THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

Managing Hemostasis in Trauma
Acute Coagulopathy of Trauma & Shock

ACOTS

NovoSeven® Efficacy and Risk
Cyclokapron® (tranexamic acid)

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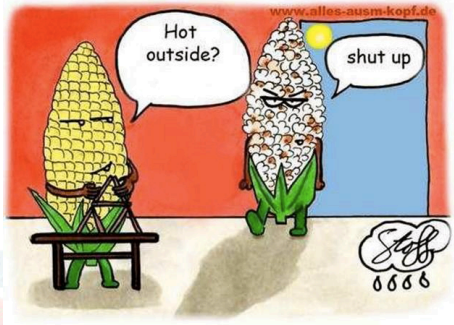
Heat Wave of 2011



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Death by Trauma: Statistics

- Unintended or intentional injury are the most common cause of death in N Americans age 1–45
  - 93,000/year in the USA
  - 3,000,000 worldwide, but exceeded by AIDS deaths
- 50% of trauma deaths are caused by neurological displacement and occur before reaching hospital
- 20,000 who reach the hospital alive die of *exsanguination* within 48 hours
  - 30–35% of blood loss *with uncompensated shock* is fatal
  - Coagulopathy may be key; failure to achieve hemostasis
  - 3000–4,000 deaths are preventable

Boffard KD, Choog PIT, Kloger Y, et al. The treatment of bleeding is to stop the bleeding! Treatment of trauma-related hemorrhage. On behalf of the NovoSeven Trauma Study Group. Transfusion 2009; 49:240–7S.

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CDC: WISQARS*

10 Leading Causes of Death, United States
2007, All Races, Both Sexes

Rank	Age Groups										All Ages
	<1	1-4	5-9	10-14	15-24	25-34	35-44	45-54	55-64	65+	
1	Congenital Anomalies 5,785	Unintentional Injury 1,598	Unintentional Injury 865	Unintentional Injury 1,209	Unintentional Injury 15,997	Unintentional Injury 14,977	Unintentional Injury 16,631	Malignant Neoplasms 80,167	Malignant Neoplasms 103,171	Heart Disease 496,095	Heart Disease 616,067
2	Short Gestation 4,857	Congenital Anomalies 646	Malignant Neoplasms 480	Malignant Neoplasms 479	Homicide 5,551	Suicide 5,279	Malignant Neoplasms 13,268	Heart Disease 37,454	Heart Disease 85,527	Malignant Neoplasms 389,730	Malignant Neoplasms 562,875
3	SIDS 2,493	Homicide 599	Congenital Anomalies 196	Homicide 213	Suicide 4,140	Homicide 4,709	Heart Disease 11,839	Unintentional Injury 30,315	Chronic Low Respiratory Disease 12,777	Cerebro-vascular 115,961	Cerebro-vascular 135,952
4	Maternal Pregnancy Comp. 1,769	Malignant Neoplasms 364	Homicide 133	Suicide 165	Malignant Neoplasms 1,653	Malignant Neoplasms 3,463	Suicide 6,722	Liver Disease 8,212	Unintentional Injury 12,193	Chronic Low Respiratory Disease 109,902	Chronic Low Respiratory Disease 127,924
5	Unintentional Injury 1,295	Heart Disease 173	Heart Disease 110	Congenital Anomalies 178	Heart Disease 1,084	Heart Disease 3,223	HIV 3,072	Suicide 7,719	Diabetes Mellitus 11,304	Alzheimer's Disease 73,797	Unintentional Injury 123,706
6	Placenta Cord Membranes 1,135	Influenza & Pneumonia 169	Chronic Low Respiratory Disease 54	Heart Disease 131	Congenital Anomalies 402	HIV 1,091	Homicide 3,062	Cerebro-vascular 6,389	Cerebro-vascular 10,930	Diabetes Mellitus 51,929	Alzheimer's Disease 74,632
7	Bacterial Sepsis 820	Septicemia 78	Influenza & Pneumonia 48	Chronic Low Respiratory Disease 50	Cerebro-vascular 195	Diabetes Mellitus 610	Liver Disease 2,970	Diabetes Mellitus 5,753	Liver Disease 8,004	Influenza & Pneumonia 43,941	Diabetes Mellitus 71,382
8	Respiratory Distress 789	Perinatal Period 70	Benign Neoplasms 41	Influenza & Pneumonia 55	Diabetes Mellitus 168	Cerebro-vascular 505	Cerebro-vascular 2,133	HIV 4,156	Suicide 5,009	Nephritis 36,492	Influenza & Pneumonia 52,717
9	Circulatory System Disease 624	Benign Neoplasms 59	Cerebro-vascular 38	Cerebro-vascular 45	Influenza & Pneumonia 163	Congenital Anomalies 417	Diabetes Mellitus 1,984	Chronic Low Respiratory Disease 4,153	Nephritis 4,443	Unintentional Injury 30,392	Nephritis 46,448
10	Neonatal Hemorrhage 597	Chronic Low Respiratory Disease 57	Septicemia 36	Benign Neoplasms 43	Three Tied 160	Liver Disease 394	Septicemia 910	Viral Hepatitis 2,815	Septicemia 4,231	Septicemia 26,362	Septicemia 34,828

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24-YO ♂, GSW in ED

A 24-YO male arrived in the ED with a gunshot wound causing massive abdominal trauma. He had been given three units of Dextran® in transit to achieve fluid resuscitation but was hemorrhaging.

