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Inside this Issue:

Dedicated to the Indomitable Spirit and Sacrifices of the SOF Medic

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The Combat Medic Aid Bag: 2025

CoTCCC Top 10 Recommended Battlefield Trauma Care Research, Development, and Evaluation Priorities for 2015

Frank K. Butler, MD; Lorne H. Blackbourne, MD; Kirby Gross, MD

Introduction

The conflicts in Afghanistan and Iraq have seen the US Military achieve the highest casualty survival rates in its history. Innovations brought about by military medical research have been a major factor in these remarkable improvements in combat casualty care.[1–3] As our nation continues to explore ways to improve combat casualty care in future conflicts, the military's Combat Casualty Care Research Program will continue to play a key role.[4–6]

One product of military medical research has been Tactical Combat Casualty Care (TCCC). TCCC is a set of evidence-based, best-practice, prehospital trauma care guidelines customized for use on the battlefield.[7,8] The TCCC Guidelines are produced by the Committee on TCCC (CoTCCC), which is the prehospital arm of the Department of Defense's Joint Trauma System (JTS).

TCCC started as a biomedical research project initiated by the Naval Special Warfare Command and expanded by the US Special Operations Command (USSOCOM) in partnership with the Uniformed Services University of the Health Sciences (USUHS). The existing, largely tradition-based, prehospital trauma care practices in place in 1993 were systematically re-evaluated, and there was found to be a need to reconsider these principles for use in combat. TCCC was introduced as a new framework on which to build trauma care guidelines customized for the battlefield.

In developing the first set of TCCC Guidelines, military-specific factors were taken into account as part of the process. These factors include the following: (1) care will be rendered in an austere prehospital environment where the enemy may be actively shooting at you, and, under the best of circumstances, "safe" is a relative term and care must be rendered expeditiously; (2) TCCC interventions are sharply focused on the causes of preventable death on the battlefield: hemorrhage, airway obstruction, and tension pneumothorax; (3) evacuation time to a medical treatment facility is often more lengthy than that encountered in urban civilian setting; (4) Combat medics are well trained but often have less trauma care experience than their civilian counterparts; and (5) Combat medics may be required to provide care in extreme environments.

Since the individuals who will be using TCCC to save lives on the battlefield are Combat medical personnel, their input into the proposed new guidelines was sought. Multiple workshops were held with military medics, corpsmen, and pararescuemen (PJs) about battlefield trauma care strategies—those in use in 1993 and the proposed new TCCC recommendations.

Since the development of TCCC, military medical research has enabled numerous advances in battlefield trauma care that now have been incorporated into the TCCC Guidelines. Prehospital care in the combat environment has been almost completely transformed from the standards used at the start of the wars in Afghanistan and Iraq.[9]

Evaluating the Evidence in Prehospital Trauma Care

The prehospital environment does not lend itself well to the conduct of carefully designed, randomized controlled trials (RCTs) in trauma care; this is especially true in combat. Informed consent is not easily obtained from the recently wounded, the administrative aspects of RCTs are not appropriate for the battlefield, and rapid transport to the hospital is often lifesaving for the critically injured patient and should not be delayed for research purposes.

The lack of RCTs, however, is not an excuse for inaction. Decisions about how best to care for the Combat wounded must be made with the evidence at hand, not deferred for want of additional or higher quality evidence. Prehospital trauma care is by no means the only

area of medicine that is compelled to make at least some decisions regarding care with evidence that is not as strong as one would wish. Tricoci et al. noted in 2009 that only 11% of the American Heart Association/ American College of Cardiology practice guidelines are based on level A evidence, while 48% of the guidelines are based on level C evidence.[10]

Another consideration with respect to RCTs is that even when they have been performed, the evidence obtained from them applies directly to clinical practice only when the patient being treated meets all of the inclusion criteria for the study and the other circumstances of his or her care reflect the care rendered in the study. As an example, the 1994 Ben Taub study on prehospital fluid resuscitation was a well-done RCT in which it was found that aggressive prehospital fluid resuscitation for hypotensive patients with uncontrolled hemorrhage from penetrating torso trauma worsens outcomes.[11] This evidence is reflected in the controlled resuscitation strategy used in TCCC.[7,12–14] Critics of this decision have noted (correctly) that the transport times in the Ben Taub study were much shorter than those typically encountered in military operations, and they have challenged the applicability of the findings of this study to combat casualties on that basis. Combat wounding patterns are also different than from the wounding patterns encountered in the Ben Taub study. These observations, however, do not negate the findings of that study; they dictate that the findings be considered with the appropriate caveats.

Another important aspect of TCCC decision-making has been that when an intervention is considered, the evidence for both the current standard of care and the proposed new intervention are considered in making the decision. Endorsing an intervention that has been the status quo for years should be treated as no less a decision then recommending a new intervention and requiring no less of an evidence base than a proposed new standard. The lack of high-quality evidence often applies just as much to the existing standards of care as to the proposed new intervention.

