

JOINT TRAUMA SYSTEM CLINICAL PRACTICE GUIDELINE (JTS CPG)



Damage Control Resuscitation

This CPG provides evidence-based guidance to minimize variation in resuscitation practices and improve the care of massively hemorrhaging, severely injured casualties.

Contributors

COL Andrew P Cap, MC, USA	RDML Darin K Via, MC, USN
COL Jennifer Gurney, MC, USA	LTC Matthew A Borgman, MC, USA
Philip C. Spinella, MD, FCCM	Maj Andrew N Beckett, MC, Canadian Forces
CDR Geir Strandenes, MC, Norwegian Special Forces	Col Tom Woolley, FRCA, RAMC
COL (ret) Martin Schreiber, MC, USAR	CAPT (ret) Joseph Rappold, MC, USN
COL (ret) John Holcomb, MC, USAR	LTC Kevin Ward, MC, USAR
LTC Jason B. Corley, MC, USA	Col Michael Reade, MC, Australian Defense Forces
Col (ret) Donald Jenkins, USAF, MC	COL Sylvain Ausset, MC, French Army
COL (ret) Brian Eastridge, MC, USAR	SGT Ricky M Ditzel Jr, MC, USA
LCDR Russell Wier, MC, USN	Col Stacy Shackelford, USAF, MC
Lt Col Brian Gavitt, USAF, MC	CDR Jacob Glaser, MC, USN

First Publication Date: 18 Dec 2004

Publication Date: 12 Jul 2019

Publication Supersedes: 03 Feb 2017

TABLE OF CONTENTS

EXECUTIVE SUMMARY	4
BACKGROUND	4
BLOOD PRODUCTS FOR DCR.....	5
Whole Blood.....	5
Red Blood Cells.....	6
Plasma	6
Platelets.....	7
HEMOSTATIC ADJUNCTS FOR DCR.....	7
Mechanical Hemorrhage Control	7
Pharmacologic Adjuncts.....	8
MANAGEMENT PRINCIPLES FOR DCR	10
Recognition of Patients Requiring DCR	10
POINT OF INJURY, EN-ROUTE, & REMOTE DCR.....	11
Optimization of Fluids	11
Adjunctive Therapies in PFC.....	11
DCR AT MEDICAL TREATMENT FACILITIES	12
Optimization of Fluids	12
Blood Product Transfusion	12
Adjunctive Therapies at MTF'S.....	12
CONCLUSION	13
PERFORMANCE IMPROVEMENT MONITORING.....	13
REFERENCES.....	15
APPENDIX A: EXAMPLE OF A MASSIVE TRANSFUSION PROCEDURE AT USCENTCOM LEVEL III FACILITY	21
APPENDIX B: PEDIATRIC CONSIDERATIONS.....	22

S U M M A R Y O F U P D A T E S

RAPID UPDATES

Aug 2023: *Calcium caution statement added.*

Jun 2023

- *Calcium administration changed to 1 gram calcium.*
- *Tranexamic acid (TXA) 2gm bolus is now favored over the traditional 1gm prehospital bolus followed by 1gm infusion over 8 hours. The 2gm TXA bolus should be given as close to the time of injury as possible and not outside of the 3 hours window.*

Jul 2019

- Greater emphasis on the use of Low Titer O Whole Blood (LTOWB) as the optimal strategy to deliver a balanced and maximally hemostatic resuscitation, with platelet functionality, safely.
- Risk factors for massive transfusion (MT), International Normalized Ratio (INR) threshold updated to > 1.5.
- Earlier calcium use recommended. One gram of calcium IV/IO should be given to patients in hemorrhagic shock during or immediately after transfusion of the first unit of blood product and with ongoing resuscitation after every 4 units of blood products. Ideally, ionized calcium should be monitored and calcium should be given for ionized calcium less than 1.2mmol/L.¹⁻⁵
- Blood pressure goals for DCR have been adjusted to a target systolic blood pressure (SBP) goal of 100 mmHg (110mmHg for traumatic brain injury (TBI)).
- Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) updated as a fielded option for the control of non-compressible torso hemorrhage. REBOA continues to be recommended for designated resuscitation teams and NOT intended to be used by the combat medic or corpsman.
- The use of hydroxyethyl starch (Hextend, Hespan) as a resuscitation fluid is NO LONGER RECOMMENDED and has been removed from the guideline.
- The use of recombinant human activated factor VII (rhFVIIa) is no longer recommended.

Damage Control Resuscitation



HEMORRHAGE is the leading cause of preventable death
DO YOUR PART TO CONTROL IT

RECOGNIZE IT

Injury Pattern

- ✓ Amputations
- ✓ Pelvic injury
- ✓ Penetrating chest/abd

eFAST

- ✓ 2 regions +



Data

- ✓ SBP < 100
- ✓ HR > 100
- ✓ HCT < 32
- ✓ pH < 7.25
- ✓ Lactate > 2.5
- ✓ INR > 1.5
- ✓ Base Deficit > 6

STOP IT

- ✓ Tourniquets
- ✓ Hemostatic dressing
- ✓ Direct pressure
- ✓ Junctional tourniquets
- ✓ TXA 2gms
- ✓ Appropriate surgical care ASAP (<1 hr)

REPLACE IT

-  **NO CRYSTALLOID**
-  **NO HEXTEND**
- ✓ LTOWB
- ✓ WFWB
- ✓ Plasma: RBC (1:1:1)
- ✓ Warmed
- ✓ TXA (< 3 hrs)
- ✓ Calcium
 - 1 gm Calcium IV/IO
 - After 1st unit
 - Then every 4th unit



- 1st Fluid is Blood
- Whole Blood
- OR**
- Plasma:RBC:Plts:Cryo(1:1:1:1)
- TXA given
- Calcium given



Clinical tips based on the Damage Control Resuscitation Clinical Practice Guideline (CPG) published by the Joint Trauma System (JTS).

JTS CPGs : https://jts.health.mil/index.cfm/pi_cpgs/cpgs

EXECUTIVE SUMMARY

Hemorrhage is the leading cause of preventable death on the battlefield.⁶ Of the 4,596 combat deaths reported in COL Brian Eastridge's 2012 review *Death on the Battlefield*, 976 casualties died with injuries that an expert panel classified as potentially survivable, and the vast majority of these deaths—just over 90%—were secondary to uncontrolled hemorrhage. Subsequent interventions focusing on point of injury hemorrhage control and prehospital Tactical Combat Casualty Care were predictably successful, and particularly when paired with rapid evacuation and prehospital blood resuscitation. In fact, data published in studies by Col Stacy Shackelford et al. showed that blood given in the prehospital setting as soon as possible after injury improved both 24 hour and 30-day survival.⁷ In short, in the setting of active hemorrhage, the combination of point-of-injury hemorrhage control (per Tactical Combat Casualty Care guidelines), rapid evacuation, and pre-hospital blood resuscitation saves lives.

BACKGROUND

Damage Control Resuscitation (DCR) is generally accepted as a complementary strategy usually paired with Damage Control Surgery (DCS), which focuses surgical interventions to those which address life-threatening injuries and delays all other surgical care until metabolic and physiologic derangements have been treated.⁸ Recognizing that this approach saved lives, DCR was developed to work synergistically with DCS and prioritize non-surgical interventions which may reduce morbidity and mortality from trauma and hemorrhage.⁹ The major principle of DCR is to restore homeostasis, prevent or mitigate the development of tissue hypoxia, oxygen debt and burden of shock, as well as coagulopathy.^{10,11} This amounts to preventing 'blood failure,' specifically with a goal of restoring blood functionality (improving oxygen delivery and tissue perfusion, reducing acidosis, preventing fibrinolysis, reducing coagulopathy, protecting the endothelium, and reducing platelet dysfunction). This is best accomplished through aggressive hemorrhage control and a blood product-based resuscitation, which restores tissue oxygenation, avoids platelet and coagulation factor dilution, and also replaces lost hemostatic potential. DCR is most effective when resuscitation replaces lost blood with whole blood, whether ideally transfused as units of whole blood (WB), or blood product components transfused in a ratio approximating whole blood (i.e. 1:1:1 ratio of FFP:Plt:RBC). Additional goals of DCR are avoidance or limiting of the use of crystalloids to avoid dilutional coagulopathy, selective use of hypotensive resuscitation (SBP of 100 or SBP of 110, if TBI suspected until surgical control is achieved, correction of coagulopathy and acidosis, maintenance of normothermia, empiric administration of Tranexamic Acid in appropriate patient populations, and expeditious evacuation to damage control and definitive surgical capabilities.