ED personnel ordered and administered four RBC units. Upon the second RBC four-unit batch order the transfusion service director recommended one plasma and one pheresis platelet concentrate. After 8 RBCs, 1 plasma, and 1 platelet, still bleeding, labs were:

PT: 20.8 s (Mean of RI 12.9); PTT: 82.5 s (MRI 30.1)

FG: 130 mg/dL (225-498 mg/dL); PLTs: 70,000/mcL

Current Typical Approach to ACOTS

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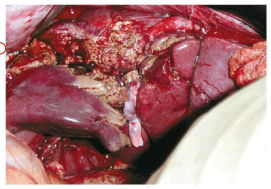
24-YO W♂, GSW in ED

In surgery, major vessels were tied, but the field was obscured by microvascular bleeds. The patient went into shock and expired.

Thanks to Margaret Fritsma, Mary Anne Krupsky, Michelle Brown, Birmingham, AL and Jose De Jesus, Tuscaloosa, AL for assistance with this case.



Current Typical Approach to ACOTS

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American Society of Anesthesiologists Surgical Practice Guidelines: *RBCs*

- Monitor BP, pulse, ABG (pH, O_2 sat), urine output, EKG when feasible
- Monitor physical blood loss
- Transfuse when HGB <6 g/dL in young, healthy patient
- Do not transfuse when HGB >10 g/dL
- Transfuse based on acuity and clinical history when HGB 6–10 g/dL
  - O_2 sat, tissue ischemia, bleeding rate, IV volume replacement, evidence for coagulopathy
- Autotransfuse (recovery) when feasible

Current Typical Approach to ACOTS
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American Society of Anesthesiologists Practice Guidelines: *Coagulopathy*

- Assess surgical field for microvascular bleeding
  - Suction canisters, surgical sponges, surgical drains
- Platelet concentrate transfusion
  - No platelets if count is >100,000/mcL
  - "Usually" give platelets if <50,000/mcL, unless…
    - Limited blood loss is anticipated based on type of surgery
    - If thrombocytopenia is due to HIT, ITP, or TTP, where platelets may be ineffective
  - From 50–100,000/mcL, use platelets if…
    - Potential of bleeding into confined space such as brain or eye
    - Antiplatelet drugs, cardiopulmonary bypass, platelet disorder

Duchesne JC, Holcomb JB. Damage control resuscitation: addressing trauma-induced coagulopathy. Br J Hosp Med (Lond) 2009; 70: 22–5.

Current Typical Approach to ACOTS
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American Society of Anesthesiologists Practice Guidelines: *Coagulopathy*

- Do not use plasma only to augment volume, use colloid plasma expanders
  - 5D: lactated Ringers saline with 5% dextrose
- Give plasma if microvascular bleeding…
  - And PT >1.5X normal ("normal" is undefined by ASA),
  - Or PTT >2X normal,
  - Or when transfused with >1 blood volume (~70 mL/kg),
  - Or needed for urgent reversal of warfarin therapy,
  - Or known factor deficiency & concentrate is unavailable.
- Dosage is 10–15 mL plasma/kg to achieve ≥30% factor concentration
  - Or 5–8 mL/kg if only for warfarin reversal

Current Typical Approach to ACOTS
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American Society of Anesthesiologists Practice Guidelines: *Coagulopathy*

- CRYO when there is microvascular bleeding and…
  - Fibrinogen <100 mg/dL or documented deficiency,
  - Or massive transfusions without opportunity to determine fibrinogen level
- CRYO delivers 150–250 mg fibrinogen
- Consider recombinant activated factor VII (NovoSeven®, rFVIIa) when RBCs, PLTs, plasma and CRYO fail

Practice guidelines for perioperative blood transfusion and adjuvant therapies: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. Anesthesiology 2006; 105: 198–208.

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Massive Tx requirement is likely in young, healthy combat casualties when…

- Systolic <110 mm Hg
- Pulse >105
- pH <7.25
- HCT <32%
- HGB <10 g/dL
- INR >1.5
  - *Is INR the correct measure?*

McLaughlin DF, Niles SE, Salinas J, et al. A predictive model for massive transfusion in combat casualty patients. J Trauma 2008;64:S57–63.
Schreiber MA, Perkins J, Kiraly L, et al. Early predictors of massive transfusion in combat casualties. J Am Coll Surg 2007;205:541–5

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RBC/Plasma 1:1?

