

State of the Art of Fluid Resuscitation 2010: Prehospital and Immediate Transition to the Hospital

Norman E. McSwain, MD, Howard R. Champion, MD, Timothy C. Fabian, MD, David B. Hoyt, MD, Charles E. Wade, PhD, Brian J. Eastridge, MD, Todd E. Rasmussen, MD, Robert R. Roussel, PhD, Frank K. Butler, MD, John B. Holcomb, MD, Martin A. Schreiber, MD, Steven R. Shackford, MD, and Lorne H. Blackbourne, MD

The Prehospital Fluid Conference was sponsored by the US Army Institute of Surgical Research and Combat Casualty Care Research, US Army Medical Research and Materiel Command. Some 65 conferees were invited in January 2010 to review the contemporary guidelines on the use of fluid resuscitation in treating combat casualties, discuss the state of the art of fluid resuscitation for combat casualties, and answer the following questions:

- Are current Tactical Combat Casualty Care (TCCC) intravenous (IV) fluid resuscitation guidelines optimal for today?
- Which IV fluid should be the top priority for future research?
- What are the current indications for fluid resuscitation in the combat trauma patient?
- What is the current practice in tactical fluid resuscitation?

The objective of this conference was to identify the fluid to be used by the prehospital provider and not to address the needs once definitive hemorrhage control has been achieved. The fluids to be used are those that will be carried into the field on the back of the combat medic or in the vehicle used to transport the medic or the patient (echelon 1 care). There are several definitions of these echelons of care (North Atlantic Treaty Organization [NATO], European forces, etc.). The definitions used in this document are those of the Joint Theater Trauma System. The use of "role" and "echelon" can be interchangeable depending on the country of origin, but the terms can vary significantly. Echelon, as used in many/most of Joint Theater Trauma System presen-

tations, will be used throughout this document to indicate a level of care facility (see Table 1).

Although discussions focused on military needs, it was understood and accepted by the consensus group that many, if not all, of the recommendations could and would be used for civilian prehospital providers with appropriate situational modifications.

The conferees explored the state of the science in three sessions:

- Crystalloids and colloids: Session chaired by Charles Wade, PhD, currently of the University of Texas Health Science Center (UTHSC), and Lorne Blackbourne, MD, Commander of the United States Institute of Surgical Research (USAISR).
- Oxygen carriers: Chaired by David Hoyt, MD, University of California Irvine Medical Center, and Howard Champion, MD, Uniformed Services University of the Health Sciences (USUHS).
- Coagulation maintenance and treatment: Chaired by Brian Eastridge, MD (USAISR), and John Holcomb, MD (UTHSC).

A consensus panel of experts was convened, and each expert presented his/her findings and recommendations. The panel in the first session was composed of Martin Schreiber, MD (Oregon Health and Science University), Fred Moore, MD (Methodist Hospital Houston), Sandro Rizoli, MD, PhD (University of Toronto), Ken Proctor, PhD (University of Miami), Peter Rhee, MD (University of Arizona Medical Center), Raul Coimbra, MD, PhD (University of California San Diego Medical Center), Eileen Bulger, MD (University of Washington), and Steven Shackford, MD (Scripps Mercy Medical Center). The panel in the second session was composed of Steve Gould, MD (University of Illinois), Joe Minei, MD (University of Texas Southwestern Medical Center), Charles Auker, MD (Naval Medical Research Center), Timothy Fabian, MD (University of Tennessee-Memphis), and Francisco Rentas, PhD (US Army Office of the Surgeon General). The panel in the third session was composed of Juan Duchesne, MD (Tulane University), Norman McSwain, MD (Tulane University), Kenji Inaba, MD (University of Southern California), Andre Cap, MD, PhD (USAISR), Ariv Amir, DVM, PhD (Core Dynamics),

Submitted for publication February 11, 2011.

Accepted for publication March 17, 2011.

Copyright © 2011 by Lippincott Williams & Wilkins

From the Department of the Army, US Army Institute of Surgical Research, Fort Sam Houston, Texas.

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or reflecting the views of the Department of the Army or Department of Defense.

Presented at the USAISR Prehospital Fluid Conference, January 8–9, 2010, Fort Worth, Texas.

Address for reprints: Norman E. McSwain, MD, 1430 Tulane Ave., Department of Surgery, Tulane University School of Medicine, New Orleans, LA 70112; email: nmcswai@tulane.edu.

DOI: 10.1097/TA.0b013e31821b201d

Report Documentation Page				Form Approved OMB No. 0704-0188	
Public reporting burden for the collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to a penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number.					
1. REPORT DATE 01 MAY 2011		2. REPORT TYPE N/A		3. DATES COVERED -	
4. TITLE AND SUBTITLE State of the art of fluid resuscitation 2010: prehospital and immediate transition to the hospital				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) McSwain N. E., Champion H. R., Fabian T. C., Hoyt D. B., Wade C. E., Eastridge B. J., Proctor K. G., Rasmussen T. E., Roussel R. R., Butler F. K., Holcomb J. B., Schreiber M. A., Shackford S. R., Blackbourne L. H.,				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) United States Army Institute of Surgical Research, JBSA Fort Sam Houston, TX				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION/AVAILABILITY STATEMENT Approved for public release, distribution unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT					
15. SUBJECT TERMS					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT UU	18. NUMBER OF PAGES 9	19a. NAME OF RESPONSIBLE PERSON
a REPORT unclassified	b ABSTRACT unclassified	c THIS PAGE unclassified			

TABLE 1. JTTS Levels of Care

Echelon/Role	Type of Care
1	Prehospital provider (e.g., combat medic)
2	Forward surgical team
3	Advanced surgical facility (e.g., combat support hospital)
4	Level II trauma center (e.g., Landstuhl Regional Medical Center)
5	Major trauma center in the continental United States (e.g., Brooke Army Medical Center)

and John Holcomb, MD (UTHSC). A synopsis of each session appears later in this article. For additional detail, please refer to the individual abstracts and their references that are presented in this supplement.

BACKGROUND

Physiology of Resuscitation

The two major components for resuscitation of the trauma patient are (1) stopping hemorrhage and (2) maintaining or restoring energy production.

