DAMAGE CONTROL RESUSCITATION AT LEVEL IIb/III TREATMENT FACILITIES

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☐ Minor Changes (*or*)		☒ ***Changes are substantial and require a thorough reading of this CPG (or)***		
☐ Significant Changes				

1. **Goal.** Outline a method of trauma resuscitation in which fluids, blood products and other adjunctive measures, e.g., Tranexamic Acid and Recombinant Factor VIIa (rFVIIa), 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 (truncal) and non-tourniquetable (axillary, neck, and groin) hemorrhage remains a largely unsolved problem, and is the leading cause of potentially preventable death on today's battlefield.[1]

   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%).[2]

   c. There is strong retrospective evidence in both civilian and military trauma populations that for patients requiring massive transfusion, a higher ratio of plasma and platelets to red cells results in improved survival (e.g., 1 unit plasma: 1 unit platelets: 1 unit of PRBCs).[3-7] Fresh whole blood delivers these products in the above ratio and retrospective analyses in combat casualties have shown that fresh whole blood is at least equivalent to component therapy and at best is independently associated with improved survival.[8, 24]

   d. Adjuncts to resuscitation include TXA and rFVIIa. Strong evidence demonstrates a significant improvement in survival following the early use of TXA.[9,10] There is both prospective and retrospective evidence that rFVIIa used early in the resuscitation of patients with massive transfusion results in decreased blood usage, however an improved survival has never been prospectively demonstrated for the use of rFVIIa.[11-15]

3. **Recognition of patients requiring damage control resuscitation.**

   a. Most casualties who require immediate use of uncrossmatched Type O blood in the ED will 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. These patients must be identified early and receive hemostatic resuscitation in the ED, OR, and ICU. Anticipating the need for a MT requires experience and the coordination of extensive resources.

b. A number of predictors for massive transfusion upon hospital admission have been identified.[18] 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 factors have approximately a 70% predicted risk of massive transfusion; patients with all 4 of the above have an 85% predicted risk.

5) Other risk factors for massive transfusion include: INR level > 1.4, NIR-derived StO2< 75%.[19]

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.

d. Rotational thromboelastometry (ROTEM®) may also facilitate early identification of patients who will require massive transfusion.[20,21]

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. Permissive Hypotension in casualties without CNS injury: Hypotensive resuscitation prior to surgical control of bleeding (i.e., pre-hospital and emergency room) focuses on maintaining a lower target SBP (around 90 mm Hg) during the early stages of treatment. Isotonic crystalloid use is limited or nonexistent as blood products are transfused in fixed ratios.[3, 25] This strategy has been studied retrospectively and has been associated with improved survival.[26] It should be emphasized that this strategy should not be utilized for patients with CNS injury in which hypotension is associated with adverse outcomes. For additional information, see USCENTCOM JTTS CPG entitled "Management of Patients with Severe Head Trauma".

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

d. 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 MTFs are apheresis platelets.
1 apheresis unit = 6 units random donor platelets = 1 “6-pack”.

Therefore, the goal of 1:1:1 resuscitation should be 6 units PRBCs: 6 units FFP: 1 unit 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, **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 developed an extensive logistical process that helps ensure that surgical hospitals 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 it is the next safest unmatched plasma product to use when supplies of AB FFP are limited or absent. 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 not-FDA compliant 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 and some Level II facilities throughout the theater. These are 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 cryopreciptate 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.[6]

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 risk of transfusion transmitted infections. Two retrospective analyses in combat casualties comparing FWB to component therapy (which included platelets) have been published. One study showed a potential survival benefit to the use of FWB during resuscitation of severe combat injuries, and the other showed FWB to be equivalent to component therapy.[16, 24] 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".

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 large prospective randomized trial demonstrated a decrease in mortality in trauma patients who received TXA within 3 hours of injury. [9] (For additional information concerning TXA, see Appendix C).

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.

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 higher temperatures may reduce or destroy the efficacy of TXA.***

c. **TXA Performance Monitoring.**

Department of Defense Trauma Registry (DoDTR) data reveals mortality of 6.7% in casualties who did not receive TXA versus 10.1% who did receive TXA in a series of 322 combat casualties who required massive transfusion from 11 January 2011 to 06 October 2012 as ongoing theater performance improvement.