- USA hospital in Baghdad Green Zone
  - Retrospective w/o controls but extensive, accurate data
  - Tx >2000 wounded, massively Tx >600 wounded
- Ratio and results
  - Receiving <1 plasma for every 4 RBCs: 65% mortality
    - Confounding data: soldiers who received >10 RBCs but died before plasma could thaw are counted in this arm of the study
  - Receiving 2 plasma for every 3 RBCs: 19% mortality
    - Surgeons report less bleeding and edema
  - Now implementing 1:1 plasma/RBC Rx
- Anticipated adverse effects; none recorded
  - Plasma supply (yes), TRALI, anaphylaxis, ARDS, MOF, thrombosis

Borgman MA, Spinella PC, Perkins JG, et al. The ratio of blood products transfused affect mortality in patients receiving massive transfusions in a combat support hospital. J Trauma 2007; 63: 805–13.

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Current Typical Approach to ACOTS 12

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Massive Trauma With Hemorrhagic Shock

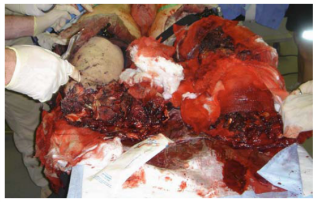

Figure 2. Severely injured patients can present with coagulopathy at the time of hospital admission. This soldier arrived in hemorrhagic shock and required massive transfusion with packed red blood cells (pRBC), coagulation products, and whole blood. Tourniquets were placed on the patient's thighs in the field to minimize blood loss.

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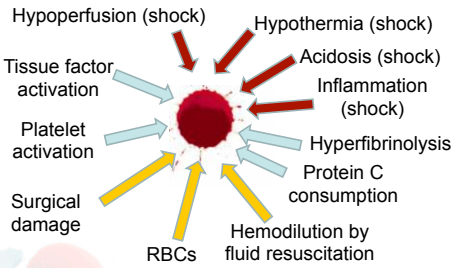
Acute Coagulopathy of Trauma-Shock (ACOTS)



Duchesne JC, Holcomb JB. Damage control resuscitation: addressing trauma-induced coagulopathy. Br J Hosp Med (Lond) 2009; 70: 22–5.

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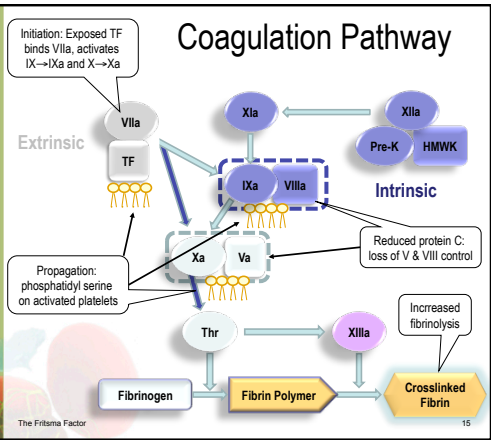
Coagulation Pathway



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1974 Injury Severity Score (ISS)

Region	Description (Examples)	Injury Score (1–6)	Highest 3 Squared
Head & neck	Cerebral contusion	3 (Serious)	9
Face	Scratches	1 (Minor)	
Chest	Sucking wound	4 (Severe)	16
Abdomen	Liver contusion Spleen rupture	2 (Moderate) 5 (Critical)	25
Extremity	Fractured femur	3 (Serious)	
External	Skin abrasions	0	
Total ISS			50

Maximum is 75. If an injury is assigned a score of 6 (unsurvivable), the ISS is automatically 75.
The ISS is the only anatomical scoring system in use and correlates linearly with mortality, morbidity and hospital stay.

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Baker SP, et al. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. J Trauma 1974;14:187–96

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Probability of Life-threatening Coagulopathy

Condition (n = 58, >10 RBCs)	Percent Coagulopathy
Injury severity score (ISS) >25 alone	10%
ISS >25 & systolic blood pressure <70 mm Hg	39%
ISS >25 & body temp <34°C	49%
ISS >25 & pH <7.10	58%
ISS >25; SBP <70 mm Hg; body temp <34°C	85%
ISS >25; SBP <70 mm Hg; temp <34°C; pH <7.10	98%

Life-threatening coagulopathy is empirically defined as PT *and* PTT >2X mean of reference interval (MRI)

Cosgriff N, Moore EE, Sauaia A, et al. Predicting life-threatening coagulopathy in the massively transfused trauma patient: hypothermia and acidosis revisited. J Trauma 1997;42:857-862

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Coagulopathy in Trauma

ISS & Coagulopathy n = 1088	% Coagulopathy by Lab Assay
Injury severity score (ISS) >15; median 20	57.7%
Injury severity score <15	10.9%
Coagulopathy at Admission	**% Mortality**
Yes (24.4%)	46%
No	10.9%
Overall mortality	19.5%

