

JOINT TRAUMA SYSTEM CLINICAL PRACTICE GUIDELINE (JTS CPG)



Damage Control Resuscitation (CPG ID: 18)

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

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BACKGROUND

Hemorrhage is the leading cause of preventable death on the battlefield.¹ Damage Control Resuscitation (DCR) emerged as an extension of a principle used by trauma surgeons called Damage Control Surgery (DCS), which limits surgical interventions to those which address life-threatening injuries and delays all other surgical care until metabolic and physiologic derangements have been treated.² Recognizing that this approach saved lives, DCR was developed to work synergistically with DCS and prioritize non-surgical interventions that may reduce morbidity and mortality from trauma and hemorrhage.³ The major principle of DCR is to restore homeostasis and prevent or mitigate the development of tissue hypoxia and oxygen debt as well as coagulopathy.⁴ This is accomplished through aggressive hemorrhage control and blood transfusion, which restores tissue oxygenation and not only avoids platelet and coagulation factor dilution, but also replaces lost hemostatic potential.

Efforts are focused on blood product transfusion with products that provide the functionality of Whole Blood (WB, either WB or a mixture of components that includes Red Blood Cells [RBCs], plasma, and platelets), limited use of crystalloids to avoid dilutional coagulopathy and other adjunctive measures used to mitigate hemorrhagic shock and acute traumatic coagulopathy, including:

- Relatively hypotensive resuscitation to avoid re-bleeding (target Systolic Blood Pressure [SBP] 80-90mmHg in adults);
- Compressive/hemostatic dressings and devices;
- Empiric use of Tranexamic Acid (TXA) which has been shown to reduce mortality in trauma, likely due to reduction in fibrinolysis;⁵
- Prevention of acidosis and hypothermia; and
- Expeditious delivery to definitive surgical control

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 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 was associated with a higher risk of dilutional coagulopathy, abdominal compartment syndrome, multiple organ failure, and death⁶; however, selection bias may have contributed to these findings. It should be noted that in recognition of these problems, the latest edition of the Advanced Trauma Life Support (ATLS) manual (9th ed.) suggests limiting the use of crystalloids to one liter during initial resuscitation and incorporating early use of blood products including plasma and platelets in patients at risk of Massive Transfusion (MT).⁷

During the conflicts in Iraq and Afghanistan, between 2003 and 2012, 14% of patients admitted to Role 3 Military Treatment Facilities (e.g., MTFs, combat support hospitals) received a transfusion of at least one blood product. Of these, 35% received a MT (MT; ≥ 10 units of RBCs and/or WB in 24 hours). The proportion of transfused patients receiving a MT reached approximately 50% by 2011 in parallel with increasing injury severity scores, decreased crystalloid and colloid use, and increasing use of blood for resuscitation.⁸ 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 of Packed RBCs [PRBCs]). MT at a 1:1:1 ratio is associated with improved survival.^{3, 9-12} 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.^{13,14} 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 in the initial resuscitation period is no longer the standard of care for major trauma.

BLOOD PRODUCTS FOR DCR

RED BLOOD CELLS

RBC units may be stored for up to 42 days under refrigeration when stored in additive solution (e.g., AS-5). In addition, “frozen” RBCs (fRBCs, stored frozen with glycerol cryoprotectant for up to 10 years at <-65°C, then thawed and rinsed in an automated process) 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.

PLASMA

Plasma can be stored frozen and 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 Citrate Phosphate Dextrose (CPD) anticoagulant solution, or 40 days in Citrate Phosphate Dextrose Adenine (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 that data regarding the hemostatic capacity of liquid plasma stored beyond 28 days are very limited.^{15,16} 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 Investigational New Drug (IND) protocol.¹⁷ 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.¹⁸ Although group AB plasma is classically considered to be the only universally compatible plasma, 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. The US military, as well as many civilian trauma centers, routinely uses A plasma as universal emergency release plasma.¹⁹⁻²²

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.²³ Platelets are vital for hemostasis and their early use in a balanced transfusion strategy is associated with increased survival in trauma.^{10,13,24,25} Platelets stored under refrigeration (1-6°C), or “Cold-Stored Platelets” (CSP), maintained without agitation for up to 3 days in plasma, are approved by the Food and Drug Administration (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.^{26,27} CSP have been proven effective in clinical trials and used successfully in combat trauma patients in the U.S. Central Command (CENTCOM) area of operations.^{23,28} Cold-stored platelets in platelet additive solution (CSP-PAS) or plasma retain function for at least 15 days.²⁹ CSP-PAS can be collected in theater and used interchangeably with other platelet products.³⁰

WHOLE BLOOD

In deployed environments, the inability to supply blood components due to logistical constraints led to the use of WB collected onsite from “walking blood banks,” especially to provide platelets for hemostatic resuscitation. It should be noted that blood products collected in the deployed setting (platelets or WB) are not prospectively tested for Transfusion-Transmitted Diseases (TTDs). Recipients of these products must be tested at 3, 6 and 12 months post-transfusion to monitor for disease transmission. WB delivers all the components of blood in the correct ratio and is independently associated with improved survival.³¹⁻³³ 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 to 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 (<1:256 by tube method) group O blood has been identified as a practical, effective universal blood product for resuscitation of exsanguinating hemorrhage.^{17,34} 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. Low Titer Group O Whole Blood (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-1.³⁵ Available data suggest that Cold-Stored WB (CWB) will provide platelet hemostatic function during the first 2 weeks of storage. Function is moderately reduced during the remaining shelf life (21 days for CPD WB and 35 days for CPDA WB), but it should be noted that WB plasma hemostatic function is comparable to that of liquid plasma and that CWB remains a relatively hemostatic product (compared to RBCs alone) throughout its shelf life.³⁶⁻³⁸ 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 and that contains fewer or effectively no platelets requires supplementation with platelet or FWB transfusion.³⁹ 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 US civilian hospitals.^{38, 40-}
⁴⁷ For guidance regarding use of fRBCs and FWB, see the Joint Trauma System (JTS) CPGs entitled Frozen and Deglycerolized Red Blood Cells, and Fresh Whole Blood Transfusion, respectively.^{48,49}

HEMOSTATIC PRODUCTS 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. Superficial wounds are amenable to novel and effective hemostatic dressings (e.g., Combat Gauze or Celox gauze). Junctional (axillary, neck, and groin) hemorrhage, previously a nearly intractable problem, can now be treated with newly-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.⁵⁰⁻⁵² Conversely, truncal internal hemorrhage is non-compressible and is the subject of intensive research. Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) may be an effective technique for truncal hemorrhage control in expert hands, but has limited literature and is not yet widely available. The development of catheters that do not require fluoroscopic guidance for placement and facilitate both resuscitation and monitoring may represent an important advance that together with appropriate transfusion may benefit certain critically injured, exsanguinating patients.⁵³⁻⁵⁵