6. Recombinant Factor VIIa (rFVIIa).

Recombinant Factor VIIa (rFVIIa) has been associated with improved hemostasis in combat casualties with a modest decrease in blood loss, however has not been clearly associated with improved survival. (see Appendix D 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.

a. Usual Dose: 100 mcg/kg intravenously; may be repeated in 20 minutes.

b. Contraindications: Active cardiac disease.

c. Storage: Room temperature stable product currently available throughout theater. The refrigerated product is no longer in USCENTCOM formulary.

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.

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:

a. The operating room must be kept as warm as possible; ideally 108°F or greater.

b. Consider a dose of rFVIIa for ongoing coagulopathic bleeding which persists despite use of TXA.

c. Administer THAM (non-bicarbonate buffer) or sodium bicarbonate to maintain pH > 7.2.

d. Administer Ca++ after every four units of FFP and/or to keep ionized Ca++ > 1.0 (via i-STAT®).

9. ICU Resuscitation.

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 for uncontrolled bleeding. However, in patients for whom surgical bleeding has been controlled, laboratory testing should primarily guide the transfusion of subsequent blood products. Additional doses of rFVIIa may be considered for coagulopathic bleeding if acid/base and hematologic parameters are sufficient for its effectiveness (pH> 7.1, PLT> 50,000, FGN > 100).

10. Rotational thromboelastography (ROTEM®) is a tool which has been proven to be feasible in the combat environment. ROTEM permits fine tuning of management of the coagulopathic combat casualty. ROTEM is a tool which is currently available at the Level III MTFs.

For bleeding patients, use ROTEM® to differentiate platelet vs. fibrinogen deficiency/dysfunction in order to guide transfusion therapy. ROTEM may also identify fibrinolysis (cryptic or overt) and prolonged clot initiation due to factor deficiency or hemodilution. This protocol represents an alternative approach to the DCR CPG ratio therapy (1:1:1:1) outlined in the Massive Transfusion Protocol. In addition to obtaining ROTEM on admission of bleeding patients, consider especially using ROTEM to guide transfusion therapy in bleeding post-operative/ICU patients. Normal ROTEM findings suggest absence of coagulopathy and indicate an anatomic defect amenable to surgical repair. See Appendix E for additional information on ROTEM.

a. Run EXTEM, FIBTEM, APTEM [start all 3 assays at same time to accelerate differential diagnosis]. If you suspect heparin effect or intrinsic factor deficiency (e.g., ICU patient on heparin, hemophilia, etc.), consider INTEM paired with HEPTEM [EXTEM is relatively insensitive to heparin as it is activated with tissue factor (extrinsic pathway) whereas INTEM is activated with elegiac acid (intrinsic pathway)].

b. If CT is prolonged out of normal range on EXTEM (>79sec), particularly with history of significant dose of crystalloid or colloid resuscitation indicating hemodilution, give FFP 10-15ml/kg (for an 70-90 kg soldier, this represents initial therapy of about 4-6 units) as tolerated by volume status.

c. If A10 or MCF is low on EXTEM (A10<43, MCF<50) look at FIBTEM. If FIBTEM MCF is normal, give 1 unit apheresis platelets (or Whole Blood, WB) as initial therapy.

d. If both EXTEM and FIBTEM MCF are depressed (FIBTEM MCF < 9 indicates fibrinogen deficiency/dysfunction, MCF < 7 indicates severe deficiency), give 10U cryoprecipitate (or 2gm fibrinogen concentrate) as starting dose. Consider giving 1U apheresis platelets as well (or WB) in a severely bleeding patient. Sequential treatment depending on rate of bleeding and degree of MCF depression, with reassessment by ROTEM and clinical exam, is reasonable in a more stable patient.

e. Check APTEM. If APTEM MCF is normal (>50) or even simply greater than EXTEM MCF, particularly in setting of depressed EXTEM and/or FIBTEM MCF, fibrinolysis is present and TXA is indicated (1gm over 10 minutes followed by 1gm over 8 hours IV). If APTEM MCF is also low (all three tests showing low MCF) and patient is bleeding, give cryoprecipitate 10U (or 2gm fibrinogen concentrate) and 1U apheresis platelets (or WB).

f. An LI30 of <94% (ML>15% at one hour) indicates excess clot lysis: give TXA as above.

g. In a patient with continued bleeding and isolated prolonged CT despite resuscitation as above (i.e., other ROTEM parameters improved and heparin effect ruled out), consider rVIIa, dose not to exceed 90mcg/kg.

h. Reassess effect of transfusion and/or TXA therapy with ROTEM as well as patient clinical status (bleeding yes/no) prior to further treatment.