Energy production depends on the Ficke principle:

- On-load oxygen (O_2) into the hemoglobin molecule in the lung.
- Deliver the hemoglobin to the tissue.
- Off-load the O_2 to the tissue cell.

In the tissue cells, aerobic metabolism produces adenosine triphosphate (ATP) at a rate that is significant to maintain life; anaerobic metabolism does not. O_2 delivery depends on an adequate supply of red blood cells (RBCs).

Hemorrhage control depends on the availability of the 13 factors in the coagulation cascade plus the definitive extrinsic factor, surgical control. In the 1960s, whole blood was used very effectively as the resuscitation solution. In the early 1970s, blood suppliers began separating whole blood into components and supplying blood products in the form of packed RBCs (PRBCs), platelets, and plasma, without data to support the use of components as being at least equally efficacious as the use of whole blood. This practice has now become standard in all civilian communities in the United States. Resuscitation fluids changed from complete/whole blood, with all of the elements needed for hemostasis, to PRBCs, crystalloid fluid (in Viet Nam), and replacement of various factors piecemeal using cryoprecipitate, fresh frozen plasma (FFP), and similar (in the 1990s). This practice was, perhaps, good for handling blood loss in the operating room, chronic blood loss from a hemorrhage from the gastrointestinal tract, and congenital or acquired coagulopathy; however, it was much less effective for the acutely hemorrhaging trauma patient. Recent emphasis on hemostasis has stressed the importance of the early use of plasma as FFP, platelets, cryoprecipitate, and, in some cases, recombinant factor VIIa. The first three are usually given with initial resuscitation in the hospital as a package and recombinant factor FVIIa as an in-hospital treatment when the first three fail to produce hemostasis.

Three crucial elements of resuscitation during hemorrhagic shock are maintaining movement of oxygen to the tissues from the lungs, forming clots to stop leaks in the vessels caused by injuries, and retaining fluid in vessels by reversing endothelial permeability and maintaining the serum oncotic pressure.

The old adage on shock management is to replace what the patient has lost.

- If blood has been lost, then blood should be replaced (hemorrhagic shock).
- If crystalloid is lost, then crystalloid should be replaced (dehydration).
- If dysrhythmia is the cause of shock, then cardiac drugs (cardiac arrest or similar problems) should be used.

This logical approach works well.

Various methods of isotonic fluid resuscitation were developed in response to the adoption of blood component therapy (instead of using of whole blood). Shires et al.¹ recommended 3 L of crystalloid for each liter of blood lost. The major reason for the large volumes of replacement was that the crystalloid rapidly distributed throughout the entire extracellular compartment; it was not confined to the vascular space. This distribution resulted in massive fluid overload producing significant edema and complications of “Da Nang Lung” (acute respiratory distress syndrome), hepatic failure, renal failure, and sepsis.

Jelenko² (burns) and Holcroft and Trunkey³ (acute trauma) recommended hypertonic saline (HTS) and colloid. The edema was not as severe and oxygen transfer was facilitated and complications were reduced. However, obstacles such as underhydration, coagulopathy, and decreased O_2 carrying capacity were not resolved. For burns, the long-term outcome was not changed; and in hemorrhagic trauma, the long-term studies do not exist. A consensus conference recommended continued use of large-volume resuscitation for burns.⁴ Mattox and coworkers⁵ recommended hypotensive resuscitation to prevent “pop-the-clot” problems and maintain the reduction of transmural pressure.

A modification of the Bernoulli theorem demonstrates that the flow from an injured vessel is proportional to the differential of the intraluminal/extraluminal pressure, the area of the defect in the vessels:

Rate of leakage

$$= \frac{\text{area of the vascular defect} \times (\text{intramural pressure} - \text{extramural pressure}) \times V^2}{\text{Density of the fluid}}$$

None of these solutions had all the necessary factors as identified above for complete resuscitation. Complication rates increased and survival was compromised.

Holcomb⁶ and others began the use of fluid replacement in severe combat injuries that was as near to whole blood as possible; i.e., blood, plasma, and platelets in a 1:1:1 ratio. The use of this ratio resulted in increased survival and decreased complications, including those of overhydration, excessive edema, and the associated complications. In a retrospective study from 16 Level I trauma centers, Holcomb et al.⁷ showed that increased plasma and platelets were

associated with decreased hemorrhagic mortality, no increase in multiorgan failure, and improved 24-hour and 30-day survival. Duchesne et al.⁸ assessed the same process in civilian injuries and produced the same positive results.⁸ The results of Duchesne demonstrated mortality improvement from ~80% to <30% in severely injured patients who required >10 units of blood in 8 hours. In addition, less blood for similar injuries was required during the hospitalization. Additional studies have demonstrated shorter length of stay and less blood required for resuscitation by using plasma rather than crystalloid for resuscitation.⁹

Dilutional resuscitation of hemorrhagic shock with either colloid, such as hetastarch, or crystalloid reduces the concentration of coagulation factors in the circulating blood volume and impairs hemostasis. Holcomb, Duchesne, and several others have demonstrated increased survival by using minimal to no crystalloid for resuscitation. Using minimal to no crystalloid most likely has three effects: early reintroduction of clotting factors into the depleted shock patient; resuscitation with a fluid that stays in the vascular system to assist in perfusion; and prevention of edema allowing increased transport of oxygen from the capillary to the tissue cell. Mattox and his team demonstrated that resuscitating patients to a “normal” blood pressure with crystalloid actually decreased survival. The likely etiology is prevention of clot popping and the reduction of transmural pressure.¹⁰ This so-called hypotensive resuscitation has become one part of the triad for prehospital resuscitation: rapid transport to a facility that can provide mechanical control of hemorrhage; hypotensive management of uncontrolled hemorrhage; and maintenance of energy production (ATP).

Resuscitation to a systolic pressure in the range of 120 mm Hg can produce several problems:

- Increasing the ratio between intramural pressure and extramural pressure will increase the pressure on the clot; if the clot is pushed off, greater blood loss from the injured vessels will result.
- Increasing the size of the hole as the vessel expands makes the initial clot less effective.
- It reduces the available factors needed for the coagulation cascade to proceed (dilution).
- It reduces the available platelets (dilution with crystalloid resuscitation).