Coagulopathy is defined prior to, and independent of fluid replacement as:
PT >18s,16.3%; PTT >60s, 24.4%; or TCT >15s, 14.2%

Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. J Trauma 2003; 54: 1127-30

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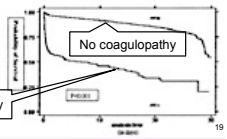
PT and PTT Predict Mortality

- Review of 7638 level I trauma admissions
- Initial PT >14s: 28% of admissions
  - 6.3% of patients with PT <14s died
  - 19.3% of patients with PT >14s died
  - Independent mortality increase 35%; OR, 3.6; p <0.0001
    - When controlling for age, ISS, BP, HCT, pH, and head injury
- Initial PTT >34s: 8% of admissions
  - Independent mortality increase 326%; OR 7.8; p <0.001

MacLeod JB, Lynn M, McKenney MG, et al. Early coagulopathy predicts mortality in trauma. J Trauma 2003;55:39-44.



Coagulopathy

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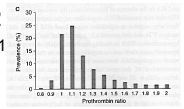
Definition and "Drivers" of ACOTS

- Retrospective cohort study
  - 3646 trauma patients at 5 international trauma centers
- Prothrombin time ratio >1.2
  - Mortality 22.7% Vs. 7.0%, p <0.001
  - RBCs 3.5 Vs. 1.2 units, p <0.001
  - Plasma 2.1 Vs. 0.8 units, p <0.001



- When ACOTS is defined as PTR >1.2, it correlates with ISS and shock
- Confirmed using rat model (not described)

Frith D, Goslings JC, Gaarder C, et al. Definition and drivers of acute traumatic coagulopathy: clinical and experimental investigations. J Thromb Haemost 2010;8: 1919-25.

Coagulopathy

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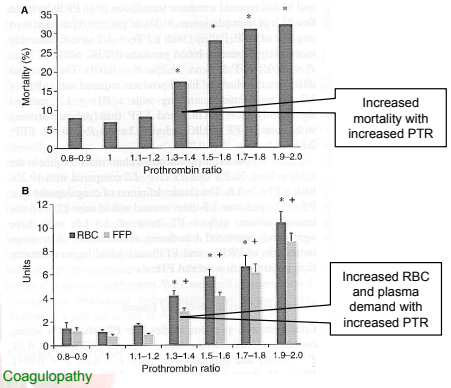

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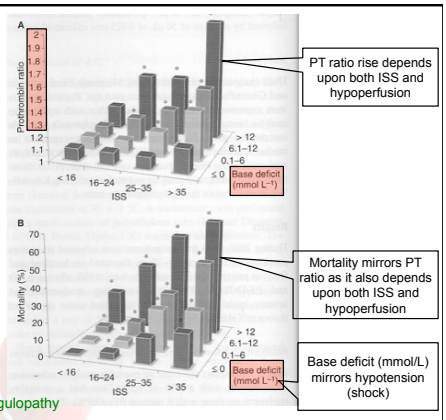

Coagulopathy

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Recombinant Activated Factor VII

- Pre-1980 (and still available)
  - Prothrombin complex concentrates (PCC) extracted from human plasma using Ba_2SO_4 absorption: Proplex®
    - Factors II, VII, IX, and X, once used for IX deficiency patients
  - Activated PCC for FVIII or FIX deficiency with inhibitors
    - FEIBA FH® and Autoplex T®
    - Variant efficacy traced to FVIIa activity
- 1980: Extract FVIIa from human plasma
  - Kisiel, Broze
- 1983: Compassionate use in two humans
- 1988: Novo Nordisk®, Bagsvaerd, Denmark, undertook to synthesize rFVIIa as orphan drug
- March 25, 1999: FDA releases NovoSeven® rFVIIa

Kisiel W. Recollections on the discovery of factor VIIa as a novel therapeutic agent for hemophiliacs with inhibitors. J Thromb Haemost 2009;7:1053–6.
Broze GJ, Majerus PW. Purification and properties of human coagulation factor VII. J Biol Chem 1980;255:1242–7.

rFVIIa

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FEIBA FH® Dosages

- Activated prothrombin complex concentrate
  - Activated II (thrombin), VII, IX, and X

Indication	Dose
Joint bleeding	50 units/kg every 12 h
Mucous membrane bleeding	50 units/kg every 6 h
Muscle bleeding	100 units/kg every 12 h
To avoid DIC, FEIBA FH dose may not exceed 200 units/kg in 24 hours and infusion rate may not exceed 2 units/kg/minute	
There is no test to monitor FEIBA directly. The patient's clinical response, e. g., bleeding or hematoma size, plus global assays, PT and PTT are the guide.	
Cost $0.50/unit, single Rx for a 70 kg patient is $1750	

rFVIIa

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rFVIIa; NovoSeven

- Secreted from baby hamster kidney cells, proteolytically converted to two-chain active form
- Limitation: γ-carboxylation of 2/3 of glutamic acids at amino terminus
  - Seems to be enough γ-carboxylated GLUs
  - Requires coexpressed γ-glutamyl carboxylase
  - Requires vitamin K

