

Fluid Resuscitation in Tactical Combat Casualty Care

TCCC Guidelines Change 21-01

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Travis Deaton, MD¹; Jonathan Auten, DO²; Richard Betzold, MD³; Frank Butler, MD⁴;
Terence Byrne, SOCM⁵; Andre Cap, MD, PhD⁶; Ben Donham, MD⁷; Joseph DuBose, MD⁸;
Andrew D. Fisher, MD, PA-C⁹; James Hancock, MD¹⁰; Victor Jourdain, MD¹¹; Ryan Knight, MD¹²;
Lanny Littlejohn, MD¹³; Matthew Martin, MD¹⁴; Kevin Toland, SOIDC¹⁵; Brendon Drew, DO¹⁶

ABSTRACT

Hemorrhagic shock in combat trauma remains the greatest life threat to casualties with potentially survivable injuries. Advances in external hemorrhage control and the increasing use of damage control resuscitation have demonstrated significant success in decreasing mortality in combat casualties. Presently, an expanding body of literature suggests that fluid resuscitation strategies for casualties in hemorrhagic shock that include the prehospital use of cold-stored or fresh whole blood when available, or blood components when whole blood is not available, are superior to crystalloid and colloid fluids. On the basis of this recent evidence, the Committee on Tactical Combat Casualty Care (TCCC) has conducted a review of fluid resuscitation for the combat casualty who is in hemorrhagic shock and made the following new recommendations: (1) cold stored low-titer group O whole blood (CS-LTOWB) has been designated as the preferred resuscitation fluid, with fresh LTOWB identified as the first alternate if CS-LTOWB is not available; (2) crystalloids and Hextend are no longer recommended as fluid resuscitation options in hemorrhagic shock; (3) target systolic blood pressure (SBP) resuscitation goals have been redefined for casualties with and without traumatic brain injury (TBI) coexisting with their hemorrhagic shock; and (4) empiric prehospital calcium administration is now recommended whenever blood product resuscitation is required.

KEYWORDS: *fluid resuscitation; blood transfusion; calcium; hemorrhage; shock; traumatic brain injury; traumatic injury; damage control resuscitation*

Proximate Cause for This Change

Whole blood was recommended by the Committee on TCCC (CoTCCC) in June of 2014 as the preferred prehospital fluid for resuscitation from hemorrhagic shock.¹ Since that update to the TCCC Guidelines, the ongoing monitoring of new papers in the medical literature conducted by the CoTCCC has noted a number of publications that attest to the benefit of earlier use of whole blood or blood components.²⁻⁵ There have also been publications that have documented increased survival with increasing SBP in TBI patients.⁶ Additionally, there

have been publications that raise concerns about the use of crystalloid and colloid solutions in hemorrhagic shock as well as literature that addresses the issue of hypocalcemia in hemorrhagic shock. These observations have necessitated a relook at the topic of fluid resuscitation for hemorrhagic shock in the TCCC environment.

Several policy and regulatory changes have influenced the practice of prehospital care in the deployed environment. These include the issuance of a Federal Drug Administration (FDA) black box warning on hetastarches including Hextend,⁷ the Armed Services Blood Program Office (ASBPO) production and sourcing of FDA licensed CS-LTOWB,⁸ and the Emergency Use Authorization of Freeze-Dried Plasma for uncontrolled hemorrhage in military trauma.⁹

Another important development in this area is that the American Association of Blood Banks has now recognized LTOWB as a universal donor whole blood product for patients in hemorrhagic shock.¹⁰ Their 2018 recommendation states that: "Recipients shall receive ABO group-compatible Red Blood Cell components, ABO group-specific Whole Blood, or low titer group O Whole Blood (for non-group O or for recipients whose ABO group is unknown)." The definition of "low titer" is deferred to local transfusion services.

When FDA-compliant CS-LTOWB is not available, a second option for whole blood for emergency transfusion in trauma patients is fresh whole blood (FWB). New programs and training courses to facilitate the use of FWB in military settings have been developed. In addition to the Ranger Group O Low-Titer (ROLO) program that was initiated in 2015,¹¹ the US Special Operations Command recently extended their FWB program to include all their component forces under the command-sanctioned Special Operations Low-Titer O Whole Blood (SOLO) Program.¹² Conventional US Marine Corps infantry forces have also reported successful training and implementation of fresh whole blood use under the Valkyrie FWB program.^{13,14} There is additional interest from prehospital providers outside of the military with FWB training programs now reported in civilian EMS and law enforcement programs including the Texas Rangers.¹⁵

¹⁻¹⁶Please see affiliations on page 134.

Finally, there have been both CoTCCC and Joint Trauma System (JTS) recommendations that CS-LTOWB be considered the preferred option for resuscitation of casualties in hemorrhagic shock. The 2018 TCCC Advanced Resuscitative Care paper stated that: “Resuscitation should be initiated with FDA-compliant, cold-stored LTOWB as the preferred option and every effort should be made to have cold-stored LTOWB available.”⁵ FDA-complaint LTOWB is now being shipped by the ASBPO to support combat operations. The logistics of cold-stored whole blood carriage remain a challenge for tactical medics, but the availability of small portable blood containers that are capable of achieving the required cold storage conditions for up to 72 hours makes CS-LTOWB use more feasible in combat operations supported by tactical vehicles or aircraft.⁵ The Joint Trauma System Clinical Practice Guideline (CPG) on Damage Control Resuscitation (DCR) was subsequently updated in July 2019 and specifically calls for (1) a greater emphasis on LTOWB as the optimally balanced and maximally hemostatic resuscitation fluid, (2) recommends early calcium use in hemorrhagic shock, (3) modifies blood pressure goals to a target SBP of 100mmHg for hemorrhagic shock or 110mmHg for TBI and (4) no longer recommends hydroxyethyl starch (Hextend, Hespan) as a resuscitation fluid.¹⁶ Similarly, the JTS CPG on Whole Blood Transfusion stresses the advantages of whole blood over component therapy and includes considerations for risks and benefits between fresh whole blood and stored whole blood.¹⁷ Finally, the JTS CPG on Damage Control Resuscitation in Prolonged Field Care, recognized as the follow-on guidance for TCCC if evacuation is delayed, also updated its recommendations to include CS-LTOWB and included the same SBP goals for resuscitation noted in the Damage Control Resuscitation CPG above.¹⁸ Consistency in recommendations throughout the spectrum of care (insofar as the tactical, equipment, and training considerations permit) starting with the initial TCCC rendered at the point of injury and continuing throughout the prehospital phase of care, remains critical to reducing variability in training and standardizing the application of critical life-saving interventions.

Incorporating the approach used by Col Stacy Shackelford in her 2016 TCCC Change Paper on circumferential pelvic compression devices in TCCC,¹⁹ the TCCC change team addressing the topic of fluid resuscitation in hemorrhagic shock identified four specific questions that needed to be addressed in this review:

- (1) Is there a specific blood product that is preferred over others for resuscitation of casualties in hemorrhagic shock in TCCC?
- (2) Should crystalloid solutions and Hextend be removed as TCCC-recommended fluids for resuscitation of casualties in hemorrhagic shock?
- (3) What is the optimal target SBP for resuscitation of hemorrhagic shock casualties, and does this change when traumatic brain injury is also present?
- (4) Should empiric calcium be added to the TCCC fluid resuscitation guideline? If so, how much and which type of calcium formulation should be used, and when in the resuscitation sequence should it be given?

Background

Clinical observations from recent Overseas Contingency Operations provide insight into the previous paradigm of large-volume crystalloid resuscitation for prehospital and initial

in-hospital resuscitation and the impacts of trauma-induced coagulopathy resulting in excess morbidity and mortality from uncontrolled hemorrhage.²⁰⁻²² From the very beginning of the TCCC program in 1996, and as continued by the National Academy of Science, Engineering and Medicine’s “Zero Preventable Deaths” initiative, civilian and military trauma experts have begun to focus on the prehospital phase of care as the most promising time period in which to reduce preventable deaths in trauma victims.²³ One of the prehospital tenants of care that has been shown to decrease mortality among the most critically injured is blood product transfusion early in the continuum of care.⁴ Additionally, data published by Shackelford et al. showed that blood products given as soon as possible following injury improved 24-hour and 30-day survival, suggesting both the choice of fluid and time of administration are key components to successful resuscitation.³

Despite the evidence backing use of blood products in resuscitation, a recent review of the military prehospital trauma registry shows that providers continue to rely on crystalloid or colloid solutions. In a 2019 retrospective study, the most commonly administered fluids were normal saline (52.4%) followed by hetastarch solution (33.3%).²⁴ Although whole blood was recommended by the CoTCCC in 2014 as the preferred resuscitation fluid for casualties in hemorrhagic shock and other blood components were recommended in the event that whole blood was not available, Hextend, lactated Ringer’s, and Plasma Lyte-A were retained on the recommended list of resuscitation fluids in the event that blood products were not available. This may have contributed to their continued use in the military. Recently, however, a civilian meta-analysis highlights the increased mortality and renal replacement therapy requirements attributed to hetastarch use among critically ill patients (including but not limited to trauma patients) requiring volume resuscitation.²⁵ Furthermore, in the trauma-specific setting, both crystalloids and colloids have been shown to worsen trauma-induced coagulopathy.²⁶ Decreasing reliance on pre-hospital crystalloid and colloid solutions for resuscitation of trauma victims represents an opportunity to further decrease death after injury.