Physiology of Hemostasis

In March 2010, the Department of Defense (DoD) and the National Heart, Lung and Blood Institute of the US Department of Health & Human Services hosted a symposium to discuss the physiology of clotting in the trauma patient. Over the course of the 2-day meeting, many scientific articles were presented and discussed. At the summation of the meeting, three concepts held general agreement:

- Dilution of the clotting factors was a major initial problem.
- A condition initiated by trauma to the tissue cells, which most likely consists of multiple components, begins immediately after wounding before the patient gets to the first medical facility and continues for 2 days to 4 days after injury.

- Hypercoagulopathy is not adequately understood in patients with traumatic injuries.

Many names have been proposed, but trauma-induced coagulopathy (TIC) is one of these and is very descriptive. Hemorrhage alters host energy metabolism, electrolyte balance, hormonal regulation, and coagulation function although little is known about these effects. Hemorrhage is a complex systemic disease, and many aspects of its underlying pathophysiological mechanisms remain unclear. One of the most serious complications after hemorrhage is the disruption of hemostasis, resulting in clinical consequences of uncontrolled bleeding and thrombotic complications. Normal physiologic coagulation requires a dynamic balance of complex systems of procoagulant, anticoagulant, and fibrinolytic processes. There are several reasons for coagulation disorders in major trauma. Major blood loss always includes the loss of clotting factors to a variable degree. Dilution-induced coagulopathy during fluid resuscitation results in critical plasma concentrations of coagulation factors.¹¹ Massive release of tissue factor from the site of injury extensively activates the coagulation cascade and consumes clotting factors, especially fibrinogen.¹² Furthermore, hypothermia, acidosis, hypovolemia, and hypoperfusion are frequent problems in severe trauma patients and lead to further deterioration of the coagulation process.¹³ The breakdown of fresh clots, a phenomenon termed hyperfibrinolysis, contributes to coagulopathy to an unknown degree. TIC occurs in 24% of patients with severe tissue injury and tissue hypoperfusion with a fourfold increase in mortality.¹⁴ The incidence and relevance of hyperfibrinolysis in patients with TIC is still unclear and is the subject of ongoing research.

Several different approaches have been offered as a solution to hemorrhage:

- Prehospital
 - Increased external pressure
 - Direct hand pressure
 - Pressure dressing
 - Hemostatic agents
 - Tourniquets
 - Liquid plasma
 - Resuscitation with long-distance transport of the patient in either a combat or rural situation
 - Hypotensive (restricted) resuscitation
- Hospital
 - 1:1:1 (RBC:plasma:platelets)
 - As needed, cryoprecipitate
 - 2:1 (RBC:plasma)
 - As needed
 - Platelets
 - Cryoprecipitate
 - Plasma = FFP, thawed plasma, and liquid plasma
 - Permissive hypotension
 - Systolic 80–90 mm Hg
 - 1:1 (RBC:plasma)
 - Crystalloid
 - Surgical hemostasis

Combat Fluid Resuscitation

In both the US civilian sector and the combat setting, the majority of deaths occur at the point of wounding or shortly after admission to a hospital and have a hemorrhagic component. Approximately 80% of those who die from combat wounds are dead at the scene or on arrival at echelon 2 or 3 facilities.^{15–18} Of the remaining 20%, the majority die shortly after admission, resulting in a total case fatality rate of ~10%. This rate excludes the ~50% of combat casualties who return to duty within 3 days.¹⁶ In the civilian sector, between 55% and 60% of deaths occur at the scene with a case fatality rate that varies from <1% to ~8%, depending on the mechanism of injury (e.g., falls, crashes, knife wounds, and gunshot wounds) and the denominator involved.¹⁹ Less than 10% of admitted civilian or military trauma patients have abnormal vital signs. Thus, it is estimated that the added value of fluid resuscitation is <2% of all those patients.²⁰

The devastating effects of injuries produced by modern weaponry is not replicated in the civilian sector. These effects, together with the tactical environment and delay in evacuation as well as the resource constraints of the combat setting, place special demands on the providers of point-of-wounding care and the resources to which they have access.

With no viable method for mechanically stopping non-compressible truncal hemorrhage, the leading opportunity for reducing mortality at the point of wounding in combat is from hemorrhage control and improved resuscitative strategies.^{17,21} The goals of resuscitation are to control hemorrhage and to restore oxygen-carrying capacity to support ATP production at the cellular level. The latter will usually restore some of the lost volume. The ideal resuscitative fluid should expand and maintain the circulating blood volume, maintain vital organ perfusion, and have a positive effect on hemostasis or homeostasis. Improved oxygen delivery, supplemented procoagulation, and metabolic downregulation may all be qualities that could be advantageously administered.

Although prehospital fluids have been widely used, their benefit in improving survival in trauma patients has not been established in prospective clinical trials. Most of the benefit of fluid replacement fluid therapy has been based on positive outcomes seen in animal models of controlled hemorrhage. For uncontrolled hemorrhage, several studies have shown either no benefit or increased mortality from aggressive prehospital fluid resuscitation.^{5,20,22} In addition, the battlefield brings special demands often not fully appreciated by civilian researchers and practitioners. If fluid resuscitation is to be undertaken in a battlefield setting, crystalloids have a short duration of action²³ and may not be suitable for casualties whose evacuation may be delayed. Colloids such as 6% hetastarch, in contrast, last for at least 8 hours and may be more suitable in this setting.²⁴

Resuscitation guidelines for military casualties are determined and recommended by the Committee on TCCC. TCCC was given structure and conceptual organization in a seminal 1996 article by Butler et al.²⁵ Shortly thereafter, these disciplines were introduced to the Special Operations community. An expert panel workshop was convened by the US Special Operations Command in 1999 to review the casualty

care lessons learned from military activities in Mogadishu and recommended that casualties with unconsciousness or altered mental status from uncontrolled hemorrhage be given prehospital fluids titrated to restore mentation.²⁶

The evolving guidelines based on evidence from combat and civilian settings^{6,27,28} have been disseminated throughout the DoD, US Allied and NATO Armed Forces largely as a result of the TCCC created in 2001 by Captain Frank Butler of Naval Special Warfare at US Special Operations Command.