~12 GLU molecules
~8 become GLA

NH_2

rFVIIa

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Physiology of rFVIIa & Tissue Factor

- rFVIIa binds TF of injured vessels, activating FX; FXa binds FV; activates II→IIa; generates fibrin
- rFVIIa activates platelets *directly* through thrombin receptors and triggers primary coagulation even in Glanzmann thrombasthenia
- rFVIIa activates *thrombin activatable fibrinolysis inhibitor* (TAFI), simultaneously reduces fibrinolysis
- rFVIIa hemostatic action is localized by TF
  - FEIBA functions systemically, causes DIC
  - DIC risk is negligible for rFVIIa

Mathew P, Young G. Recombinant factor VIIa in paediatric bleeding disorders —a 2006 review. Haemophilia 2006;12:457–72.
Hedner U, Kisiel W. Use of human factor VIIa in the treatment of two hemophilia A patients with high-titer inhibitors. J Clin Invest 1983;71:1836–41.

rFVIIa

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Coagulation Pathway

Initiation: rFVIIa binds TF, triggers IX→IXa and X→Xa

Extrinsic
VIIa
TF
Xa
Va
Common
Propagation: rFVIIa exposes phosphatidyl serine on activated platelet
Thr
XIIIa
Fibrinogen
Fibrin Polymer
Crosslinked Fibrin
IXa
VIIIa
Intrinsic
XIa
XIIa
Pre-K
HMWK

Fritsma MG, Fritsma GA. Overview of Hemostasis and Coagulation. In Rodak BF, Fritsma GA, Keohane E. Hematology, 4th Edition, Elsevier 2011

rFVIIa

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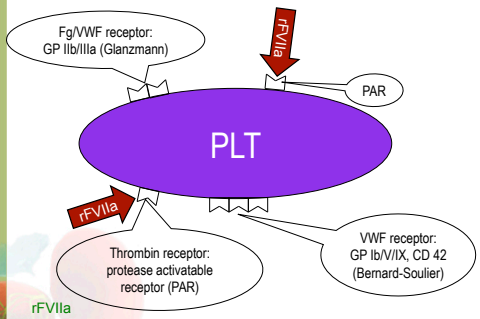
rFVIIa Activates Thrombin Receptors



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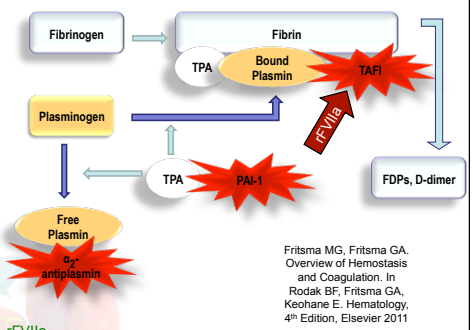
rFVIIa Activates TAFI



Fritsma MG, Fritsma GA. Overview of Hemostasis and Coagulation. In Rodak BF, Fritsma GA, Keohane E. Hematology, 4th Edition, Elsevier 2011

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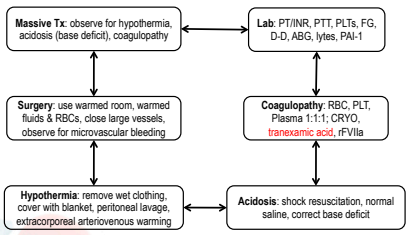
Summary: Caring for ACOTS



Modified from: Tieu BH, Holcomb JB, Schreiber MA. Coagulopathy: Its pathophysiology and treatment in the injured patient .World J Surg 2007 31: 1055–64

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rFVIIa 3/25/99 FDA Indications

Cleared Indication	IV Bolus Dose
Bleeding episode in hemophilia A or B with inhibitor	90 mcg/kg every 2 h until hemostasis is achieved
Surgery in hemophilia A or B or with inhibitor	90 mcg/kg immediately before and every 2 h during surgery
After minor surgery in hemophilia A or B with inhibitor	90 mcg/kg every 2 h for 48 h, then every 2–6 h until healed
After major surgery in hemophilia A or B with inhibitor	90 mcg/kg every 2 h for 5 d then every 2 h until healed
Congenital FVII deficiency—bleeding episode or surgery	15–30 mcg/kg every 4–6 h until healed
Acquired hemophilia—bleeding episode or surgery	70–90 mcg/kg every 2–3 h until hemostasis is achieved
Cost $1.00/mcg, single Rx for a 70 kg patient is $6300	

NovoSeven® RT Coagulation Factor VIIa (Recombinant) Room Temperature Stable

rFVIIa
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Off-label Applications for NovoSeven®