PHARMACOLOGIC ADJUNCTS

Hemostatic pharmaceutical adjuncts to limit blood loss are another subject of considerable investigation. 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 with 3 hours of injury, after which mortality is higher.^{5,56-58} Prospective and retrospective evidence from a decade ago suggested that rFVIIa used early in the resuscitation of patients with MT results in decreased blood transfusion, but not higher survival. 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.⁵⁹⁻⁶³ 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 should not be used in trauma outside the context of a clinical trial as they may cause harm due to excessive thrombogenicity.⁶⁴ 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.^{11,65-67}

MANAGEMENT PRINCIPLES FOR DCR

RECOGNITION OF PATIENTS REQUIRING DCR

Patients receiving uncrossmatched 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 transfusional 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.⁶⁸ 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 < 110 mm Hg
- Heart rate > 105 bpm
- Hematocrit < 32%
- pH < 7.25

Other risk factors associated with MT or at least need for aggressive resuscitation:⁶⁹⁻⁷²

- 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 ≥ 1.2 -1.4
- Near Infrared Spectroscopy (NIR)-derived StO₂ < 75% (in practice, rarely available)
- 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 MTF 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 (Thromboelastography [TEG] or Rotational Thromboelastometry [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.^{73,74} 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.^{75,76}

POINT OF INJURY, EN-ROUTE, AND REMOTE DCR

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.^{3,77}

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

The order of priority for fluid administration should be:

- whole blood (Group O low titer preferred);
- blood components at a 1:1:1 ratio;
- RBCs plus plasma = 1:1 ratio;
- plasma with or without RBCs; and
- RBCs alone.⁷⁸

During prolonged evacuations and in the absence of available blood products, crystalloid and non-blood colloid fluids may be needed for casualties at risk of imminent death, but administration should be balanced against the risk of worsening coagulopathy contributing to further blood loss. If only plasma or RBCs are available, either of these is preferable to crystalloid infusion, which should be the therapy of last resort in severely bleeding patients. Albumin (5% or 25%) provides effective and more physiologic volume expansion than other colloids, but given alone contributes to hemodilution. Consideration should be given to supplementing albumin with fibrinogen concentrate and TXA, if available.

Hextend or Hespan use should be avoided as these products worsen coagulopathy.^{79,80}

Hypertonic Saline does not improve mortality in hemorrhagic shock and should only be used for patients with Traumatic Brain Injury (TBI) and evidence of raised Intracranial Pressure (ICP).^{81,84}

A key element of fluid optimization is careful documentation of all fluids, interventions, and medications given in the pre-hospital phase – for more information, see the JTS CPG titled [Battle and Non-Battle Injury Documentation: The Resuscitation Record](#).⁸²

BLOOD PRODUCT TRANSFUSION

The availability of blood products is limited in the pre-hospital setting. When operationally possible and trained personnel are available to donate and collect, FWB is life-saving during prolonged evacuations of casualties in hemorrhagic shock.

“Golden hour boxes” or similar isothermal transport devices containing blood components should be available on patient transport vehicles (Casualty Evacuation [CASEVAC], Medical Evacuation [MEDEVAC]).

WB (Group O low titer preferred) or blood components given at a 1:1:1 ratio should be transfused when shock is present or expected.

Frequent reassessment of casualty status is imperative during transfusion, both to gauge adequacy of the intervention and to diagnose adverse reactions.

Blood products that are fully tested in FDA-registered testing facilities for TTDs should be used whenever possible. Whole blood from donors recently tested for TTDs with known blood type represents the next best available option, particularly if rapid, point-of-care TTD testing is also available.

Blood from untested donors should be limited to emergency use and should be stratified by risk determined from the donor history and blood compatibility.⁸³

U.S. personnel transfused with blood products collected in the deployed setting must be followed up with infectious disease testing at 3, 6, and 12 months following re-deployment to the U.S. according to policy set forth by the U.S. Assistant Secretary of Defense for Health Affairs.

Calcium (consider one 10 ml ampule of 10% calcium chloride, or 30 ml of 10% calcium gluconate) should be given to patients in shock after approximately 4 units of citrated blood products transfused. Ideally, ionized calcium should be monitored.

Blood products should ideally be warmed with approved in-line blood heaters with the goal of transfusing products warmed to 37°C.

ADJUNCTIVE THERAPIES

Hypotensive Resuscitation

In casualties without Central Nervous System (CNS) injury, resuscitation prior to surgical control of bleeding focuses on maintaining a relatively lower target SBP (< 90 mm Hg) to reduce re-bleeding by minimizing intravascular hydrostatic pressure. While empirically attractive, this approach represents a significant logistical challenge due to the difficulties in obtaining frequent and high fidelity SBP monitoring between the time of injury and definitive care, and due to the limited interventions possible in challenging environments. Acute changes in mental status or pulse quality have been used to detect impending hypotensive shock, but have not been adequately tested and can be misleading in the acute setting by the concomitant use of analgesics and

sedatives such as ketamine. Hypotensive resuscitation should not be utilized for patients with CNS injury because of associated adverse outcomes in this population. In general, patients with CNS injury benefit from avoidance of even transient hypotension and hypoxia. For additional information, see the CPG entitled *Neurosurgery and Severe Head Injury*.⁸⁴

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 providers.

Empiric use of TXA

In casualties at high risk of hemorrhagic shock, TXA reduces mortality IF GIVEN WITHIN THREE (3) HOURS of injury. TXA given > 3 hours post-injury increases the risk of mortality. For eligible casualties (see section above titled [Recognition of Patients Requiring DCR](#)), one (1) gram of I.V. TXA should be administered in 100 ml of normal saline over 10 minutes, followed by another 1 gram dose delivered over 8 hours; the first dose must be given within three (3) hours of injury. 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.

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 MTF, 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 CPG *Hypothermia Prevention* for additional information.⁸⁵ 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.⁸⁶

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 only focus on control of hemorrhage and 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 StO₂ 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) WB or blood components at a 1:1:1:1 ratio (RBCs:plasma:platelets:CRYO);
- WB or blood components at a 1:1:1:1 ratio from a recently tested donor (NOTE: this option is only acceptable in the hospital for emergency indications when fully FDA TTD tested products are not available);
- RBCs plus plasma=1:1 ratio;
- plasma with or without RBCs; and
- 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 CPG titled Whole Blood Transfusion.⁴⁹

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 PT/INR, Activated Partial Thromboplastin Time (aPTT), and viscoelastic testing (ROTEM® or TEG if available).