The purpose of the Committee was to bring best practices to point-of-wounding care in combat settings and to address the inconsistencies in both training content and practice throughout the military. The Committee consisted of military medical combat casualty care experts from all services, a small number of civilian trauma surgeons, and a membership that consisted of at least 50% point-of-wounding combat care providers (e.g., medics). The Committee meets four times a year and invites participation from civilian tactical emergency medical services and Allied and NATO Armed Forces personnel.

The Committee continues to review best practices, training, and equipment and to make recommendations that are widely adopted. In 2009, the Committee gained official standing in DoD and is now reporting through the Injury Subcommittee of the Defense Health Board, an advisory board to the Office of the Secretary of Defense. Its recommendations are published on the Web site and instantiated in the *Prehospital Trauma Life Support Manual* (7th Edition).²⁹

Conferences on Combat Fluid Resuscitation

In 2001, the same year as the founding of the TCCC Committee, two conferences on combat fluid resuscitation were held. The 38 articles presented were published in the Supplement to the *Journal of Trauma*.²⁷ The first conference, funded by the Office of Naval Research, was held at USUHS in June 2001; and the second, funded by Defense R&D Canada, was held in Toronto in October 2001. The findings of these conferences differ because of the availability of HTS and hypertonic saline dextran (HSD) outside the United States.

Conference 1: Recommendations/Findings, USUHS²⁷

- The primary recommendation was that fluid resuscitation should be instituted for a systolic blood pressure of <80 mm Hg to 85 mm Hg, a falling blood pressure, or decreasing ability to mentate without evidence of head injury.
- In addition to determining the mechanism of wounding, anatomic location, and potential severity of the wounds, physiologic assessment of the patient should include assessment of mental status and presence of radial pulse.
- No fluids should be instituted in the presence of a strong radial pulse and normal mentation.
- Fluids should be initiated for weak or absent radial pulse or decreasing level of consciousness in the absence of head injury.
- Hetastarch (hydroxyethyl starch) was narrowly recommended as the colloid of choice for early care given in

an amount of 500 mL by gravity infusion. (Hextend is a hetastarch in a balanced salt solution.)

Conference 2: Recommendations/Findings, Toronto²⁷

- The current practice of using large-volume isotonic crystalloid infusion alone for combat resuscitation is not optimal.
- Fluid resuscitation of controlled hemorrhage in the battlefield, when indicated, should be an initial 250-mL infusion of 7.5% HTS combined with 6% HSD, administered slowly over 10 minutes to 15 minutes. This initial volume of HSD may be followed by a second 250-mL dose of HSD only in those patients who fail to stabilize. The infusion of HSD may be followed by isotonic crystalloids alone as care progresses.
- Although the recommended HSD regimen is mainly based on investigations in animal studies, its clinical efficacy in treating traumatic hypovolemic injury should be validated.
- International, multicenter, standardized human clinical trials and basic research should be conducted to confirm the efficacy of HSD for fluid resuscitation and to obtain regulatory approval.

The findings of the June USUHS conference was the basis for subsequent Fluid Resuscitation Guidelines propagated by TCCC and published in the Prehospital Trauma Life Support manual.³⁰

TCCC Resuscitation Guidelines

- Hypotensive resuscitation – Give fluid only if the patient has an altered mental status or an absent or weak radial pulse.
- Give fluid (500 ml of Hextend) and repeat $\times 1$ if the patient is still in shock.
- Hemorrhage control is paramount.

Current Status of Combat Casualty Care Resuscitation

As of January 2010, there have been 32,000 combat injury casualties in overseas contingency operations, predominantly in Iraq and Afghanistan. The wealth of experience gained in combat casualty care and resuscitation of the devastating injuries encountered in the theaters of operation with fresh whole blood and blood component therapy, together with tantalizing data on improved outcome at echelons 2 and 3 extending through acute hospitalization at level V, prompted this review. The focus was point-of-wounding care and echelon 1 resuscitation strategies.

Missing at the time of conference, but obtained shortly thereafter, were data to support impressions gained and articulated by the conferees on contemporary practice in Iraq and Afghanistan (Table 2). These data from a single Ranger regiment support the general impression of the conferees that despite the guidelines, more than 60% of combat fluid resuscitation at the point of wounding is initiated with isotonic crystalloid solutions, despite the cube (volume) weight trans-

TABLE 2. Data Set 331 Battle and Nonbattle Injuries From 2009*

Fluid	Number	Volume
Hetastarch	19	15 $\times$ 500 mL, 3 $\times$ 250 mL, 1 $\times$ 100 mL
Lactated Ringer's solution	2	2 $\times$ 500 mL
Normal saline	31	1 $\times$ 1,500 mL, 5 $\times$ 1,000 mL, 24 $\times$ 500 mL, 1 $\times$ 250 mL

* 52 (~15% if N = 331) were given IV fluid.

Source: Entered into Ranger Prehospital Trauma Registry. Data courtesy of LTC R. S. Kotwal, MD, MPH, 75th Ranger Regiment.

porting disadvantage of these fluids in the tactical environment. Several of the conferees also confirmed this from their own experience. It was apparent that wide variations in initial fluid management prevailed.

Session 1 Summary: Intravenous Crystalloids and Colloids for Battlefield Resuscitation

Because the disadvantages of normal saline outweigh the advantages, lactated Ringer's solution is still considered the crystalloid of choice for field resuscitation. The primary disadvantage of these fluids in combat is cube/weight (volume of the product versus the weight of the product) effect compared with other fluids (hetastarches require less fluid volume to produce the same vascular volume expansion as crystalloid).²⁶ PlasmaLyte, Hespan, Dextran, and Hextend were further discussed as were albumin, HTS, and HSD.

Recent clinical data from the Army Trauma Training Center at University of Miami Ryder Trauma Center on the clinical use of Hextend were presented. This prospective nonrandomized observational study compared Hextend to the standard of care at Ryder and showed an improved initial survival largely related to reduced early death with hemorrhage. There was, however, an increase in late deaths from organ failure, resulting in no difference in mortality by 2 weeks after injury. More patients given Hextend were admitted to the intensive care unit (ICU) than the patients given only lactated Ringer's solution. Of note, Hextend did not seem to be associated with coagulopathy in any of the patients receiving it (Fig. 1; Table 3).