When considering the optimal resuscitation fluid choice, there is an ample body of work demonstrating the superiority of blood products. In the laboratory setting, whole blood has been noted to be superior to both crystalloids and colloids in a prehospital translational shock model.²⁷ Further evidence comes from the field. Over the past decade, NATO prehospital teams such as the United Kingdom’s Medical Emergency Response Team Enhanced (MERT-E) have successfully integrated hemostatic resuscitation with packed red blood cells (PRBCs) and fresh frozen plasma (FFP) as part of en-route care.²⁸ In addition, Israeli Defense Forces Medical Corps have also documented successful prehospital utilization of LTOWB.²⁹ Our own clinical data from nearly two decades of conflict suggest that whole blood is safe, effective, and far superior to crystalloid and colloid resuscitation fluids.^{2,30-32}

Traditionally, the principal argument for nonhemostatic prehospital fluid resuscitation options like Hextend has been related to the logistics of blood component availability close to the point of injury and training requirements for combat medical personnel.¹ With the increasing body of evidence supporting the superiority of whole blood and blood components over crystalloids in resuscitating combat casualties in hemorrhagic shock, the continued use of crystalloid solutions for

hemorrhagic shock needs to be reevaluated and the military focus on prehospital blood products as the resuscitation fluid of choice for combat injuries requiring resuscitation needs to be strengthened.³³

The following is a review of fluid resuscitation options in hemorrhagic shock with recent literature updates included.

Discussion

(1) *Is there a specific blood product that is preferred over others for resuscitation of casualties in hemorrhagic shock in TCCC?*

Whole Blood – A Brief History of Combat Use

The use of whole blood as the best option for resuscitating wartime casualties in hemorrhagic shock is a lesson that has been learned by the US military three separate times in three separate conflicts. Dr. Walter Cannon was a strong advocate for using whole blood to treat casualties in hemorrhagic shock in World War I. During the period after World War I, however, physicians and physiologists began to consider shock as being primarily due to loss of plasma volume from the intravascular space, suggesting that plasma might be just as good as whole blood. It was also logistically easier to ship units of dried plasma to frontline troops.

These two factors combined to make plasma the preferred fluid to use for resuscitation from hemorrhagic shock at the start of World War II. As a result, early in World War II, the US Army Surgeon General declined to supply whole blood to combat units. During the course of the war, however, surgeons like Colonel Edward Churchill noted that American casualties who were being treated with plasma were faring less well than British casualties who were being treated with whole blood.³⁴ Additionally, the use of pooled plasma products entailed an increased risk of hepatitis.

Colonel Churchill subsequently requested that whole blood be supplied to US Army combat forces. Churchill's request was denied. This story subsequently found its way to the *New York Times*. The *Times* ran a story in August of 1943 and the US military restarted its whole blood program shortly thereafter. In Okinawa alone, over 40,000 pints of whole blood were reportedly used for casualties.³⁴

Despite whole blood having been “re-discovered” by the US military as the preferred resuscitation fluid for casualties in shock in World War II, this important aspect of care was again lost in the mid-1970s, when transfusion practice moved from the use of whole blood to using individual blood component (RBCs, plasma, or platelet) therapy after blood fractionation became technologically feasible. This change occurred despite the lack of evidence for the benefit of this strategy when used for patients in hemorrhagic shock.¹

Another development in fluid resuscitation that occurred during the Vietnam era was the thought that adequate fluid resuscitation could be accomplished with crystalloid solutions if the volume provided was approximately three times the volume of estimated blood lost in order to account for the fact that only about one-third of the crystalloid solution infused remained in the intravascular space. This led to the emergence of fluid overload syndromes during the Vietnam conflict. Excess fluid in the pulmonary system was dubbed “Da Nang Lung” and was the best-known entity, but fluid overload in the abdomen and the brain can be deadly as well.

Several studies in recent Overseas Contingency Operations have demonstrated improved survival when whole blood was used to resuscitate casualties in hemorrhagic shock.^{2,30,31} The 2014 TCCC reexamination of fluid resuscitation options for casualties in hemorrhagic shock found that whole blood was the optimal fluid for that purpose.¹ This demonstrated survival benefit is much enhanced when the casualties being treated are critically injured and when whole blood administration begins as soon as possible after the onset of shock.

Whole Blood – Modern Use on the Battlefield

Whole blood is a generic term for unfractionated blood collected in a single bag that includes an anticoagulant solution to sustain red blood cell integrity. To understand the risks and benefits of whole blood transfusions, it is important to differentiate the various methods of collection, storage, and use. There are four primary options for whole blood on the modern battlefield.⁵

- CS-LTOWB is collected by blood banks, screened for transfusion-transmittable infections, and tested to ensure low titers of anti-A and anti-B antibodies. It is thus FDA compliant and is a universal donor option for blood transfusions. The ASBPO has increased the production and delivery of this type of stored blood to combat theaters. It does, however, require storage in the recommended cold conditions, which imposes logistical issues for combat units. Both safety and Department of Defense policy require that FDA-compliant blood products be used for combat casualties unless such products are not available or are deemed to be not clinically effective by the providing physician.³⁵ The increasing availability of portable blood coolers for use on the battlefield now often makes this option feasible even in far-forward environments, especially when the military operation being supported entails the use of tactical aircraft or vehicles.⁵
- Fresh LTOWB is collected from donor pools of individuals who have been prescreened to ensure that they were free from transfusion-transmittable infections and that their Type O blood contains low titers of anti-A and anti-B antibodies. These prescreened donors are thus able to act as relatively low-risk sources of universal donor whole blood when needed in far-forward environments. The 75th Ranger Regiment has demonstrated the feasibility of establishing such a program in frontline combat units with their Ranger Type O Low Titer (ROLO) effort.¹¹ Fresh whole blood can be stored at room temperature for 24 hours, and some data suggests this timeframe may be safely extended to 72 hours.³⁶ It can also be refrigerated within 8 hours at which point it becomes known as stored whole blood.
- Fresh group O unititered whole blood is also collected from donor pools in combat settings when neither of the first two options for whole blood are available. The risk of transfusion reactions from type O donors with unknown levels of anti-A and anti-B antibodies has been shown to be low, but the risk of transfusion-transmittable infections remains. This option for obtaining whole blood when FDA-compliant whole blood is not available has been used widely in combat support hospitals.³¹
- Type-specific fresh whole blood provides for ABO-identical transfusions but entails the risk of a fatal hemolytic reaction in the event of an ABO-mismatch due

to an administrative or blood typing error. Type-specific blood has been used as a source of fresh whole blood on forward surgical teams embarked on naval surface combatant vessels. A recent case series described the use of 39 units of type-specific whole blood during a mass casualty event on the USS Bataan.³⁷

Cold-Stored Low-Titer Group O Whole Blood

Following US military implementation of a cold-stored whole blood program, several US civilian trauma centers and pre-hospital providers began incorporating CS-LTOWB into their respective trauma resuscitation protocols.³⁸ Williams et al. reported a decrease in post-emergency department blood product utilization and two-fold increased likelihood of survival with CS-LTOWB when controlling for age and severity of injury.³⁹ In a separate prospective observational study, Duchesne et al. evaluated trauma patients receiving whole blood as part of their initial emergency department resuscitation.⁴⁰ They found that CS-LTOWB patients received significantly fewer PRBCs and FFP during hospitalization. They also observed a decreased incidence of ARDS, but contrary to Williams et al, found no survival benefit in those receiving CS-LTOWB.⁴⁰ A third recently published study again found no difference in 24-hour or 30-day mortality between groups receiving component therapy or CS-LTOWB.⁴¹ Importantly, the studies mentioned previously have thus far demonstrated no increased rate of complications in comparison to component therapy in the civilian trauma setting. Furthermore, the use of CS-LTOWB has recently expanded to the fields of obstetrics and pediatric trauma.⁴²⁻⁴⁴ With increased adoption in the civilian trauma setting as well as in other medical specialties, a greater base of knowledge and evidence regarding the use of CS-LTOWB is already developing.