ADJUNCTIVE THERAPIES

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 (90 mm Hg) 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. For additional information, see the JTS CPG titled *Neurosurgery and Severe Head Injury*.⁸⁴

Compressive/hemostatic dressings and devices

Until definitive surgical control is established, prevent further hemorrhage with direct pressure, topical or intratruncal hemostatic dressings, and/or tourniquets to avoid the development of shock. In extremis, procedures such as resuscitative thoracotomy or REBOA 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 hyper fibrinolysis

TXA should be given to casualties at risk of hemorrhagic shock who have not already received a dose during the pre-hospital phase. **IF GIVEN UPON ARRIVAL TO THE MTF, THE CASUALTY SHOULD STILL BE 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](#)), one (1) gram of I.V. TXA should be administered in 100 ml of normal saline solution over 10 minutes, followed by another 1 gram dose delivered over 8 hours.

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 (1:1:1) in combination with early hemorrhage control. Crystalloid or colloid resuscitation will contribute to the acidosis (as well as dilutional coagulopathy) 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. 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, fluid blankets, ventilators, warm environments, and rapid surgical care to minimize blood and heat loss.

Expedient 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.

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 safe 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 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.⁸⁷ 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,⁸⁸ there are studies of TXA use in pediatric cardiac, orthopedic and cranial surgeries showing overall safety and decreased

transfusion requirements.⁸⁹⁻⁹² 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.⁹³

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.⁹⁴ Viscoelastic testing should not be used to withhold TXA during initial resuscitation of bleeding trauma patients.⁹⁵

As noted above, use of rFVIIa is associated with risks and its utility in DCR has not been established.

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.⁹⁶

CONCLUSION

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.

PERFORMANCE IMPROVEMENT (PI) MONITORING

INTENT (EXPECTED OUTCOMES)

- All MT patients who receive TXA will have initial dose administered < 3 hours from time of injury.
- All patients receiving > 4 units of blood product also receive calcium.
- All MT patients receive transfusion of PRBC and FFP in a ratio between 1:1 and 1:2.
- All MT patients receive platelet or WB transfusion.
- All MT patients receive cryoprecipitate or WB.

PERFORMANCE/ADHERENCE MEASURES

- All MT patients who receive TXA will have initial dose administered < 3 hours from time of injury.
- All MT patients will receive TXA, unless ROTEM® data indicates no TXA indicated
- All patients receiving > 4 units of blood product also receive calcium.
- All MT patients receive transfusion of PRBC and FFP in a ratio between 1:1 and 1:2.
- All MT patients receive platelet or WB transfusion.
- All MT patients receive cryoprecipitate or WB.

DATA SOURCE

- Patient Record
- Out of Hospital Documentation: DD Form 1380, DA Form 4700
- Medication Administration Record (MARS) and/or Anesthesia Record
- Department of Defense Trauma Registry (DoDTR)

SYSTEM REPORTING AND 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 Joint Trauma System (JTS) Director and the JTS Performance Improvement 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.

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APPENDIX A: EXAMPLE OF A MASSIVE TRANSFUSION PROCEDURE AT AN 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 PRBC, FFP, platelets 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 PRBC to approximate 1:1:1 resuscitation.

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

- Pack One: 4u PRBC, 4u FFP, 1u apheresis platelets, 1 10-unit bag cryo . Strongly consider the early use of TXA: Infuse 1 gram of tranexamic acid in 100 ml of 0.9% NS over 10 minutes intravenously in a separate IV line from any containing blood and blood products. (More rapid injection has been reported to cause hypotension.). Hextend® should be avoided as a carrier fluid. Infuse a second 1-gram dose intravenously over 8 hours infused with 0.9% NS carrier.
- Pack Two: 4u PRBC and 4u FFP
- Pack Three: 4u PRBC, 4u FFP, 1u apheresis platelets, 1 10-unit bag of cryo and +/- rFVIIa (obtained from Pharmacy)
- Pack Four: 4u PRBC and 4u FFP
- Pack Five: 4u PRBC, 4u FFP, 1u apheresis platelets, and 1 10-unit bag of cryo

A reassessment of the progress of the resuscitation, hemostasis and the need to continue the MT Procedure should be conducted between the providers taking care of the patient at that time.

- Packs Six and Seven are identical to packs Four and Five
- Packs Eight and Nine are identical to packs Four and Five

Definitions

Emergency Release: Uncrossmatched 4u PRBC (O+ or O- for males, O- for females) and 4u AB or A FFP (NOTE: A FFP is not a universal donor but its use in massive transfusion patients when supplies of AB FFP are limited or absent may improve survival and help preserve resources with a low risk to the patient. The decision to use A FFP or to switch from AB FFP to A FFP in the same patient should be a decision based on the interaction of the medical/surgical staff in concert with laboratory staff. Once the patient's type has been identified, type-specific plasma should be given as soon as possible).

APPENDIX B: LAST IN, FIRST OUT (LIFO) POLICY

Goal. In patients requiring massive transfusion (MT), a concerted effort is made to transfuse fresh units of PRBCs (i.e., preferably less than 14 days old, but the freshest available nonetheless).

The rationale for this policy is as follows:

1. Multiple retrospective analyses of various patient groups have suggested increased complications of transfusion with "older" units of PRBCs, presumably due to the development of a "storage lesion": which includes increased pro-inflammatory factors, acidosis, increased free hemoglobin, and decreased RBC deformability, 2,3 DPG and ATP.
2. The people most likely to suffer the consequences of complications of "older" units of blood are those requiring a higher dose (e.g., multiple transfusions).
3. Therefore an effort is being made in theater to utilize the freshest blood available for MT patients and those suspected of needing MT upon presentation to the MTF.

APPENDIX C: TRANEXAMIC ACID (TXA)

BACKGROUND**Hemorrhage**

Hemorrhage is the leading cause of preventable death among combat casualties. Patients at the greatest risk of exsanguination often present with a clinically significant coagulopathy that has recently been linked to systemic anticoagulation through a Protein C-dependent pathway, and activation of fibrinolysis.¹ The activation of fibrinolysis accompanying the massive generation of thrombin in the period immediately following trauma has been well described by several groups and is readily observed in the elevated levels of D-dimer, fibrin split products (FSP) and plasmin-antiplasmin complexes found in blood samples drawn from trauma patients on presentation.² Fibrinolysis can occasionally overwhelm the ability to clot following trauma, a phenomenon that can be directly observed in real time by thromboelastography (TEG) or rotational thromboelastometry (ROTEM). Such hyperfibrinolysis occurs in the most severely injured patients (approximately 4% of trauma patients in major civilian US trauma centers) and portends poor outcomes.³

