

Joint Theater Trauma System Clinical Practice Guideline

DAMAGE CONTROL RESUSCITATION AT LEVEL IIb/III TREATMENT FACILITIES

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Supersedes:	Damage Control Resuscitation at Level IIb / III Treatment Facilities, updated 30 Mar 11		
<input type="checkbox"/> Minor Changes (or)	<input checked="" type="checkbox"/> <i>Changes are substantial and require a thorough reading of this CPG (or)</i>		
<input type="checkbox"/> Significant Changes	Tranexamic acid added as another drug to consider when treating patients with significant hemorrhage		

1. Goal

Outline a method of trauma resuscitation in which fluids, blood products and other adjunctive measures, e.g. Recombinant Factor VIIa (rFVIIa) and Tranexamic Acid, are used to reverse or prevent coagulopathy and aid in management of ongoing hemorrhage.

2. Background

- a. Utilizing the Tactical Combat Casualty Care (TCCC) guidelines, medics and corpsmen use tourniquets and hemostatic dressings to treat most compressible hemorrhage on the battlefield. Non-compressible hemorrhage (i.e., truncal, axillary, neck, and groin) remains a largely unsolved problem, as well as one of the leading causes of death on today's battlefield.
- b. Following Advanced Trauma Life Support guidelines, physicians have traditionally initiated resuscitation with large-volume crystalloid infusion, followed by the addition of pRBCs and finally plasma. This approach in major civilian trauma has demonstrated a greater incidence of abdominal compartment syndrome (16% vs. 8%), multiple organ failure (22% vs. 9%), and death (27% vs. 11%).
- c. There is strong retrospective evidence in both civilian and military trauma populations, that for patients requiring massive transfusion, a higher proportion of plasma and platelets, when compared to red cells, results in improved survival (e.g. 1 unit plasma: 1 unit platelets: 1 unit of PRBCs). Fresh whole blood delivers these products in the above ratio and is independently associated with improved survival in a retrospective analysis. Finally, there is both prospective and retrospective evidence that rFVIIa used early in the resuscitation of patients with massive transfusion results in decreased blood usage without an increase in thromboembolic complications.

3. Recognition of patients requiring damage control resuscitation

- a. Most casualties that receive hemostatic resuscitation in the ED or the OR require a massive transfusion (MT). Defined as equal to as, or greater than, 10u pRBCs/24 hours, MT patients present a unique challenge both in the ED and OR, as well as the ICU post-operatively. Anticipating the need for a MT requires experience and the coordination of extensive resources.

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b. A number of risk factors for massive transfusion upon hospital admission have been identified. In a patient with **serious injuries**, these include:

- 1) Systolic blood pressure < 110 mm Hg
- 2) Heart rate > 105 bpm
- 3) Hematocrit < 32%
- 4) pH < 7.25

Note: Patients with 3 of the above 4 risk factors have approximately a 70% risk of massive transfusion; patients with all 4 of the above have an 85% risk.

5) Other risk factors for massive transfusion include: INR level > 1.4, NIR-derived StO₂ < 75%.

c. Examples of clinical scenarios that are associated with the need for massive transfusion include: Uncontrolled truncal, axillary, neck, or groin bleeding, uncontrolled bleeding secondary to large soft tissue injuries, proximal amputation or mangled extremity, clinical signs of coagulopathy, or severe hypothermia associated with blood loss.

4. Management Principles for Damage Control Resuscitation

a. The major principle of damage control resuscitation is to prevent development of coagulopathy by dilution of factors needed to provide hemostasis. In order to support this goal, the system must provide components at an appropriate ratio throughout the resuscitation process.

b. It is critical to communicate with the blood bank at the medical treatment facility when a potential massive transfusion patient has been identified. Most blood banks within theater have developed procedures for providing blood products in the appropriate proportion to support resuscitative efforts.

c. Component therapy: The goal in transfusion of the patient with need for massive transfusion is to deliver a ratio of PRBCs to plasma to platelets of 1:1:1.