Advanced Trauma Life Support (ATLS) guidelines historically advocated a linear resuscitation strategy beginning with an emphasis on crystalloid infusion, particularly during the pre-hospital phase, followed by the addition of red blood cells (RBCs), and finally plasma. Platelets were delayed until a low platelet count was documented and reserved either for severe thrombocytopenia or thrombocytopenia in the presence of active hemorrhage. As documented in retrospective reports from the civilian trauma literature, this approach resulted in excessive crystalloid use and is associated with a risk of dilutional coagulopathy, abdominal compartment syndrome, multiple organ failure, and death¹². Although selection bias may have contributed to these findings, it should be noted that the ATLS 10th edition identifies that resuscitation with greater than 1.5L of crystalloid is associated with increased mortality and suggests limiting crystalloid use to no more than one liter during the initial resuscitation. Instead, current ATLS recommendations for bleeding patients are for early administration of blood products, including plasma and platelets, while focusing on rapidly achieving hemorrhage control.¹³

During the conflicts in Iraq and Afghanistan between 2003 and 2012 14% of patients admitted to Role 3 military treatment facilities (e.g., combat support hospitals) received a transfusion of at least one blood product. Of these, 35% received MT. (MT is defined as ≥ 10 units of RBCs and/or WB in 24 hours. The proportion of transfused patients receiving MT reached approximately 50% by 2011 in parallel with increasing injury severity scores, use of blood resuscitation, and decreased use of crystalloid and colloid use.¹⁴ During this period mortality fell as military clinicians became experts in the treatment of very severe multisystem trauma accompanied by massive hemorrhage. Civilian ATLS-based practice gave way to a hemostatic resuscitation approach designed to mimic WB functionality.

There is now strong retrospective evidence in both civilian and military trauma populations that patients requiring MT benefit from a higher ratio of plasma and platelets to red cells (e.g., 1 unit plasma: 1 unit platelets: 1 unit RBCs). MT at a 1:1:1 ratio is associated with improved survival.^{9, 15-18} Recently, prospective randomized data from the Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial revealed that mortality at 3 hours after injury due to exsanguination was lower in patients resuscitated with a 1:1:1 ratio compared to 1:1:2.¹³ These were important findings given that the differences between resuscitation strategies were small—and probably best characterized by an early vs. late platelet approach. There was no difference in overall mortality at 24 hours or 30 days, likely due to the confounding effect of head injury. Balanced resuscitation was not associated with increased complication rates.^{19,20}

Although physicians continue to debate the lessons of the PROPPR trial and the relative benefits of specific blood component ratios, the practice of giving large amounts of crystalloid or RBCs alone during the initial resuscitation is no longer standard practice. As stated above, in combat casualties with bleeding, EARLY blood product resuscitation (ideally within 36 minutes of injury) provides the lowest early and late mortality rates.² Available data on balanced resuscitation comes from component-based resuscitation. We know that any blood product combination represents an advantage over salt-based crystalloids for the bleeding casualty. However, LTOWB represents the best way to deliver a functional resuscitation early, clinically as well as logistically.

B L O O D P R O D U C T S F O R D C R

W H O L E B L O O D

Whole blood delivers all the components of blood in the same ratio in which they were lost; WB is independently associated with improved survival.²¹⁻²³ In deployed environments, the logistical challenges of maintaining a supply of blood components have led to the use of WB collected onsite from “walking blood banks,” specially to provide platelets for hemostatic resuscitation. Depending on where the blood products have been collected, some of the whole blood products in the deployed setting (platelets or WB) are not prospectively tested for Transfusion-Transmitted Diseases (TTDs). Rapid TTD test kit use is encouraged to screen for HIV, Hepatitis B and C, and malaria or other diseases for which kits are available. Recipients of these blood products must be tested at 3-, 6- and 12-months post- transfusion to monitor for disease transmission.

Type-Specific Whole Blood (TSWB), often referred to as Fresh Whole Blood (FWB), is collected from donors in the deployed setting and must be an ABO match with the recipient. The availability of TSWB may be limited due the constrained pool of donors who must be tested for TTDs and blood group compatibility with recipients. In addition, the chaotic conditions of mass casualty scenarios complicate the matching of blood types between donors and recipients, increasing the risk of clerical errors causing hemolytic transfusion reactions.

In order to improve the availability and safety of WB, low anti-A and anti-B titer (<256 by tube method, though the definition of ‘low titer’ can vary by medical agency or facility) group O blood has been identified

as a practical, effective universal blood product for resuscitation of exsanguinating hemorrhage.^{24,25} Like all blood donors, “O low titer” donors should be tested for TTDs and undergo confirmatory typing and an antibody screen (type and screen) in addition to testing for anti-A and anti-B antibodies. LTOWB can be collected from pre-screened walking blood banks in the deployed setting or collected in Armed Services Blood Program donor centers and stored refrigerated for 21 days in CPD or 35 days in CPDA-1.²⁶ It is important to note that LTOWB has been used safely in the military setting since WW1, with hundreds of thousands of units transfused and only one recorded hemolytic reaction, due to a clerical error.²⁷

In 2014 the U.S. Army Rangers developed and instituted the Ranger O Low titer blood (ROLO) program. Low Titer Rangers were identified as a screened donor pool serving as an immediate WBB capability (approximately 2/3 of the group O Ranger population is naturally low titer, generally accepted as having anti-A and anti-B levels less than 1:256 concentration). Every Ranger is trained in how to set up and administer a Fresh Whole Blood buddy transfusion. This program represents a success story of leadership and since 2015 every Ranger task force has deployed with a functional ROLO program. This model is currently being broadened to other prehospital communities.

Available data suggest that Cold-Stored WB (CWB) will provide robust platelet hemostatic function during the first 2 weeks of storage. When using anticoagulants and preservatives such as CPD and CPD-A, function is moderately reduced during the remaining shelf life (21 days for Citrate Phosphate Dextrose (CPD) WB and 35 days for Citrate Phosphate Dextrose Adenine (CPDA-1) WB), but it should be noted that some platelet function remains and that WB plasma hemostatic function is comparable to that of liquid plasma. Throughout its shelf life, CWB remains a relatively hemostatic product compared to RBCs and plasma alone.²⁸⁻³⁰ Patients receiving MT with CWB stored for more than 2 weeks may require additional support with platelet transfusions or FWB (consider a ratio of 3:1 of CWB: FWB as available). Similarly, CWB that has been leukoreduced with a filter that does not spare platelets and that contains fewer or effectively no platelets require supplementation with platelet or FWB transfusion.³¹ Cold-stored LTOWB and TSWB have been used successfully and safely to treat trauma and other causes of massive hemorrhage, such as obstetric emergencies and bleeding in cardiac surgery, in leading U.S. civilian hospitals.^{30,32-40}

WB is standard practice for resuscitation of combat casualties. For guidance regarding use of FWB, see the [Joint Trauma System \(JTS\) CPG entitled *Fresh Whole Blood Transfusion*](#).⁴¹

RED BLOOD CELLS

RBC units may be stored for up to 42 days under refrigeration when stored in additive solution (e.g., AS-5) or 35 days if stored in CPDA1. In addition, “frozen” RBCs (stored frozen with glycerol cryoprotectant for up to 10 years at <-65°C, then thawed and rinsed in an automated process prior to transfusion) are used interchangeably and successfully with standard RBC units when needed, although these units require at least an hour and a half and specialized equipment to prepare. Transfusion of thawed fRBC units without removal of glycerol is absolutely contraindicated and is lethal to the recipient. Thawed and deglycerolized RBCs can be stored for 14 days with refrigeration. For guidance regarding use of fRBCs see the [JTS CPG entitled *Frozen and Deglycerolized Red Blood Cells*](#).⁴²

PLASMA

Plasma can be stored frozen and then thawed on-demand (FFP), or pre-thawed and stored refrigerated for up to 5 days (so-called “thawed plasma”). The delay in treatment imposed by slow thawing of FFP (up to 30 minutes or more) has necessitated the widespread maintenance of thawed plasma inventories for immediate, emergency use. This typically results in significant waste due to the 5-day post-thaw shelf life. Plasma can also be supplied as “liquid” (never frozen) plasma and stored for 26 days in CPD anticoagulant

solution, or 40 days in CPDA-1. Available data suggest that “thawed” and “liquid” plasma may be functionally interchangeable in most trauma patients. Note that no randomized trials have compared these products and the data regarding the hemostatic capacity of liquid plasma stored beyond 28 days are very limited.^{42,43} Although group AB plasma is classically considered the universal donor, it is now widely recognized that A plasma can, in fact, be considered universal since group A individuals do not generally make high titer anti-B antibodies and B red cells express the B antigen at low density, thus making them much less susceptible to hemolysis than A red cells.