Coagulation

Coagulation system responses to trauma and surgery are broadly similar and activation of fibrinolysis has been observed in surgical patients. Anti-fibrinolytic agents, including TXA, have been used to decrease bleeding and the need for blood transfusions in coronary artery bypass grafting, orthotopic liver transplantation, hip and knee arthroplasty, and other surgical setting. 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)⁵. 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 administered as a loading dose of 1gram over 10 minutes followed by an infusion of 1 gram over 8 hours. The primary outcome was death in hospital within 4 weeks of injury. Secondary outcomes included vascular occlusive events, transfusions, and surgical interventions. Patients were randomized and treated within 8 hours of injury. Patients were excluded from randomization only if the treating physician considered the patient to have either a clear indication for use of TXA or a clear contraindication. 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. 16.0%, RR 0.91, CI 0.85-0.97; p = 0.0035). This 1.5% absolute risk reduction means that one would have to treat 67 trauma patients with TXA to prevent one from dying of any cause (number needed to treat = 1/absolute risk reduction). The authors also reported a reduction in relative risk of death due to bleeding of 15% (4.9% vs. 5.7%, RR 0.85, CI 0.76-0.96; p = 0.0077). Similarly, the authors reported a relative risk reduction in death due to bleeding on the day of randomization of 20% (2.8% vs. 3.5%, RR 0.80, CI 0.68-0.93; p = 0.0036). It was in this group of most severely injured patients that use of TXA was associated with the greatest reduction in risk of death. Further subgroup analysis suggested that the benefit of TXA was greater in patients treated within 3 hours of injury compared to those treated later and in patients with a presenting systolic blood pressure of ≤ 75 mmHg compared to those with normal systolic blood pressures. There was no difference in rate of vascular occlusive events between the two arms of the study (1.7% for TXA vs. 2.0% for placebo, p = 0.084). No unexpected adverse events were reported. A post-hoc analysis⁶ showed that TXA given < 1 hour from injury resulted in the greatest reduction in death from bleeding (5.3% vs. 7.7%, RR 0.68, CI 0.57-0.82, p<0.0001). TXA given 1-3 hours from injury also reduced death from bleeding (4.8% vs. 6.1%, RR 0.79, CI 0.64-0.97, p=0.03). Treatment given after 3 hours seemed to increase the risk of death from bleeding (4.4% vs. 3.1%, RR 1.44, CI 1.12-1.84, p=0.004).

TXA EXPERIENCE IN COMBAT-RELATED HEMORRHAGE

A registry-based study of combat injured troops receiving blood in Afghanistan⁷ (January 2009 - December 2010) at the Bastion Role 3 facility demonstrated a decreased mortality with TXA use in this population. In a review of 896 combat casualties treated at Bastion, 32.7% (N=293) received TXA (mean $\pm$ SD dose: 2.3 ± 1.3 g) while 67.2% (N=603) did not receive TXA. 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; $p < 0.001$), and 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 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). For all patients requiring at least one unit of blood after combat injury, patients receiving TXA had higher rates of DVT (2.4% vs. 0.2%, $p = 0.001$) and PE (2.7% vs. 0.3%, $p = 0.001$), but were also more likely to have injury patterns associated with higher risk of thromboembolic events; including higher mean ISS (25 vs. 23, $p < 0.001$), more severe extremity injuries (extremity AIS ≥ 3 66.6% in TXA group, 47.3% non-TXA, $p < 0.001$), and more commonly GCS ≤ 8 (63.3% vs. 35.6%, $p < 0.001$).

JTS analysis of 849 combat casualties receives TXA, the largest military cohort yet analyzed, was underpowered but showed a trend similar towards xxx mortality benefit to the CRASH-2 study.⁷

The survival benefit associated with TXA supports the use of TXA, in conjunction with damage control resuscitation following combat injury. This association is most prominent in those requiring massive transfusion.⁸

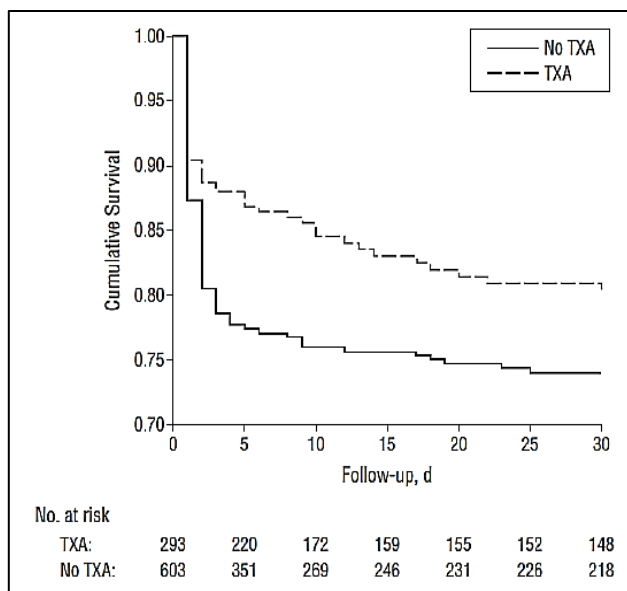


Figure 1. Kaplan-Meier Survival curve of the overall cohort, patients receiving TXA or no TXA, $p = 0.006$ (Wilcoxon Statistic)⁷

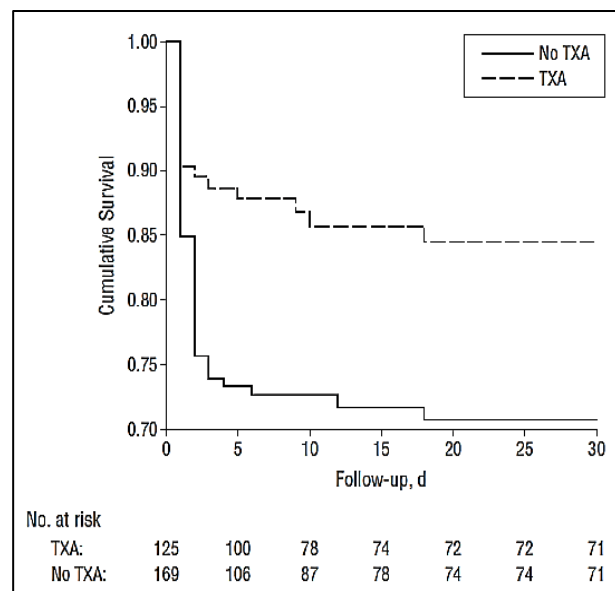


Figure 2. Kaplan-Meier survival curve of the massive transfusion group receiving TXA MT or no TXA MT, $p = 0.004$ (Wilcoxon Statistics)⁷

FDA POSITION

FDA-approved use

Intravenous administration of TXA was approved by the FDA in 1986 for prevention or reduction of bleeding in patients with hemophilia undergoing dental procedures. The FDA approved use of the oral form of TXA to control heavy menstrual cyclic bleeding in 2009.