As noted previously, both safety considerations and DoD policy make CS-LTOWB the option of choice when logistic considerations make that a feasible choice. This option also eliminates the time delay caused by the need to draw a unit of fresh whole blood from a member of the donor pool. Finally, it avoids having to take blood from a combatant who is still on the battlefield and could possibly be wounded during ongoing combat action.⁵

Fresh Whole Blood

Experience during Operation Enduring Freedom and Operation Iraqi Freedom has demonstrated that FWB is safe and that outcomes after FWB administration are equivalent, if not superior, to outcomes following component therapy.^{30,31,45}

Risks associated with the use of FWB include transfusion-transmittable infections and the potential for acute hemolytic reactions due to ABO mismatch. The risk, however, has thus far been very low. Recent data encompassing approximately 10,000 FWB transfusions to US personnel during OIF/OEF have resulted in one hepatitis C (HCV) infection, one human T-lymphocyte virus (HTLV) seroconversion, and one fatal case of transfusion-associated graft-versus-host disease that was potentially due to an FWB transfusion.⁴⁶⁻⁴⁸

In the prehospital setting, a structured approach such as the Ranger Type O Low (ROLO) or Marine Corps Valkyrie program^{11,13} minimizes the chance of an ABO mismatch by clearly identifying the LTOWB donor pool before the unit leaves for combat operations, rather than having to take the time to test potential donors with Eldon cards in the midst of a casualty

response on the mission. Further, the use of Eldon cards to determine blood type was found by Bienek and Perez in 2013 to be only 80% accurate when compared to the ABO group in the subjects' medical record.⁴⁹ The subjects in this study included physicians, corpsmen, and medical service corps officers.

The use of a prescreened type O low-titer donor pool also minimizes the risk for a reaction to high anti-A and anti-B antibody titers by eliminating those type O individuals with high titers from the donor pool during the predeployment screening process.¹¹

Prehospital Considerations

Several factors must be considered in developing prehospital fluid resuscitation strategies for casualties in hemorrhagic shock, including the fact that medics and corpsmen will deliver the preponderance of medical care in the tactical environment. CS-LTOWB is the safest option as an FDA-complaint universal blood product, but it requires significant logistical support for cold chain requirements. This requirement may make the use of cold stored whole blood and blood components (plasma and RBCs) infeasible in some tactical settings.

Where cold chain storage cannot be maintained, freeze dried plasma and fresh whole blood remain reasonable options for fluid resuscitation. While the FDA Emergency Use Authorization remains in place for the French freeze-dried plasma product (FLyP), the producer has not yet increased the supply of FLyP to quantities sufficient to meet US military demand. Military logistics systems are therefore not able to reliably supply this product to combat units.

If units decide to implement prescreened fresh LTOWB as an option, formal training and education on the safe collection and utilization of fresh whole blood must be implemented. Donham et al. addressed prior concerns that fresh whole blood training was excessively high risk for operational units, and published experiences with over 3,400 autotransfusion cases with no anaphylactic or hemolytic reactions in the training environment.⁵⁰ Similarly, the Ranger O Low Titer, Special Operations O Low Titer, Naval Special Warfare Special Operations Tactical Medic Course and Marine Corps Valkyrie Fresh Whole Blood training programs have developed curricula with didactic and practical exercises to successfully support this emerging capability.

(2) Should crystalloid solutions and Hextend be removed as TCCC-recommended fluids for resuscitation of casualties in hemorrhagic shock?

Hextend and Other Hetastarches (HESs)

There are significant variations in the composition and properties of HESs. The different HES products are commonly described by their weight-averaged molecular weight. The physiologic effects of hetastarch solutions may vary depending on both the type of hetastarch molecule, the concentration of the solution, the diluent fluid, and the volume of fluid infused. Hextend (6% HES in physiological solution) is a physiologically balanced, first-generation, high-molecular-weight HES preparation that was included in prior TCCC recommendations.^{51,52}

The 2013 Zarachanski study found that hetastarches administered to critically ill patients did not improve survival and resulted in an increased risk of acute kidney injury.^{25,53} The authors of the Zarachanski study recommended against the

use of hetastarch solutions. A subsequent 2016 meta-analysis found that even low-molecular-weight HES products reduced coagulation competence when compared to crystalloids and albumin.⁵⁴ A 2018 paper from Germany found that severely injured patients receiving more than 1000mL of synthetic colloid solutions (predominantly hetastarch) had a higher rate of renal and multiple organ failure but did not find any effect on mortality.⁵⁵

The FDA issued a safety communication on HES solutions in November 2013 that noted an increased risk in mortality and renal replacement therapy associated with the use of HES to treat critically ill patients.⁷ A further Cochrane Review concluded that HES slightly increased the need for blood transfusion and renal replacement therapy while albumin or FFP had minimal impact.⁵⁶ Hextend had previously remained the TCCC-recommended resuscitation fluid when blood products were not available, and represented the best available colloid based on available evidence in 2014. However, as noted by more recent reviews, both high- and low-molecular HES products adversely affect coagulation competence, increase kidney injury, and increase the incidence of subsequent surgeries.^{54,57}

Crystalloids – General

Once considered the prehospital standard of care, early and aggressive administration of crystalloid fluid has fallen out of favor in hemorrhagic shock. This approach was replaced by damage control resuscitation, which for the casualty in hemorrhagic shock, focuses on not increasing the blood pressure to the point where hydrostatic pressure may interfere with the body's attempts at hemostasis, on avoiding dilutional coagulopathy, and on providing an increased ratio of plasma administered with RBCs and the use of platelets when available, in a 1:1:1 ratio.⁵⁸

Crystalloids are distributed throughout the interstitium as well as the intravascular space, resulting in the expansion of the entire interstitial space instead of the desired effect of intravascular expansion. For example, an infused volume of 1L of 0.9% sodium chloride adds 275mL to the plasma volume and 825mL to the interstitial volume after equilibration. This can lead to clinical complications like acute respiratory distress syndrome, hypoxemia, and abdominal compartment syndrome.⁵⁹⁻⁶⁴

Current clinical practice guidelines for damage control resuscitation highlight that crystalloid fluids should be reserved for specific clinical uses, such as carrier fluid for intravenous medication or other nonresuscitative uses.¹⁶ The minimization of crystalloids is part of balanced resuscitation of patients with hemorrhagic shock that avoids worsening the coagulopathy of trauma.^{65,66}

Crystalloids – Lactated Ringer's and Plasma-Lyte A

The crystalloid solutions currently recommended in TCCC are lactated Ringer's solution (LR) and Plasma-Lyte A. LR appears to be better than Normal Saline (NS) in traumatic resuscitation because it does not produce the degree of hyperchloremic acidosis that large volume NS resuscitation does.⁶⁷ LR, NS, Plasma-Lyte A, and Plasma-Lyte R were compared in a translational animal model where LR produced the highest 2-hour survival rate among the four crystalloids studied.⁶⁸ LR for fluid replacement during vascular surgery has trended toward less acidosis and less intraoperative blood loss, but with no decrease in mortality when compared to NS.⁶⁹

Plasma-Lyte A has a neutral pH (7.4), an osmolarity of 295mOsm/L, and no calcium. This is in contrast to LR, which has a lower pH, is slightly hypotonic with an osmolarity of 273mOsm/L and contains calcium. Plasma-Lyte A was compared with NS in a study of 46 trauma patients and was associated with improved acid-base status and less hyperchloremia at 24 hours postinjury, although no improvement in survival was found.⁷⁰ In a separate observational study of 30,994 patients who received NS during major surgery compared with 926 patients who received Plasma-Lyte A, the patients who received Plasma-Lyte A had a lower incidence of postoperative infection, renal failure requiring dialysis, and the need for blood transfusion.⁷¹ Plasma-Lyte A may have a physiological advantage over NS and LR, but like all crystalloids, does not have the intravascular volume expansion properties of colloids or FFP.⁷²

Recent evidence, however, has demonstrated the superiority of whole blood or blood components over crystalloid solutions.^{2-4,73,74} Further, other studies have shown that large volumes of crystalloid are associated with poorer outcomes in resuscitating trauma patients.^{75,76}

In summary, the currently available evidence indicates that neither crystalloids nor Hextend are acceptable options for the prehospital fluid resuscitation of trauma patients in hemorrhagic shock.

(3) What is the optimal target SBP for resuscitation of hemorrhagic shock casualties, and does this change when traumatic brain injury is also present?

Isolated Hemorrhagic Shock Without TBI

Over the past decade and a half, resuscitation strategies for military trauma have shifted from liberal fluid administration toward a controlled hypotensive resuscitation with various SPB goals between 70 and 100mmHg. Bickell et al. demonstrated that delaying aggressive fluid resuscitation until after surgical control of noncompressible hemorrhage in penetrating trauma patients significantly decreased mortality.⁷⁷ The primary aim of hypotensive resuscitation is to maintain SBP (or mean arterial pressure) in order to sustain organ perfusion.⁷⁸ It was proposed that permissively moderate SBP goals would avoid further hemorrhage due to dilution coagulopathy, reduce hypothermia and avoid dislodging hemostatic blood clots.^{79,80}

Two recent meta-analyses were published that evaluated controlled hypotension vs. aggressive fluid resuscitation in traumatic hemorrhagic shock.^{81,82} While both studies found a survival benefit in the controlled hypotension strategy, several confounding factors need to be addressed. First, the various studies included in these meta-analyses had a wide variation of target SBPs in the controlled hypotension arms ranging from 50mmHg to 100mmHg. Additionally, many of the studies that met inclusion criteria were performed prior to the era of blood product use in initial fluid resuscitation. Finally, both groups of authors also note that many of the included studies were insufficiently powered to find statistical significance and they were of poor-to-moderate quality due to insufficient protocol reporting and lack of blinding.