The CoTCCC and the TCCC Working Group

The original TCCC paper came out in *Military Medicine* in 1996 and proposed the first set of TCCC Guidelines,[8] but the need to provide a mechanism through which TCCC could evolve as new medical technology and evidence became available was recognized from the outset. The CoTCCC proposed in the 1996 paper was established at the Naval Operational Medicine Institute in 2001, with funding from the USSOCOM. Through the efforts of the CoTCCC, TCCC has been regularly updated over the ensuing 14 years. The battlefield trauma care management strategies developed by this body have now been well documented to improve survival in combat casualties,[2,9,15–17] and TCCC has been adopted throughout the US Military and by many allied nations.[9,15]

The CoTCCC is made up of trauma surgeons, emergency medicine physicians, combatant unit physicians, physician assistants, and combat medical educators. Additionally, any group making decisions about what Combat medics should do on the battlefield should include those individuals as part of the decision-making process. Very importantly, by tradition, and now through its Mission Statement, the CoTCCC must have no less than 30% of its membership made up of active or former Combat medics, corpsmen, and PJs. This 42-member group, at present, has representation from all of the US Armed Services and has 100% deployed experience. The CoTCCC was relocated in 2007 to the Defense Health Board (DHB) and, in 2013, to the JTS. Figure 1 is the CoTCCC logo.

Figure 1
CoTCCC logo.

At its meetings and teleconferences, the CoTCCC meets with designated TCCC subject matter experts (SMEs) and with liaisons from other military organizations, interagency groups, and allied nations, as well as speakers invited to present on specific topics in which they are SMEs.

Changes in TCCC are developed based on direct input from Combat medical personnel, an ongoing review of the published prehospital medical literature, new research coming from military medical research organizations, lessons learned from US and Allied Service medical departments, and from opportunities to improve prehospital trauma care noted in the JTS Performance Improvement process. Proposed changes to the TCCC Guidelines must pass by a supermajority (i.e., two-thirds of the voting membership) of the CoTCCC to be approved.

Voting members of the CoTCCC monitor the emerging prehospital trauma care literature and take part in multiple forums in which the care of US Military casualties is reviewed and opportunities to improve combat casualty

care are identified. Any voting member of the CoTCCC may propose a change to the current TCCC guidelines. The order in which changes are presented to the CoTCCC is determined by the chairman, in consultation with the director of the JTS. The proposed change and the evidence that supports it are compiled into a draft position paper. The paper is then discussed by the voting members of the CoTCCC and by additional SMEs and liaisons from the Service medical departments, Combat Command Surgeons' staffs, other government agencies, and allied nations that collectively compose the TCCC Working Group. This review of proposed changes is accomplished either at meetings or via teleconference. Once the proposed change has been reviewed and items of contention have been discussed and addressed, the change is reworded to reflect the consensus views and opinions presented during the review process, and the position paper is revised and distributed. An electronic vote is then conducted among the 42 voting members of the CoTCCC.

Once the proposed change is approved by the CoTCCC and, subsequently, by the director of the JTS, the change paper is finalized and submitted to the US Army Institute of Surgical Research (USAISR) for publication approval. After approval, the TCCC change papers are published in the *Journal of Special Operations Medicine*. Interim change notices are sent out to a TCCC distribution group and posted on several websites that post TCCC material as soon as the paper is approved by USAISR and the training slides needed to train the change have been developed. The *Prehospital Trauma Life Support* textbook is updated every 3–4 years and new changes are also reflected in each updated version of the PHTLS textbook. The TCCC change papers for 2013 through 2015 are included in the references for this article.[12,18–25]

Each of the TCCC change papers has a section in which additional research, development, test, and evaluation (RDT&E) items of interest that emerged during the discussions of the proposed change are noted. These research items are believed by the authors of that paper to be of potential benefit to future CoTCCC decisions in that aspect of prehospital trauma care. These potential research items were compiled and placed into a consolidated list of potential RDT&E topics. Also included in this list are research priorities identified by the CoTCCC and endorsed by the DHB in previous years,[26,27] and RDT&E issues noted in the two Joint Training System (JTS)/US Central Command assessments of prehospital trauma care in Afghanistan.[28,29]

Current CoTCCC RDT&E Recommendations

In April 2015, voting members of the CoTCCC were provided with the compiled list of 116 proposed RDT&E projects and asked to identify the 10 research projects that each member believed to be most important. Members were asked to consider the following in selecting their Top 10 projects:

- Will the project help to identify the causes of preventable death on the battlefield?
- Will the project help reduce preventable deaths on the battlefield?
- Will the project help reduce long-term disability?
- Is the intervention in the project feasible for prehospital care providers?
- What other methods to accomplish the desired effect for the casualty are currently available?
- How long would the project take to complete?
- How much will the project cost?
- How much will the new equipment or medication cost to field?
- What is the likelihood of successful completion of the project?

The following list contains the Top 10 priorities for battlefield trauma care RDT&E as established by the votes of the CoTCCC.

1. Explore all options to make a US Food and Drug Administration (FDA)-approved dried plasma product available for all US Military Combat medical providers. This product should be able to be transfused to casualties of any blood type, should be able to withstand the temperatures encountered in military prehospital settings, should have a long shelf life, and should not be packaged in breakable containers.

