HBOC has almost all these characteristics, and may hold the future of resuscitation.

The concerns about the potential side effects (vascular toxicity, pulmonary and systemic hypertension, and myocardial infarction) are slowly being resolved. These side effects are due to the scavenging properties of free deoxygenated hemoglobin on nitric oxide, which renders it unavailable for blood vessel dilation. A novel technology that allows free nitrite or nitrites methemoglobin to be added to stromal-free HBOC will lead to the elimination of the side effects that prevent its FDA approval. When free nitrites are added to HBOC, nitric oxides (NO and NO_2O_3) are produced. These by-products are able to escape the scavenging properties of free deoxyhemoglobin, and thus are available to dilate blood ves-

sels. The ability to produce free nitric oxide will eliminate the concerns of systemic or pulmonary hypertension and myocardial infarction associated with HBOC.[78]

The more clinical and laboratory research is performed, the more fuel is added to the controversy regarding choice of fluid, how fast and how much volume should be infused, and the ideal parameter to guide resuscitation strategies. Since most of these studies do not include human trials, it's hard to extrapolate their findings to clinical practice. Until we have adequately paired randomized, controlled studies involving human subjects to validate the finding in animals, the controversy will continue to rage. HTS and HBOC may be the future of resuscitation, since more promising human trials are beginning to confirm results from animal models.

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CNE/CME Objectives

Upon completing this program, the participants will be able to:

a.) discuss conditions that should increase suspicion for traumatic injuries;
b.) describe the various modalities used to identify different traumatic conditions;
c.) cite methods of quickly stabilizing and managing patients; and
d.) identify possible complications that may occur with traumatic injuries.

CNE/CME Instructions

Physicians and nurses participate in this continuing medical education/continuing education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. **After completing this activity, you must complete the evaluation form provided and return it in the reply envelope provided in order to receive a letter of credit.** When your evaluation is received, a letter of credit will be mailed to you.

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CNE/CME Questions

1. The concern for hemoglobin-based oxygen carriers' utility in traumatic brain injury patient is:
   a. Its high oxygen affinity
   b. Its negative effect on cerebral perfusion pressure
   c. Its vasoactive properties
   d. Its immunomodulating properties

2. According to Vella et al, the most important predictor of pediatric fluid resuscitation is:
   a. Age
   b. Revised trauma score
   c. Injury severity score
   d. Mechanism of injury

3. In the head-injured younger child, the goal for cerebral perfusion pressure should be:
   a. 10–20 mmHg
   b. 20–25 mmHg
   c. Greater than 40 mmHg
   d. Greater than 60 mmHg

4. According to the ATLS guidelines for pediatric fluid resuscitation, if after two boluses of crystalloid are given the patient is still hypotensive, the next choice is:
   a. blood at 20 mL/kg.
   b. colloid at 20 mL/kg.
   c. blood at 10 mL/kg.
   d. colloid at 10 mL/kg.

5. All of the following are characteristics of D-isomer Ringer's lactate that have deleterious effect on resuscitation *except*:
   a. inhibits lactic acid clearance
   b. stimulates neutrophil oxidative bursts
   c. damages the endothelium
   d. inhibits neutrophil oxidative burst

6. The exception to the "scoop-and-run" mantra for pre-hospital personnel is the:
   a. Hypotensive blunt trauma patient
   b. Hypotensive penetrating trauma patient
   c. Multi-trauma head injury victim
   d. Entrapped patient

7. Using the radial pulse as a parameter for adult fluid resuscitation, the presence of pulse is equivalent to what systolic blood pressure?
   a. 60–70 mmHg
   b. 70–80 mmHg
   c. 80–90 mmHg
   d. Greater than 100 mmHg

8. Which of following are potential side effects of hemoglobin-based oxygen carriers (HBOC)?
   a. Nephrotoxicity
   b. Vasoconstriction
   c. Methemoglobinemia
   d. All of the above

9. The characteristics of hypertonic saline that make it a promising resuscitative fluid include all of the following *except*:
   a. Direct vasodilatory effect
   b. Reduction of venous capacitance
   c. Positive ionotropic effect through action on myocardial cells
   d. Increasing tissue edema

10. Based on the available data, the current resuscitation trend in hemorrhaging trauma patients includes all the following *except*:
    a. Low-volume resuscitation
    b. Permissive hypotension
    c. Carefully monitored resuscitation
    d. Aggressive fluid resuscitation of patients with a blood pressure of 90 mmHg

Answers: 1. C; 2. C; 3. C; 4. C; 5. D; 6. D; 7. C; 8. D; 9. D; 10. D

In Future Issues: **Organ Donation and Procurement**

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CNE/CME Evaluation — Fluid Management in the Adult and Pediatric Trauma Patient
Please take a moment to answer the following questions to let us know your thoughts on the CNE/CME program. Fill in the appropriate space and return this page in the envelope provided. **You must return this evaluation to receive your letter of credit. ACEP members — Please see reverse side for option to mail in answers.** Thank you.

CORRECT ● **INCORRECT** ⊘ ✓ ✗ ⚠

1. In which program do you participate? ○ CNE ○ CME
2. If you are claiming physician credits, please indicate the appropriate credential: ○ MD ○ DO ○ Other _____
3. If you are claiming nursing contact hours, please indicate your highest credential: ○ RN ○ NP ○ Other _____

After participating in this program, I am able to:	**Strongly Disagree**	**Disagree**	**Slightly Disagree**	**Slightly Agree**	**Agree**	**Strongly Agree**
4. Discuss conditions that should increase suspicion for traumatic injuries.	○	○	○	○	○	○
5. Describe the various modalities used to identify different traumatic conditions.	○	○	○	○	○	○
6. Cite methods of quickly stabilizing and managing patients.	○	○	○	○	○	○
7. Identify possible complications that may occur with traumatic injuries.	○	○	○	○	○	○
8. The test questions were clear and appropriate.	○	○	○	○	○	○
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11. This activity reaffirmed my clinical practice.	○	○	○	○	○	○
12. This activity has changed my clinical practice.	○	○	○	○	○	○

If so, how? _____

13. How many minutes do you estimate it took you to complete this activity? Please include time for reading, reviewing, answering the questions, and comparing your answers with the correct ones listed. _____ minutes.
14. Do you have any general comments about the effectiveness of this CNE/CME program?

_____

I have completed the requirements for this activity.

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Company: _____

Address: _____

City: _____ State: _____ Zip _____

Fax: _____ Phone: _____

E-mail: _____

Optional for ACEP members: In accordance with ACEP requirements, below we provide the option for ACEP members to submit their answers for this CME activity. If you wish to submit answers for this activity, please refer to this issue (Vol. 10, No. 3) and circle the correct responses.

1. A
   B
   C
   D

2. A
   B
   C
   D

3. A
   B
   C
   D

4. A
   B
   C
   D

5. A
   B
   C
   D

6. A
   B
   C
   D

7. A
   B
   C
   D

8. A
   B
   C
   D

9. A
   B
   C
   D

10. A
    B
    C
    D