Hemorrhagic Shock With Concurrent TBI

The evaluation of a military trauma patient in hemorrhagic shock is complicated by the ever-present risk of either occult or obvious concurrent TBI. High-energy kinetic weapons, explosions, vehicle accidents, and falls from heights all contribute to the likelihood of concurrent brain injury. Management

strategies for TBI must focus on preventing secondary injury by avoiding hypotension and hypoxia while maintaining appropriate cerebral perfusion pressure.⁸³ The need to maintain a normal physiologic arterial blood pressure in TBI is in conflict with the principles of controlled hypotensive resuscitation in hemorrhagic shock.

Similar to resuscitation SBP goals in isolated hemorrhagic shock, there remains an absence of definitive evidence to support specific SBP goals for patients in hemorrhagic shock with concurrent TBI. Extrapolating from isolated TBI data, Chi et al. reported 28% mortality when a secondary insult (SPB less than 90mmHg or oxygen saturation less than 92%) was present in the prehospital setting compared to 20% mortality for those without such insults.⁸⁴

In a subgroup analysis performed by the authors of the previously mentioned meta-analysis for controlled hypotensive resuscitation, there appeared to be a mortality benefit for concurrent TBI when SBP goals were at or above 90mmHg. It is important to note that no functional outcomes were reported on the TBI patients, and the authors conclude the data is not compelling enough to strongly recommend hypotensive resuscitation in traumatic hemorrhagic shock patients with TBI.⁸²

In summary, the consensus opinion of the authors and currently available evidence indicates that fluid resuscitation of casualties in hemorrhagic shock should be continued to a target SBP of 100mmHg, unless the casualty has concurrent TBI, in which case the target SBP should be 100–110mmHg.

(4) Should empiric calcium be added to the TCCC fluid resuscitation guideline? If so, how much and which type of calcium formulation should be used, and when in the resuscitation sequence should it be given?

Calcium Management in Fluid Resuscitation

Ionized calcium is essential to many physiologic functions important to the trauma patient. It is a cofactor to several components of the clotting cascade and is essential to platelet adhesion. Ionized calcium has a direct effect on the contractility of myocardial cells and smooth muscle cells, thus affecting cardiac output, vascular contractility, and thrombus formation.^{85,86}

Trauma patients at baseline have an increased risk of being hypocalcemic from ischemia, reperfusion, hypothermia, and parathyroid and liver dysfunction. Hypocalcemia on initial presentation, prior to resuscitation efforts, has a reported incidence between 50% and 75% in major trauma patients.^{87–89} It has also been shown by multiple investigations that blood product resuscitation increases the incidence of hypocalcemia, especially for patients with massive transfusions. This is likely due to a combination of dilution and binding of calcium by citrate in the transfused blood products.^{90–93}

Evidence suggests that hypocalcemia has a linear, concentration-dependent relationship with mortality as Ho et al. reported an odds ratio of 1.25 per 0.1mmol/L decrement ($p = .02$) in a cohort study of 353 consecutive patients requiring massive transfusion.⁹¹ Further studies corroborate these findings and suggest ionized calcium <1.0mmol/L increases mortality and further worsening to levels below 0.9mmol/L increases mortality 2- to 3-fold.^{93,94,96} Consistent with anecdotal prehospital reporting, Desai et al. reported a direct association between hypocalcemia and hypotension among intensive care unit patients.⁹⁷

Moore et al. provided the most recent analysis on hypocalcemia by investigating two DoD-funded studies that focused on the use of prehospital plasma in the civilian trauma setting, the Prehospital Plasma during Air Medical Transport in Trauma Patients at Risk of Hemorrhage (PAMPPer) and the Control of Major Bleeding After Trauma (COMBAT) trials. They concluded that prehospital plasma is associated with hypocalcemia, which in turn predicts lower survival (adjusted hazard ratio, 1.07; 95% CI, 1.02–1.13; $p = .01$) and need for massive transfusion (adjusted relative risk, 2.70; 95% CI, 1.13–6.46; $p = .03$).⁹⁸

Prehospital military experiences regarding hypocalcemia were published in a retrospective review of patients transported by the UK Medical Emergency Response Team in Afghanistan between 2010 and 2014. Their overall incidence of hypocalcemia in the group not given prehospital calcium was 70.0% (n=166), compared with 28.3% (n = 17) in the patients treated with intravenous calcium ($p < .001$).⁹⁹

While estimates suggest that ionized calcium drops approximately 0.05mmol/L per unit of blood product transfused,¹⁰⁰ the literature is in disagreement on specific dosing requirements. MacKay et al. also noted a 22% incidence of hypercalcemia in massive transfusion patients in a civilian trauma center suggesting that care should be taken in redosing calcium without laboratory measurements available.¹⁰¹ It is also appropriate to note that slow IV/IO push of calcium salts is prudent due to the potential risks of adverse cardiovascular effects or extravasation into surrounding tissues.¹⁰²

In summary, the authors believe that the available evidence supports the administration of 1g of calcium (30mL of 10% calcium gluconate or 10mL of 10% calcium chloride) IV/IO given after the first transfused product when blood products are being administered.

Conclusions

The conclusions and recommendations of this working group include the following answers to the previously posed questions:

(1) Is there a specific blood product that is preferred over others for resuscitation of casualties in hemorrhagic shock in TCCC?

The preferred fluids for resuscitation of casualties in hemorrhagic shock, in descending order of preference, are:

- Cold stored low titer O whole blood
- Pre-screened low titer O fresh whole blood
- Plasma, red blood cells (RBCs), and platelets in a 1:1:1 ratio
- Plasma and RBCs in a 1:1 ratio
- Plasma or RBCs alone

NOTE: *Prescreened low-titer O fresh whole blood and most platelets obtained in forward deployed locations are not currently FDA compliant.

Cold-stored low titer O whole blood is the safest and most beneficial fluid for resuscitation of casualties in hemorrhagic shock due to the hemostatic and oxygen-carrying properties of whole blood and the associated FDA compliant testing for blood type, antibody titers and transfusion transmissible infections. However, the authors do recognize that cold chain storage requirements limit the use of CS-LTOWB in some tactical situations and alternative fluid resuscitation products may be required.

In settings such as tactical field care or mass casualty scenarios, the use of type O fresh whole blood of unknown anti-A and anti-B titer may be safer than attempting to match blood groups between donors and recipients. The risk of hemolysis from major mismatch is greater than the risk of transfusing a very high-titer group O unit (very high titers being relatively uncommon) to a non-group O recipient.

Dried plasma remains an acceptable fluid for resuscitation in trauma, particularly in tactical situations where cold chain storage of alternative blood products is not practical. Units that do not have the capability to use cold-stored or fresh LTOWB for casualties who require fluid resuscitation should make a maximal effort to obtain a dried plasma product and train their medics in its use.

(2) Should crystalloid solutions and Hextend be removed as TCCC-recommended fluids for resuscitation of hemorrhagic shock?

The preponderance of available evidence demonstrates improved outcomes and survival in hemorrhagic shock when blood products are utilized to resuscitate these casualties rather than crystalloids or colloids. While Hextend, lactated Ringer's, and Plasma-Lyte A have been removed from the fluid resuscitation guidelines for traumatic hemorrhage, crystalloid solutions are used for other purposes in tactical field care such as burns and reconstitution fluids.

(3) What is the optimal target SBP for resuscitation of hemorrhagic shock casualties, and does this change when traumatic brain injury is also present?

End points of fluid resuscitation may be challenging to measure in tactical field care with limited monitoring equipment and fluid resuscitation may therefore need to be titrated to a palpable radial pulse or improved mentation. If blood pressure measurements are available; however, the updated recommendation is that fluid resuscitation of casualties in hemorrhagic shock should be continued to a target SBP of 100mmHg unless the casualty has concurrent TBI, in which case the target SBP should be 100–110mmHg. While further data may refine these recommendations, it aligns and synchronizes the TCCC guidelines with current damage control resuscitation and prolonged casualty care recommendations.

(4) Should empiric calcium be added to the TCCC fluid resuscitation guideline? If so, how much and which type of calcium formulation should be used, and when in the resuscitation sequence should it be given?