Freeze-dried plasma (FDP) was identified at the January 8–9, 2011, USAISR Medical Research and Materiel Command Fluid Resuscitation Conference as the most promising near-term fluid for damage-control resuscitation in circumstances when Special Operations Forces (SOF) medics or other Combat medical personnel must provide casualty care in remote locations where evacuation may be delayed for several hours or days. FDP was recommended as a top research priority by the SMEs at this conference.[30]

As a resuscitation fluid, plasma restores fibrinogen and other hemostatic factors, as well as volume, in contrast to crystalloids and colloids, which restore volume without any hemostatic factors and, thus, contribute an iatrogenic component to trauma-associated coagulopathy. Early administration of plasma to casualties in hemorrhagic shock is an essential part of the JTS damage control resuscitation (DCR) strategy.[31] DCR is also now widely used in the US civilian sector.[32–35]

Plasma was preferred over crystalloids and colloids in the recent TCCC review of resuscitation fluids.[12] FDP

is used by the United Kingdom, France, Germany, The Netherlands, and Israel,[12,36] but there is still no FDA-approved dried plasma product available to US Forces. The US Special Operations Command (USSOCOM) has spearheaded efforts to obtain approval for an FDP product to be used by SOF medics. The Commander of USSOCOM emphasized the urgent need for this approval in a letter to the acting Assistant Secretary of Defense for Health Affairs in 2010.[37] In the absence of an FDA-approved dried plasma product, the French FDP product is currently being used by a select few Special Operations units under a treatment protocol (Figure 2), but the administrative burden and the expense of that approach severely limit the benefit of the French FDP to US Forces.

Figure 2 *Bottle of freeze-dried plasma used by US SOF under a treatment protocol.*

Photo courtesy of SGM F. Bowling

The establishment of an FDA approval process specifically designed to meet the needs of US Combat troops—a Department of Defense (DoD)–FDA Military Use Panel—could greatly expedite the process. At present, there are mechanisms in place to provide special considerations for military use in the approval of devices but not for medications or blood products. This topic is discussed further in the second RDT&E priority below. In the absence of an approved dried plasma product, most US Combat medics are compelled to use colloids (not an optimal choice for resuscitation from hemorrhagic shock) or crystalloids (an even worse choice.)

Since Combat medics are generally unable to carry blood components on the battlefield, there is also a significant need for a prospective, randomized trial to be initiated in the US civilian sector to evaluate the use of plasma as the sole prehospital resuscitation fluid for patients in hemorrhagic shock, especially those with noncompressible hemorrhage. This study would provide valuable information about the magnitude of the lifesaving benefit derived from using plasma alone in the prehospital setting. To better translate the findings of this study to the military setting, the study should preferably be done in emergency medical services systems that have relatively long prehospital evacuation times. The prehospital resuscitation fluid choice may be less likely to improve outcomes in trauma patients with only a 10- or 15-minute transport time to the hospital. Surrogate outcome measures for survival, such as improvement in coagulation status, may also be a useful outcome measure in studies on prehospital plasma use.

2. Establish a Military Use Panel as a shared effort between the DoD and the FDA. One purpose of this panel would be to consider the approval of a military indication label for medications that are currently labeled for other indications but have applicability for military use. Examples include oral transmucosal fentanyl citrate, ketamine, and tranexamic acid. A second purpose of the proposed DoD–FDA Military Use Panel would be to evaluate products that have been approved for use by North Atlantic Treaty Organization (NATO) allies and have applications for the US Military but which have not been approved by the FDA for use in the United States. The French and German dried plasma products are examples of such items.

The usefulness of such a panel with respect to blood products is discussed above. This panel could also help improve combat casualty care through modifications in the existing regulatory approach to medications of particular interest to battlefield trauma care.

Obtaining an approved indication for a new drug is a complex, expensive, and time-consuming process. Further, there is little incentive for pharmaceutical companies to seek new indications when both they and physicians know that it is entirely legal and accepted for physicians to prescribe a medication approved for one indication to treat a patient who has another condition (so-called off-label use). This has given rise to a number of seemingly anomalous labeling and prescribing practices. Off-label use of medications by physicians in the United States is very common, especially in specialties such as pediatrics and obstetrics, where useful medications often have no approved indication in those populations.[38,39] The lack of drugs approved for obstetric indications in the United States is especially notable. As of 2010, no new medications had been approved for an obstetric indication since 1995.[38]

Although physicians are authorized to use medications for off-label indications as they believe appropriate

according to their clinical judgment, current FDA regulations prohibit medications from being marketed or packaged by their manufacturer for off-label uses. This is an very significant problem on the battlefield, where combat medics, corpsmen, and PJs provide the vast majority of prehospital combat casualty care under the most challenging circumstances imaginable. Medications being used for off-label indications, such as subdissociative doses of ketamine for analgesia, cannot be packaged in autoinjectors or other formats that facilitate their use for off-label uses. This regulatory anomaly therefore requires Combat medical providers to draw up doses of medications on the battlefield from multidose containers in the middle of battlefield casualty scenarios, as depicted in Figure 3. This is clearly not optimal practice. It slows the delivery of care for casualties, it increases the likelihood of dosing errors, and it may cause both medic and casualty to be at risk from hostile fire for longer periods of time as suboptimal medication administration practices are used.