None of the data presented in this study would change the current resuscitation strategy advocated by the TCCC Guidelines, which support the use of Hextend as a colloid for low cube weight or low volume/weight ratio compared with lactated Ringer's solution. There should be reliance on limited volume resuscitation. Despite the recommendations of TCCC, and supported by the DoD as the best initial fluid to use in combat, a significant number (as many as one-half) of the military prehospital providers still used lactated Ringer's or normal saline at the time of the meeting.

Session 2 Summary: Oxygen Carriers

The substantial challenges of, and failed attempts in, obtaining FDA approval for hemoglobin-based oxygen carriers were recounted together with lessons learned with

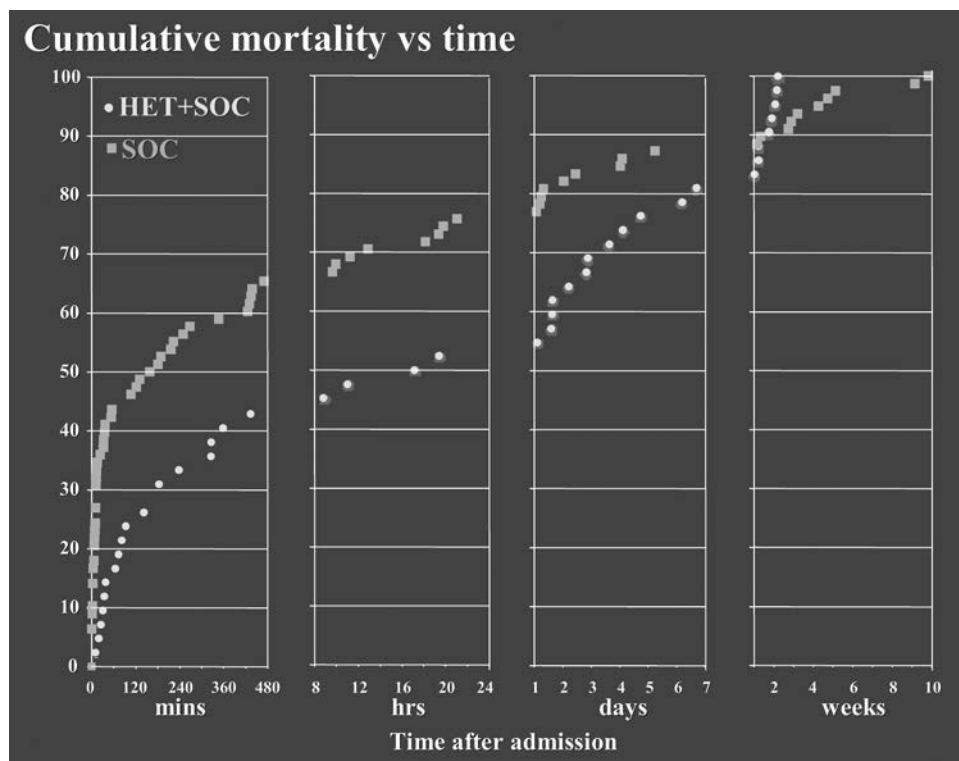


Figure 1. Effects of Hextend versus Standard of Care on mortality rates at a single major trauma center.³¹

TABLE 3. Effects of Hextend vs. Standard of Care on Early and Late Mortality Rates at a Single Major Trauma Center

Time	Hetastarch + SOC	SOC	<i>P</i>
Died <30 min	4 (0.1%*)	28 (3.1%*)	<0.0001
Died >30 min	38 (4.7%*)	53 (6.0%*)	0.2808

* Percent timing of death.³¹

PolyHeme and Biopure. Similarly, the attempted use of perfluorocarbons as a resuscitation fluid has not progressed over the past decade, although research in this area continues to produce third-generation perfluorocarbons that may be of particular value for patients with head injuries.

Frozen red cells are widely available and used in both the United States and Israel. Most of this use has been in-hospital and not in the tactical or prehospital environment. The advantage of using these frozen cells is that it obviates the “storage lesion” of RBC products stored for long periods at 4°C. The United States currently has several thousand units of frozen RBCs stored and available for use.

The blood pharming program of the Defense Advanced Research Programs Agency, which produces red cells from stem cells, was evidence of the continued research commitment of the DoD that holds significant future potential to provide oxygen-carrying capabilities for early combat casualty resuscitation. The bottom line is that there are no new oxygen carriers in the foreseeable future, and blood <14 days old may be better than older blood.³²

Session 3 Summary: Coagulation Maintenance and Treatment

The massive wounds of war and aggressive resuscitation strategies at the combat support hospital have prompted early use of a variety of coagulation factors and procoagulants in Operation Enduring Freedom and Operation Iraqi Freedom. A retrospective evaluation of patients receiving massive transfusion in a combat support hospital with a high ratio of red cells to FFP showed a substantial reduction in mortality. This in turn prompted a retrospective evaluation of high-ratio use of coagulation factors in civilian trauma centers and the coining of the term “damage control resuscitation”.⁹ This preplanned resuscitation strategy calls for limited use of isotonic crystalloids, early identification of patients who are likely to require massive transfusion, and aggressive use of FFP and platelets as a predetermined routine in these patients. The early use of FFP and other products seems to reduce transfusion requirements suggesting a decrease in the rate of early hemorrhage, which in itself produces increased survival.

There has been a significant reduction in the incidence of coagulopathy during and after resuscitation with the limited use of crystalloid and increased use of reconstructed whole blood in resuscitation (RBCs: plasma: platelets in a 1:1:1 ratio) in theater.⁹ This has caught on in the civilian community and proved effective as well.^{34,35} Reductions in complications due to overhydration, such as acute respiratory distress syndrome, acute renal failure, acute hepatic failure, and abdominal compartment syndrome, and reduced RBC use are thought to be due to the early control of hemorrhage

and the early administration of procoagulants. The controversy continues on whether use of all of the factors together (plasma) or the use of only isolated factors is the best approach.

The current state of the science in frozen and lyophilized coagulation factors including fibrinogen and plasma was reviewed. Perhaps the product with the most apparent potential for improving resuscitation in the near term is freeze-dried plasma.