The available evidence suggests that hypocalcemia is common in trauma and that it is advisable that calcium levels be addressed and repleted to avoid the deleterious effects of hypocalcemia on platelet function, coagulation and contractility, and potentially impact survivability in hemorrhagic trauma patients. While recognizing that military trauma patients with hemorrhagic shock may present with varying severity of hypocalcemia, it is understood that measurement of ionized calcium in a tactical environment can be challenging. If a laboratory guided replenishment protocol is not feasible, a single empiric dose of 1g calcium equivalent should be given IV or IO. In order to not delay fluid resuscitation, consideration was given to recommend calcium administration after the initial blood product was transfused. Additional calcium may well be required in large volume resuscitations; however, follow-on dose recommendations remain outside the scope of

TCCC and are better addressed in prolonged casualty care and JTS CPGs.

Proposed Change to the TCCC Guidelines

Current Wording

Tactical Field Care and TACEVAC Care

e. Fluid resuscitation

- Assess for hemorrhagic shock (altered mental status in the absence of brain injury and/or weak or absent radial pulse).
- The resuscitation fluids of choice for casualties in hemorrhagic shock, listed from most to least preferred, are: whole blood*; plasma, red blood cells (RBCs) and platelets in a 1:1:1 ratio*; plasma and RBCs in a 1:1 ratio; plasma or RBCs alone; Hextend; and crystalloid (lactated Ringer's or Plasma-Lyte A).

NOTE: *Hypothermia prevention measures [Section 7] should be initiated while fluid resuscitation is being accomplished.

- If not in shock:
 - No IV fluids are immediately necessary.
 - Fluids by mouth are permissible if the casualty is conscious and can swallow.
- If in shock and blood products are available under an approved command or theater blood product administration protocol:
 - Resuscitate with whole blood*, or, if not available
 - Plasma, RBCs, and platelets in a 1:1:1 ratio*, or, if not available
 - Plasma and RBCs in a 1:1 ratio, or, if not available
 - Reconstituted dried plasma, liquid plasma, or thawed plasma alone or RBCs alone
 - Reassess the casualty after each unit. Continue resuscitation until a palpable radial pulse, improved mental status, or SBP of 80–90mmHg is present.
- If in shock and blood products are not available under an approved command or theater blood product administration protocol due to tactical or logistical constraints:
 - Resuscitate with Hextend, or if not available
 - Lactated Ringer's or Plasma-Lyte A
 - Reassess the casualty after each 500mL IV bolus.
 - Continue resuscitation until a palpable radial pulse, improved mental status, or SBP of 80–90mmHg is present.
 - Discontinue fluid administration when one or more of the above end points has been achieved.
- If a casualty with an altered mental status due to suspected TBI has a weak or absent radial pulse, resuscitate as necessary to restore and maintain a normal radial pulse. If BP monitoring is available, maintain a target SBP of at least 90mmHg.
- Reassess the casualty frequently to check for recurrence of shock. If shock recurs, recheck all external hemorrhage control measures to ensure that they are still effective and repeat the fluid resuscitation as outlined above. NOTE: *Currently, neither whole blood nor apheresis platelets collected in theater are FDA compliant because of the way they are collected. Consequently, whole blood and 1:1:1 resuscitation using apheresis platelets should be used only if all of the FDA-compliant blood products needed to support 1:1:1 resuscitation are not available, or if 1:1:1 resuscitation is not producing the desired clinical effect.

Proposed change

Tactical Field Care and TACEVAC Care

d. Fluid resuscitation

- Assess for hemorrhagic shock (altered mental status in the absence of brain injury and/or weak or absent radial pulse).
- The resuscitation fluids of choice for casualties in hemorrhagic shock, listed from most to least preferred, are: **cold stored low titer O whole blood; pre-screened low titer O fresh whole blood**; plasma, red blood cells (RBCs) and platelets in a 1:1:1 ratio*; plasma and RBCs in a 1:1 ratio; plasma or RBCs alone.

NOTE: *Hypothermia prevention measures [Section 7] should be initiated while fluid resuscitation is being accomplished.

- If not in shock:
 - No IV fluids are immediately necessary.
 - Fluids by mouth are permissible if the casualty is conscious and can swallow.
- If in shock and blood products are available under an approved command or theater blood product administration protocol:
 - Resuscitate with **cold stored low titer O whole blood**, or, if not available
 - **Pre-screened low titer O fresh whole blood, or, if not available**
 - Plasma, RBCs and platelets in a 1:1:1 ratio, or, if not available
 - Plasma and RBCs in a 1:1 ratio, or, if not available
 - Reconstituted dried plasma, liquid plasma or thawed plasma alone or RBCs alone
 - Reassess the casualty after each unit. Continue resuscitation until a palpable radial pulse, improved mental status or **SBP of 100mmHg is present**.
 - Discontinue fluid administration when one or more of the above end points has been achieved.
- If blood products are **transfused, administer one gram of calcium (30mL of 10% calcium gluconate or 10mL of 10% calcium chloride) IV/IO after the first transfused product.**
- **Given increased risk for a potentially lethal hemolytic reaction, transfusion of unscreened group O fresh whole blood or type-specific fresh whole blood should only be performed under appropriate medical direction by trained personnel.**
- **Transfusion should occur as soon as possible after life-threatening hemorrhage in order to keep the patient alive. If Rh-negative blood products are not immediately available, Rh-positive blood products should be used in hemorrhagic shock.**
- If a casualty with an altered mental status due to suspected TBI has a weak or absent radial pulse, resuscitate as necessary to restore and maintain a normal radial pulse. If BP monitoring is available, maintain a target systolic BP **between 100 and 110mmHg**.
- Reassess the casualty frequently to check for recurrence of shock. If shock recurs, re-check all external hemorrhage control measures to ensure that they are still effective and repeat the fluid resuscitation as outlined above.

CoTCCC Vote: This change was approved by the required three-quarters or greater majority of the voting members of

the CoTCCC and published in the updated guidelines on 5 November 2020.

Level of evidence (AHA/ACC)

The levels of evidence used by the American College of Cardiology and the American Heart Association were described by Tricoci in 2009:¹⁰³

Level A: Evidence from multiple randomized trials or meta-analyses.

Level B: Evidence from a single randomized trial or non-randomized studies.

Level C: Expert opinion, case studies or standards of care.

According to this taxonomy, the levels of evidence assigned to the following aspects of fluid resuscitation from hemorrhagic shock are provided below.

- 1) *Is there a specific blood product that is preferred over others for resuscitation of casualties in hemorrhagic shock in TCCC? Yes – Cold stored low titer O whole blood. **Level B***
- 2) *Should crystalloid solutions and Hextend be removed as TCCC-recommended fluids for resuscitation of casualties in hemorrhagic shock? Yes. **Level A***
- 3) *What is the optimal target SBP for resuscitation of hemorrhagic shock casualties, and does this change when traumatic brain injury is also present? A target SBP of 100mmHg for casualties without TBI and a range of 100–110mmHg for those with TBI. **Level C***
- 4) *Should empiric calcium be added to the TCCC fluid resuscitation guideline? If so, how much and which type of calcium formulation should be used, and when in the resuscitation sequence should it be given? Yes – 1g of calcium given IV or IO after the first transfused product. **Level C***

Considerations for Further Research and Development

1. Radial pulse, mental status, and, where available, noninvasive blood pressure measurements provide surrogate markers for tissue perfusion. The need exists for lightweight and portable biosensors to provide easily discernable information on oxygen debt and endpoints for resuscitation to guide prehospital fluid strategies.
2. Clinical decision-making is limited in TCCC by the lack of available laboratory data. Lightweight and portable point-of-care lactate and calcium testing would provide critical information for initiating resuscitation, continuing blood product utilization in a resource-constrained environment and provide guidance for continued calcium administration when appropriate.
3. Available data on albumin in fluid resuscitation remains mixed, especially with regard for moderate to severe TBI in multi-trauma patients. Further investigation into the optimal osmotic balance and dose may provide another fluid resuscitation option that does not require cold storage and minimizes transfusion transmitted illness risks.
4. For low titer group O donors, current guidelines require anti-A and anti-B titers less than 1:256. Historical data suggests the risk of hemolytic reaction is minimal despite the measurement of anti-A and anti-B titers. Funding for determining the safety profiles and refinement of the definition for low titer group O whole blood may increase the number of eligible donors and decrease the cost of screening potential donor pools.

5. Current evidence suggests initial calcium supplementation is warranted in major trauma, especially for patients who may require massive transfusion. At this point, there is conflicting evidence on the type of calcium salt administered, specific initial dose and pursuant re-dosing recommendations.
6. Many whole blood donor protocols exclude females as potential candidates because of concern that blood from female donors may entail a higher risk of transfusion-related acute lung injury (TRALI). Given the significant number of female service members who serve in deployed and combat positions, further investigation into the donor and recipient safety profiles for female whole blood transfusions are required.
7. For the trauma patient in extremis, initiation of fluid resuscitation is dependent upon obtaining rapid vascular access. Emergent intraosseous (IO) access is twice as likely to be successful as peripheral intravenous attempts. Optimal IO blood infusion strategies that will provide sufficient volume to meet resuscitation demands but that avoid the potential complications, such as hemolysis in the infused blood, that may result from overpressurized IO infusion techniques. Further research is needed to help develop improved recommendations for prehospital IO infusion strategies.