- Cardiac, thoracic, aortic and spinal surgery; hepatic resection; hysterectomy, post-partum bleeding
- Severe multiple trauma
- Non-traumatic intracranial hemorrhage if <4 hours from onset
- Reversal of antithrombotic (warfarin) overdose

rFVIIa
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Off-label Guidelines for NovoSeven®

- Evaluate underlying disorder
- Evaluate salvageability of the patient
- Ensure no inherent thrombophilia, prior AMI or stroke
- Exhaust current treatment options
  - RBCs, plasma, PLTs, CRYO
- Document amount of blood products used
- Ensure pH >7.25

Mathew P, Simon TL, Hunt KE, Crookston KP. How we manage requests for recombinant factor VIIa (NovoSeven). Transfusion 2007;47:8–14.

rFVIIa
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Generalized Off-label Guidelines for NovoSeven®

- Always offer rFVIIa when bleeding continues after conventional Tx therapy
  - RBC, plasma, platelets, and CRYO
  - rFVIIa doesn't work when coagulation factors <30%
  - 40–90 mcg/kg in adults for all emergent scenarios
- Contraindicated in previous thrombosis
  - Stroke: ensure it is intracranial hemorrhage
  - Assume no thrombosis in young trauma victims
- 20–40 mcg/kg in non-emergent warfarin reversal

Personal communication, R. Sarode, MD, Director, Transfusion Medicine and Hemostasis Reference Laboratory, UT Southwestern MC, Dallas, TX

rFVIIa
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Off Label Use in Trauma: 2005

- Israeli soldier with bleeding rescued by rFVIIa
- Approved by USA surgeon general for battlefield
- Case reports of efficacy and research protocols by Col. John B. Holcomb, MD
  - Commander of the US Army Institute of Surgical Research, Ft Sam Houston, TX, and Trauma Consultant for The Army Surgeon General

Alten JA, Benner K, Green K, et al. Pediatric off-label use of recombinant factor VIIa. Pediatrics 2009;123:1066–72.
Levi M, Peters M, Buller HR. Efficacy and safety of recombinant factor VIIa for treatment of severe bleeding: a systematic review. Crit Care Med 2005;33:883–90.
Tatoulis J, Theodore S, Meswani M, et al. Safe use of recombinant activated factor VIIa for recalcitrant postoperative haemorrhage in cardiac surgery. Interact Cardiovasc Thorac Surg 2009;9:459–62.
Martinowitz U, Michaelson M. Guidelines for the use of recombinant activated factor VII (rFVIIa) in uncontrolled bleeding: a report by the Israeli Multidisciplinary rFVIIa Task Force. J Thromb Haemost 2005;3:640–8.

rFVIIa
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Spinella: Iraq Combat Trauma

- Retrospective case-control study of 124 severe Iraq combat trauma patients
  - ≥10 units RBCs/24h
- Determine if rFVIIa reduces 24 h and 30 d mortality
- Determine association of rFVIIa with severe VTE

One 120 mcg/kg dose	Means	
Transfusion	75 Controls	49 rFVIIa
RBC (units)	14	16
Plasma (units)	8	10
Fresh whole blood (units)	0	4
Cryo (units)	0	10

Spinella PC, Perkins JG, McLaughlin DF, et al. The effect of recombinant activated factor VII on mortality in combat-related casualties with severe trauma and massive transfusion. J Trauma 2008; 4: 286–93.

rFVIIa
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Your Interactive Hemostasis Resource

Spinella: Mortality Rate in Iraq

All-cause Mortality	75 Controls	49 rFVIIa	P
12 h	25 (33%)	6 (12%)	.008
24 h (cumulative)	26 (35%)	7 (14%)	.01
30 d (cumulative)	38 (51%)	15 (31%)	.03
Thromboembolism	0	2	.15
37 patients died from hemorrhage	29 (78%)	8 (57%)	.12

rFVIIa

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Harrison: General Trauma

- Prospective study of rFVIIa-treated trauma patients matched to historic controls
- Mortality rates 41% in rFVIIa, 40% in controls (NS)
- Thromboemboli in 6.9% of rFVIIa, 19.7% of controls; (P=0.2)

1–2 40 mcg/kg doses	Means (SD not shown)		P
Immediate Transfusion	72 Controls	29 Cases	
RBC (units)	22.0	18.3	.036
Plasma (units)	14.1	14.2	NS
PLT (5-pack units)	2.3	1.4	.01
Cryo (5-pack units)	1.5	0.59	.006

Harrison TD, Laskosky J, Jazaeri O, et al. "Low-dose" recombinant activated factor VII results in less blood and blood product use in traumatic hemorrhage. J Trauma 2005; 59: 150–4.