11. 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.

12. Performance Improvement (PI) Monitoring.

a. Intent (Expected Outcomes).

1) All MT patients who receive TXA will have initial dose administered < 3 hrs from time of injury.

b. Performance/Adherence Measures.

1) All MT patients who received TXA had the initial dose administered < 3 hrs from time of injury

2) All MT patients will receive TXA, unless ROTEM® data indicates no TXA indicated

c. Data Source.

1) Patient Record

2) Out of Hospital documentation

3) MARS (Medication Administration Record)or Anesthesia Record

4) Joint Theater Trauma Registry (JTTR)

d. System Reporting & Frequency.

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

The system review and data analysis will be performed by the Joint Theater Trauma System (JTTS) Director, JTTS Program Manager, and the Joint Trauma System (JTS) Performance Improvement Branch.

13. 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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Approved by USCENTCOM JTTS Director, JTS Director and USCENTCOM SG

Opinions, interpretations, conclusions, and recommendations are those of the authors and are not necessarily endorsed by the Services or DoD.

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). **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).**

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

- **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.
   - Initiate "Emergency Release" of uncrossmatched 4u PRBC and 4u FFP.
   - Initiate MT procedure: Blood Bank begins creating Batch One (Emergency Release can be used to start, but is not counted as Pack One).
   - Consider whole blood drive.
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.

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.

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 surgical facilities in the USCENTCOM AOR are adequately supported with the newest and freshest pRBCs, with current time from donation to availability in theater averaging 7 days.

APPENDIX C

TRANEXAMIC ACID (TXA)

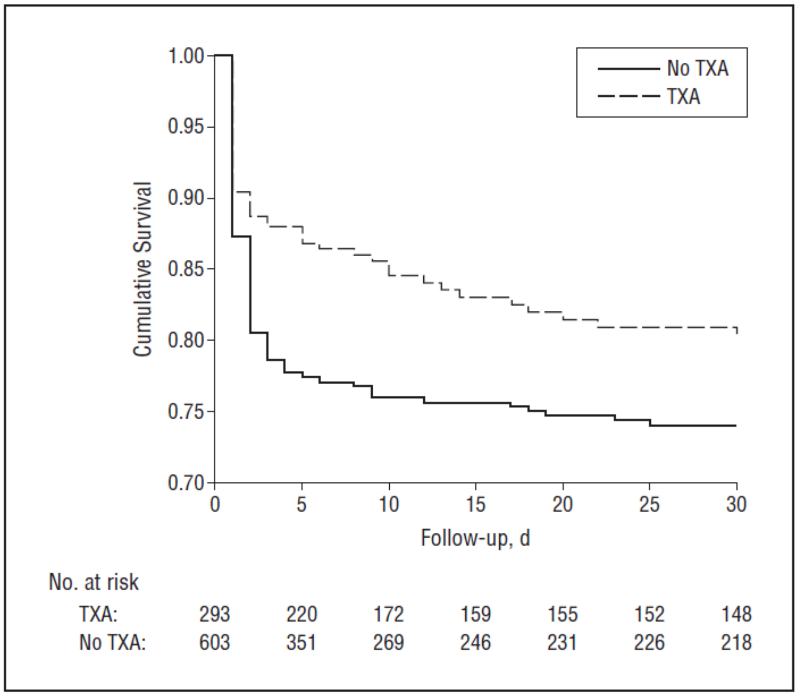
1. **Background.**

   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-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]