Freeze-Dried Plasma (FDP) was used by U.S. Forces during World War II and has been in use by the French military since the 1940s. French military FDP is available to U.S. Special Operations Forces under an Emergency Use Authorization from the Food and Drug Administration (FDA).²⁴ FDP is considered functionally interchangeable with other plasma products for trauma resuscitation. FDP or Spray-Dried Plasma (SDP) may become more broadly available to U.S. Forces in the near future.⁴⁴⁻⁴⁵

PLATELETS

In contrast to red cells and plasma, platelets collected in theater by apheresis traditionally have been stored at room temperature (20-24°C), under constant agitation, for a maximum of 5 days with an extension to 7 days total if shipped to another facility. These storage conditions are optimized to extend in vivo platelet circulation, but not hemostatic function, safety, or availability.⁴⁶ Platelets are vital for hemostasis and their early use in a balanced transfusion strategy is associated with increased survival in trauma.^{16,19,47,48} Platelets stored under refrigeration (1-6°C), or “Cold-Stored Platelets” (CSP), maintained without agitation for up to 3 days in plasma, have long been approved by the FDA for treatment of bleeding patients. Refrigerated storage better preserves platelet hemostatic function and clearly reduces the risk of bacterial growth, the major hazard of transfusing room temperature-stored platelets.^{49,50} CSP have been proven effective in clinical trials and used successfully in combat trauma patients in the U.S. Central Command area of operations.⁵³ Cold-stored platelets in platelet additive solution (CSP-PAS) or plasma retain function for at least 15 days and are compatible with blood warmers and rapid infusers.⁵¹ CSP can be collected in theater and used interchangeably with other platelet products.⁵²

Fibrinogen concentrate has not been studied adequately in trauma patients either, but several factors suggest that it may be helpful. These include: 1) fibrinogen is the fundamental substrate of clot formation; 2) fibrinogen is rapidly consumed in trauma; and 3) cryoprecipitate, a less purified source of fibrinogen, has been shown to be an essential component of MT protocols for mitigating the dilutional coagulopathy caused by red cell additive solution and anticoagulant.^{17,53-56}

Prothrombin Complex Concentrates (PCCs) are only indicated for patients requiring urgent warfarin reversal and have not been adequately studied in a broad trauma population. PCCs could be considered if: 1) the patient is anticoagulated; or 2) there is clear evidence of delayed initiation of clot formation refractory to platelets, fibrinogen, or cryoprecipitate and TXA (e.g., prolonged thrombelastography rapid time [TEG-R] or rotational thromboelastometry clotting time [ROTEM CT]). PCCs should not be routinely used in trauma outside the context of a clinical trial as they may cause harm due to excessive thrombogenicity.⁵⁷

HEMOSTATIC ADJUNCTS FOR DCR

MECHANICAL HEMORRHAGE CONTROL

In addition to blood replacement, DCR strategies also focus on limiting blood loss with hemorrhage control devices and adjunctive pharmaceutical therapies. Availability and usefulness of interventions are determined by the type of injury and location of bleeding. Effective tourniquets (e.g., Combat Application

Tourniquet, Special Operations Forces Tactical Tourniquet) have been developed for extremity injury and may be responsible for saving more wounded service members in Iraq and Afghanistan than any other single medical intervention. Junctional (axillary, neck, and groin) hemorrhage, previously a nearly intractable problem, can now be treated with approved junctional tourniquets (e.g., Combat Ready Clamp, SAM® Junctional Tourniquet, Junctional Emergency Treatment Tool) and the XSTAT™ device, which injects absorbent sponges into deep wounds to tamponade bleeding.⁵⁸⁻⁶⁰ Superficial wounds are amenable to novel and effective hemostatic dressings (e.g., Combat Gauze or Celox/Celox Rapid gauze).

Truncal internal hemorrhage is non-compressible and is the subject of intensive research. Resuscitative Endovascular Occlusion of the Aorta (REBOA) has emerged as a technique for truncal hemorrhage control. The newest device available does not require fluoroscopic guidance and has become widely available; in expert hands on teams with appropriate training, REBOA may improve survival from non-compressible truncal hemorrhage. There is no 24-hour outcome data on the use of REBOA in the combat environment. Teams that use this technique should be submitting clinical data to the JTS in order to better understand this capability and how it effects outcomes from hemorrhage. The ideal application of REBOA in the combat environment is evolving, but the technique, when used appropriately, has the potential to significantly improve outcomes from non-compressible truncal hemorrhage. Currently, REBOA use is supported for austere surgical teams, and teams that have an immediate surgical capability are using REBOA. See the [JTS REBOA for Hemorrhagic Shock CPG](#).⁶¹⁻⁶⁷

PHARMACOLOGIC ADJUNCTS

Hemostatic pharmaceutical adjuncts to limit blood loss are another subject of considerable investigation.

Tranexamic acid (TXA) is the only therapy in this class that has been found to reduce mortality in a large Randomized Controlled Trial (RCT). Strong evidence demonstrates a significant improvement in survival following the early use of TXA, but only when given within 3 hours of injury.^{68,69} Significant trauma-- in particular, penetrating trauma with hemorrhage--has been associated with coagulopathy, in part secondary to the activation of fibrinolysis.^{1,70} Such hyperfibrinolysis occurs in the most severely injured patients (approximately 4% of trauma patients in major civilian U.S. trauma centers) and portends poor outcomes.^{9,71} Anti-fibrinolytic agents, including TXA, have been used to decrease bleeding and to reduce the need for blood transfusions in coronary artery bypass grafting, orthotopic liver transplantation, hip and knee arthroplasty, obstetrics, and other surgical settings. The safety and efficacy of using TXA to treat trauma patients was evaluated in a large randomized, placebo-controlled clinical trial *The Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage (CRASH-2)*.⁷² In this trial, 20,211 adult trauma patients in 274 hospitals in 40 countries with, or at risk of, significant bleeding (HR>110, SBP<90, clinical judgment) were randomized to either TXA or placebo. The authors reported that TXA use resulted in a statistically significant reduction in the relative risk of all-cause mortality of 9% (14.5% vs.

%, RR 0.91, CI 0.85-0.97; p = 0.0035). It was in this group of most severely injured patients that use of TXA was associated with the greatest reduction in risk of death.

A registry-based study of combat-injured troops receiving blood in Afghanistan (January 2009 - December 2010) demonstrated a decreased mortality with TXA use in this population. The TXA group was more severely injured (ISS: 25.2±16.6 vs. 22.5±18.5; p<0.001), required more blood (11.8±12.1 vs. 9.8±13.1 pRBC units; p<0.001), had a lower Glasgow Coma Score (7.3±5.5 vs. 10.5±5.5; p<0.001) and initial systolic blood pressure (112±29.1 vs. 122.5±30.3 mmHg), but also had a lower unadjusted mortality than the no-TXA group (17.4% vs. 23.9%; p=0.028). In the massive transfusion cohort (N=321; 24-hour transfusion: 21.9±14.7 pRBC; 19.1±13.3 FFP and 3.5±3.2 apheresis platelet units), mortality was also lower in the TXA group compared to the no-TXA group (14.4% vs. 28.1%; p=0.004). In a multivariate regression model, TXA use in the massive transfusion cohort was independently associated with survival (odds ratio: 7.28; 95% confidence interval:

3.02-17.32). A subsequent larger retrospective analysis of TXA use outcomes in military casualties documented an increased rate of venous thromboembolism in patients receiving TXA.⁷³ Estimates of TXA effects on mortality suggested that an adequately powered study would likely observe an effect size in line with CRASH-2 findings.

This survival benefit associated with TXA supports its use in conjunction with damage control resuscitation following combat injury. This association is most prominent in those requiring massive transfusion.^{14,74} In casualties at high risk of hemorrhagic shock, ***TXA reduces mortality IF GIVEN WITHIN THREE (3) HOURS OF injury***, optimal use of TXA requires that it be given

as soon as possible when indicated rather than suggesting that TXA administration any time within 3 hours after injury is acceptable.^{75,76} TXA given empirically greater than 3 hours post-injury increases the risk of mortality. For eligible casualties, 2 grams of TXA should be administered IV or IO. (See next section *Recognition of Patients*

Requiring DCR to determine eligible casualties.) TXA is ideally administered in 100 ml of normal saline over 10 minutes, but faster administration in more concentrated form can be considered. Administration of undiluted TXA by slow IV push (given over 10 minutes) is acceptable if supplies or tactical situation prevents 100mL IV infusion.⁷⁷ It should be noted that rapid infusion of TXA has been infrequently associated with transient hypotension. Although Lactated Ringer's (LR) solution is compatible with TXA, its use should be avoided in this setting since the mixing of calcium containing LR with blood products in chaotic resuscitation settings may cause clotting of blood products and thromboembolic phenomena. Normal saline and PlasmaLyte A are the only crystalloid solutions compatible with blood products.

CAUTION: Do not mix medications and blood products in the same IV line. Use a separate line or flush well between giving medications and blood products.

Hypocalcemia is a problem in most actively bleeding trauma patients on presentation, and administration of even one unit of citrated blood product can further lower ionized calcium to levels approaching critical values (<0.9mmol/l). One gram of calcium IV/IO should be given to patients in hemorrhagic shock during or immediately after transfusion of the first unit of blood product and with ongoing resuscitation after every 4 units of blood products. At a minimum, one gram of calcium should be administered after no more than 4 units of blood product have been infused to avoid citrate toxicity. Ideally, ionized calcium should be monitored and calcium should be given for ionized calcium less than 1.2mmol/L. This should be done at the first level of care capable of monitoring these patients, typically a Role 2 equivalent or above. Appropriate calcium solutions should otherwise be administered per protocol for signs and symptoms of hypocalcemia (e.g., prolonged QTc, ventricular arrhythmias, decreased cardiac output/cardiovascular collapse, coagulopathy, tetany, laryngospasm, seizures, and paresthesia).