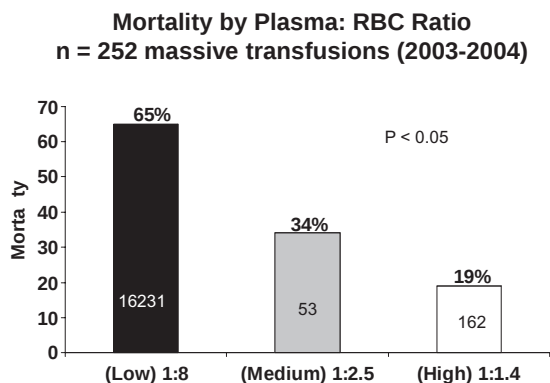
The conferees concluded that a major attempt should be made to establish a well-structured robust clinical trial that would investigate the effects on perfusion and coagulation of freeze-dried plasma in early resuscitation.

There have been multiple publications addressing the switch from crystalloid to plasma resuscitation, examples of which are listed below. They demonstrated improved survival and reduced length of stay. Unfortunately, the informed consent rules in the United States make the development of randomized studies that would definitively answer the questions of emergency care in a conventional way a significant challenge. However, several nonrandomized descriptive studies have shown the association between high plasma:RBC ratios (approaching 1:1) and improved outcome. Here are three examples (Figs. 2 and 3 and Table 4).

The importance of managing hemorrhage using plasma and coagulation factors is noted in the study below, which compares resuscitation using plasma and resuscitation using crystalloids.

SUMMARY

At the end of the 20th century, the Institute of Medicine reviewed the state of the art for combat casualty and civilian trauma care; IV saline (or crystalloid) solutions were typically the first-line therapy for hypovolemic shock patients to compensate for acute blood loss before transfusions could be safely administered.³⁷ In the first decade of the 21st century, little has changed; isotonic crystalloids remain the standard of care. There is promising data on the salutary actions of several different colloid or hypertonic solutions relative to isotonic crystalloids^{38–43}; but to date, no randomized con-



The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. Borgman MA, et al., J Trauma, 2007.

Figure 2. Effects of ratio of blood products on mortality in massively transfused patients at a combat support hospital.³³

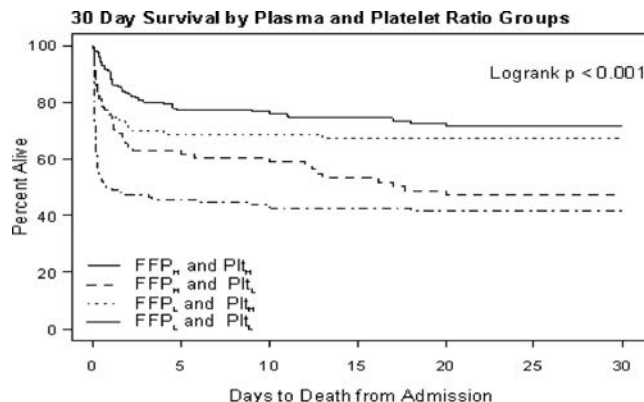


Figure 3. Effects of ratio of blood products on mortality in massively transfused patients at 16 Level I trauma centers.⁷

TABLE 4. Mean TICU LOS and Overall 30-Day Survival for DCL Patients During Study Periods

Outcome	DCL and CRE	DCL and DCR	p
ICU LOS	20	11	0.01
30-d survival	54.8%	73.6%	0.009

DCL, damage control laparotomy; DCR, damage control resuscitation; CRE, conventional resuscitation efforts.

Duchesne et al., 2010.³⁶

trolled trial has reported a significant survival benefit of these novel solutions. Controlled trials indicate the benefit of hypotensive resuscitation or low-volume resuscitation in the field, in the emergency department, and in the ICU and has become an accepted method of care.

- As of 2006, there were at least 32 randomized controlled trials comparing albumin to crystalloid solutions in 8,452 critically ill patients with hypovolemia or burns and no evidence that albumin reduced mortality.⁴⁴
- As of 2007, there were at least 55 randomized controlled trials of colloids compared with crystalloids and no evidence that colloids reduced the risk of death compared with crystalloids in 7,754 patients with trauma, burns, or after surgery.⁴⁵
- As of 2008, a review of 70 trials in 4,375 patients found no evidence that any one colloid solution is safer or more effective than any other.⁴⁶
- Because artificial colloids are not associated with an improvement in survival and because they are more expensive than crystalloids, some have suggested that the continued use of colloids in civilian trauma patients cannot be justified outside the context of randomized controlled trials.⁴⁵

For the military, on the other hand, colloids and other low-volume resuscitation solutions are attractive alternatives because they have unique advantages in austere environments where supplies are limited and evacuation times can be prolonged. For these logistical reasons and because of its reduced weight and size relative to saline solutions, Hextend (6% hetastarch in lactated electrolyte buffer; Hospira, Inc.) was

recommended for fluid resuscitation of combat casualties.^{6,26,27} Hextend is approved by the FDA for use in hypovolemia during elective surgery.⁴⁷ Despite these recommendations, saline solutions are still commonly used on the battlefield. Furthermore, many civilian and military clinicians avoid any artificial colloid solutions after trauma because of generalized concerns about anaphylaxis,⁴⁸ coagulopathy,⁴⁹ and/or catastrophic bleeding.⁵⁰ There have only been a few, inconclusive studies that have addressed the coagulation profile of Hextend.^{51,52} There are no data on the safety and efficacy of Hextend at the doses typically used for initial trauma resuscitation. However, recent work has suggested that Hextend administered in volumes up to 1 L has no adverse effect on the coagulation profile of trauma patients.³¹

RECOMMENDATIONS FOR MILITARY RESUSCITATION

Clinical

1. The TCCC guidelines should be continued unchanged.
 - a. The hypotensive resuscitation process should be used until hemorrhage control is obtained.
 - b. This process has not been refuted.
2. Prehospital
 - a. 1:1 resuscitation should be used as much as conditions and resources permit.
 - b. This type of resuscitation is not readily available for point-of-wounding care in prehospital combat or in the prehospital environment in the civilian community.
3. In hospital
 - a. 1:1:1 resuscitation should be the goal until hemorrhage is controlled. (This goal is based on retrospective studies.)
 - b. Use low-volume resuscitation as appropriate in hospital.
 - c. Management of the initial coagulopathy of severe blood loss is best achieved by early plasma infusion.
4. No current data are available to indicate that Hextend is superior to other fluids for field resuscitation.