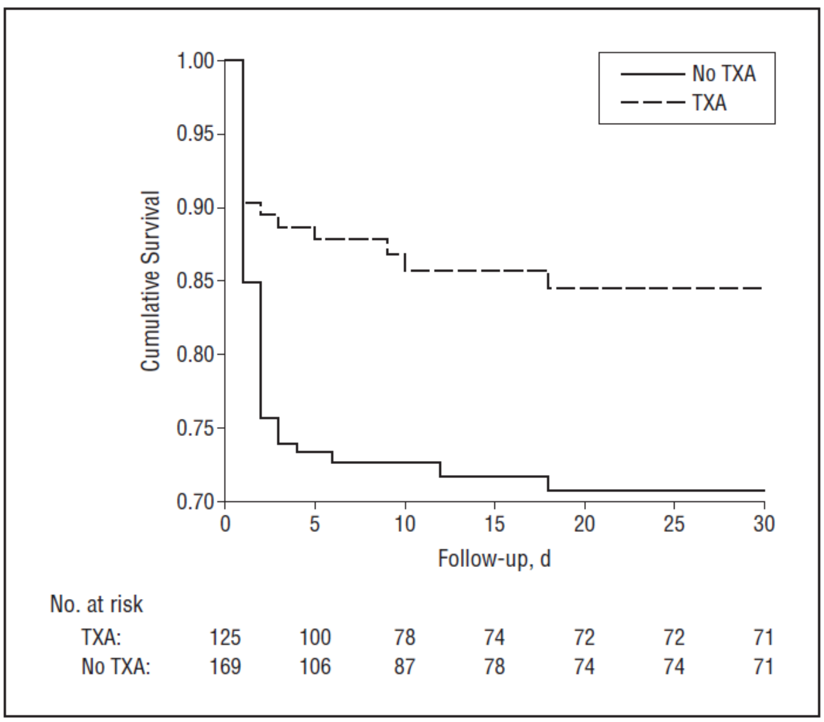
   b. Coagulation system responses to trauma and surgery are broadly similar and activation of fibrinolysis has been observed in surgical patients. Anti-fibrinolytic agents, including TXA, have been used to decrease bleeding and the need for blood transfusions in coronary artery bypass grafting, orthotopic 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 0.0.64-0.97, 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).

c. **TXA experience in combat-related hemorrhage:** A registry-based study of combat injured troops receiving blood in Afghanistan[7] (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 ± SD dose: 2.3 ± 1.3g) 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).

d. 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.[7]



Kaplan-Meier survival curve of the overall cohort, patients receiving TXA or no-TXA, p = 0.006 (Wilcoxon Statistic)[7]



Kaplan-Meier survival curve of the massive transfusion group receiving TXA^{MT} or no-TXA^{MT}, p = 0.004 (Wilcoxon Statistic).[7]

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 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 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 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 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.

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.**

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.

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

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APPENDIX D

RECOMBINANT FACTOR VIIa (rFVIIa)

1. **Background.** The most critically injured casualties often present hypothermic (T < 96°F), acidemic (base deficit >5), and coagulopathic (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 study[2], 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 (30-33°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 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 (ISS > 15) and massive transfusion (pRBCs ≥ 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 trial[7] (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.

2. **FDA Position.**

   a. <u>FDA Approved Use</u>: Recombinant Factor VIIa is FDA-approved for use during critical bleeding or surgery in hemophiliac patients with inhibitors to Factor VIII or IX.

   b. <u>Unlabeled Use</u>: 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.

   c. <u>Potential adverse events</u>:[9] 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.[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.

4. **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 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 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.**