Figure 3 *75th Ranger Regiment medical officer drawing up a dose of ketamine at night using a night-vision device during a training exercise.*

Photo courtesy of MAJ Ethan Miles

The perceived need is a mechanism by which the FDA can recognize the unique circumstances of the battlefield and establish a new regulatory process to address medications and blood products of particular interest to the military—a Military Use Panel. As noted above, the FDA already has such a mechanism for dealing with medical devices and with medications to be used for biological threats, but not for other medications or blood products. Far more US Servicemembers have died of trauma in recent military operations than from biological weapons. The recent DHB report on trauma care lessons learned in Iraq and Afghanistan included the following recommendation in its findings: "Establish an interagency mechanism with the Food and Drug Administration to approve proposed projects and indications for use by the Services in deployed combat environments."[15]

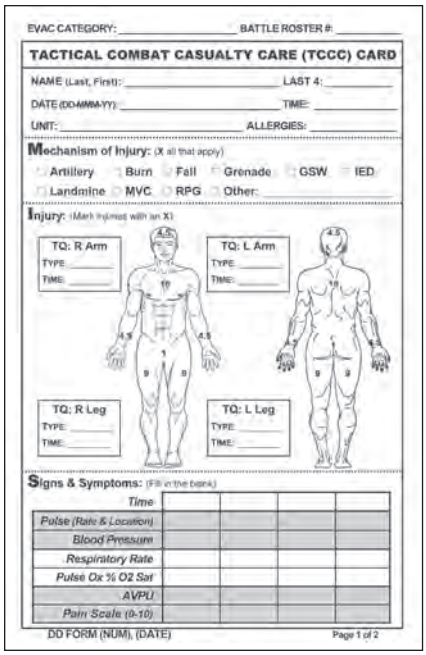
3. Efforts to leverage technology and to develop electronic methods of capturing prehospital medical care should be encouraged and funded.

Reliable documentation of care rendered in the prehospital environment is critical but has proven difficult to accomplish. An accurate record of prehospital care rendered is important for several reasons: (1) it may help guide further care that will be rendered to the casualty at medical treatment facilities; (2) prehospital care is an essential part of the casualty's electronic health record; and (3) accurate records of prehospital care are crucial to combat casualty care performance improvement efforts conducted by the military's JTS.

There are multiple reports showing that prehospital care documentation needs to be an area of increased focus in the DoD, both on the part of medical leaders and of line commanders.[25,28,29,40]

The CoTCCC recently approved recommendations to upgrade the TCCC casualty card (DD 1380).[25] The newly approved DoD Form 1380 is shown in Figures 4 and 5. What is needed is a way to make this documentation of care easier and faster for the Combat medic, who may not have any hands or attention to spare when dealing with multiple casualties on the battlefield. Enhanced voice-to-text or other information capture technology should be able to provide such a solution. Well-designed methodology that optimizes the use of existing technology may also facilitate the capture of both wounding information and care rendered in unit-based prehospital trauma registries. This approach was used very successfully by the

Figure 4 *TCCC casualty card (front; DD Form 1380).*


EVAC CATEGORY: _____ BATTLE ROSTER #: _____

TACTICAL COMBAT CASUALTY CARE (TCCC) CARD

NAME (Last, First): _____ LAST 4: _____

DATE (DD-MMM-YY): _____ TIME: _____

UNIT: _____ ALLERGIES: _____

Mechanism of Injury: (X all that apply)

Artillery Burn Fall Grenade GSW IED

Landmine MVC RPG Other: _____

Injury: (Mark injuries with an X)

TQ: R Arm TYPE: TIME:

TQ: L Arm TYPE: TIME:

TQ: R Leg TYPE: TIME:

TQ: L Leg TYPE: TIME:

Signs & Symptoms: (Fill in the blank)

Time				
Pulse (Rate & Location)				
Blood Pressure				
Respiratory Rate				
Pulse Ox % O2 Sat				
AVPU				
Pain Scale (0-10)				

DD FORM (NUM), (DATE) Page 1 of 2

Photo courtesy of US Government

Figure 5 *TCCC casualty card (back; DD Form 1380).*


EVAC CATEGORY: _____ BATTLE ROSTER #: _____

Treatments: (X all that apply, and fill in the blank)

C: Extremity-TQ Junctional-TQ Pressure-Dressing

Hemostatic-Dressing Type: _____

A: Intact NPA CRIC ET-Tube SGA Type: _____

B: O2 Needle-D Chest-Tube Chest-Seal Type: _____

C:	Name	Volume	Route	Time
Fluid				
Blood Product				

MEDS:	Name	Dose	Route	Time
Analgesic (e.g. Ketamine, Fentanyl, Morphine)				
Antibiotic (e.g. Moxifloxacin, Ertapenem)				
Other (e.g. TXA)				

OTHER: Combat-Pill-Pack Eye-Shield (R L) Splint

Hypothermia-Prevention Type: _____

NOTES: _____

FIRST RESPONDER

NAME (Last, First): _____ LAST 4: _____

DD FORM (NUM), (DATE) Page 2 of 2

Photo courtesy of US Government

75th Ranger Regiment: electronic TCCC after-action reports were used to record and supplement the information captured on the paper TCCC casualty card.[17,25]

4. Fund the continued development and expedited fielding of technologies that enable prehospital Combat medical personnel to better judge the adequacy of fluid resuscitation. Specific examples of candidate technologies include the tissue oxygen saturation monitor and the cardiovascular reserve index monitor.