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Disclaimers

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Defense Health Agency or the Department of Defense. This recommendation is intended to be a guideline only and is not a substitute for clinical judgment.

Disclosures

The authors have no disclosures to report.

Release

This document was reviewed by the Director of the Joint Trauma System and by the Public Affairs Office and the Operational Security Office at the DoD's Defense Health Agency. It is approved for unlimited public release.

and a Navy undersea medical officer with more than 20 years of experience providing medical support to Special Operations Forces. Dr Butler has served as the command surgeon at the US Special Operations Command and was the chairman of the Department of Defense's Committee on TCCC for 11 years. He currently serves as a consultant to both the JTS and the CoTCCC. ⁵SO1 Terence Byrne, USN, is a Special Operations SEAL Medic and Special Operations Combat Medic (SOCM). He previously served as the medical leading petty officer for SOTM, Naval Special Warfare, Advanced Training Command and is now a first-year medical student at Tulane University. ⁶COL Andrew Cap MD, PhD, MC, USA, is the division chief, Acute Combat Casualty Care Research, US Army Institute of Surgical Research. He first trained and worked as an EMT and then as an internist, hematologist, oncologist, and specialist in stem cell transplantation, coagulation disorders, and transfusion medicine. He is the hematology and oncology consultant to the Army Surgeon General and has consulted extensively for the Joint Trauma System and Special Operations Command. He serves as co-chair of the NATO Blood Panel. ⁷LTC Benjamin Donham, MD, USA, is the commander of the 261st Multifunctional Medical Battalion and has multiple deployments with austere surgical teams in support of overseas contingency operations. ⁸Colonel Joseph J. DuBose, MD, USAF, serves as director, Center for the Sustainment of Trauma and Readiness Skills (CSTARS) at R Adams Cowley Shock Trauma Center/University of Maryland in Baltimore, Maryland. Col DuBose is a professor of surgery at USUHS and the University of Maryland and is board certified in general surgery, vascular surgery, and surgical critical care. He has over 230 published peer review publications as an active-duty military surgeon with the United States Air Force and has deployed seven times as a trauma surgeon to combat theaters in both conventional and JSOC roles. ⁹MAJ Andrew D. Fisher, MD, PA-C, ARNG, is a physician assistant in the Texas Army National Guard, a recent graduate from the Texas A&M University College of Medicine, and a general surgery resident at the University of New Mexico School of Medicine. He previously served on active duty as a physician assistant within USASOC. ¹⁰RDML James Hancock, MD, USN, is an emergency physician with multiple combat deployments. He has served as a flight surgeon, as OIC of a fleet surgical team and as OIC of a shock trauma platoon. He is currently serving as the Medical Officer of the Marine Corps/director, Health Services, Headquarters Marine Corps with additional duty as the Chief of the Medical Corps for the Navy. ¹¹LCDR Victor Jourdain, MD, USN, is an emergency medicine physician and senior medical officer at the Naval Medical Center San Diego Emergency Department. As a Fleet Marine Force qualified officer, he completed multiple combat deployments in support of Role 1 and Role 2 echelons of care. ¹²LTC Ryan Knight, MD, USA, was an infantry platoon leader, leading platoons in Afghanistan and Iraq, prior to becoming a physician. As an emergency physician he served seven years at Ft. Bragg, NC deploying numerous times to Afghanistan and austere locations in Africa with a Joint Task Force. He has extensive experience training medics, APPs, and physicians in austere/operational medicine. Ryan is currently serving as the regimental surgeon for the 75th Ranger Regiment and is the primary author of the 2019 and 2020 Ranger Medic Handbooks. ¹³CAPT Lanny Littlejohn, MD, USN, is a prior US Marine who now serves as an emergency physician for the US Navy. He has served as a flight surgeon, diving medical officer, shock trauma platoon leader, and command surgeon for multiple US Marine Corps and US Special Operations command units. He is currently the force surgeon for Naval Special Warfare Command. ¹⁴Colonel Matthew J. Martin, MD, US Army (retired), is a trauma and acute care surgeon at Scripps Mercy Hospital and the Navy Medical Center San Diego. He recently retired from active military service as the trauma director and director of surgical research at Madigan Army Medical Center, where he established and directed a highly productive basic science and translational trauma research lab. He served in a variety of clinical and leadership positions during five deployments in support of combat operations in Iraq and Afghanistan. ¹⁵HMC Kevin Toland, USN, is a Special Operations independent duty corpsman (SOIDC) and advanced tactical paramedic (ATP). He is currently serving as a Special Operations combat medic (SOCM) course instructor and is the NCOIC of the Prolonged Casualty Care (PCC) section. He has deployed multiple times in both conventional and SOF roles. ¹⁶CAPT Brendon Drew, DO, USN, is the Chair of the Joint Trauma System Committee on Tactical Combat Casualty Care. He currently serves as the I Marine Expeditionary Force Surgeon. He has 8 deployments across Asia, Afghanistan, Iraq, Africa and 11 ships in support of both USMC and SOCOM units.

¹CAPT Travis Deaton, MD, USN, is the 1st Marine Division surgeon and most recent chair of Emergency Medicine at Naval Medical Center San Diego. As a prior flight surgeon and dive medical officer, he has 13 deployments in support of USMC and SOCOM units. ²CDR Jonathan Auten, DO, USN, is the program director of the Emergency Medicine Residency at Naval Medical Center San Diego. He has served as a carrier airwing flight surgeon, US Marine Corps shock trauma platoon leader, and detachment OIC for SOUTHCOM humanitarian efforts. He has a wide area of research involvement in prehospital and austere medicine with specific interests in pediatric trauma, hemostatic resuscitation and intraosseous blood transfusion. ³Maj Richard Betzold, MD, USAF, is a trauma surgeon who has multiple deployments with the Joint Special Operations Command. He currently works at the R Adams Cowley Shock Trauma Center and is an instructor in the Air Force Center for Sustainment of Trauma and Readiness Skills program. ⁴CAPT (Ret) Frank Butler, USN, was a Navy SEAL platoon commander before becoming a physician. He is an ophthalmologist