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 1u platelets
      2) Redose rFVIIa 90-120 mcg/kg IV push[1]
6. **Administration Limits.**
   a. 3 doses within a 6 hour period
   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. Room temperature stable product currently available throughout theater. The refrigerated product is no longer in USCENTCOM formulary.
   b. Reconstitution is with sterile water for injection at room temperature.
   c. The reconstituted solution may be used up to 24 hours after reconstitution.
8. **Relative Contraindications.**[9] Known hypersensitivity to rFVIIa or any of its components. Known hypersensitivity to mouse, hamster, or bovine proteins.
9. **Absolute Contraindications.** Active cardiac disease.
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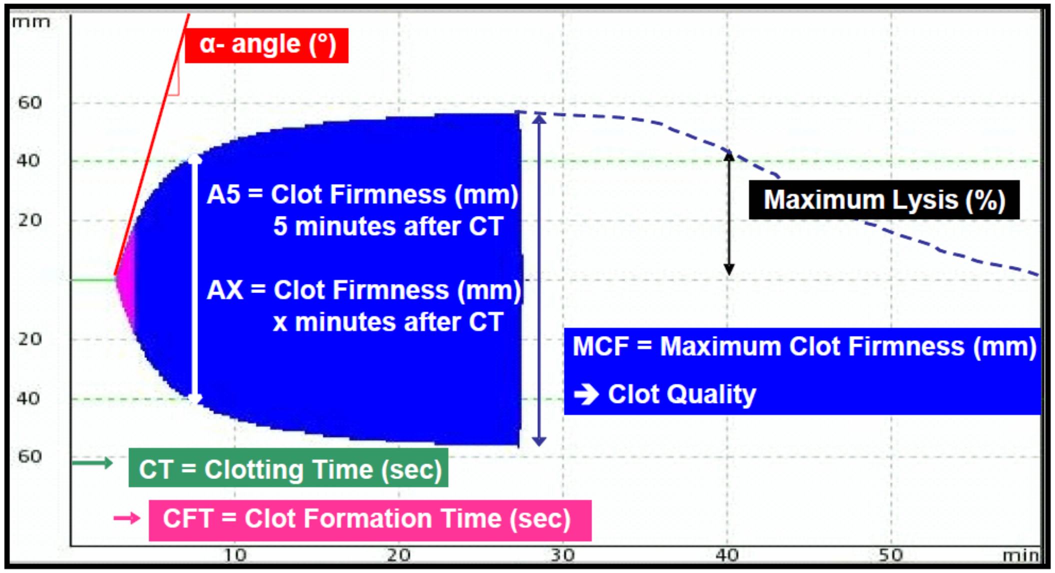
APPENDIX E

ROTEM® MANUFACTURER'S GUIDELINES

ROTEM® 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 [4]	150-700 [4]	30-70 [4]			35-60 [4]		40-65 [4]	94-100 [4]	< 15 [4]

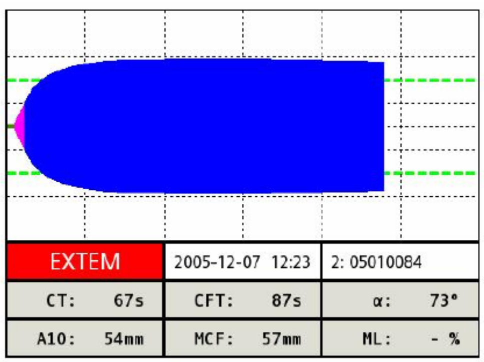
Referenz: Lang T, Bauters A, Braun SL, Poetzsch B, von Pape K-W, Kolde H-J, Lakner M. Multi-centre investigation on reference ranges for ROTEM® thromboelastometry (eingereicht in Blood Coagulation and fibrinolysis)