Unlabeled use

Tranexamic acid is not FDA-approved to stop uncontrolled hemorrhage in severe trauma patients. It has been studied in randomized trials to control bleeding during surgery, and most recently in trauma as discussed above. It may be given at the discretion of individual providers, based on their assessment of the clinical condition of the patient.

Potential adverse events

Adverse events associated with TXA use have been reported. These include acute gastrointestinal disturbances (nausea, vomiting and diarrhea, generally dose-related), visual disturbances (blurry vision and changes in color perception, especially with prolonged use), and occasional thromboembolic events (e.g., deep venous thrombosis, pulmonary embolism, generally observed in the setting of active intravascular clotting such as thrombotic DIC). Its use is thus contraindicated in the settings of acquired defective color vision and active intravascular clotting. TXA should be used with caution in the setting of urinary tract bleeding as ureteral obstruction due to clotting has been reported. TXA should not be given with activated prothrombin complex concentrate or factor IX complex concentrates as this may increase the risk of thrombosis.

MECHANISM

TXA is an anti-fibrinolytic that inhibits both plasminogen activation and plasmin activity, thus preventing clot break-down rather than promoting new clot formation. TXA (trans-4-(aminomethyl) cyclohexanecarboxylic acid) is a small molecule (MW 157.2) inhibitor of plasminogen activation, and inhibitor of plasmin activity. It occupies the lysine-binding sites on plasminogen thus preventing its binding to lysine residues on fibrin. This reduces plasminogen activation to plasmin. Similarly, blockade of lysine-binding sites on circulating plasmin prevents binding to fibrin, and thus prevents clot break-down. TXA is 10 times more potent *in vitro* than an older drug of the same class, aminocaproic acid. At therapeutically relevant concentrations, TXA does not affect platelet count or aggregation or coagulation parameters. It is excreted largely unchanged in urine and has a half-life of about 2 hours in circulation. Dosing should be adjusted for renal impairment, but no adjustment is needed for hepatic impairment. TXA (intravenous trade name: cyklokapron) is supplied in ampoules of 1000 mg in 10 ml water for injection.

CONSIDERATIONS FOR USE

- a. TXA has been studied in patients with subarachnoid hemorrhage (SAH), but no published data are available regarding its use in traumatic brain injury (TBI). TXA was shown to reduce bleeding in SAH, but increase cerebral ischemia, possibly due to vasospasm or increased microvascular thrombosis. Since TXA use had no effect on mortality or quality of life in these studies, its use is not recommended in this population. At this time, there is no role for TXA or other antifibrinolytics in managing SAH.
- b. It should be noted that treatment with TXA in these studies was modeled on the prolonged (3-4 times per day for 2-8 days) dosing used in hemophilia. A dosing regimen shorter in duration might avoid this outcome, and remains a topic for further investigation.

- c. Critics of the CRASH-2 study have noted that it would have been helpful to know outcomes for patients with TBI, since TXA has not proven to be beneficial in subarachnoid hemorrhage (SAH). The CRASH-2 trial did not exclude TBI patients, but separate detailed outcomes for this cohort were not reported. It is worth noting, as discussed above, that the relative contraindication to using antifibrinolytics in SAH was known prior to the initiation of CRASH-2. Thus, it is possible that treating physicians tended to exclude patients with TBI from trial enrollment. Nevertheless, about 18% of patients had a GCS score of 3-8 (17.8% for TXA, 18.2% for placebo), probably indicating severe TBI, and 13.4% had GCS scores of 9-12 ($p>0.05$, NS, for both groups), indicating moderate TBI. Mild or no TBI (GCS 13-15) was present in 68.7% (TXA) and 68.3% (placebo). While GCS scores can be depressed for a variety of reasons such as global hypoperfusion, it would be reasonable to expect that a substantial fraction of trauma patients with depressed GCS had in fact sustained a TBI. The authors did report that death from head injury was the same in both groups (6.0% for TXA and 6.2% for placebo, RR 0.97, CI 0.87-1.08, $p=0.6$). They also reported that stroke rates (0.6% for TXA and 0.7% for placebo) and neurosurgery rates (10.3% for TXA and 10.5% for placebo) were similar between the groups. These data are reassuring; if a major safety concern were present for perhaps one third of the patients in the trial (those with depressed GCS among whom TBI patients are common) a negative effect on outcomes would be expected.
- d. Hextend® is commonly used as a resuscitation fluid in combat casualties. Several studies have demonstrated that this product may interfere with hemostasis through a number of mechanisms including fibrinolysis. Due to poorly defined potential interactions between Hextend and TXA, which may blunt the antifibrinolytic activity of TXA, TXA should not be given through the same IV as Hextend, and Hextend should not be used as a carrier fluid for this medication.
- e. Use of this drug in conjunction with pro-coagulant drugs sometimes administered to trauma patients, such as recombinant factor VIIa (Novoseven) or activated prothrombin complex concentrate (APCC), could result in thrombotic complications. Of note, only 17 patients enrolled in the CRASH-2 trial received Novoseven (13 in the TXA group and 4 in the placebo group).
- f. It is also possible that a subgroup of patients not identified in the CRASH-2 trial, such as those with traumatic brain injury, may be at particularly high risk of thrombotic or other complications if treated with TXA. It is very reassuring, however, that no increase in vascular occlusive events was observed in this study, despite the significantly increased baseline risk of such complications in this population. The rate of deep vein thrombosis reported is difficult to interpret due to the lack of a consistent screening procedure, and the variable clinical importance of this complication. However, the rates of myocardial infarction, stroke and pulmonary embolism may be more informative. These complications are relatively simple to diagnose, and are of clinical importance. None of these complications were more common in the treatment arm, while Guideline Only/Not a Substitute for Clinical Judgment Feb 2013 Page 19 of 32 Damage Control Resuscitation At Echelon IIb/III Treatment Facilities myocardial infarction was significantly less common in the TXA group ($p=0.035$). These data strongly argue against a safety problem with respect to vascular occlusive events.

GUIDELINES FOR ADMINISTRATION IN THE DEPLOYED SETTING

The early use of TXA should be considered strongly for any patient requiring blood products in the treatment of combat-related hemorrhage and is most strongly advocated in patients judged likely to require massive transfusion (e.g., significant injury and 3 or 4 risk factors of Massive Transfusion). It should be the judgment of the physician that the casualty has a life-threatening hemorrhagic injury and high potential for development of coagulopathy or presence of coagulopathy. If the treating physician has access to TEG or ROTEM® results, and fibrinolysis is diagnosed, administration of TXA can be expected to result in improved hemostasis. Use of TXA within 3 hours of injury is associated with the greatest likelihood of clinical benefit.

CONSIDERATIONS FOR USE

TXA (intravenous trade name: Cyklokapron) is supplied in ampoules of 1000 mg in 10 ml water for injection.