Determination of the adequacy of tissue perfusion is less simple than it might seem, and fluid resuscitation has the potential to be harmful as well as beneficial. Blood pressure is the traditional way to measure the volume of blood in the intravascular space, as well as the functioning of the heart as it generates the mechanical force to circulate this blood. When blood is being lost due to hemorrhage, however, the body's compensatory mechanisms serve to maintain both blood pressure and the perfusion of critical organs, such as the brain and the heart. These physiologic responses to blood loss will maintain the blood pressure at a normal or near-normal level despite significant blood loss. Once a threshold point is reached, however, the compensatory mechanisms fail, and the body goes into shock.[41]

It is important not to overshoot the mark on fluid resuscitation; animal studies have shown that, in the presence of an unrepaired vascular injury, raising the blood pressure beyond a critical threshold through excessive fluid resuscitation may result in disruption of the forming clot, rebleeding, and death.[42]

There are a number of monitoring devices that have the potential to guide fluid resuscitation with more precision than is possible by relying on blood pressure measurements. One example is the cardiovascular reserve indicator, which uses the characteristics of the arterial pulse waveform to generate a more precise determination of intravascular volume status. Another option is to measure tissue oxygen saturation, which monitors the adequacy of oxygen delivery by determining the level of oxygen present in tissues. A third candidate technology is a device that could provide prehospital measurements of serum lactate. The latter two devices have the added benefit of providing a quantitative measure of the adequacy of tissue oxygenation, which requires both adequate intravascular volume and adequate oxygen-carrying capacity.

For any of these three devices to be used most effectively in TCCC, they will need to be small, rugged, light, and inexpensive enough to be fielded widely to military medics. Additionally, it would be useful to have studies that show that the use of such monitors in the prehospital setting improves outcomes in trauma patients.

5. Evaluate the impact of individual and collective TCCC prehospital care interventions recommended by the JTS on combat casualty outcomes, using data from the DoD Trauma Registry.

As noted previously, decisions regarding prehospital trauma care must often be made with relatively low-quality evidence. This is especially true for prehospital combat casualty care. Further, even in those instances when high-quality prehospital trauma care evidence is available from the civilian sector, it must be considered with caveats when extrapolating the evidence to the military environment. This necessitates the use of robust feedback methodology so that the impact of TCCC-recommended interventions can be monitored carefully and performance improvement measures implemented, as necessary. Studies such as those performed by COL John Kragh on tourniquet use, LTC Bob Mabry on surgical airways, COL Ian Wedmore on HemCon dressings, COL (Ret) Robb Mazzoli on eye shields, COL Russ Kotwal on oral transmucosal fentanyl citrate, and Col Stacy Shackelford on prehospital analgesia are essential to either confirm the success of currently recommended interventions or identify the need to reconsider management recommendations for the aspect of care being studied.[18,20,43–47]

This is a complex undertaking in that outcomes for casualties are typically impacted by multiple interrelated factors and isolating the contribution of any one intervention to survival may be challenging. Despite the challenges, each aspect of prehospital care needs to be

monitored to determine as precisely as possible its impact on casualty outcomes. It is important to note that valuable information in this area may be provided from civilian settings, as noted in the previously mentioned study by Bickell in 1994[11] and by the recent evaluation of the TCCC controlled volume resuscitation plan done by Shrieber and colleagues.[48] New combat casualty care strategies identified in conflicts often have direct applicability to civilian trauma patients,[9,49–52] and this type of focused examination of TCCC-recommended prehospital trauma care interventions will increase the evidence base as the civilian sector considers adopting these recommendations.

6. Explore all options to make 50mg intramuscular (IM) ketamine autoinjectors available for use by US combat forces.

Morphine has been used for the control of battlefield pain since the US Civil War. The US Military currently fields morphine in autoinjectors, but IM morphine has several disadvantages. It is absorbed relatively slowly when given IM and the onset of analgesia is delayed. This leads to repeated doses and the risk of overdose.[53] It also depresses both cardiac and respiratory function and is contraindicated in casualties with hemodynamic or pulmonary compromise.[7,22,54–56] Hemorrhagic shock continues to be the leading cause of potentially preventable death in combat casualties.[2] Avoiding hypotension and hypoxia is especially important in patients with traumatic brain injury, in whom even moderate decreases in blood pressure or oxygen saturation can lead to secondary brain injury.[12,57]

Ketamine is now recommended as the analgesic agent of choice when a casualty who requires pain medication is in, or at significant risk for, hemorrhagic shock.[22] It also has the advantage of being absorbed quickly when given IM,[58] leading to a more rapid relief of pain than is possible with IM morphine.