Note: All platelets at US Level III facilities are apheresis platelets.

1 apheresis unit/pack = 6 units random donor platelets.

Therefore, the goal of 1:1:1 resuscitation should be 6 units PRBCs: 6 units FFP: 1 unit/pack apheresis platelets). This goal should be discussed at appropriate intervals between members of the trauma team and blood bank with efforts made to develop a massive transfusion procedure (see Appendix A).

1) Packed red blood cells (PRBCs): There is evidence that as PRBCs are stored, that **there is development of a “storage lesion” that may have deleterious effects.** These effects are potentially more significant in patients requiring MT. For MT patients the policy of “Last in/First Out” (LIFO) will be applied for all PRBCs provided to the surgical/ICU team. The USCENTCOM (U.S. Central Command) Blood Bank staff, in conjunction with in-theater personnel and the USAF, has

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developed an extensive logistical process that helps ensure that major Level III facilities within the theater are adequately supported with the newest and freshest pRBCs (see appendix B). Frozen and deglycerolized RBCs are available at several facilities within the USCENTCOM area of responsibility (AOR). Use of these products is somewhat limited due to the time necessary for preparation (90 min-2 hours). Further information on this product is available in the USCENTCOM JTTS CPG entitled “Frozen and Deglycerolized Red Blood Cells”.

- 2) Thawed plasma for emergency use should be type AB or A (**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**). An effort should be made to rapidly obtain the casualty’s blood type, with the goal to provide type-specific transfusions as quickly as possible during the resuscitation process.
- 3) Platelets: Apheresis platelets collected in theater are non-FDA approved due to the lack of complete infectious disease testing of donors prior to collection. Efforts have been made to push platelets as a component of therapy to Level III facilities throughout the two theaters. These are typically available as platelet pheresis packs that are obtained from donors within theater.
- 4) Cryoprecipitate may be added to component therapy to enhance replacement of fibrinogen. One unit of fresh whole blood contains approximately 1000 mg of fibrinogen. One unit of FFP contains 400 mg of fibrinogen and 1 unit of platelets contains 80 mg. Therefore, transfusion of FFP and platelets alone may not adequately replace fibrinogen in MT patients. Ten units of cryoprecipitate contain 2500 mg of fibrinogen. The transfusion of high ratios of fibrinogen:RBCs or cryoprecipitate:RBCs have both been associated with improved survival in retrospective studies.
- 5) Warm fresh whole blood (FWB): FWB offers an appropriate ratio of components, with the benefits of lack of storage lesion, excellent platelet activity, and field availability. While broadly available and used, this treatment option is not FDA-approved due to a slight risk of transmission of infection. Recent retrospective data show a potential survival benefit to the use of FWB during resuscitation of severe combat injuries. Fresh whole blood can be used at any phase of the resuscitation if it is the judgment of the provider that the casualty has a life-threatening hemorrhagic injury and one of the blood components (platelets, plasma, RBCs) is not available OR when stored components are not adequately resuscitating a patient receiving component therapy (e.g. worsening coagulopathy and shock). For additional information, see USCENTCOM JTTS CPG entitled “Fresh Whole Blood (FWB) Transfusion”.

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5. Tranexamic Acid

Tranexamic acid (TXA), an anti-fibrinolytic agent, has been used to decrease bleeding and the need for blood transfusions in coronary artery bypass grafting (CABG), orthotopic liver transplantation, hip and knee arthroplasty, and other surgical settings. A recent meta-analysis reported that TXA is effective for preventing blood loss in surgery and reducing transfusion, and was not associated with increased vascular occlusive events.⁴ (For additional information concerning TXA, see Appendix D).