Research

1. Lyophilized plasma is the first priority for research and development and represents the greatest need on the battlefield.
2. A DoD-funded multicenter trial comparing frozen RBCs to older RBCs and fresh RBCs is indicated.
3. Further research comparing Hextend, HTS, and 25% albumin would be reasonable.
4. Hemoglobin substitutes and perfluorocarbons are not ready for serious consideration at this time. Future advances in technology may make them candidates in the near future.
5. Component products such as lyophilized fibrinogen, prothrombin complex concentrate, and freeze-dried platelets may be beneficial.
6. Freeze-dried blood and blood pharming are very exciting, but they require further advances in technology.

7. Research on point-of-wounding treatments should focus on efficacy (i.e., hemodynamic parameters) and effectiveness (patient is alive at the next echelon of care) of early treatment rather than on 30-day survival.
8. A prehospital trial of plasma resuscitation is indicated to establish a baseline for future lyophilized plasma trials.

CONCLUSIONS

Significant development in fluid management has occurred in the use of hospital fluid resuscitation by the military in combat which has been adapted by the civilian community for resuscitation, operative management, and in the ICU. This development has been in the use of that major and critical fluid that has been lost by the patient—whole blood.⁵³ Therefore, reconstituted blood (1:1:1 PRBC:plasma:platelets) has been found to be nearly as effective for resuscitation. Many studies have shown the benefit in both military and civilian trauma. Unfortunately, the storage of these products has prevented their use in the field. Nonetheless, field care has matured, and specific indications for their use have been formulated. Most important is restricted use of crystalloids for resuscitation to prevent fluid overload and compartment syndrome in the abdomen, head, and lungs combined with early hemorrhage control using tourniquets and hemostatic solutions for wounds on which tourniquets cannot be applied (such as torso, head, and neck injuries). For long-term field care and in combat situations, hetastarches such as Hextend have not been found to improve survival but on the other side have not been found to produce coagulopathy or other negative effects. Therefore, in combat and at times when cube/weight ratios are important, Hextend has been found to be beneficial.

- TCCC guidelines are supported unchanged.
- Hypotensive resuscitation with fluid restriction is supported.
- Rapid control of hemorrhage with pressure, tourniquets, and hemostatic agents is advised.

REFERENCES

1. Shires GT, Carrico CJ, Coln D. The role of the extracellular fluid in shock. *Int Anesthesiol Clin*. 1964;2:435–454.
2. Jelenko C 3rd. Fluid therapy and the HALFD method. *J Trauma*. 1979;19(11 Suppl):866–867.
3. Holcomb JW, Trunkey DD. Extravascular lung water following hemorrhagic shock in the baboon: comparison between resuscitation with Ringer's lactate and Plasmanate. *Ann Surg*. 1974;180:408–417.
4. Schwartz SI. Consensus summary on fluid resuscitation. *J Trauma*. 1979;19(11 Suppl):876–877.
5. Bickell WH, Wall MJ, Pepe PE, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *N Engl J Med*. 1994;331:1105.
6. Holcomb JB. Fluid resuscitation in modern combat casualty care: lessons learned from Somalia. *J Trauma*. 2003;54(5 Suppl):46–51.
7. Holcomb JB, Wade CE, Michalek JE, et al. Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. *Ann Surg*. 2008;248:447–458.
8. Duchesne JC, Hunt J, Wahl G, et al. Review of current blood transfusions strategies in a mature level I trauma center: were we wrong for the last 60 years? *J Trauma*. 2009;67:216; author reply 216–217.
9. Holcomb JB, Jenkins D, Rhee P, et al. Damage control resuscitation: directly addressing the early coagulopathy of trauma. *J Trauma*. 2007;62:307–310.