Ketamine has been widely used by both US Military and British Armed Forces in Afghanistan,[47,57,59] but since analgesia for wounds sustained in combat is an off-label use of this medication, it cannot be supplied by manufacturers in an autoinjector format for use on the battlefield. This results in our battlefield medical personnel (typically medics, corpsmen, or PJs) having to draw up the desired dose of ketamine from multidose vials in the chaos of a casualty scenario. This is clearly not optimal and having ketamine available as an autoinjector would greatly reduce the potential for dosing errors in this setting. As noted previously, having a DoD–FDA Military Use Panel empowered to consider the special circumstances of combat casualty care and approve additional military-only indications for selected medications, when appropriate based on the available evidence and without requiring civilian-based phase III trials, could be of great benefit to our nation's combat wounded.

7. (Tie) Perform an analysis of the use of ketamine at the point of injury and during tactical evacuation care from DoD Trauma Registry data: optimal dosing, efficacy, and incidence of side effects, to include dysphoric and emergence reactions, and their impact on casualty outcome.

The use of ketamine as a prehospital analgesic option is relatively new in the US Military. This analgesic option was used extensively by British forces during the war in Afghanistan and adopted early in the US Military by the Air Force pararescue community.[22,47,57] It was recommended by the CoTCCC and the DHB for battlefield analgesia in 2011.[57] The multiyear survey of Combat medical providers' experiences with prehospital trauma care technology and techniques, conducted by the Navy Operational Medicine Lessons Learned Center, indicated that ketamine outperformed opioid analgesic agents.[60]

This evidence notwithstanding, many US physicians are not familiar with ketamine. They have heard reports of dissociative states and other dysphoric events occurring during emergence from ketamine anesthesia but may be unaware that ketamine used in subdissociative doses for analgesia does not typically result in significant difficulties from these phenomena, as was noted in a recent civilian report on prehospital ketamine use.[61]

To strengthen the evidence base for ketamine use on the battlefield, a study examining the available evidence from the DoD Trauma Registry on ketamine, to include analgesic efficacy, incidence of side effects, impact on hemodynamic and pulmonary status, and other aspects of ketamine use would be of great value.

7. (Tie) Develop methodology, training, and equipment to improve the ability of far-forward medical personnel to transfuse whole blood where possible.

Cap et al. recently noted: "The historic role of crystalloid and colloid solutions in trauma resuscitation represents the triumph of hope and wishful thinking over physiology and experience."[62] There is an increasing awareness that fluid resuscitation for casualties in hemorrhagic shock is best accomplished with fluid that is identical to that lost by the casualty: whole blood.[12,62–64]

Storage logistics for blood components make them difficult to use in the far-forward battlefield environment, although the innovative use of electrically powered coolers has enabled blood products to be used in mounted

patrols in the British Armed Forces.[65] The use of blood products in association with other advanced capabilities on evacuation platforms has been associated with an increase in survival.[66–68]

Combatant-to-combatant "buddy" transfusions have been used successfully in US Military operations,[69] and may be life saving. Type O, low A-, low B-titer whole blood has been proposed as the universal donor for whole-blood transfusions,[62,63,70] and some Combat units are now actively working to implement this mode of resuscitation.[71] Figure 6 depicts a Ranger medic preparing for a whole-blood transfusion in a training exercise. Figure 7 shows a field blood-transfusion kit, and Figure 8 shows a leukocyte-reducing platelet-sparing filter.

Figure 6 *Ranger medic preparing for a whole-blood transfusion in a training exercise.*

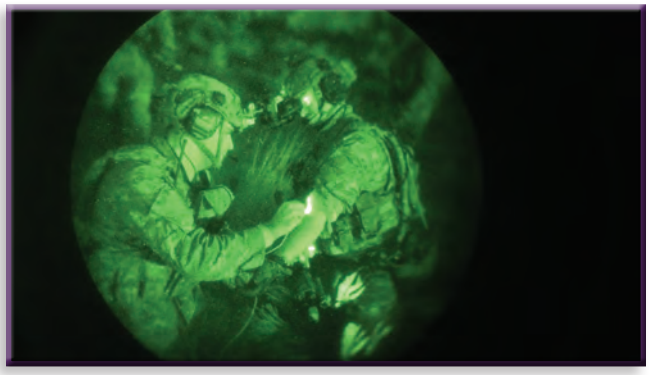


Photo courtesy of MAJ Ethan Miles

Figure 7 *Field blood-transfusion kit.*

Photo courtesy of Dr Warren Dorlac

There is overlap of this research requirement with the one discussed immediately above. While transfusion programs using freshly collected type O, low anti-A/anti-B–titer whole blood are an option being explored by the US Military, other options need to be explored as well. Techniques and technology to enhance the storage life and usability of both cold-stored type O, low anti-A/anti-B–titer whole blood, as well as stored red

Figure 8 *Leukocyte-reducing, platelet-sparing filter for fresh whole-blood transfusions.*

Photo courtesy of Dr Warren Dorlac

cells, plasma, and platelets, need to be explored and optimized. Although component therapy has not provided outcomes as good as the results obtained with fresh whole blood, resuscitation with balanced blood-component therapy is clearly better than resuscitation with either crystalloids or colloids for casualties in hemorrhagic shock.[12]

9. (Tie) Perform comparative studies of resuscitative endovascular balloon occlusion of the aorta (REBOA) versus the abdominal aortic junctional tourniquet (AAJT) versus polyurethane self-expanding foam, with an evaluation of the advantages and disadvantages of each option.