The early use of TXA (i.e. *as soon as possible after injury* but ideally not later than 3 hours post injury) should be strongly considered 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 risk factors of massive transfusion). It may be utilized in circumstances when in the judgment of the physician, a casualty has life-threatening hemorrhagic injury and high potential for development of coagulopathy or outright presence of coagulopathy. Use of TXA within 3 hours of injury is associated with the greatest likelihood of clinical benefit. Initial use of TXA after 3 hours post injury may have no benefit and may in fact worsen survival. ***Therefore it is strongly recommended that TXA not be administered to patients when the time from injury is known to be or suspected to be greater than 3 hours.***

a. Considerations for Use

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

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.

There are presently no data from randomized controlled trials to support administration of further doses to trauma patients. However, if a patient has received the initial dosing of TXA and continues to show signs of ongoing hemorrhage, strong consideration should be given to re-dosing the patient as above.

TXA may be administered to patients requiring MT even if they have an associated TBI.

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In patients who continue to have life-threatening hemorrhage despite TXA use and adequate 1:1:1 resuscitation, clinical judgment is warranted as to the use of additional pro-coagulant agents such as rFVIIa.

b. Storage

Room temperature (15-30° Celsius / 59-86° Fahrenheit). *Storage at temperatures great than these may reduce or destroy the efficacy of TXA.*

6. Recombinant Factor VIIa (rFVIIa)

Recombinant Factor VIIa (rFVIIa) has recently been associated with improved hemostasis in combat casualties, decreasing blood loss by 23% (see Appendix C for more information on the use of rFVIIa). The use of this product should be reserved for those patients likely to require massive transfusion (e.g. significant injury and risk factors) and is at the discretion of the treating physician. It should be the judgment of the provider that the casualty has a life-threatening hemorrhage and coagulopathy.

- 1) Usual Dose: 100 mcg/kg intravenously; may be repeated in 20 minutes.
- 2) Contraindications: Active cardiac disease.
- 3) Storage: Refrigerate (2–8°C/36–46°F) prior to reconstitution and use. The FDA recently approved a room temperature stable product. This will be distributed throughout the USCENTCOM AOR as the current supplies are exhausted.

7. Emergency Department (ED) Resuscitation

Damage control resuscitation (pRBC, plasma and platelets (1:1:1 ratio) ± rFVIIa) should be initiated for patients with signs noted in section 3 above. Transfusion of products and administration of rFVIIa should be based on clinician judgment and the response of the patient to resuscitative therapy. Crystalloid and nonsanguinous colloid therapy should be limited in the patient with significant ongoing bleeding.

8. OR Resuscitation.

- a. The goal of resuscitation in the OR is to stop bleeding, to normalize casualty temperature, and to prevent/reverse coagulopathy and shock. In addition to ongoing resuscitation with component therapy the following measures are suggested:
 - 1) The operating room must be kept as warm as possible; ideally 108°F or greater.
 - 2) Consider a dose of rFVIIa for ongoing coagulopathic bleeding.
 - 3) Administer THAM (non-bicarbonate buffer) to maintain pH > 7.2.
 - 4) Administer Ca⁺⁺ after every four units of pRBCs and/or to keep ionized Ca⁺⁺ > 1.0 (via i-STAT[®]).

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9. ICU Resuscitation

- a. For patients who continue to have massive bleeding in the ICU the 1:1:1 approach in addition to all other DCR principles are still required. Additional doses of rFVIIa may also be indicated if acid/base and hematologic parameters are sufficient for its effectiveness (pH > 7.1, PLT > 50,000, FGN > 100).

10. Conclusion

- a. The approach to a critically injured soldier, marine, sailor, or airmen requires a significant expenditure of resources and the coordination of a diverse group of health care providers. This is frequently performed in the face of multiple casualties and limited resources. It is incumbent upon the lead trauma surgeon at each facility to be fully versed on available resources, and to employ them judiciously and appropriately.
- b. Patients requiring massive transfusion should be resuscitated using damage control resuscitation principals as noted above.

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Approved by USCENTCOM JTTS Director, JTS Director
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APPENDIX A

EXAMPLE OF A MASSIVE TRANSFUSION PROCEDURE AT A 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).