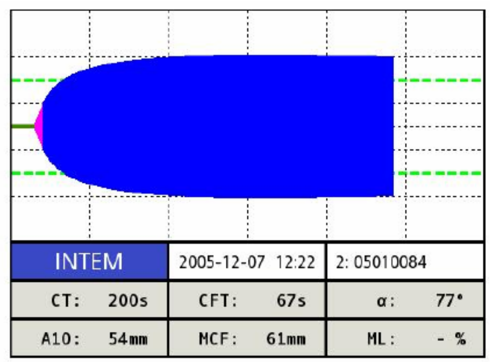
Test specificities: EXTEM & INTEM

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





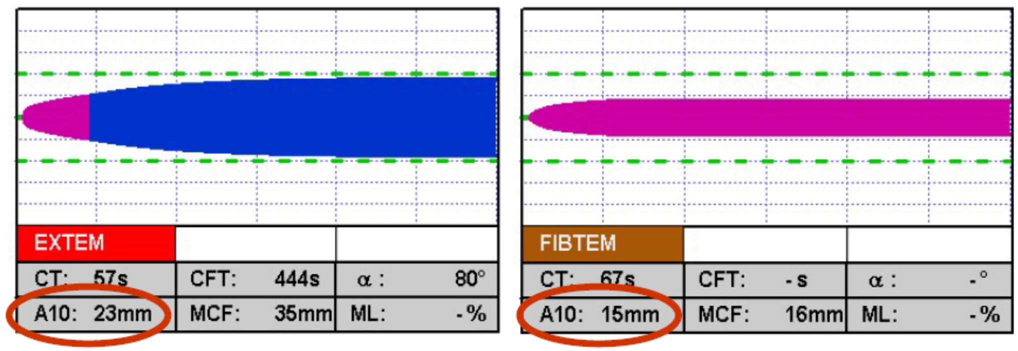
Test specificities: FIBTEM

FIBTEM:
- activation as in EXTEM
- platelet inhibition reagent added

→ TEMogram shows isolated fibrinogen contribution to Clot firmness

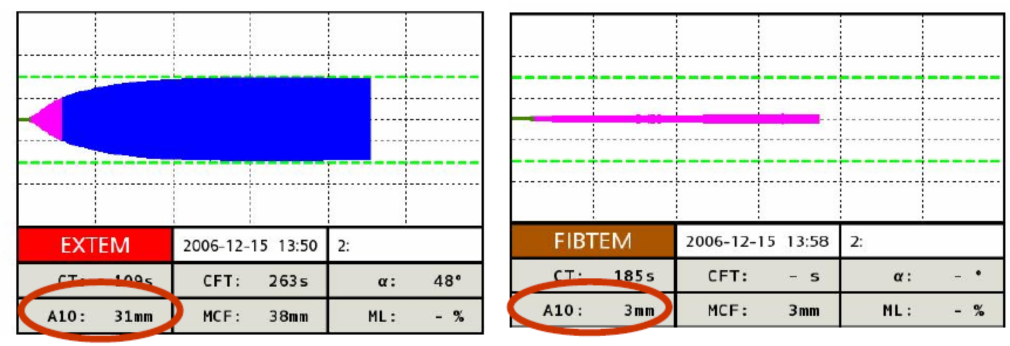
A)
- EXTEM: amplitude low
- FIBTEM: amplitude normal

=> fibrinogen level OK
=> platelet deficiency



B)
- EXTEM: amplitude low
- FIBTEM: amplitude low

=> fibrinogen deficiency



Test specificities: APTEM

APTEM:

- activation as in EXTEM
- fibrinolysis inhibition with aprotinin

=> TEMogram identifies hyperfibrinolysis

A) • EXTEM: clear hyperfibrinolysis (ML 100%)

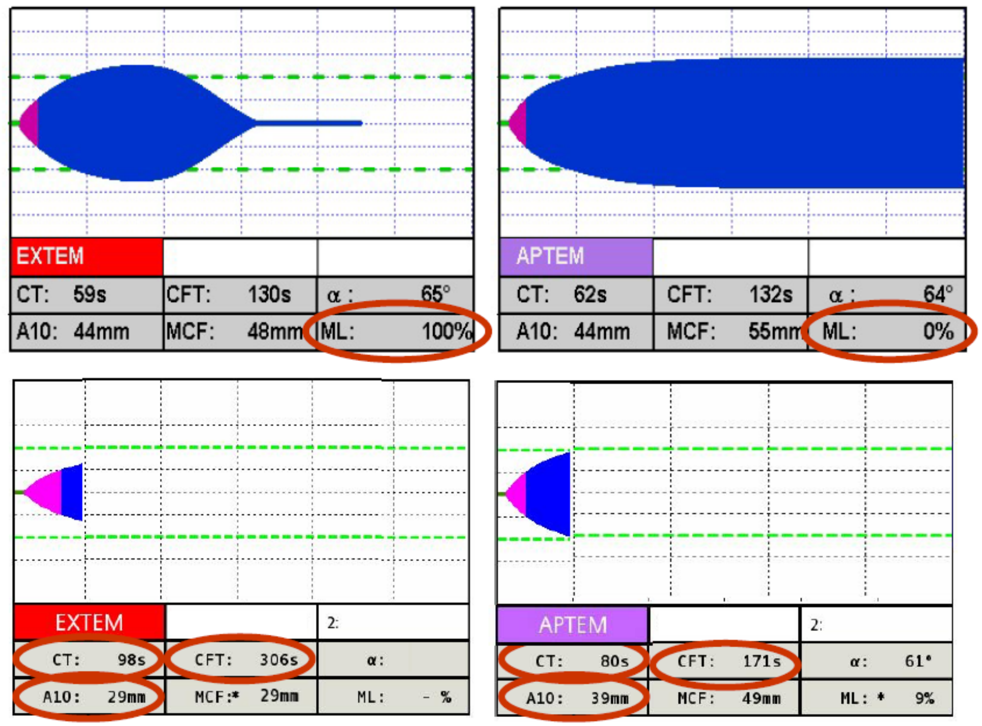
• APTEM: fibrinolysis inhibited (ML <15%)