The US Military has had excellent success with the use of tourniquets and hemostatic dressings to control external hemorrhage, especially extremity hemorrhage, with a resulting dramatic drop in preventable deaths from this cause.[2] Multiple junctional pressure devices are also available now to control junctional hemorrhage.[23] Exsanguination from noncompressible hemorrhage, however, remains the leading cause of preventable death on the battlefield and offers the greatest challenge to medical researchers. The use of tranexamic acid (TXA); controlled volume fluid resuscitation from hemorrhagic shock; avoidance of platelet-inhibiting nonsteroidal anti-inflammatory drug use in combat theaters; and prevention of hypothermia in combat casualties are the first steps toward reducing mortality in noncompressible hemorrhage.

Additionally, a number of promising new technologies to assist in controlling noncompressible hemorrhage are being evaulated, including REBOA; the AAJT™; intraperitoneally injected polyurethane self-expanding foam (ResQFoam™); and the pelvic hemostasis belt.

REBOA entails an endovascular balloon occlusion of the aorta. Although generally inserted in medical treatment

facilities under fluouroscopic guidance, with modifications, the device might be feasible for use by prehospital medical providers.

The AAJT can be used at junctional sites but is also cleared by the FDA for abdominal application, in which configuration it controls distal hemorrhage by occluding the aorta at the level of its bifurcation, distal to the level of the renal arteries. This eliminates flow to distal abdominal, pelvic, and lower-extremity vessels.

In the ResQFoam™ technology being developed jointly by the DoD and DARPA in their Wound Stasis program, two precursor materials are mixed and then injected percutaneously into the peritoneal cavity to control intra-abdominal hemorrhage (Figure 9). The foam mixture expands to approximately 35 times its original volume and, in doing so, exerts hemostatic pressure on bleeding sites.[72–74]

Figure 9 *Self-expanding polyurethane foam (ResQFoam™; Arsenal Medical; http://www.arsenalmedical.com) components contained in the injection device.*

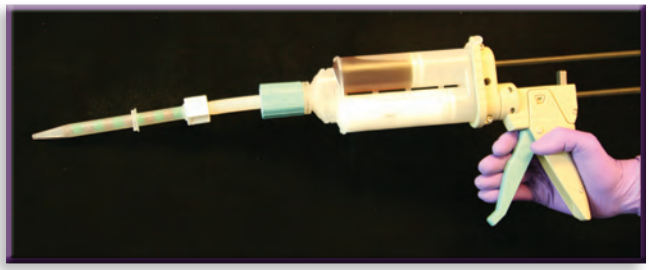


Photo courtesy Dr. David King

The pelvic hemostasis belt is a circumferential device that, when tightened, transmits pressure directly into the pelvic cavity, thereby reducing hemorrhage.[75]

While some preliminary studies of these options for prehospital use are promising,[73–77] others are cautionary (B. Kheirabadi, personal communication, 2015).[78,79] Use of relatively invasive hemorrhage control techniques by Combat medical providers in the prehospital setting is an area of potential concern. The externally applied devices, which do not require arterial vascular access or intraperitoneal delivery, involve occlusion of the abdominal aorta, with the potential for untoward events due to ischemia or elevated intra-abdominal pressure. There is also concern that devices that occlude the abdominal aorta may actually increase the rate of hemorrhage if there is vascular injury proximal to the site of the occlusion.

Considering that there is a great need for interventions to successfully control intra-abdominal hemorrhage in TCCC but that all of the devices mentioned above also entail the potential to harm the casualty, determining with as much precision as possible the relative merits and disadvantages of each of these noncompressible hemorrhage control options should be undertaken as soon as possible. Attention should also be directed toward determining the injury patterns and physiologic indicators that identify the casualties most likely to benefit from these interventions and application strategies that optimize this potential benefit. These devices should be evaluated, as appropriate, on animal models, and then transitioned to clinical use with careful monitoring of outcomes and further adjustments made based on initial clinical experience.

9. (Tie) Gather information from Combat medics, corpsmen, and PJs regarding the efficacy of all of the hemostatic devices and dressings that they have personally used to treat combat injuries on the battlefield. The TCCC Equipment Feedback project, conducted by the Naval Operational Medical Lessons Learned Center (NOMLLC), is the best current model for gathering this type of information.

Published reports on the experiences of seasoned Combat medics/corpsmen and PJs with the battlefield trauma care equipment that they carry are remarkably lacking in the medical literature, considering that our nation has been at war for 14 years. Laboratory testing of such equipment is appropriate and necessary, but such testing provides an incomplete picture of the merits and weaknesses of the equipment item. Such important questions as ease of use, durability, performance under environmental extremes, common causes of failure in combat use, and overall suitability for battlefield use can be answered with more fidelity by a systematic collection of input from the medics, corpsmen, and PJs who have actually used the device in combat conditions.

The NOMLLC conducted an excellent TCCC equipment after-action evaluation program for several years that allowed for quantitative evaluations and specific comments about the merits and/or shortcomings of currently fielded combat medical equipment to be obtained from individuals with experience in using these items in combat. This program has now unfortunately been discontinued, but should be restarted and continued as a permanent feature of the DoD military medical lessons learned or combat casualty care research program.