Pack One: 4u PRBC and 4u FFP, should consider 6pk Platelets, 1 10 unit bag cryo and +/- Factor VII (obtained from Pharmacy) at this time if patient received 4uPRBC/4uFFP Emergency release blood. **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, 6pk Platelets, 1x 10 unit bag of cryo and +/- Factor VII (obtained from Pharmacy)

Pack Four: 4u PRBC and 4u FFP

Pack Five: 4u PRBC, 4u FFP, 6pk platelets, and 1x 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 (2u O+ and 2u O-) 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).

Pack: A single group of type-specific, crossmatched 4u PRBC and 4u FFP, which later in the procedure, may include cryo, Platelets and/or Factor VII

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- **Flow/order of resuscitation using MT Procedure**

1. Patient arrives in ED. Initial survey, securing of airway and resuscitation are initiated by ED provider. Trauma Team begins consideration of blood transfusion needs.
2. Surgeon who will be taking the patient to the OR decides:
 - Blood is not needed at the present time.
 - Only use “Emergency Release” of uncrossmatched 4u PRBC and 4u FFP.
 - Initiate MT Procedure: 4u PRBC and 4u FFP immediately, Blood Bank begins creating Batch One (Emergency Release can be used to start, but is not counted as Pack One).
3. In the OR, the anesthesia provider, in ongoing evaluation of hemodynamics, lab studies and hemostatic control as per the operating surgeon, decides to continue the MT Procedure, initiate it if not already done so in the ED or terminate it and notify the Blood Bank of that decision if the patient has remained stable.
4. Once in the ICU, the critical care provider now has responsibility for initiating, continuing or terminating the MT Procedure (and notifying the Blood Bank as appropriate) as the patient’s condition and lab studies dictate.

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APPENDIX B

Last in, First Out (LIFO) Policy

Goal: In patients requiring massive transfusion (MT), a concerted effort is made to give patients younger units of PRBCs (i.e. preferably less than 14 days old, but the youngest 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 "younger" (LIFO) blood for MT patients and those suspected of needing MT upon presentation to the MTF.

For all MT patients, the policy of "LIFO" will be applied for all blood products provided to the surgical/ICU team. The USCENTCOM Command Surgeon's staff, in conjunction with USCENTCOM J4, the Armed Services Blood Program (ASBP) and in-theater personnel, have developed an extensive logistical process that helps ensure that certain Level III facilities in the USCENTCOM AOR are adequately supported with the newest and freshest pRBCs, with current time from donation to availability in theater as low as 4 days.

APPENDIX C

RECOMBINANT FACTOR VIIa (rFVIIa)

- 1. Background.** The most critically injured casualties often present hypothermic ($T < 96^{\circ}\text{F}$), acidemic (base deficit < 6), 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 recent prospective, randomized human trauma study², rFVIIa was shown to be effective in decreasing transfusion requirements, including those patients requiring massive transfusion (pRBCs ≥ 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 recently published retrospective review³ of records for trauma admissions to Combat Support Hospitals in Iraq between Jan 04 and Oct 05, a total of 117 patients requiring a massive transfusion and receiving rFVIIa were identified. Complete records were available for review in 61 patients. Of those, 17 received rFVIIa early, or before 8 units of pRBCs had been transfused, while 44 received the drug late, or after 8 units pRBCs were given. At admission, temperature, Glasgow Coma Scale score, base deficit, hemoglobin, platelets, prothrombin time/International Normalized Ratio, and Injury Severity Score were similar in both groups, as were the number of administered units of fresh frozen plasma, fresh whole blood, cryoprecipitate, and crystalloid. Although no statistically significant survival benefit was seen, this review demonstrated that early administration of rFVIIa decreased red blood cell use by 20% (5 units) in trauma patients requiring massive transfusion. It is well documented that increased exposure to blood products increases the risk of infection, multi-organ failure, and mortality. In addition, the FDA has acknowledged that decreased blood transfusion is an appropriate end-point when considering the evaluation of resuscitation interventions.