References

1. Butler FK, Holcomb JB, Schreiber MA, et al. Fluid resuscitation for hemorrhagic shock in Tactical Combat Casualty Care: TCCC guidelines change 14-01-2. *J Spec Oper Med.* 2014;14(3):13-38.
2. Gurney J, Staudt A, Cap A, et al. Improved survival in critically injured combat casualties treated with fresh whole blood by forward surgical teams in Afghanistan. *Transfusion.* 2020;60:S180-S188.
3. Shackelford SA, Del Junco DJ, Powell-Dunford N, et al. Association of prehospital blood product transfusion during medical evacuation of combat casualties in Afghanistan with acute and 30-day survival. *JAMA.* 2017 Oct 24;318(16):1581-1591.
4. Sperry JL, Guyette FX, Brown JB, et al. Prehospital plasma during air medical transport in trauma patients at risk for hemorrhagic shock. *N Engl J Med.* 2018 Jul 26;379(4):315-326.
5. Butler FK Jr, Holcomb JB, Shackelford S, et al. Advanced resuscitative care in Tactical Combat Casualty Care: TCCC guidelines change 18-01:14 October 2018. *J Spec Oper Med.* 2018;18:37-55.
6. Spaite DW, Hu C, Bobrow BJ, et al. Mortality and prehospital blood pressure in patients with major traumatic brain injury: implications for the hypotension threshold. *JAMA Surg.* 2016. Published online December 7, 2016.
7. Federal Drug Administration. Product Information Package Insert—HEXTEND (6% Hetastarch in Lactated Electrolyte Injection).
8. Department of Defense Armed Services Blood Program Office. Memorandum. Low Titer Group O Whole Blood for Contingency Support dated 11 Apr 2016.
9. Office of the Secretary, Department of Health and Human Services. Emergency use of treatment for uncontrolled hemorrhage due to agents of military combat. *Fed Reg.* 2018;83(147):36941-36942.
10. Yazer M, Cap A, Spinella P. Raising the standard on whole blood. *J Trauma Acute Care Surg.* 2018;84:S14-S17.
11. Fisher AD, Miles EA, Cap AP, et al. Tactical damage control resuscitation. *Mil Med.* 2015;180(8):869-875.
12. Office of the Chief of Staff, United States Special Operations Command. Memorandum. Special Operations Low-Titer O Whole Blood Program dated 11 May 2020.
13. Kotora JG. Fresh whole blood transfusion, what's being done in the 2dMarDiv. *Marine Corps Gazette.* 2020;5:WE4-WE6.
14. Marine Program Could Get More Troops Off the Battlefield Alive. The American Legion online 11 Dec 2019.
15. Fisher AD, Dunn J, Pickett JR, et al. Implementation of a low titer group O whole blood program for a law enforcement tactical team. *Transfusion.* 2020;60(Suppl 3):S36-S44.
16. Joint Trauma System. Clinical Practice Guideline. Damage Control Resuscitation. 17 Jul 2019.
17. Joint Trauma System. Clinical Practice Guideline. Whole Blood Transfusion. 15 May 2018.
18. Joint Trauma System. Clinical Practice Guideline. Damage Control Resuscitation in Prolonged Field Care. Oct 2018.
19. Shackelford S, Hammesfahr R, Morrisette D, et al. The use of pelvic binders in Tactical Combat Casualty Care. TCCC guidelines change 1602. *J Spec Oper Med.* 2016;16:135-147.
20. Hess JR, Lelkens CC, Holcomb JB, Scalea TM. Advances in military, field, and austere transfusion medicine in the last decade. *Transfus Apher Sci.* 2013 Dec;49(3):380-386.
21. Holcomb JB, Jenkins D, Rhee P, et al. Damage control resuscitation: directly addressing the early coagulopathy of trauma. *J Trauma.* 2007 Feb;62(2):307-310.
22. 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 Oct;63(4):805-813.
23. Janak J, Stockinger Z, Mazuchowski E, et al. Military preventable death conceptual framework: a systematic approach for reducing battlefield mortality. *Mil Med.* 2018 Sep 1;183(Suppl 2):15-23.
24. Schauer SG, Naylor JF, Bellamy MA, et al. A descriptive analysis of casualties undergoing CASEVAC from the point-of-injury in the Department of Defense Trauma Registry. *Mil Med.* 2019 Jul 1;184(7-8):e225-e229.
25. Zarychanski R, Abou-Setta AM, Turgeon AF, et al. Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: a systematic review and meta-analysis. *JAMA.* 2013 Feb 20;309(7):678-688.
26. Sevcikova S, Durila M, Vymazal T. Rotational thromboelastometry assessment of balanced crystalloid, hydroxyethyl starch and gelatin effects on coagulation: a randomized trial. *Rev Bras Anesthesiol.* 2019 Jul-Aug;69(4):383-389.
27. Sheppard FR, Mitchell TA, Cap AP, et al. Prehospital whole blood resuscitation prevents coagulopathy and improves acid-base status at hospital arrival in a nonhuman primate hemorrhagic shock model. *Transfusion.* 2019 Jul;59(7):2238-2247.
28. O'Reilly DJ, Morrison JJ, Jansen JO, et al. Prehospital blood transfusion in the en route management of severe combat trauma: a matched cohort study. *J Trauma Acute Care Surg.* 2014 Sep;77(3 Suppl 2):S114-S120.
29. Allon R, Epstein D, Shavit I. Prehospital transfusion of low titer cold-stored whole blood through the intraosseous route in a trauma patient with hemorrhagic shock. *Transfusion.* 2020 Apr;60(4):875-878.
30. Spinella PC, Perkins JG, Grathwohl KW, et al. Warm fresh whole blood is independently associated with improved survival for patients with combat-related traumatic injuries. *J Trauma.* 2009;66(4 Suppl):S69-S76.
31. Nessen SC, Eastridge BJ, Cronk D, et al. Fresh whole blood use by forward surgical teams in Afghanistan is associated with improved survival compared to component therapy without platelets. *Transfusion.* 2013;53(Suppl 1):107S-113S.
32. Auten JD, Lunceford NL, Horton JL, et al. The safety of early fresh, whole blood transfusion among severely battle injured at US Marine Corps forward surgical care facilities in Afghanistan. *J Trauma Acute Care Surg.* 2015 Nov;79(5):790-796.
33. Jones TB, Moore VL, Shishido AA. Prehospital whole blood in SOF: current use and future directions. *J Spec Oper Med.* 2019 Winter;19(4):88-90.
34. Black JA, Pierce VS, Kerby JD, Holcomb JB. The evolution of blood transfusion in the trauma patient: whole blood has come full circle. *Semin Thromb Hemost.* 2020 Mar;46(2):215-220.
35. Rice CL. Policy on the use of non-US Food and Drug Administration compliant blood products [letter]. Assistant Secretary of Defense for Health Affairs letter dated 19 March 2010.
36. Hughes JD, Macdonald VW, Hess JR. Warm storage of whole blood for 72 hours. *Transfusion.* 2007;47(11):2050-2056.
37. Miller BT, Lin AH, Clark SC, et al. Red tides: mass casualty and whole blood at sea. *J Trauma Acute Care Surg.* 2018;85(1S Suppl 2):S134-S139.
38. Condron M, Scanlan M, Schreiber M. Massive transfusion of low-titer cold-stored O-positive whole blood in a civilian trauma setting. *Transfusion.* 2019;59(3):927-930.
39. Williams J, Merutka N, Meyer D, et al. Safety profile and impact of low-titer group O whole blood for emergency use in trauma. *J Trauma Acute Care Surg.* 2020;88(1):87-93.
40. Duchesne J, Smith A, Lawicki S, et al. Single institution trial comparing whole blood vs balanced component therapy: 50 years later. *J Am Coll Surg.* 2020;S1072-7515(20):32534-32535.
41. Gallaher J, Dixon A, Cockcroft A, et al. Large volume transfusion with whole blood is safe compared with component therapy. *J Trauma Acute Care Surg.* 2020;89(1):238-245.
42. Bahr TM, DuPont TL, Morris DS, et al. First report of using low-titer cold-stored type O whole blood in massive postpartum hemorrhage. *Transfusion.* 2019;59(10):3089-3092.
43. Newberry R, Winckler CJ, Luellwitz R, et al. Prehospital transfusion of low-titer O+ whole blood for severe maternal hemorrhage: a case report. *Prehosp Emerg Care.* 2020;24(4):566-575.
44. Leeper CM, Yazer MH, Cladis FP, et al. Cold-stored whole blood platelet function is preserved in injured children with hemorrhagic shock. *J Trauma Acute Care Surg.* 2019;87(1):49-53.
45. Perkins JG, Cap AP, Spinella PC, et al. Comparison of platelet transfusion as fresh whole blood versus apheresis platelets for massively transfused combat trauma patients (CME). *Transfusion.* 2011;51(2):242-252.