9. (Tie) Evaluate the impact of immediate (immediately after wounding) versus delayed (1 hour and 3 hour) administration of intravenous (IV) TXA on survival in noncompressible hemorrhage.

Hemorrhagic shock is the leading cause of potentially preventable deaths in US combat casualties. Eastridge found that 24% of combat fatalities were potentially preventable and that most of these deaths occurred in the prehospital setting. Ninety-one percent of preventable

deaths were due to hemorrhage, of which two-thirds resulted from noncompressible hemorrhage.[2]

The Clinical Randomization of Antifibrinolytics in Significant Hemorrhage (CRASH-2) trial was a large, multinational, placebo-controlled trial that examined the effect of the administration of TXA on death, vascular occlusive events, and blood transfusion requirements in trauma patients with, or at risk for, significant hemorrhage. This study found that TXA significantly reduced the risk for death with few adverse effects.

The subsequent CRASH-2 subgroup analysis and the Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERS) study, both published in 2011, strengthened the evidence that TXA reduces mortality in casualties with significant hemorrhage, especially when the medication is administered within the first hour after injury. TXA was subsequently recommended by the CoTCCC and the DHB for use in selected casualties.[80]

The CRASH-2 subgroup analysis clearly showed that TXA is most effective at reducing mortality when the medication is administered within 1 hour of injury. Further, multiple papers reporting the use of TXA to reduce bleeding in elective orthopedic, spinal, and cardiac surgeries have clearly shown that TXA is effective at reducing blood loss in this setting without causing increasing thromboembolic complications.[81,82] TXA, when used in elective surgery, is given either preoperatively or, in orthopedic surgery, just before tourniquet release. Thus, the TXA is on board and acting before the onset of bleeding.

There are presently no published studies in trauma patients that look at TXA administered immediately after wounding as compared with TXA administered 1 hour after wounding or not at all. This information is of great interest to the US Military, since noncompressible hemorrhage is the leading cause of death on the battlefield, even in a combat theater with relatively short evacuation times to surgical care. This information will be even more important for casualties in an immature combat theater where evacuations to surgical care may be delayed far beyond those currently seen in Afghanistan.

TXA is a tool has been specifically authorized for combat medic use by the Assistant Secretary of Defense for Health Affairs and it is critically important that the use of this effective, safe, and inexpensive medication be optimized in battlefield trauma care.[80,83]

9. (Tie) Evaluate the use of an undiluted IV bolus of TXA in noncompressible hemorrhage versus the currently used 10-minute infusion of TXA diluted in 100mL of normal saline.

The CRASH-2 study administered 1g of TXA diluted in 100mL of normal saline administered over 10 minutes, followed by a second 1g dose administered over 8 hours.[84] Since the CRASH-2 study is, at present, the strongest evidence for the efficacy of TXA in trauma patients, this dosing technique for TXA is often used. The MATTERS study, however, used an IV bolus of TXA rather than the CRASH-2 dosing method. Elective surgery studies of TXA have also used IV bolus dosing.[85]

Simplifying and optimizing the dosing regimen for TXA would be of benefit to Combat medics who may have multiple casualties to care for in a combat scenario.

Summary

While the list presented here is by no means a comprehensive list of all of the research areas of interest in battlefield trauma care, much less a list of research needs across the entire continuum of combat casualty care, it does provide the collective judgment of the CoTCCC about the highest priorities for RDT&E that relate to battlefield trauma care.

Two additional observations should be made regarding that point: (1) As the landmark Eastridge et al.[2] 2012 study convincingly documented, most combat fatalities occur in the prehospital phase of care, so research efforts that enable Combat medics, corpsmen, and PJs to care for their casualties more effectively will convey the highest probability of further reducing the case fatality rate and preventable deaths among US Combat casualties; and (2) inasmuch as the mission of the CoTCCC is to update the TCCC Guidelines as needed, this group has excellent visibility of the most important current research questions in battlefield trauma care.

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Disclaimer

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 Department of the Army 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 nothing to disclose.

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CAPT (Ret.) Butler was a Navy SEAL platoon commander before becoming a physician. He is an ophthalmologist and a Navy Undersea Medical Officer with over 20 years of experience providing medical support to Special Operations Forces. Dr Butler has served as the Command Surgeon for the US Special Operations Command. He is currently the chair of the Department of Defense's CoTCCC and director of Prehospital Trauma Care at the Joint Trauma System.

COL Blackbourne is a trauma surgeon at the San Antonio Military Medical Center, San Antonio, Texas. He was previously the Commander of the US Army Institute of Surgical Research and the director of the Army Trauma Training Center at the Ryder Trauma Center in Miami, Florida.

COL Gross is a trauma surgeon with prior experience with the US Special Operations Command and combat-deployed forward surgical teams. He has over 50 months of deployed service providing surgical care to our nation's combat wounded in Afghanistan and Iraq and is the Trauma Consultant to the Army Surgeon General. He was previously the Director of the Joint Trauma System and is presently the Director of the Defense Medical Readiness Training Institute.