CAUTION: Calcium gluconate is safer for peripheral use. Calcium chloride may cause severe skin necrosis if extravasation occurs through a partially dislodged IV or IO catheter. The risk of bone necrosis with IO injection of calcium chloride is not known. When using peripheral IV or IO access, use extreme caution to ensure the device is in good intravascular position and no extravasation occurs.

Note that hypomagnesemia is also common in trauma patients and is worsened by citrate- containing blood products. Hypomagnesemia may contribute to increased cardiac irritability and risk of fatal arrhythmias. Consideration should be given to replacing magnesium in the setting of severe hypocalcemia and massive transfusion.^{4,78-80}

The use of rFVIIa is no longer recommended in most trauma patients since it has not been shown to reduce mortality and may increase risk of adverse events.⁸¹⁻⁸⁵

MANAGEMENT PRINCIPLES FOR DCR

RECOGNITION OF PATIENTS REQUIRING DCR

Patients receiving uncross matched Type O blood in the Emergency Department (ED) or resuscitation area and later receiving cumulative transfusions of 10 or more RBC units in the initial 24 hours post-injury (MT) are widely recognized as being at increased risk of morbidity and mortality due to exsanguination. Ideally, these patients should be rapidly identified and hemostasis established at the earliest level of care possible in order to prevent or mitigate shock and coagulopathy. Due to diagnostic challenges, particularly in the case of truncal hemorrhage, anticipating the transfusion needs of these patients requires experience and the coordination of extensive resources, including development of MT protocols.

Robust pre-hospital data are lacking, but a number of factors predict the need for MT support in trauma.⁸⁶ In a patient with serious injuries, the presence of 3 of the 4 features below indicates a 70% predicted risk of MT and 85% risk if all 4 are present:

- Systolic blood pressure < 100 mm Hg
- Heart rate > 100 bpm
- Hematocrit < 32%
- pH < 7.25

Other risk factors associated with MT or at least need for aggressive resuscitation.⁸⁶⁻⁹⁰

- Injury pattern (above-the-knee traumatic leg amputation especially if pelvic injury is present, multi-amputation, clinically obvious penetrating injury to chest or abdomen)
- >2 regions positive on FAST scan
- Lactate concentration on admission >2.5
- Admission INR ≥ 1.5
- BD > 6 mEq/L

Recognition of clinical patterns associated with the need for MT is essential for effective triage. These include uncontrolled truncal or junctional bleeding, uncontrolled major bleeding secondary to large soft tissue injuries, proximal, bilateral, or multiple amputations, a mangled extremity, clinical signs of coagulopathy (e.g., paucity of clots or petechial bleeding), or severe hypothermia. It is critical to communicate with the blood bank at the medical treatment facility when a potential MT patient has been identified. Blood banks within theater have developed procedures for providing blood products in the appropriate proportion to support resuscitative efforts. Upon arrival to the ED, laboratory evaluation such as viscoelastic testing (TEG or ROTEM) may also facilitate early identification of patients who will require MT, although this technology is not widely available in the deployed setting, particularly at Role 2 facilities.^{91,92} It should be noted that many point-of-care coagulation tests that measure Prothrombin Time/International Normalized Ratio (PT/INR) have linear ranges only between INR 2.0-3.0 and are unreliable in clinical conditions characterized by loss of fibrinogen. These devices should not be relied upon to evaluate the coagulation function in trauma patients.^{93,94}

P O I N T O F I N J U R Y , E N - R O U T E , & R E M O T E D C R

For detailed recommendations on prolonged field care (PFC) damage control resuscitation, see the [JTS Damage Control Resuscitation for PFC CPG, 01 Oct 2018](#).

OPTIMIZATION OF FLUIDS

Volume resuscitation, particularly crystalloid and colloid, should be used sparingly in the pre-hospital setting, given the potential for harm and the limited resources; blood products are preferred for hemorrhagic shock resuscitation.^{9,95} WB (Group O low titer preferred) or blood components given ideally at a 1:1:1 (plasma, platelets, RBC) ratio should be transfused when shock is present or expected. Blood products should ideally be warmed with approved in-line blood heaters with the goal of transfusing products warmed to 37°C.

Casualties at low risk of developing shock should NOT receive IV fluids or adjunctive medications.

Hypertonic Saline does NOT improve mortality in hemorrhagic shock and should only be used for patients with TBI and evidence/suspicion of raised Intracranial Pressure (ICP).^{96,97} Vasopressors are NOT recommended for the treatment of hemorrhagic shock.

A key element of fluid optimization is careful documentation of all fluids, interventions, and medications given in the pre-hospital phase.

ADJUNCTIVE THERAPIES IN PFC**Compressive / hemostatic dressings and devices**

Prevent further hemorrhage with direct pressure, topical hemostatic dressings, and/or tourniquets, if possible, to minimize the risk of shock. REBOA can be highly effective if rapidly implemented by skilled and designated teams.

Prevention of acidosis and hypothermia

Metabolic acidosis resulting from acute trauma is a consequence of inadequate tissue perfusion leading to lactic acid production and is best addressed with resuscitation with WB or equal ratio components. Crystalloid resuscitation will contribute to the acidosis and should be avoided. Hypothermia is multifactorial and strategies should address as many causes as are identified, including cold exposure, cold resuscitation fluids, significant blood loss, and shock. Hypoperfusion contributes to development of hypothermia due to decreased heat production. Prior to arrival at the military treatment facility, heated fluids, fluid blankets, and ventilators may not be available, but wounds should be covered, “space blankets” (e.g., HPMK) used to cover the casualty, and shock avoided or treated. See [JTS Hypothermia Prevention CPG](#) for additional information.⁹⁸ In patients with isolated extremity injuries treated with tourniquets, the extremity distal to the tourniquet should be left exposed and cooled relative to the patient’s core in order to increase the likelihood of preserving the ischemic limb’s viability.⁹⁹

Expeditious delivery to definitive surgical control

Casualties may require care as described and emergency procedures for life-threatening conditions in the pre-hospital setting; however, these should be balanced against the need to expeditiously deliver the patient to definitive care. DCS at Role 2 forward surgical units should focus only on control of hemorrhage and prevention of ongoing contamination. Only absolutely necessary procedures should be performed. In

general, every effort should be made to deliver the critically injured casualty to the highest available level of care as rapidly as possible.

DCR AT MEDICAL TREATMENT FACILITIES

Although principles remain the same, DCR in medical facilities differs in that there are more resources available, including access to operative surgical control. Also, some therapies such as TXA may have already been given in the pre-hospital phase. Resuscitation to physiologic endpoints such as lactate and base deficit should be considered since tissue hypoxia and oxygen debt are known drivers of coagulopathy. Reversal of tissue hypoxia should thus be a central tenet of hospital-based resuscitation. Specifically:

OPTIMIZATION OF FLUIDS

Volume resuscitation with crystalloids should NOT be first line of care in MTFs due to the potential for harm. Crystalloid fluids should be reserved for specific clinical uses, such as carrier fluid for intravenous medication or other non-resuscitative uses. The order of priority for fluid administration should be:

- Fully TTD tested (performed in FDA registered testing facility/FDA approved) whole blood
- Blood components at a 1:1:1:1 ratio (plasma:platelets:RBC:CRYO)
Note that apheresis platelets may be collected in theater and therefore are not FDA approved and fully tested prior to transfusion.
- Whole blood from a recently tested donor (**NOTE: this option is only acceptable in the hospital for emergency indications when full component therapy is not available**)
- RBCs plus plasma=1:1 ratio
- Plasma with or without RBCs
- RBCs alone

BLOOD PRODUCT TRANSFUSION

Cryoprecipitate is available in hospital settings and should be added to the component mix to create a 1:1:1:1 ratio of products in order to adequately supply fibrinogen and other clotting factors (Factors VIII, XIII, and vWF).

When operationally necessary due to component shortages, WB from walking blood banks can be life-saving. For additional information, refer to the [JTS Whole Blood Transfusion CPG](#).⁴¹

Continual reassessment of the casualty status is needed during and between transfusions. As the patient stabilizes, component ratios should be replaced by 'goal-directed' therapy guided by laboratory evaluation, including CBC, blood gases, calcium levels, PT/INR, Activated Partial Thromboplastin Time (aPTT), and viscoelastic testing (ROTEM® or TEG) if available.