=> Fulminant hyper-fibrinolysis

B) • APTEM:

CT > 10% shorter &
CFT > 20% shorter &
A10 higher than EXTEM
(or 2 out of 3)

=> Consider mild hyper-fibrinolysis which will become visible later during measurement



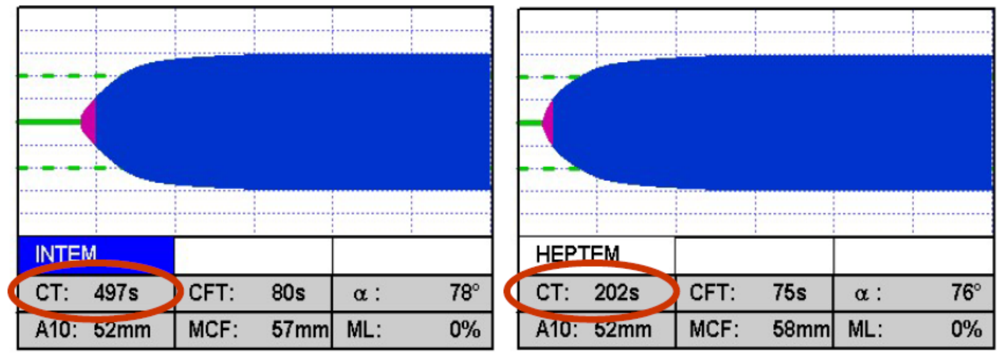
Test specificities: HEPTEM

HEPTEM:
- activation as in INTEM
- heparin inhibition with heparinase

⇒ TEMogram identifies heparin effects

A)
- INTEM: CT long
- HEPTEM: CT normalised

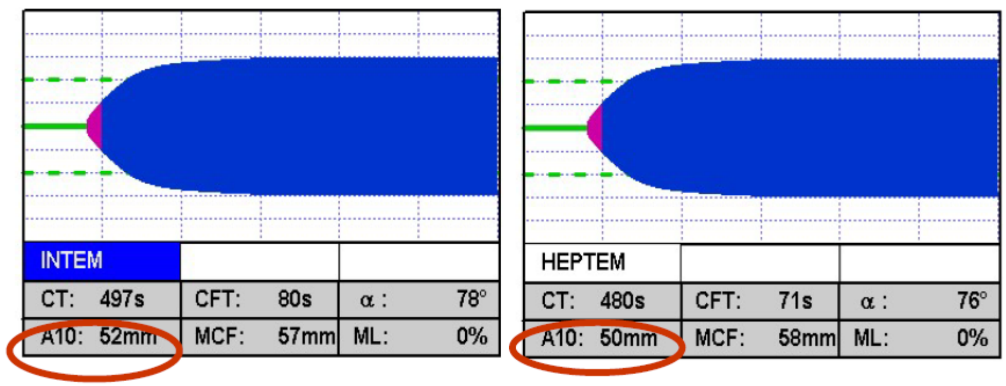
⇒ Heparin effect

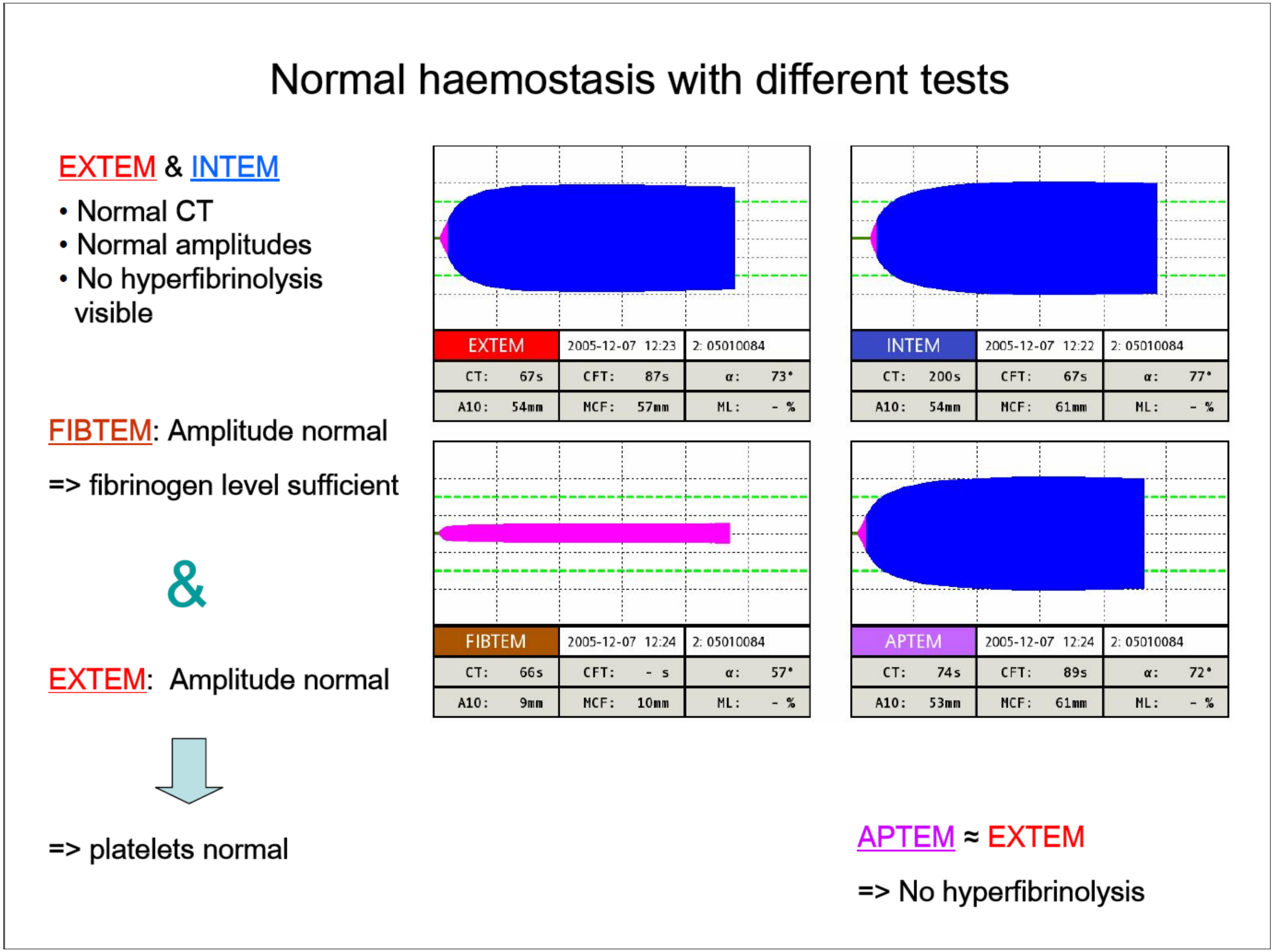


B)
- INTEM: CT long
- HEPTEM: CT also long

⇒ No heparin effect

⇒ Factor deficiency (limited sensitivity to isolated single factor deficiency)




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
EXTEM 2005-12-07 12:23 2: 05010084
CT: 67s CFT: 87s α: 73°
A10: 54mm MCF: 57mm ML: - %
INTEM 2005-12-07 12:22 2: 05010084
CT: 200s CFT: 67s α: 77°
A10: 54mm MCF: 61mm ML: - %
FIBTEM 2005-12-07 12:24 2: 05010084
CT: 66s CFT: - s α: 57°
A10: 9mm MCF: 10mm ML: - %
APTEM 2005-12-07 12:24 2: 05010084
CT: 74s CFT: 89s α: 72°
A10: 53mm MCF: 61mm ML: - %
APTEM ≈ EXTEM
=> No hyperfibrinolysis

APPENDIX F

ADDITIONAL INFORMATION REGARDING OFF-LABEL USES IN CPGs

1. **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.
2. **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.
3. **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.
4. **Additional Procedures**.
    a. 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.

    b. 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.

    c. 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.