1. Infuse 1 gram of tranexamic acid in 100 ml of 0.9% NS over 10 minutes intravenously (more rapid injection has been reported to cause hypotension). Hextend® should be avoided as a carrier fluid.
2. Infuse a second 1-gram dose intravenously over 8 hours infused with 0.9% NS carrier.
3. There are presently no data from randomized controlled trials to support administration of further doses to trauma patients.

STORAGE

Room temperature (15-30 °Celsius / 59-86° Fahrenheit)

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APPENDIX D: RECOMBINANT FACTOR VIIA (rFVIIA)

BACKGROUND

The most critically injured casualties often present hypothermic ($T < 96^{\circ}\text{F}$), acidemic (base deficit >5), and coagulopathic ($\text{INR} > 1.5$). All three conditions contribute to worsening bleeding. Interventions aimed at reversing coagulopathy, starting as soon after arrival as possible, may improve casualty survival.¹

In a 2005 prospective, randomized human trauma study², rFVIIa was shown to be effective in decreasing transfusion requirements, including those patients requiring massive transfusion ($\text{pRBCs} \geq 10$ units/24 hours), in humans with life-threatening hemorrhage, including patients with hypothermia ($30\text{--}33^{\circ}\text{C}$). Although this study was not powered to show safety, with 301 patients randomized, trends in favor of positive outcomes, adverse events, mortality, ventilator-free days, and ICU-free days were observed. Randomized patients had a $\text{pH} > 7.1$ because in vitro data suggest that rFVIIa is inactivated in patients with profound acidosis.

In a 2007 retrospective review of records for trauma admissions to Combat Support Hospitals in Iraq between Jan 2004 and Oct 2005, a total of 117 patients requiring a massive transfusion and receiving rFVIIa were identified.⁴ Although no statistically significant survival benefit was seen, this review demonstrated that early administration of rFVIIa was associated with decreased red blood cell use by 20% (5 units) in trauma patients requiring massive transfusion.

A retrospective review of combat casualty patients with severe trauma ($\text{ISS} > 15$) and massive transfusion ($\text{pRBCs} \geq 10$ units/24 hours) admitted to one Combat Support Hospital in Baghdad, Iraq, was conducted.⁵ When rFVIIa was given at a median of 2 hours from admission, an association with decreased mortality was seen. There was no statistical difference in the incidence of severe thrombotic events (DVT, PE, stroke) between the study groups.

A 2010 randomized, prospective trial⁷ (CONTROL trial) compared rFVIIa to placebo in actively bleeding patients who had received 4-8 units RBC within 12 hours of injury. Enrollment in the study was terminated due to futility after enrolling one third of the planned patients. Mortality was lower than predicted, attributed to advances in modern trauma care, and rFVIIa did not affect mortality compared to placebo.

Data from the Joint Theater Trauma Registry in US combat casualties receiving any blood transfusion from 2003 to 2009 compared patients who received rFVIIa with those who did not. This study did not show an increase in the rate of complications or mortality in patients receiving rFVIIa.¹⁹

Most recently in 2012, a Cochrane data base review was published.⁸ This review included 29 randomized controlled trials with 4290 surgical patients. The trials showed modest reductions in total blood loss or red cells transfused (equivalent to less than one unit of red cell transfusion) with the use of rFVIIa. They also observed an increase in the risk of having a blood clot in the arteries (such as a heart attack or stroke) in those patients receiving rFVIIa. When taken together, this review stated that the data supporting the off-license use of recombinant rFVIIa are weak. The authors concluded that the use of rFVIIa outside its current licensed indications should be restricted to clinical trials.

FDA POSITION**FDA Approved Use**

Recombinant Factor VIIa is FDA-approved for use during critical bleeding or surgery in hemophiliac patients with inhibitors to Factor VIII or IX.

Unlabeled Use

Recombinant Factor VIIa is not FDA-approved to stop uncontrolled hemorrhage in severe trauma patients, but has been studied in randomized trials and is in use in many civilian trauma centers. It may be given at the discretion of individual providers, based on their assessment of the clinical condition of the patient.

Potential Adverse Events⁹

In November 2005 (following publication of the data in Reference 2) the FDA issued new “Warnings and Adverse Reactions” to the labeling for Novoseven® Coagulation Factor VIIa (Recombinant). This new information is based on data from post-marketing studies and routine safety surveillance. The additional adverse events that were added are based on clinical studies of off-label uses (non-hemophilia patients) and on post-marketing safety surveillance. The following additional adverse events were reported in both labeled and unlabeled indications: high D-dimer levels and consumptive coagulopathy; thromboembolic events including myocardial infarction, myocardial ischemia, cerebral infarction, and/or ischemia; thrombophlebitis, arterial thrombosis, deep vein thrombosis and related pulmonary embolism, and isolated cases of hypersensitivity. In January 2010, the FDA issued the following Black Box Warning for use of NovoSeven RT: “Serious Thrombotic Events and Off-Label Use: Postmarketing cases of arterial and venous thrombotic/thromboembolic events, including fatal, have been reported; increased arterial thromboembolism risk when administered outside approved indications; counsel pts on thrombosis risk and s/sx; monitor pts for coagulation system activation and thrombosis s/sx; safety/efficacy not established outside approved indications.”

MECHANISM

Recombinant Factor VIIa is activated in combination with tissue factor at sites of endothelial injury. High doses of rFVIIa result in the accelerated generation of thrombin. The resulting clots are stronger and more resistant to fibrinolysis than normal clots.¹⁰ The potential effectiveness of rFVIIa degrades with time in the patient with poorly controlled hemorrhage due to fibrinogen, platelet and coagulation factor consumption, and dilution. These patients may require clotting factors and platelet supplementation prior to administration of rFVIIa. In the forward surgical setting this supplementation is available by the early administration of fresh whole blood followed by rFVIIa.

Considerations for Use

Coagulopathy is a major contributing factor to bleeding-related mortality, particularly when associated with metabolic acidosis and hypothermia. Additional factors contributing to coagulopathy in trauma patients are hemodilution and platelet dysfunction resulting from massive blood transfusion or fluid resuscitation. Patients who receive rFVIIa should be monitored for signs or symptoms of thrombosis.

Faced with the increase rate of massive transfusion inherent after military wounding, military clinicians have developed aggressive guidelines to pre-empt or reverse coagulopathy in patients requiring massive transfusions in the Echelon IIb/III facilities. These guidelines fall under the term “Damage Control Resuscitation” and include the use of thawed plasma (1:1 ratio with pRBCs), apheresis platelets, pooled cryoprecipitate, fresh whole blood, and rFVIIa. Recombinant activated factor VIIa was originally developed for the treatment of patients with hemophilia who developed inhibitors to Factor VIII or Factor IX. The majority of US civilian trauma centers use rFVIIa in severely injured patients, although use has steadily decreased over time due to lack of proven survival benefit.