ADJUNCTIVE THERAPIES AT MTF'S

Hypotensive resuscitation

As in the pre-hospital period, resuscitation of casualties without CNS injury prior to definitive surgical control should maintain a lower target SBP (100 mmHg, range 90-110mmHg) to reduce hemorrhage by minimizing intravascular hydrostatic pressure. Hypotensive resuscitation should not be utilized for patients with

isolated CNS injury because of associated adverse outcomes in this population (goal SBP >110mmHg). For additional information, see the [JTS Neurosurgery and Severe Head Injury CPG](#).⁹⁷

Compressive / hemostatic dressings and devices

Until definitive surgical control is established, prevent further hemorrhage with direct pressure, topical or truncal hemostatic dressings, and/or tourniquets or REBOA to avoid the development of shock. In extremis, procedures such as resuscitative thoracotomy are indicated. Use of these devices should occur as rapidly as hemorrhage is identified and should not unnecessarily delay transport to the operating room.

Prevention or correction of hyperfibrinolysis

TXA should be given to casualties at risk of hemorrhagic shock who have not already received a dose during the pre-hospital phase. THE CASUALTY SHOULD ONLY RECEIVE INITIAL TXA IF ADMINISTERED WITHIN THREE (3) HOURS OF INJURY. When given > 3 hours post-injury, TXA increases the risk of mortality. The mortality data were not analyzed in patients with hyperfibrinolysis documented by viscoelastic testing (ROTEM® or TEG). However, documented hyperfibrinolysis in the setting of ongoing hemorrhage should be treated according to clinical judgment. For eligible casualties (see section above titled Recognition of Patients Requiring DCR), 2 grams of TXA should be administered IV or IO. TXA is ideally administered in 100 ml of normal saline over 10 minutes, but faster administration in more concentrated form can be considered. It should be noted that rapid infusion of TXA has been infrequently associated with transient hypotension.

Prevention of acidosis and hypothermia

Hypothermia is multifactorial and strategies should address as many causes as are identified, including cold exposure, cold resuscitation fluids, significant blood loss, and shock. Hypothermia occurs even when ambient temperatures are elevated and medical personnel are uncomfortably warm, due to blood loss and hypoperfusion. Treatment should include urgent, active re-warming with all available means including heated fluids, heated blankets, ventilators, warm environments, and rapid surgical care to minimize blood and heat loss.

Expeditious delivery to definitive surgical control

As with casualties in the pre-hospital setting, pre-surgical care should be balanced against the need to expeditiously deliver the patient to the operating room.

C O N C L U S I O N

The DCR approach to the initial management of a critically injured casualty requires a significant expenditure of resources and the coordination of a diverse group of health care providers. This is frequently performed in a clinical scenario of multiple casualties and limited resources. It is incumbent upon the clinical leaders at each level of care to be fully versed on available resources and to employ them judiciously and appropriately. Patients requiring MT should be resuscitated using DCR principles and should undergo early DCS.

P E R F O R M A N C E I M P R O V E M E N T M O N I T O R I N G

POPULATION OF INTEREST

1. All patients who receive blood product transfusion within 3 hours of injury

2. All patients with severe traumatic injury (ISS ≥ 16 and ≥ 2 body regions injured with AIS severity ≥ 2 AND SBP < 100 OR HR > 100 OR hematocrit $< 32\%$ OR pH < 7.25 within 3 hours of injury)
3. Massive transfusion includes all patients who received 10 or more units of RBC + WB within first 24 hours.

INTENT (EXPECTED OUTCOMES)

1. All patients in the population of interest receive TXA within 3 hours after injury.
2. All patients in the population of interest who receive 1 or more units of blood product also receive calcium.
3. All MT patients receive transfusion of plasma:RBC in a ratio between 0.5:1 to 1:1.5.
4. All MT patients receive platelet or WB transfusion.
5. All MT patients receive cryoprecipitate or WB.
6. For the population of interest, the first resuscitation fluid given after injury is a blood product, ideally cold-stored LTOWB.

PERFORMANCE/ADHERENCE METRICS

1. Number and percentage of patients in the population of interest who receive TXA within 3 hours after injury (or documented ROTEM indicating no fibrinolysis).
2. Number and percentage of patients in the population of interest receiving 1 or more units of blood product who also receive calcium.
3. Number and percentage of MT patients who receive plasma:RBC in a ratio between 0.5:1 to 1:1.5. (calculate ratio for first 24 hours).
4. Number and percentage of MT patients who receive platelet or WB transfusion.
5. Number and percentage of MT patients who receive cryoprecipitate or WB.
6. Number and percentage of patients in population of interest who received a blood product as the first resuscitation fluid.
7. Number and percentage of patients in population of interest who received cold-stored LTOWB as the first resuscitation fluid.

DATA SOURCES

- Patient Record
- Department of Defense Trauma Registry (DoDTR)
- Theater Medical Data Store

SYSTEM REPORTING & FREQUENCY

The above constitutes the minimum criteria for PI monitoring of this CPG. System reporting will be performed annually; additional PI monitoring and system reporting may be performed as needed.

The system review and data analysis will be performed by the JTS Chief and the JTS PI Branch.

RESPONSIBILITIES

It is the trauma team leader's responsibility to ensure familiarity, appropriate compliance, and PI monitoring at the local level with this CPG.

REFERENCES

1. Giancarelli A, Birrer KL, Alban RF, et al. Hypocalcemia in trauma patients receiving massive transfusion. *J Surg Res*, 2016 May 1;202(1):182-7. Epub 2015 Dec 30
2. 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.
3. MacKay EJ, Stubna M, Holena D, 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*, Sep 2017. 125(3):895–901.
4. 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*, Feb 2018;35:176-179.
5. Webster S, Todd S2, Redhead J, Wright C, et al. Ionised calcium levels in major trauma patients who received blood in the Emergency Department. *Emerg Med J*, 2016 Aug;33(8):569-72.
6. Eastridge BJ, Mabry RL, Seguin P, et al. Death on the battlefield (2001-2011): Implications for the future of combat casualty care. *J Trauma Acute Care Surg*, 2012. 73(6 Suppl 5): p. S431-7.
7. 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.
8. Rotondo MF, Schwab CW, McGonigal MD, et al., Damage control: an approach for improved survival in exsanguinating penetrating abdominal injury. *J Trauma*, 1993. 35(3): p. 375-82; discussion 382-3.
9. Holcomb JB, Jenkins D, Rhee P, et al., Damage control resuscitation: directly addressing the early coagulopathy of trauma. *J Trauma*, 2007. 62(2): p. 307-10.
10. Bjerkvig CK, Strandenes G, Eliassen HS, et al., "Blood failure" time to view blood as an organ: How oxygen debt contributes to blood failure and its implications for remote damage control resuscitation. *Transfusion*, 2016. 56 Suppl 2: p. S182-9.
11. Woolley T, Thompson P, Kirkman E, et al. Trauma Hemostasis and Oxygenation Research Network position paper on the role of hypotensive resuscitation as part of remote damage control resuscitation. *J Trauma Acute Care Surg*, 2018 Jun;84(6S Suppl 1):S3-S13.
12. Balogh Z, McKinley BA, Cocanour CS. Supranormal trauma resuscitation causes more cases of abdominal compartment syndrome. *Arch Surg*, 2003. 138(6): p. 637-42; discussion 642-3.
13. American College of Surgeons, Advanced Trauma Life Support (ATLS), 10th Edition 2018.
14. Pidcoke HF, Aden JK, Mora AG, et al. Ten-year analysis of transfusion in Operation Iraqi Freedom and Operation Enduring Freedom: Increased plasma and platelet use correlates with improved

- survival. *J Trauma Acute Care Surg*, 2012. 73(6 Suppl 5): p. S445-52.
15. Borgman MA, Spinella PC, Perkins JG, et al. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. *J Trauma*, 2007. 63(4): p. 805-13.
 16. Holcomb JB, Wade CE, Michalek JE, et al. Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. *Ann Surg*, 2008. 248(3): p. 447-58.
 17. Stinger HK, Spinella PC, Perkins JG, et al. The ratio of fibrinogen to red cells transfused affects survival in casualties receiving massive transfusions at an army combat support hospital. *J Trauma*, 2008. 64(2 Suppl):p. S79-85; discussion S85.
 18. Shaz BH, Dente CJ, Nicholas J, et al. Increased number of coagulation products in relationship to red blood cell products transfused improves mortality in trauma patients. *Transfusion*, 2010. 50(2): p. 493-500.
 19. Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: The PROPPR randomized clinical trial. *JAMA*, 2015. 313(5): p. 471-82.
 20. Nascimento B, Callum J, Tien H, et al. Effect of a fixed-ratio (1:1:1) transfusion protocol versus laboratory- results-guided transfusion in patients with severe trauma: a randomized feasibility trial. *CMAJ*, 2013. 185(12): p. E583-9.
 21. 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): p. S69- 76.
 22. Spinella PC, Dunne J, Beilman GJ, et al. Constant challenges and evolution of U.S. military transfusion medicine and blood operations in combat. *Transfusion*, 2012. 52(5): p. 1146-53.
 23. 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. *Transfusion*, 2011. 51(2): p. 242-52.
 24. Fisher AD, Miles EA, Cap AP, et al. Tactical Damage Control Resuscitation. *Mil Med*, 2015. 180(8): p. 869-75.
 25. Strandenes G, Berseus O, Cap AP, et al. Low titer group O whole blood in emergency situations. *Shock*, 2014. 41 Suppl 1: p. 70-5.
 26. Taylor AL, Eastridge BJ. Advances in the use of whole blood in combat trauma resuscitation. *Transfusion*, 2016. 56: p. 15a-16a.
 27. Army Medical Research Laboratory, Armed Services Blood Program Report 1943-1973: Lessons learned applicable to civil disasters and other considerations, 1973.
 28. Taylor AL, Eastridge BJ. Advances in the use of whole blood in combat trauma resuscitation. *Transfusion*, 2016. 56: p. 15a-16a.
 29. Pidcoke HF, McFaul SJ, Ramasubramanian AK, et al. Primary hemostatic capacity of whole blood: a comprehensive analysis of pathogen reduction and refrigeration effects over time. *Transfusion*, 2013. 53 Suppl 1: p. 137S-149S.
 30. Strandenes G, Austlid I, Apelseh TO, et al. Coagulation function of stored whole blood is preserved for 14 days in austere conditions: A ROTEM feasibility study during a Norwegian antipiracy mission