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Holcomb: Tx Requirements 48 Hours After First Dose of rFVIIa

	Placebo		rFVIIa		P
	N	Median	N	Median	
RBC (units)	65	6.6	48	2.9	<0.001
Plasma (mL)	54	1400	35	660	0.001
PLT (mL)	62	300	46	50	0.01

- Incidence of MOF or ARDS was 20% for placebo, 3% for rFVIIa, P=.004
- Incidence of thromboembolic events was 4% for placebo and 3% for rFVIIa, P=1.00

Duchesne JC, Holcomb JB. Damage control resuscitation: addressing trauma-induced coagulopathy. Br J Hosp Med 2009;70: 22–5.

rFVIIa

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For Patients Alive at 48 Hours

Median RBC Units					
Blunt Trauma			Penetrating Trauma		
Placebo	rFVIIa	P	Placebo	rFVIIa	P
7.5 (n=72)	7.0 (n=52)	.02*	4.2 (n=52)	3.9 (n=64)	.10

ARDS or Multi-organ Failure					
Blunt Trauma			Penetrating Trauma		
Placebo	rFVIIa	P	Placebo	rFVIIa	P
49 (66%)	44 (64%)	NS	36 (56%)	36 (51%)	NS

Thromboembolic Events					
Blunt Trauma			Penetrating Trauma		
Placebo	rFVIIa	P	Placebo	rFVIIa	P
3 (4%)	2 (3%)	NS	3 (5%)	4 (6%)	NS

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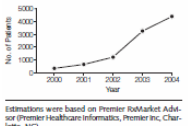
FDA Reports Thromboembolic Events

Divs. of Epidemiology and Hematology collected adverse event data 3/25/99–12/31/04, all US and non-US patients including post-licensure clinical trials

Figure 1. Estimated Number of Patients Treated With Recombinant Human Coagulation Factor VIIa by Year



Estimations were based on Premier RxMarket Advisor (Premier Healthcare Informatics, Premier Inc, Charlotte, NC).

Table 1. Number of Thromboembolic Event Reports With Use of rFVIIa by Report Source and Reason for Use and Bleeding Status

	No. of Reports (%)	
	Trial (n = 59)	Spontaneous (n = 109)
Reason for use		
Surgery (bleeding or prophylaxis)	27 (46)	48 (44)
Intracranial bleeding	13 (22)	5 (4)
Bleeding, nonsurgical	8 (14)	26 (24)
Trauma, nonsurgical	5 (9)	9 (8)
Hemophilia	0	17 (16)
Unknown*	0	4 (4)
Bleeding status		
Active bleeding	35 (59)	80 (73)
Prophylaxis	24 (41)	22 (20)
Unknown*	0	7 (7)

Abbreviation: rFVIIa, recombinant human coagulation factor VIIa.
*Indicates no information about reason for use or whether patient was bleeding or not.

O'Connell KA, Wood JJ, Wise RP, et al. Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. JAMA 2006;295:293–8.

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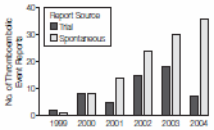
Thrombotic Events and Deaths

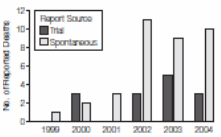
168 reports: 183 thrombotic events, 52 deaths

Figure 3. Number of Thromboembolic Event Reports With Recombinant Human Coagulation Factor VIIa Reported to FDA by Source and Year



FDA indicates US Food and Drug Administration. Some reports had more than 1 thromboembolic event.

Figure 4. Number of Reported Deaths Among Patients Administered Recombinant Human Coagulation Factor VIIa With a Thromboembolic Event by Year and Source



FDA indicates US Food and Drug Administration.

rFVIIa Thrombosis

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Thrombotic Event Sites

Site	Number (%)
Ischemic stroke	39 (21.3%)
Acute myocardial infarction	34 (18.6%)
Peripheral artery occlusion	26 (14.2%)
Deep venous thrombosis	42 (22.9%)
Pulmonary embolus	32 (17.5%)
Occluded line	10 (5.5%)
Total	**183 (100%)**
Patients in 5-y survey	~10,700
Rate of thrombotic events	0.017%

rFVIIa Thrombosis

THE FRITSMA FACTOR
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London Times, September 17, 2006

"*Wounded Iraq Troops Given Danger Drug*"

"*The Ministry of Defense has been accused of playing 'Russian roulette' with soldiers' lives after it admitted using an unlicensed drug linked to 67 deaths in America. Troops suffering severe injuries in Iraq have been treated with NovoSeven®, a drug licensed only for hemophiliacs.*"

Warning: Serious thrombotic adverse events are associated with the use of NovoSeven® RT outside labeled indications

Arterial and venous thrombotic and thromboembolic events following administration of NovoSeven® have been reported during postmarketing surveillance. Clinical studies have shown an increased risk of arterial thromboembolic adverse events with NovoSeven® RT when administered outside the current approved indications. Fatal and non-fatal thrombotic events have been reported. Discuss the risks and explain the signs and symptoms of thrombotic and thromboembolic events to patients who will receive NovoSeven® RT. Monitor patients for signs or symptoms of activation of the coagulation system and for thrombosis. **See WARNINGS AND PRECAUTIONS section of prescribing information.**

Safety and efficacy of NovoSeven® RT has not been established outside the approved indications.

rFVIIa Thrombosis

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Baltimore Sun, May 16, 2010

Federal agents probing Army's use of trauma drug

Criminal investigation looking at military's use of blood-clotting injections for treating war casualties

May 16, 2010 | By Robert Little, The Baltimore Sun

Sun photo by Monica Loposssay

Federal criminal investigators are exploring the Army's use of a controversial and expensive blood-clotting drug injected into wounded troops in Iraq and Afghanistan.