GUIDELINES FOR ADMINISTRATION IN THE DEPLOYED SURGICAL SETTING

The use of this product should be reserved for those patients likely to require massive transfusion (e.g., significant injury and risk factors of MT) and is at the discretion of the treating physician. It should be the judgment of the provider that the casualty has a life-threatening hemorrhagic injury and high potential for development of coagulopathy or presence of coagulopathy.

Considerations for Use

- Infuse rFVIIa at dose of 90-120 mcg/kg IV push.
- If coagulopathic bleeding continues 20 minutes after infusion:
 - Administer 2 additional units fresh whole blood or 4 U FFP and/or 1u platelets
 - Redose rFVIIa 90-120 mcg/kg IV push¹

Administration Limits

- 3 doses within a 6 hour period
- If bleeding persists after 3 doses, attention should be directed toward conservation of resources. Consult senior surgeon at the MTF before administering additional rFVIIa.

Storage

- Room temperature stable product currently available throughout theater. The refrigerated product is no longer in USCENTCOM formulary.
- Reconstitution is with sterile water for injection at room temperature.
- The reconstituted solution may be used up to 24 hours after reconstitution.

Relative Contraindications⁹

- Known hypersensitivity to rFVIIa or any of its components.
- Known hypersensitivity to mouse, hamster, or bovine proteins.

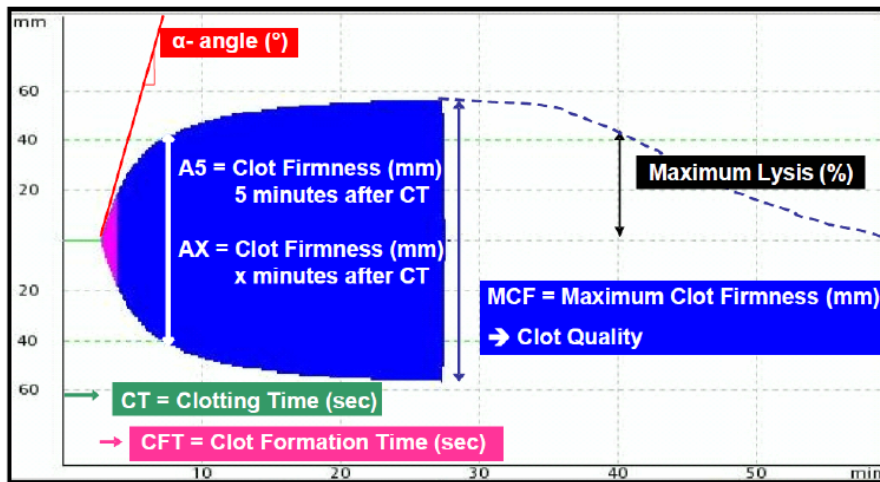
Absolute Contraindications

Active cardiac disease

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APPENDIX E: ROTEM[®] MANUFACTURER'S GUIDELINESROTEM[®] parameters

CT (clotting time): time from start of measurement until initiation of clotting
 => initiation of clotting, thrombin formation, start of clot polymerisation

CFT (clot formation time): time from initiation of clotting until a clot firmness of 20mm is detected
 => fibrin polymerisation, stabilisation of the clot with thrombocytes and F XIII

MCF (maximum clot firmness): firmness of the clot
 => increasing stabilisation of the clot by the polymerised fibrin, thrombocytes as well as F XIII

ML (maximum lysis): reduction of the clot firmness after MCF in relation to MCF
 => stability of the clot (ML < 15%) or fibrinolysis (ML > 15% within 1h)

ROTEM[®] Reference values

test name (reagent)	CT (s)	CFT (s)	α Angle	A10(mm)	A15(mm)	A20(mm)	A25(mm)	MCF(mm)	CLI 30(%)	ML (%) ²
INTEM	100-240	30-110	70-83	44-66	48-69	50-71	50-72	50-72	94-100	< 15
HEPTEM	Comparison with INTEM. A better clot quality in HEPTEM as compared to INTEM indicates the presence of heparin or heparin-like anticoagulants in the sample.									
EXTEM	38-79	34-159	63-83	43-65	48-69	50-71	50-72	50-72	94-100	< 15
APTEM	Comparison with EXTEM. A better clot formation with ap-TEM [®] or APTEG-S when compared to ex-TEM [®] is an early sign of hyperfibrinolysis.									
FIBTEM	n.d	n.d	n.d	7-23	n.d	8-24	n.d	9-25	n.d	n.d
MCF < 9 mm is a sign of decreased fibrinogen or disturbed clot polymerisation. MCF > 25 mm is a sign of elevated fibrinogen levels (which may lead to a normal EXTEM or INTEM in spite of thrombocytopenia).										
NATEM	300-1000 ¹	150-700 ¹	30-70 ¹			35-80 ¹		40-85 ¹	94-100 ¹	< 15 ¹

Reference: Lang, T Bauters A, Braun SL, Poetzch B, von Pape K-W, Kolde H-J, Lakner M. Multicenter investigation on reference ranges for ROTEM thromboelastometry (eingereicht in Blood Coagulation and fibrinolysis).

Test specificities: EXTEM & INTEM

EXTEM:

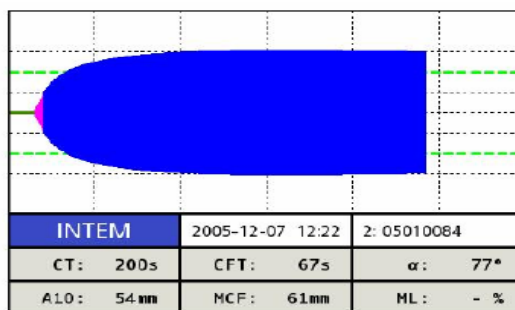
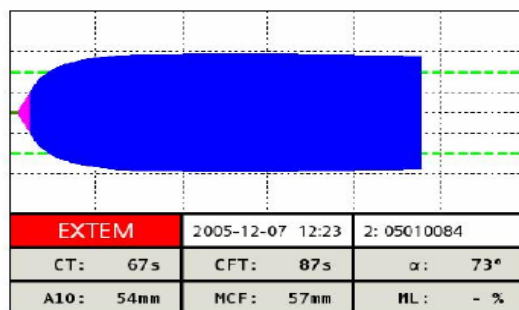
- extrinsic screening test
- CT not sensitive for heparin (up to 4 U/ml UFH in blood)

INTEM:

- intrinsic screening test
- CT sensitive for heparin (UFH)
- CT prolongation from > 0,15 U/ml UFH in blood