- and comparison to equal ratio reconstituted blood. *J Trauma Acute Care Surg*, 2015. 78(6 Suppl 1): p. S31-8.
31. Jobes D, Wolfe Y, O'Neill D, et al. Toward a definition of "fresh" whole blood: an in vitro characterization of coagulation properties in refrigerated whole blood for transfusion. *Transfusion*, 2011. 51(1): p. 43-51.
 32. Cotton BA, Podbielski J, Camp E, et al. A randomized controlled pilot trial of modified whole blood versus component therapy in severely injured patients requiring large volume transfusions. *Ann Surg*, 2013. 258(4): p. 527-32; discussion 532-3.
 33. Bahr MP, Yazer MH, Triulzi DJ, et al. Whole blood for the acutely haemorrhaging civilian trauma patient: a novel idea or rediscovery? *Transfus Med*, 2016.
 34. Seheult JN, Triulzi DJ, Alarcon LH, et al. Measurement of haemolysis markers following transfusion of uncrossmatched, low-titer, group O+ whole blood in civilian trauma patients: initial experience at a level 1 trauma centre. *Transfus Med*, 2016.
 35. Yazer MH, Jackson B, Sperry JL, et al. Initial safety and feasibility of cold-stored uncrossmatched whole blood transfusion in civilian trauma patients. *J Trauma Acute Care Surg*, 2016. 81(1): p. 21-6.
 36. Stubbs JR, Zielinski MD, Jenkins D. The state of the science of whole blood: Lessons learned at Mayo Clinic. *Transfusion*, 2016. 56 Suppl 2: p. S173-81.
 37. Zielinski MD, Jenkin DH, Hughes JD, et al. Back to the future: The renaissance of whole-blood transfusions for massively hemorrhaging patients. *Surgery*, 2014. 155(5): p. 883-6.
 38. Alexander JM, Sarode R, McIntire DD, et al. Whole blood in the management of hypovolemia due to obstetric hemorrhage. *Obstet Gynecol*, 2009. 113(6): p. 1320-6.
 39. Jobes DR, Sesok-Pizzini D, Friedman D. Reduced transfusion requirement with use of fresh whole blood in pediatric cardiac surgical procedures. *Ann Thorac Surg*, 2015. 99(5): p. 1706-11.
 40. Manno CS, Hedberg Kw, Kim HC, et al. Comparison of the hemostatic effects of fresh whole blood, stored whole blood, and components after open heart surgery in children. *Blood*, 1991. 77(5): p. 930-6.
 41. Joint Trauma System, Whole blood transfusion clinical practice guideline, 15 May 2018. https://jts.health.mil/index.cfm/PI_CPGs/cpgs
 42. Joint Trauma System, Frozen Deglycerolized Red Blood Cells Clinical Practice Guideline, 11 Jul 2016. https://jts.health.mil/index.cfm/PI_CPGs/cpgs
 43. Spinella PC, Frazier E, Pidcoke HF, et al. All plasma products are not created equal: Characterizing differences between plasma products. *J Trauma Acute Care Surg*, 2015. 78(6 Suppl 1): p. S18-25.
 44. Matijevic N, Wang Y, Cotton BA, et al. Better hemostatic profiles of never-frozen liquid plasma compared with thawed fresh frozen plasma. *J Trauma Acute Care Surg*, 2013. 74(1): p. 84-90.
 45. Pusateri, A.E., Given, M.B., Schreiber, M.A., et al., Dried plasma: state of the science and recent developments. *Transfusion*, 2016. 56 Suppl 2: p. S128-39.
 46. Pidcoke HF, Spinella PC, Borgman MA, et al. Refrigerated platelets for the treatment of acute bleeding: A review of the literature and reexamination of current standards. *Shock*, 2014. 41 Suppl 1: p. 51-3.
 47. Perkins JG, Cap AP, Spinella PC, et al. An evaluation of the impact of apheresis platelets used in the

- setting of massively transfused trauma patients. *J Trauma*, 2009. 66(4 Suppl): p. S77-84.
48. Cap AP, Spinella PC, Borgman MA, et al. Timing and location of blood product transfusion and outcomes in massively transfused combat casualties. *J Trauma Acute Care Surg*, 2012. 73(2 Suppl 1): p. S89-94.
49. Reddoch KM, Pidcock HF, Montgomery RK, et al. Hemostatic function of apheresis platelets stored at 4 degrees C and 22 degrees C. *Shock*, 2014. 41 Suppl 1: p. 54-61.
50. Nair PM, Pidcock HF, Cap AP, et al. Effect of cold storage on shear-induced platelet aggregation and clot strength. *J Trauma Acute Care Surg*, 2014. 77(3 Suppl 2): p. S88-93.
51. Corley JB, Implementation of Cold Stored Platelets for Combat Trauma Resuscitation. *Transfusion*, 2016. 56: p. 16a-17a.
52. Getz, T.M., Montgomery, R.K., Bynum, J.A., et al. Storage of platelets at 4 degrees C in platelet additive solutions prevents aggregate formation and preserves platelet functional responses. *Transfusion*, 2016. 56(6): p. 1320-8.
53. Cap AP. Platelet storage: a license to chill! *Transfusion*, 2016. 56(1): p. 13-6.
54. Collins PW, Solomon C, Sutor K, et al. Theoretical modelling of fibrinogen supplementation with therapeutic plasma, cryoprecipitate, or fibrinogen concentrate. *Br J Anaesth*, 2014. 113(4): p. 585-95.
55. Schlump CJ, Schochl H. The role of fibrinogen in trauma-induced coagulopathy. *Hamostaseologie*, 2014. 34(1): p. 29-39.
56. Schochl H, Schlump CJ, Maegele M. Tranexamic acid, fibrinogen concentrate, and prothrombin complex concentrate: data to support prehospital use? *Shock*, 2014. 41 Suppl 1: p. 44-6.
57. Schochl H, Voelckel W, Maegele M, et al. Endogenous thrombin potential following hemostatic therapy with 4-factor prothrombin complex concentrate: A 7-day observational study of trauma patients. *Crit Care*, 2014. 18(4): p. R147.
58. Blackburn LH, Baer DG, Eastridge BJ, et al. Military medical revolution: prehospital combat casualty care. *J Trauma Acute Care Surg*, 2012. 73(6 Suppl 5): p. S372-7.
59. Kragh JF, Jr., Aden JK, Steinbaugh J, et al. Gauze vs XSTAT in wound packing for hemorrhage control. *Am J Emerg Med*, 2015. 33(7): p. 974-6.
60. Sims K, Montgomery HR, Dituro P, et al. Management of External Hemorrhage in Tactical Combat Casualty Care: The Adjunctive Use of XStat Compressed Hemostatic Sponges: TCCC Guidelines Change 15-03. *J Spec Oper Med*, 2016. 16(1): p. 19-28.
61. Pezy P, Flaris AN, Prat NJ, et al. Fixed-distance model for balloon placement during fluoroscopy-free resuscitative endovascular balloon occlusion of the aorta in a civilian population. *JAMA Surg*, 2016.
62. Napolitano LM. Resuscitative endovascular balloon occlusion of the aorta: indications, outcomes, and training. *Crit Care Clin*, 2017. 33(1): p. 55-70.
63. Sokol KK, Black GE, Shawhan R, et al. Efficacy of a novel fluoroscopy-free endovascular balloon device with pressure release capabilities in the setting of uncontrolled junctional hemorrhage. *J Trauma Acute Care Surg*, 2016. 80(6): p. 907-14.
64. Brenner M, Inaba K, Aiolfi A, et al. Resuscitative endovascular balloon occlusion of the aorta and resuscitative thoracotomy in select patients with hemorrhagic shock: Early results from the American Association for the Surgery of Trauma's Aortic Occlusion in Resuscitation for Trauma and Acute Care