A retrospective review of combat casualty patients with severe trauma ($\text{ISS} > 15$) and massive transfusion (pRBCs ≥ 10 units/24 hours) admitted to one Combat Support Hospital in Baghdad, Iraq, was conducted.⁶ Admission vital signs and laboratory data, blood products, Injury Severity Score (ISS), 24-hour and 30-day mortality, and severe thrombotic events were compared between patients who received rFVIIa and those who did not receive rFVIIa. Of 124 patients who received massive transfusion, 49 patients received rFVIIa and 75 patients did not. ISS scores and vital signs did not differ between the two groups. A statistically significant decrease in mortality was demonstrated in the group who received rFVIIa at 12 hours, 24 hours, and 30 days. 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.

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2. FDA Position.

- a. 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.
- b. 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 civilian trauma centers. It may be given at the discretion of individual providers, based on their assessment of the clinical condition of the patient.
- c. Potential adverse events:⁷ 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.”

3. **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.⁸ 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.

4. Considerations for Use.

The extent of the risk of thrombotic adverse events after treatment with rFVIIa is not known precisely, but recent data (unpublished) from the Joint Theater Trauma Registry shows that the risk of thromboembolic complications in patients receiving massive transfusion during the past two years was essentially the same in patients who received rFVIIa as those who did not get the drug. 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.

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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 Level 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 VII 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.. In the 2008 Annals of Surgery paper attached, of 10 major Level I centers that treated 466 massive transfused trauma patients, about 15% of those patients received rFVIIa.

In a paper from the journal American Surgeon Use of rFVIIa in the trauma setting--practice patterns in United States trauma centers was reviewed. They sent surveys to 435 trauma centers, most of which were ACS verified and level I and II. 156 centers responded. The article shows that 68% of centers responding use it and 59% have a procedure for its use in trauma patients.

Although rFVIIa has been associated with pathologic thrombosis, in the only prospective, randomized study of injured patients receiving rFVIIa compiled to date, the clinical venous thromboembolic (VTE) rate was no different between patients who received rFVIIa and those that did not (2% vs. 3% in blunt trauma; 4% vs. 3% in penetrating trauma).² At a recent DOD review, a group of Senior Civilian Surgeons reviewed data on 615 severely injured combat casualties from 2004-2006 compiled from the Joint Theater Trauma Registry. The DVT rate was 7.5%, with a PE incidence of 3.8% and there was no apparent difference in VTE between groups that received rFVIIa and those who did not. Among the most severely injured combat casualties who required a massive transfusion, the thrombotic rate in patients who did not receive rFVIIa was 13% vs. 18% for those who did (not significantly different). Conversely, rFVIIa significantly improved survival in a subgroup of severely injured and massively transfused casualties (p <0.05).⁶

5. 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.

- a. **Considerations for Use** Infuse rFVIIa at dose of 90-120 mcg/kg IV push.
- b. If coagulopathic bleeding continues 20 minutes after infusion:
 - 1) Administer 2 additional units fresh whole blood or 4 U FFP and/or 6 pack platelets
 - 2) Redose rFVIIa 90-120 mcg/kg IV push and repeat ii)¹

6. Administration Limits.

- a. 3 doses within a 6 hour period

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

7. Storage.

- a. Refrigeration at 4° C (range 2-8° C).
- b. Reconstitution is with sterile water for injection at room temperature.
- c. The reconstituted solution may be used up to 24 hours after reconstitution.
- d. **The FDA has recently approved a non-heat sensitive rFVIIa. This product will be distributed throughout the AOR to replace expended stocks.**

8. Relative Contraindications.⁷ Known hypersensitivity to rFVIIa or any of its components. Known hypersensitivity to mouse, hamster, or bovine proteins.