EXTEM & INTEM amplitude and CFT influenced by:

- fibrinogen
- platelets



Test specificities: FIBTEM

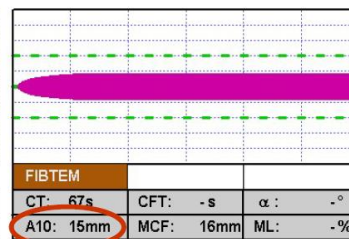
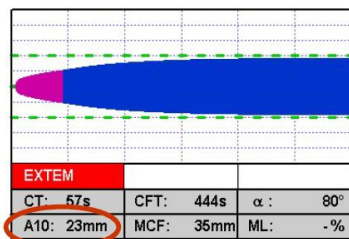
FIBTEM:

- activation as in **EXTEM**
- platelet inhibition reagent added

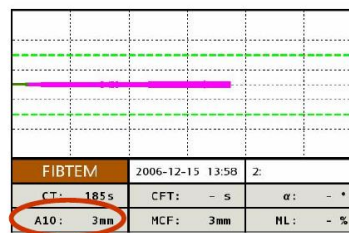
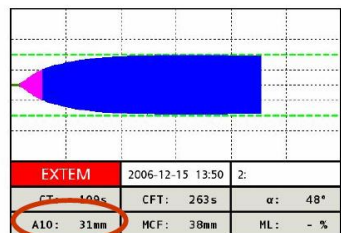


TEMogram shows isolated fibrinogen contribution to Clot firmness

- A) • **EXTEM**: amplitude low
• **FIBTEM**: amplitude normal
=> fibrinogen level OK
=> platelet deficiency



- B) • **EXTEM**: amplitude low
• **FIBTEM**: amplitude low
=> fibrinogen deficiency



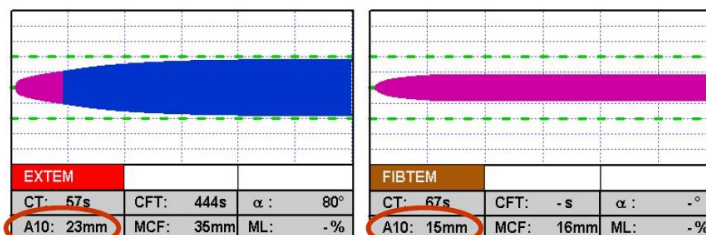
Test specificities: FIBTEM

FIBTEM:

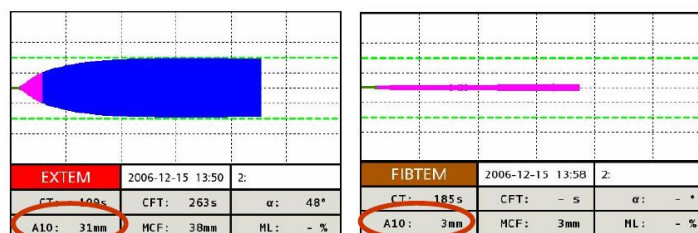
- activation as in **EXTEM**
- platelet inhibition reagent added

→ TEMogram shows isolated fibrinogen contribution to Clot firmness

- A) • **EXTEM**: amplitude low
• **FIBTEM**: amplitude normal
=> fibrinogen level OK
=> platelet deficiency



- B) • **EXTEM**: amplitude low
• **FIBTEM**: amplitude low
=> fibrinogen deficiency



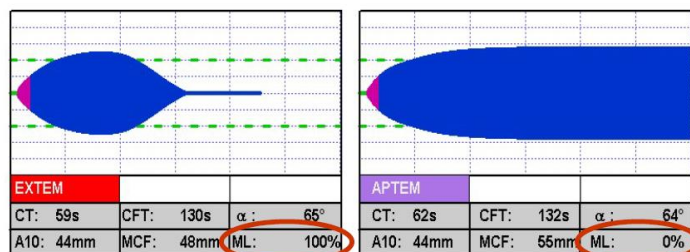
Test specificities: APTTEM

APTEM:

- activation as in **EXTEM**
- fibrinolysis inhibition with aprotinin

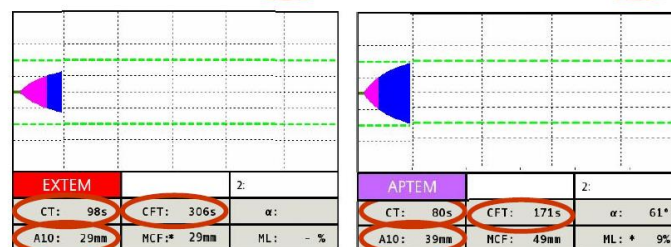
→ TEMogram identifies hyperfibrinolysis

- A) • **EXTEM**: clear hyperfibrinolysis (ML 100%)
• **APTEM**: fibrinolysis inhibited (ML <15%)
=> Fulminant hyperfibrinolysis



- B) • **APTEM**:
CT > 10% shorter &
CFT > 20% shorter &
A10 higher than **EXTEM**
(or 2 out of 3)

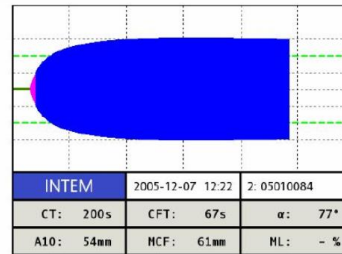
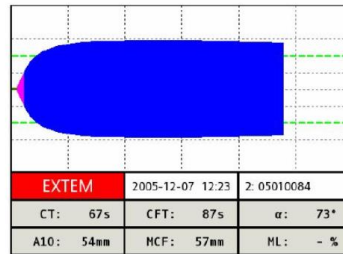
=> Consider mild hyperfibrinolysis which will become visible later during measurement



Normal haemostasis with different tests

EXTEM & **INTEM**

- Normal CT
- Normal amplitudes
- No hyperfibrinolysis visible

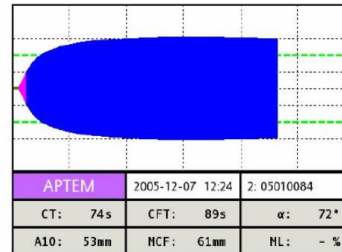
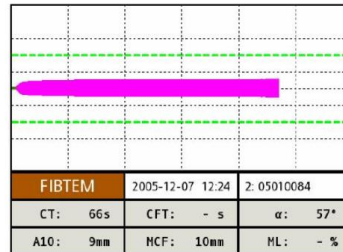
**FIBTEM**: Amplitude normal

=> fibrinogen level sufficient

&

EXTEM: Amplitude normal

=> platelets normal

**APTEM** $\approx$ **EXTEM**

=> No hyperfibrinolysis

APPENDIX F: ADDITIONAL 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 of care. 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.