46. Gilstad C, Roschewski M, Wells J, et al: Fatal transfusion-associated graft-versus-host disease with concomitant immune hemolysis in a group A combat trauma patient resuscitated with group O fresh whole blood. *Transfusion* 2012;52(5):930–935.
47. Spinella PC, Perkins JG, Grathwohl KW, et al. Risks associated with fresh whole blood and red blood cell transfusions in a combat support hospital [published correction appears in *Crit Care Med*. 2008 Apr;36(4):1396]. *Crit Care Med*. 2007;35(11):2576–2581.
48. Cap AP, Beckett A, Benov A, et al. Whole blood transfusion. *Mil Med*. 2018;183(Suppl 2):44–51.
49. Bienek DR, Perez NM. Diagnostic accuracy of a point-of-care blood typing kit conducted by potential end users. *Mil Med* 2013; 178:599–592.
50. Donham B, Barbee GA, Deaton TG, et al. Risk associated with autologous fresh whole blood training. *J Spec Oper Med*. 2019;19 (3):24–25.
51. Holcomb J. Fluid resuscitation in modern combat casualty care: lessons learned in Somalia. *J Trauma*. 2003;54:S46–S51.
52. Champion HR. Combat fluid resuscitation: introduction and overview of conferences. *J Trauma*. 2003;54:7.
53. Antonelli M, Sandroni C. Hydroxyethyl starch for intravenous volume replacement: more harm than benefit. *JAMA* 2013;309: 723–724.
54. Rasmussen KC, Secher NH, Pedersen T. Effect of perioperative crystalloid or colloid fluid therapy on hemorrhage, coagulation competence, and outcome: a systematic review and stratified meta-analysis. *Medicine (Baltimore)*. 2016 Aug;95(31):e4498.
55. Hilbert-Carius P, Schwarzkopf D, Reinhart K, et al. Synthetic colloid resuscitation in severely injured patients: analysis of a nationwide trauma registry. *Sci Rep*. 2018;8:1–8.
56. Mutter TC, Ruth CA, Dart AB. Hydroxyethyl starch (HES) versus other fluid therapies: effects on kidney function. *Cochrane Database Syst Rev*. 2013 Jul 23;(7).
57. Lewis SR, Pritchard MW, Evans DJ, et al. Colloids versus crystalloids for fluid resuscitation in critically ill people. *Cochrane Database Syst Rev*. 2018 Aug 3;8(8).
58. Holcomb JB, Jenkins D, Rhee P, et al. Damage control resuscitation: directly addressing the early coagulopathy of trauma. *J Trauma*. 2007;62:307–310.
59. McSwain NE, Champion HR, Fabian TC, et al. State of the art of fluid resuscitation 2010: prehospital and immediate transition to the hospital. *J Trauma*. 2011 May;70(5 Suppl):S2–S10.
60. Dries D. Fluid resuscitation: less is more. *Crit Care Med*. 2014 Apr;42(4):1005–1006.
61. Cotton BA, Podbielski J, Camp E, et al; Early Whole Blood Investigators. A randomized controlled pilot trial of modified whole blood versus component therapy in severely injured patients requiring large volume transfusions. *Ann Surg*. 2013 Oct;258(4): 527–532; discussion 532–533.
62. Robinson BR, Cotton BA, Pritts TA, et al; PROMMTT Study Group. Application of the Berlin definition in PROMMTT patients: the impact of resuscitation on the incidence of hypoxemia. *J Trauma Acute Care Surg*. 2013 Jul;75(1 Suppl 1):S61–S67.
63. Balogh Z, McKinley BA, Holcomb JB, et al. Both primary and secondary abdominal compartment syndrome can be predicted early and are harbingers of multiple organ failure. *J Trauma*. 2003 May;54(5):848–859; discussion 859–861.
64. Butler FK Jr, Hagmann J, Butler EG. Tactical combat casualty care in special operations. *Mil Med*. 1996 Aug;161(Suppl):3–16.
65. Holcomb JB, Pati S. Optimal trauma resuscitation with plasma as the primary resuscitative fluid: the surgeon's perspective. *Hematology*. 2013;656–659.
66. Holcomb JB, del Junco DJ, Fox EE, et al. The Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) study. *Arch Surg*. 2012.
67. Schreiber M. The use of normal saline for resuscitation in trauma. *J Trauma*. 2011;70:S13–S14.
68. Traverso LW, Lee WP, Langford MJ. Fluid resuscitation after an otherwise fatal hemorrhage. I. Crystalloid solutions. *J Trauma*. 1986;26:168–175.
69. Waters JH, Gottlieb A, Schoenwald P, et al. Normal saline versus lactated Ringer's solution for intraoperative fluid management in patients undergoing abdominal aortic aneurysm repair: an outcome study. *Anesth Analg*. 2001;93:817–822.
70. Young JB, Utter GH, Schermer CR, et al. Saline versus Plasma-Lyte A in initial resuscitation of trauma patients. *Ann Surg*. 2014 Feb; 259(2):255–262.
71. Shaw AD, Bagshaw SM, Goldstein SL, et al. Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared with Plasma-Lyte. *Ann Surg*. 2012;255: 821–829.
72. Pape A, Kutschker S, Kertscho H, et al. The choice of the intravenous fluid influences the tolerance of acute normovolemic anemia in anesthetized domestic pigs. *Crit Care*. 2012 Dec 12;16(2): R69.
73. Guyette FX, Sperry JL, Peitzman AB, et al. Prehospital blood product and crystalloid resuscitation in the severely injured patient: a secondary analysis of the Prehospital Air Medical Plasma Trial. *Ann Surg*. 2021;273:358–364.
74. Elster EA, Bailey J. Prehospital blood transfusion for combat casualties. *JAMA*. 2017 Oct 24;318(16):1548–1549.
75. Duchesne JC, Heaney J, Guidry C, et al. Diluting the benefits of hemostatic resuscitation: a multi-institutional analysis. *J Trauma Acute Care Surg*. 2013 Jul;75(1):76–82.
76. Gurney J, Staudt A, Cap A, et al. Improved survival in critically injured combat casualties treated with fresh whole blood by forward surgical teams in Afghanistan. *Transfusion*. 2020;60:S180–S188.
77. Bickell WH, Wall MJ Jr, Pepe PE, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *N Engl J Med*. 1994;331:17.
78. Bouglé A, Harrois A, Duranteau J. Resuscitative strategies in traumatic hemorrhagic shock. *Ann Intensive Care*. 2013;3:1.
79. Rezende-Neto JB, Rizoli SB, Andrade MV, et al. Permissive hypotension and desmopressin enhance clot formation. *J Trauma*. 2010;68(1):42–50.
80. Geeraedts LM Jr, Kaasjager HA, van Vugt AB, Frolke JP. Exsanguination in trauma: a review of diagnostics and treatment options. *Injury*. 2009;40(1).
81. Tran A, Yates J, Lau A, et al. Permissive hypotension versus conventional resuscitation strategies in adult trauma patients with hemorrhagic shock: a systematic review and meta-analysis of randomized controlled trials. *J Trauma Acute Care Surg*. 2018 May; 84(5):802–808.
82. Owattanapanich N, Chittawatanarat K, Benyakorn T, Sirikun J. Risks and benefits of hypotensive resuscitation in patients with traumatic hemorrhagic shock: a meta-analysis. *Scand J Trauma Resusc Emerg Med*. 2018 Dec 17;26(1):107.
83. Abdelmalik PA, Draghic N, Ling GSF. Management of moderate and severe traumatic brain injury. *Transfusion*. 2019 Apr;59 (S2):1529–1538.
84. Chi JH, Knudson MM, Vassar MJ, et al. Prehospital hypoxia affects outcome in patients with traumatic brain injury: a prospective multicenter study. *J Trauma*. 2006;61(5):1134–1141.
85. Vincent JL, Bredas P, Jankowski S, Kahn RJ. Correction of hypocalcaemia in the critically ill: what is the haemodynamic benefit? *Intensive Care Med*. 1995;21(10):838–841.
86. Brass LF, Zhu L, Stalker TJ. Minding the gaps to promote thrombus growth and stability. *J Clin Invest*. 2005;115(12):3385–3392.
87. Webster S, Todd S, Redhead J, et al. Ionised calcium levels in major trauma patients who received blood in the emergency department. *Emerg Med J*. 2016 Aug;33(8):569–572.
88. Vasudeva M, Mathew JK, Fitzgerald MC, et al. Hypocalcaemia and traumatic coagulopathy: an observational analysis. *Vox Sang*. 2020;115(2):189–195.
89. Vivien B, Langeron O, Morell E, et al. Early hypocalcemia in severe trauma. *Crit Care Med*. 2005;33:1946–1952.
90. Kyle T, Greaves I, Beynon A, et al. Ionised calcium levels in major trauma patients who received blood en route to a military medical treatment facility. *Emerg Med J*. 2018;35:176–179.
91. Ho KM, Leonard AD. Concentration-dependent effect of hypocalcaemia on mortality of patients with critical bleeding requiring massive transfusion: a cohort study. *Anaesth Intensive Care*. 2011 Jan;39(1):46–54.
92. Webster S, Todd S, Redhead J, et al. Ionised calcium levels in major trauma patients who received blood in the emergency department. *Emerg Med J*. 2016 Aug;33(8):569–572.

93. Giancarelli A, Birrer KL, Alban RF, et al. Hypocalcemia in trauma patients receiving massive transfusion. *J Surg Res.* 2016 May 1; 202(1):182–187.
94. Cherry RA, Bradburn E, Carney DE, et al. Do early ionized calcium levels really matter in trauma patients? *J Trauma.* 2006;61:774–779.
95. Brass LF, Zhu L, Stalker TJ. Minding the gaps to promote thrombus growth and stability. *J Clin Invest.* 2005;115(12):3385–3392.
96. Lier H, Krep H, Schroeder S, Stuber F. Preconditions of hemostasis in trauma: a review. The influence of acidosis, hypocalcemia, anemia, and hypothermia on functional hemostasis in trauma. *J Trauma.* 2008;65:951–960.
97. Desai TK, Carlson RW, Thill-Baharozian M, Geheb MA. A direct relationship between ionized calcium and arterial pressure among patients in an intensive care unit. *Crit Care Med.* 1988; 16(6):578–582.
98. Moore HB, Tessmer MT, Moore EE, et al. Forgot calcium? Admission ionized-calcium in two civilian randomized controlled trials of prehospital plasma for traumatic hemorrhagic shock. *J Trauma Acute Care Surg.* 2020;88(5):588–596.
99. Kyle T, Greaves I, Beynon A, et al. Ionised calcium levels in major trauma patients who received blood en route to a military medical treatment facility. *Emerg Med J.* 2018 Mar;35(3):176–179.
100. Webster S, Todd S, Redhead J, Wright C. Ionised calcium levels in major trauma patients who received blood in the emergency department. *Emerg Med J.* 2016 Aug;33(8):569–572.
101. MacKay EJ, Stubna MD, Holena DN, et al. Abnormal calcium levels during trauma resuscitation are associated with increased mortality, increased blood product use, and greater hospital resource consumption: a pilot investigation. *Anesth Analg.* 2017; 125(3):895–901.
102. Kagen MH, Bansal MG, Grossman M. Calcinosis cutis following the administration of intravenous calcium therapy. *Cutis.* 2000;65(4):193–194.
103. Tricoci P, Allen JM, Kramer JM, et al. Scientific evidence underlying the ACC/AHA clinical practice guidelines [published correction appears in *JAMA.* 2009 Apr 15;301(15):1544]. *JAMA.* 2009;301(8):831–841.