- Surgery Registry. Presented at the American Association for the Surgery of Trauma 76th Annual Meeting, Baltimore, MD, Sep 2017.
65. Manley JD, Mitchell BJ, DuBose JJ, Rasmussen TE. A modern case series of Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) in an out-of-hospital, combat casualty care setting. *J Spec Oper Med*, Spring 2017;17(1):1-8.
 66. Smith SA, Hilsden R, Beckett A, McAlister VC. The future of resuscitative endovascular balloon occlusion in combat operations. *J R Army Med Corps*, Aug 9, 2017.
 67. Joint Trauma System, Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) for Hemorrhagic Shock CPG, 06 Jul 2017, https://jts.health.mil/index.cfm/PI_CPGs/cpgs
 68. Shakur, H., Roberts, I., Bautista, R., et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo- controlled trial. *Lancet*, 2010. 376(9734): p. 23-32.
 69. Roberts I, Prieto-Merino D, Manno D. Mechanism of action of tranexamic acid in bleeding trauma patients: an exploratory analysis of data from the CRASH-2 trial. *Crit Care*, 2014. 18(6): p. 685.
 70. Brohi K, Cohen MJ, Ganter MT, Schultz MJ, Levi M, Mackersie RC, Pittet JF. Acute coagulopathy of trauma: hypoperfusion induces systemic anticoagulation and hyperfibrinolysis. *J Trauma*, 2008;64(5):1211-7.
 71. Hess JR, Brohi K, Dutton RP, et al. The coagulopathy of trauma: a review of mechanisms. *J Trauma*, 2008;65(4):748-54.
 72. CRASH-2 collaborators, Roberts I, Shakur H, et al., The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet*, 2011. 377(9771): p. 1096-101, 1101 e1-2.
 73. Howard JT, Stockinger ZT, Cap AP, Bailey JA, Gross KR. Military use of tranexamic acid in combat trauma: Does it matter? *J Trauma Acute Care Surg*, 2017 Oct;83(4):579-588.
 74. Morrison JJ, Dubose JJ, Rasmussen TE. Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study. *Arch Surg*, 2012. 147(2): p. 113-9.
 75. Gayet-Ageron A, Prieto-Merino D, Ker K, et al. Effect of treatment delay on the effectiveness and safety of antifibrinolytics in acute severe haemorrhage: A meta-analysis of individual patient-level data from 40138 bleeding patients. *Lancet*, 2018;391:125–132.
 76. Ramirez R, Spinella P, Bochichio G. Tranexamic acid update in trauma. *Crit Care Clin*, 2017;33:85–99.
 77. Joint Trauma System, Damage Control Resuscitation for Prolonged Field Care Clinical Practice Guideline, 01 Oct 2018. https://jts.health.mil/index.cfm/PI_CPGs/cpgs
 78. Giancarelli A, Birrer KL, Alban RF, et al. Hypocalcemia in trauma patients receiving massive transfusion. *J Surg Res*, 2016 May 1;202(1):182-7.
 79. 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 Sep;125(3):895-901.
 80. 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):569-72.
 81. Boffard KD, Riou B, Warren B, et al. Recombinant factor VIIa as adjunctive therapy for bleeding

- control in severely injured trauma patients: two parallel randomized, placebo-controlled, double-blind clinical trials. *J Trauma*, 2005. 59(1): p. 8-15; discussion 15-8.
82. Dutton RP, McCunn M, Hyder M, et al. Factor VIIa for correction of traumatic coagulopathy. *J Trauma*, 2004. 57(4): p. 709-18; discussion 718-9.
83. Holcomb JB. Use of recombinant activated factor VII to treat the acquired coagulopathy of trauma. *J Trauma*, 2005. 58(6): p. 1298-303.
84. Holcomb JB, Hoots K, Moore FA. Treatment of an acquired coagulopathy with recombinant activated factor VII in a damage-control patient. *Mil Med*, 2005. 170(4): p. 287-90.
85. Hauser CJ, Boffard K, Dutton R, et al. Results of the CONTROL trial: efficacy and safety of recombinant activated Factor VII in the management of refractory traumatic hemorrhage. *J Trauma*, 2010. 69(3): p. 489- 500.
86. Schreiber MA, Perkins JG, Kiraly L, et al. Early predictors of massive transfusion in combat casualties. *J Am Coll Surg*, 2007. 205(4): p. 541-5.
87. Ogura T, Nakamura Y, Nakano M, et al. Predicting the need for massive transfusion in trauma patients: the Traumatic Bleeding Severity Score. *J Trauma Acute Care Surg*, 2014. 76(5): p. 1243-50.
88. Moore FA, Nelson T, McKinley Ba, et al. Massive transfusion in trauma patients: tissue hemoglobin oxygen saturation predicts poor outcome. *J Trauma*, 2008. 64(4): p. 1010-23.
89. Brown JB, Lerner BE, Sperry JL, et al. Prehospital lactate improves accuracy of prehospital criteria for designating trauma activation level. *J Trauma Acute Care Surg*, 2016. 81(3): p. 445-52.
90. Brohi K, Cohen MJ, Ganter Mt, et al. Acute coagulopathy of trauma: hypoperfusion induces systemic anticoagulation and hyperfibrinolysis. *J Trauma*, 2008. 64(5): p. 1211-7; discussion 1217.
91. Leemann H, Lustenberger T, Talving P, et al. The role of rotation thromboelastometry in early prediction of massive transfusion. *J Trauma*, 2010. 69(6): p. 1403-8; discussion 1408-9.
92. Doran CM, Woolley T, Midwinter MJ. Feasibility of using rotational thromboelastometry to assess coagulation status of combat casualties in a deployed setting. *J Trauma*, 2010. 69 Suppl 1: p.S40-8.
93. Solvik UO, Roraas TH, Petersen PH, et al. Effect of coagulation factors on discrepancies in international normalized ratio results between instruments. *Clin Chem Lab Med*, 2012. 50(9): p. 1611-20.
94. Kim SJ, Lee EY, Park R, et al. Comparison of prothrombin time derived from CoaguChek XS and laboratory test according to fibrinogen level. *J Clin Lab Anal*, 2015. 29(1): p. 28-31.
95. Duchesne JC, Barbeau JM, Islam TM, et al. Damage control resuscitation: from emergency department to the operating room. *Am Surg*, 2011. 77(2): p. 201-6.
96. Strandvik GF. Hypertonic saline in critical care: A review of the literature and guidelines for use in hypotensive states and raised intracranial pressure. *Anaesthesia*, 2009. 64(9): p. 990-1003.
97. Joint Trauma System, Neurosurgery and Severe Head Injury CPG, 02 Mar 2017. https://jts.health.mil/index.cfm/PI_CPGs/cpgs
98. Joint Trauma System, Hypothermia prevention, monitoring and management CPG, 20 Sep 2012. https://jts.health.mil/index.cfm/PI_CPGs/cpgs
99. Percival TJ, Rasmussen TE. Reperfusion strategies in the management of extremity vascular injury with ischaemia. *Br J Surg*, 2012. 99 Suppl 1: p. 66-74.

APPENDIX A: EXAMPLE OF A MASSIVE TRANSFUSION PROCEDURE AT USCENTCOM LEVEL III FACILITY

CONSIDERATIONS FOR USE WITH MASSIVE TRANSFUSION (MT)

- A flexible procedure for use in the Emergency Department (ED), Operating Room (OR) and Intensive Care Unit (ICU) which can be initiated or ceased by the site-specific provider as dictated by the patient's needs when in that specific venue. It consists of batches as defined below, which vary in composition, but are directed toward approximating a 1:1:1:1 ratio of FFP, platelets, RBC, and cryoprecipitate (CRYO). Note: one unit of apheresis platelets is approximately the equivalent of 6 units random donor platelets, therefore 1u apheresis platelets should be given for every 6 units of RBC to approximate 1:1:1 resuscitation. Crystalloid infusion should be minimized and limited to use as carrier fluid. Hextend® should not be used.
- Note that the MT protocol described below is designed for use with blood components and is designed to provide the functionality of WB. If using WB for MT, the considerations that can be applied from the protocol below include early use of TXA and calcium. Also, if using primarily CWB that has been stored for more than 2 weeks, consider supplementing with additional platelets, either from FWB (consider a ratio of 3:1 of CWB: FWB as available) or from apheresis platelets (consider adding 1 unit of platelets after every 6-10 CWB units if clinically indicated).

Initiate MT procedure if patient has received 4u RBC/4u FFP emergency release blood products.