9. Absolute Contraindications. Active cardiac disease.

10. References.

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APPENDIX D

TRANEXAMIC ACID (TXA)

1. Background

- a. 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-dimers, fibrin split products (FSP) and plasmin-antiplasmin complexes found in blood samples drawn from trauma patients on presentation.² Fibrinolysis can occasionally overwhelm the tendency to clot following trauma, a phenomenon that can be directly observed in real time by thromboelastography (TEG) or rotational thromboelastometry (ROTEM). Such hyperfibrinolysis occurs only in the most severely injured patients (approximately 4% of trauma patients in major civilian US trauma centers) and portends extremely poor outcomes.³

- b. Coagulation system responses to trauma and surgery are broadly similar and activation of fibrinolysis has been observed in a 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 recently evaluated in a large randomized, placebo-controlled clinical trial called “The Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage” (CRASH-2)⁴. 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. This randomization scheme reflects application of the uncertainty principle, or clinical equipoise in decision-making. Only 14 patients out of 20,225 screened were excluded from randomization, because they died before they could be randomized. (Personal communication with study director, Ian Roberts) The treatment and placebo groups were well-balanced across a wide range of prognostic variables. The overall mortality rate in the cohort studied was 15.3%, of whom

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35.3% died on the day of randomization. A total of 1063 died due to hemorrhage, of whom 59.9% died on the day of randomization. A subgroup at particularly high risk of death included those patients presenting with a SBP<75 (3,161 of 20,125; 15.7%). Overall, this study included a large and very diverse trauma population, with most patients facing a relatively low mortality risk. Nevertheless, over 3,000 patients in the study would likely have been candidates for treatment under a damage control resuscitation (and possibly massive transfusion) procedure. 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). Note that this NNT reflects the underlying mortality risk in the CRASH-2 study (15%). 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. There were no differences in need for transfusion or surgery between the two arms (blood product transfused in 50.4% of patients for TXA vs. 51.3% for placebo, p = 0.21; any surgery in 47.9% of patients for TXA and 48.0% for placebo, p = 0.79). A recent post-hoc analysis of the CRASH-2 data suggests that the greatest benefit of TXA administration is likely to occur when patients receive the medication soon after injury. In this analysis, TXA given between 1 and 3 hours post-trauma reduced the risk of death due to bleeding by 21% (147/3037 [4.8%] vs. 184/2996 [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 due to bleeding (144/3272 [4.4%] vs. 103/3362 [3.1%], RR 1.44, CI 1.12-1.84; p=0.004).⁶

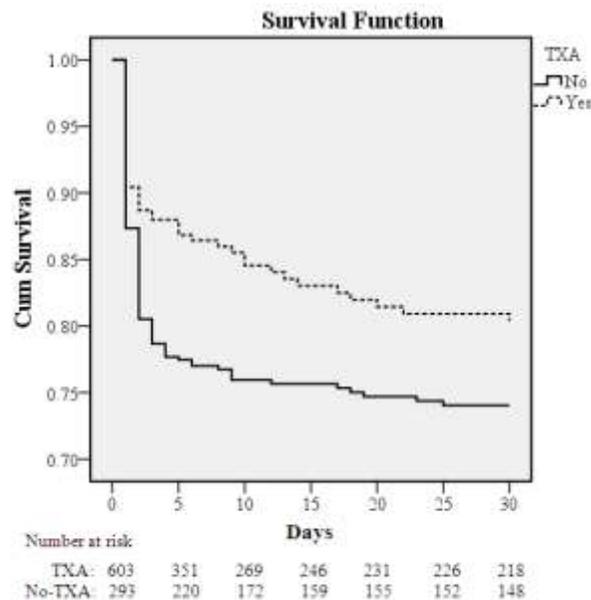
- c. **TXA experience in combat-related hemorrhage:** A recent registry-based study of combat injured troops receiving blood in Afghanistan (January 2009 - December 2010) at the Bastion Role 3 facility has demonstrated findings supportive of TXA use in this population. In a review of 896 combat casualties treated at Bastion over this time frame, 32.7% (N=293) received TXA (mean \pm SD dose: 2.3 \pm 1.3g) while 67.2% (N=603) did not receive TXA. In the overall cohort, the TXA group was more severely injured (ISS:

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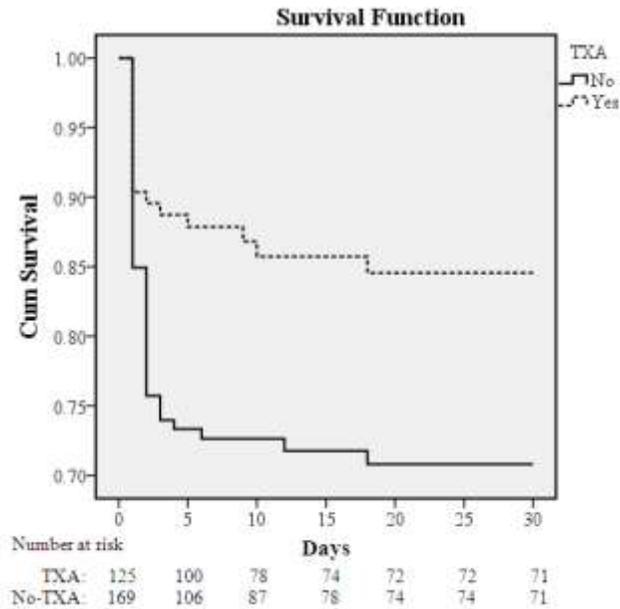
25.2±16.6 vs. 22.5±18.5; $p < 0.001$), required more blood (11.8±12.1 vs. 9.8±13.1 pRBC units; $p < 0.001$), and had a lower Glasgow Coma Score (7.3±5.5 vs. 10.5±5.5; $p < 0.001$) and initial systolic blood pressure (112±29.1 vs. 122.5±30.3 mmHg), but also had a lower unadjusted mortality than the no-TXA 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 (mean ± SD dose: 2.4 ± 1.4g) 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%, $p < 0.001$). These survival benefit findings associated with TXA use support the hypothesis that the use of this adjunct, in conjunction with component-based resuscitation following combat injury, is associated with improved survival. This association is most prominent in those requiring massive transfusion. (MATTERS Study – In press)



Kaplan-Meier survival curve of the overall cohort, patients receiving TXA or no-TXA, $p = 0.006$ (Wilcoxon Statistic)

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Kaplan-Meier survival curve of the massive transfusion group receiving TXA^{MT} or no-TXA^{MT}, $p = 0.004$ (Wilcoxon Statistic).

2. FDA position

- a. **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.
- b. **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 is widely used in non-trauma surgeries and has been used on a limited basis by at least one major US civilian trauma center (Massachusetts General Hospital; panel discussion, Dr. Hasan Alam, AAST 2010, Boston, MA). It may be given at the discretion of individual providers, based on their assessment of the clinical condition of the patient.
- c. **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

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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.

3. 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.

4. 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. 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.
- b. 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

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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.

- c. Hextend[®] is commonly used as a resuscitation fluid in trauma patients. 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.
- d. 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). 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 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.

5. Guidelines for administration in the deployed setting

- a. 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

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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 tranexamic acid can be expected to result in improved hemostasis. Use of tranexamic within 3 hours of injury is associated with the greatest likelihood of clinical benefit.

6. Considerations for Use

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

- a. 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.
- b. Infuse a second 1-gram dose intravenously over 8 hours infused with 0.9% NS carrier.
- c. *There are presently no data from randomized controlled trials to support administration of further doses to trauma patients.*

7. Storage

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

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APPENDIX E

ADDITIONAL INFORMATION REGARDING OFF-LABEL USES IN CPGs

A. 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.

B. 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.

C. 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.

D. Additional Procedures.

1. 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.

2. 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.

3. 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.

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