10. Sondeen JL, Coppes VG, Holcomb JB. Blood pressure at which rebleeding occurs after resuscitation in swine with aortic injury. *J Trauma*. 2003;54:S110–S117.
11. Dickneite G, Doerr B, Kaspereit F. Characterization of the coagulation deficit in porcine dilutional coagulopathy and substitution with a prothrombin complex concentrate. *Anesth Analg*. 2008;106:1070–1077.
12. Lampl L, Seifried E, Tisch M, Helm M, Maier B, Bock KH. Hemostatic disorder following polytrauma—the role of physiologic coagulation inhibitors during the preclinical phase [in German]. *Anesthesiol Intensivmed Notfallmed Schmerzther*. 1992;27:31–36.
13. Cosgriff N, Moore E, Sauaia A, Kenny-Moynihan M, Burch JM, Galloway B. Predicting life-threatening coagulopathy in the massively transfused trauma patient: hypothermia and acidosis revisited. *J Trauma*. 1997;42:857–862.
14. Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. *J Trauma*. 2003;54:1127–1130.
15. Champion HR, Bellamy RF, Roberts P, Leppaniemi A. A profile of combat injury. *J Trauma Suppl*. 2003;54:S5:S13–S19.
16. Holcomb JB, Stansbury LG, Champion HR, Wade C, Bellamy RF. Understanding combat casualty care statistics. *J Trauma*. 2006;60:397–401.
17. Kelly JF, Ritenour AE, McLaughlin DF, et al. Injury severity and causes of death from Operation Iraqi Freedom and Operation Enduring Freedom: 2003–2004 versus 2006. *J Trauma*. 2008;64:S21–S28.
18. Holcomb JB, McMullin NR, Pearse L, et al. Causes of death in U.S. special operations forces in the global war on terrorism: 2001–2004. *Ann Surg*. 2007;245:986–991.
19. Potenza BM, Hoyt DB, Coimbra R, et al. The epidemiology of serious and fatal injury in San Diego County of an 11-year period. *J Trauma*. 2004;56:68–75.
20. Kaweski SM, Sise MJ, Virgilio RW. The effect of prehospital fluids on survival in trauma patients. *J Trauma*. 1990;30:1215.
21. Blackburne LH, Czarnik J, Mabry R, et al. Decreasing killed in action and died of wounds rates in combat wounded. *J Trauma*. 2010;69:S1–S4.
22. Cotton BA, Guy JS, Morris JA Jr, Abumrad NN. The cellular, metabolic, and systemic consequences of aggressive fluid resuscitation strategies. *Shock*. 2006;26:115–121.
23. Marino PL. Colloid and crystalloid resuscitation. In: Marino PL, ed. *The ICU Book*. Malvern, PA: Lea & Febiger; 1991:233–254.
24. Mortelmans Y, Merckx E, van Nerom C, et al. Effect of an equal volume replacement with 500 mL 6% hydroxyethyl starch on the blood and plasma volume of healthy volunteers. *Eur J Anesth*. 1995;12:259.
25. Butler FK, Hagmann J, Butler EG. Tactical combat casualty care in special operations. *Milit Med*. 1996;161:Suppl:3–16.
26. Butler FK, Hagmann JH, Richards DT. Tactical management of urban warfare casualties in special operations. *Mil Med*. 2000;165:Suppl:1–48.
27. Champion HR. Combat fluid resuscitation: introduction and overview of conferences. *J Trauma*. 2003;54(5 Suppl):7–12.
28. Champion HR. *Casualty Evacuation Delay and Outcomes*. Final technical report, US Special Operations Command (SOCOM) Contract USZA22-00-C-0003; 2003.
29. McSwain NE Jr, Salomone J, Pons P, Bitner M, Callaway D, Guy J (eds). *PHTLS: Prehospital Trauma Life Support*. 7th ed. St. Louis, MO: Mosby, Inc.; 2010.
30. McSwain NE Jr, Salomone J, Pons P, Giebner S (eds). *PHTLS: Basic and Advanced Prehospital Trauma Life Support*. 6th ed. St. Louis, MO: Mosby, Inc.; 2006.
31. Ogilvie MP, Pereira BMT, McKenney MG, et al. First report on the safety and efficacy of hetastarch solution for initial resuscitation at a level 1 trauma center. *J Am Coll Surgeons*. 2010;210:5, 870–880.
32. Weinberg JA, McGwin G Jr, Griffin RL, et al. Age of transfused blood: an independent predictor of mortality despite universal leukoreduction. *J Trauma*. 2008;65:279–284.
33. Borgman MA, Spinella PC, Perkins JG, et al. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. *J Trauma*. 2007;63:805–813.
34. Duchesne JC, Islam TM, Stuke L, et al. Hemostatic resuscitation during surgery improves survival in patients with traumatic induced coagulopathy. *J Trauma*. 2009;67:33–37; discussion 37–39.
35. Snyder CW, Weinberg JA, McGwin G Jr, et al. The relationship of blood product ratio to mortality: survival benefit or survival bias? *J Trauma*. 2009;66:358–364.
36. Duchesne JC, Kimonis K, Marr AB, et al. Damage control resuscitation in combination with damage control laparotomy: a survival advantage. *J Trauma*. 2010;69:46–52.
37. Longnecker DE, Baxt WG, Fratantoni JC, et al. Protocols of care at the site of injury. In: Pope A, French G, Longnecker DE, eds. *Fluid Resuscitation: State of the Science for Treating Combat Casualties and Civilian Injuries*. Washington, DC: National Academy Press; 1999:97–108.
38. Smith GJ, Kramer GC, Perron P, Nakayama S, Gunther RA, Holcroft JW. A comparison of several hypertonic solutions for resuscitation of bled sheep. *J Surg Res*. 1985;39:517–528.
39. Halvorsen L, Gunther RA, Dubick MA, Holcroft JW. Dose response characteristics of hypertonic saline dextran solutions. *J Trauma*. 1991;31:785–793; discussion 793–794.
40. Halvorsen L, Bay BK, Perron PR, et al. Evaluation of an intraosseous infusion device for the resuscitation of hypovolemic shock. *J Trauma*. 1990;30:652–658; discussion 658–659.
41. Jelenko C 3rd, Solenberger RI, Wheeler ML, Callaway BD. Shock and resuscitation. III. Accurate refractometric COP determinations in hypovolemia treated with HALFD. *JACEP*. 1979;8:253–256.
42. Jelenko C, Wheeler ML, Callaway BD, Divilio LT, Bucklen KR, Holdredge TD. Shock and resuscitation. II. Volume repletion with minimal edema using the HALFD (Hypertonic Albuminated Fluid Demand) regimen. *JACEP*. 1978;7:326–333.
43. Kramer GC, Perron PR, Lindsey DC, et al. Small-volume resuscitation with hypertonic saline dextran solution. *Surgery*. 1986;199:239–247.
44. Alderson P, Bunn F, Lefebvre C, et al. Human albumin solution for resuscitation and volume expansion in critically ill patients. *Cochrane Database Syst Rev*. 2004;4:CD001208.
45. Perel P, Roberts I. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev*. 2007;4:CD000567.
46. Bunn F, Trivedi D, Ashraf S. Colloid solutions for fluid resuscitation. *Cochrane Database Syst Rev*. 2008;1:CD001319.
47. Roche AM, Mythen MG, James MF. Effects of a new modified balanced hydroxyethyl starch preparation (Hextend) on measures of coagulation. *Br J Anaesth*. 2004;92:154–155.
48. Barron ME, Wilkes MM, Navickis RJ. A systematic review of the comparative safety of colloids. *Arch Surg*. 2004;139:552–563.
49. Avorn J, Patel M, Levin R, Winkelmayer WC. Hetastarch and bleeding complications after coronary artery surgery. *Chest*. 2003;124:1437–1442.
50. Damon L, Adams M, Stricker RB, Ries C. Intracranial bleeding during treatment with hydroxyethyl starch. *N Engl J Med*. 1987;317:964–965.
51. Boldt J, Haisch G, Suttner S, Kumble B, Schellhaass A. Effects of a new modified, balanced hydroxyethyl starch preparation (Hextend) on measures of coagulation. *Br J Anaesth*. 2002;89:722–728.
52. Gan TJ, Bennett-Guerrero E, Phillips-Bute B, et al. Hextend, a physiologically balanced plasma expander for large volume use in major surgery: a randomized phase III clinical trial. *Anesth Analg*. 1999;88:992–998.
53. Spinella PC, Perkins JG, Grathwohl KW, Beekley AC, Holcomb JB. Warm fresh whole blood is independently associated with improved survival for patients with combat-related traumatic injuries. *J Trauma*. 2009;66:S69–S76.