- Pack One: 6u RBC, 6u FFP, 1u apheresis platelets, 1-2 5-unit bags of cryo. Give TXA empirically if within 3 hours of injury: Infuse 2 grams of TXA in 100 ml of 0.9% NS over 10 minutes intravenously in a separate IV line from any containing blood and blood products. (A more concentrated or rapid injection can be considered but rapid TXA infusion has been infrequently reported to cause transient hypotension.) Give one gram calcium during or immediately after first blood product administered and another gram after every four units of blood product.
- Pack Two: 6u RBC, 6u FFP, 1u apheresis platelets, 1-2 5-unit bags of cryo. Continue to monitor ionized calcium or give 1gm calcium after every 4 blood products.
- Pack Three and beyond: identical to Pack Two

Definitions

Emergency Release: Uncross matched 4u RBC (generally O+ but may be O- for females under the age of 50 if available) and 4u AB or A plasma (NOTE: A plasma is not "universal" but risk of hemolysis in B or AB patients is very low and its use in massive transfusion patients when supplies of AB FFP are limited or absent may improve survival and help preserve resources. A plasma is commonly used as emergency release plasma throughout the United States.)

APPENDIX B: PEDIATRIC CONSIDERATIONS

There are no prospective studies of transfusion resuscitation in pediatric trauma. Most major children's centers extrapolate from adult literature and are using similar damage control resuscitation strategies in major hemorrhage. There are currently no data determining which patients may benefit from these strategies. See [Appendix A](#) for a suggested MT Protocol.

For children under a weight of 30 Kilograms (KG), transfusions of RBC units, FFP, or apheresis platelets should be given in "units" of 10-15 ml/kg. One unit of cryoprecipitate is typically administered for every 10 kg of body weight. Blood volume in children can be estimated at between 60-80ml/kg. Bear in mind that a "trauma pack" containing 6 U RBCs + 6 U FFP + 1 U apheresis platelets will deliver between 3000- 4000ml of intravascular volume. A child of 30kg may have a TOTAL blood volume of 1800-2400ml. Over- resuscitation contributes to morbidity and mortality. It may be more convenient and safer to resuscitate children with WB since this product delivers full oxygen delivery and hemostatic functionality and may support more accurate volume dosing. For example, a typical unit of whole blood contains about 500- 600ml (depending on bag type and volume: 450 or 500ml blood volume plus anticoagulant). For a severely injured, shocked child, a quarter to a half of a WB unit may provide adequate initial resuscitation, which can then be further titrated.

Pediatric approved Intraosseous (IO) devices can be used for transfusion if required. Note that sternal IOs designed for adults may pierce a child's sternum and deliver fluids or blood products into the mediastinum.

A MT in pediatrics has been defined as $\geq 40\text{ml/kg}$ of blood products in 24 hours.¹ The circulating blood volume in children is approximately 60-80 ml/kg. Children are at high risk of developing hypocalcemia, hypomagnesemia, metabolic acidosis, hypoglycemia, hypothermia, and hyperkalemia during MTs.

Therefore, frequent monitoring and correction of acid/base status, electrolytes, and core temperature is essential during the resuscitation of pediatric casualties. An approved blood warmer and other transdermal temperature management system devices are recommended for the prevention and treatment of hypothermia.

Although there are limited retrospective data demonstrating the benefit of TXA in pediatric trauma,² there are studies of TXA use in pediatric cardiac, orthopedic, and cranial surgeries showing overall safety and decreased transfusion requirements.³⁻⁶ There is no prospectively validated dosing available for pediatric trauma but loading doses of 10-100 mg/kg IV followed by 5-10 mg/kg/hour infusion doses are commonly used in elective surgery. The UK Royal College of Pediatrics and Child Health has recommended a loading dose of 15mg/kg (up to 1 gm) followed by 2mg/kg/hr over 8 hours (or up to 1gm over 8 hours). This regimen reflects standard adult dosing in trauma.⁷

Viscoelastic clot testing (e.g., TEG or ROTEM®) can be utilized to direct transfusion requirements as in adults utilizing the same thresholds discussed in this CPG.⁸ Viscoelastic testing should not be used to withhold TXA during initial resuscitation of bleeding trauma patients.⁹

Prolonged CPR > 20-30 min is generally futile in children who have cardiac arrest with trauma related injuries. Children with traumatic injuries with in-hospital cardiac arrest have a very high mortality after 20-30 min of cardiac arrest.¹⁰

References for Pediatric Considerations:

1. Neff LP, Cannon JW, Morrison JJ, et al. Clearly defining pediatric massive transfusion: cutting through the fog and friction with combat data. *J Trauma Acute Care Surg*, 2015. 78(1): p. 22-8; discussion 28-9.
2. Eckert MJ, Wertin TM, Tyner SD, et al. Tranexamic acid administration to pediatric trauma patients in a combat setting: the pediatric trauma and tranexamic acid study (PED-TRAX). *J Trauma Acute Care Surg*, 2014. 77(6): p. 852-8; discussion 858.
3. Tzortzopoulou A, Cepeda MS, Shchumann R, et al. Antifibrinolytic agents for reducing blood loss in scoliosis surgery in children. *Cochrane Database Syst Rev*, 2008(3): p. CD006883.
4. Schouten ES, van de Pol AC, Schouten AN, et al. The effect of aprotinin, tranexamic acid, and aminocaproic acid on blood loss and use of blood products in major pediatric surgery: a meta-analysis. *Pediatr Crit Care Med*, 2009. 10(2): p. 182-90.
5. Basta MN, Stricker PA, Taylor JA. A systematic review of the use of antifibrinolytic agents in pediatric surgery and implications for craniofacial use. *Pediatr Surg Int*, 2012. 28(11): p. 1059-69.
6. Grassin-Delyle S, Couturier R, Abe E, et al. A practical tranexamic acid dosing scheme based on population pharmacokinetics in children undergoing cardiac surgery. *Anesthesiology*, 2013. 118(4): p. 853-62.
7. Health, R.C.o.P.a.C. Major trauma and the use of tranexamic acid in children: Evidence statement. 2012 [cited 2016 July 14].
8. Nylund CM, Borgman MA, Holcom JB, et al. Thromboelastography to direct the administration of recombinant activated factor VII in a child with traumatic injury requiring massive transfusion. *Pediatr Crit Care Med*, 2009. 10(2): p. e22-6.
9. Inaba K, Rizoli S, Veigas PV, et al. 2014 Consensus conference on viscoelastic test-based transfusion guidelines for early trauma resuscitation: Report of the panel. *J Trauma Acute Care Surg*, 2015. 78(6): p. 1220-9.
10. Matos RI, Watson RS, Nadkarni VM, et al. Duration of cardiopulmonary resuscitation and illness category impact survival and neurologic outcomes for in-hospital pediatric cardiac arrests. *Circulation*, 2013. 127(4): p. 442-51.

APPENDIX C: INFORMATION REGARDING OFF-LABEL USES IN CPGS

PURPOSE

The purpose of this Appendix is to ensure an understanding of DoD policy and practice regarding inclusion in CPGs of “off-label” uses of U.S. Food and Drug Administration (FDA)–approved products. This applies to off-label uses with patients who are armed forces members.

BACKGROUND

Unapproved (i.e. “off-label”) uses of FDA-approved products are extremely common in American medicine and are usually not subject to any special regulations. However, under Federal law, in some circumstances, unapproved uses of approved drugs are subject to FDA regulations governing “investigational new drugs.” These circumstances include such uses as part of clinical trials, and in the military context, command-required, unapproved uses. Some command-requested, unapproved uses may also be subject to special regulations.

ADDITIONAL INFORMATION REGARDING OFF-LABEL USES IN CPGS

The inclusion in CPGs of off-label uses is not a clinical trial, nor is it a command request or requirement. Further, it does not imply that the Military Health System requires that use by DoD health care practitioners or considers it to be the “standard practice.” Rather, the inclusion in CPGs of off-label uses is to inform the clinical judgment of the responsible health care practitioner by providing information regarding potential risks and benefits of treatment alternatives. The decision is for the clinical judgment of the responsible health care practitioner within the practitioner-patient relationship.

ADDITIONAL PROCEDURES**Balanced Discussion**

Consistent with this purpose, CPG discussions of off-label uses specifically state that they are uses not approved by the FDA. Further, such discussions are balanced in the presentation of appropriate clinical study data, including any such data that suggest caution in the use of the product and specifically including any FDA-issued warnings.

Quality Assurance Monitoring

With respect to such off-label uses, DoD procedure is to maintain a regular system of quality assurance monitoring of outcomes and known potential adverse events. For this reason, the importance of accurate clinical records is underscored.

Information to Patients

Good clinical practice includes the provision of appropriate information to patients. Each CPG discussing an unusual off-label use will address the issue of information to patients. When practicable, consideration will be given to including in an appendix an appropriate information sheet for distribution to patients, whether before or after use of the product. Information to patients should address in plain language: a) that the use is not approved by the FDA; b) the reasons why a DoD health care practitioner would decide to use the product for this purpose; and c) the potential risks associated with such use.