The drug, called Factor VII, was hailed as a lifesaving breakthrough by military leaders and administered to hundreds of soldiers and Marines earlier in the wars. It has since proved largely ineffective in clinical trials and been the subject of safety warnings by U.S. and European regulators, who say it can cause potentially deadly blood clots.

Within the past several weeks, agents from the Army's Criminal Investigation Command have interviewed scientists and officers at the Army's medical laboratory in San Antonio about Factor VII, according to military sources with knowledge of the investigation. Researchers in San Antonio were among the first to explore Factor VII's role in treating trauma patients and have produced some of the few scientific studies suggesting that the drug saves lives in combat.

The manufacturer, the Danish drug company Novo Nordisk, said it had received a subpoena in January from the Defense Department's inspector general's office. Company officials said they are cooperating with the U.S. attorney's office in Baltimore, which is overseeing the investigation.

rFVIIa Thrombosis

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Meta-analysis of Off-label rVIIa: Mortality

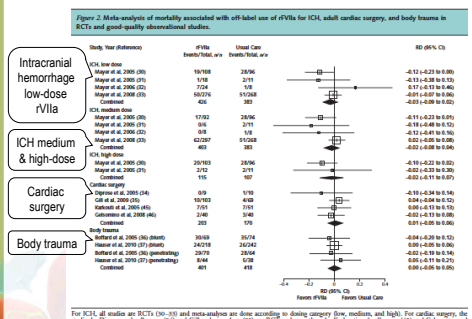

Figure 2. Meta-analysis of mortality associated with off-label use of rFVIIa for ICH, adult cardiac surgery, and body trauma in RCTs and good-quality observational studies.

Intracranial hemorrhage low-dose rVIIa
ICH medium & high-dose
Cardiac surgery
Body trauma

rFVIIa Thrombosis

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Meta-analysis of Off-label rVIIa: Thrombosis

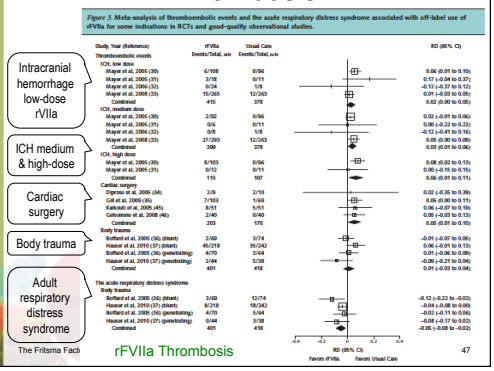

Figure 3. Meta-analysis of thromboembolic events and the acute respiratory distress syndrome associated with off-label use of rFVIIa for some indications in RCTs and good-quality observational studies.

Intracranial hemorrhage low-dose rVIIa
ICH medium & high-dose
Cardiac surgery
Body trauma
Adult respiratory distress syndrome

rFVIIa Thrombosis

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Meta-analysis Conclusion

- In-hospital off-label use of rVIIa does not reduce mortality for ICH, cardiac surgery, body trauma, brain trauma, liver transplantation, or prostatectomy
- Use of rFVIIa increases thromboembolic events in ICH and cardiac surgery
- 97% of rFVIIa use is off-label
- Cost remains ~$10,000/dose

Yank V, Tuohy CV, Logal AC, et al. Systematic review: benefits and harms of in-hospital use of recombinant factor VIIa for off-label indications. Ann Intern Med 2011;154:529-40.

rFVIIa Thrombosis

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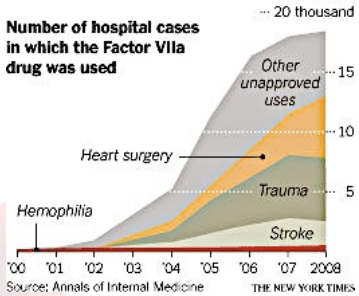
Using a Powerful Clotting Drug

A hemophilia drug that costs $10,000 a dose is being used extensively to treat other types of bleeding, though studies show no survival benefit from the unapproved uses.



The Fritsma Factor 49

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Suit Over Drug Used on GIs Settled

June 11, 2011

San Antonio Express-News

A drug company has agreed to pay $25 million to the federal government, 24 states including Texas and two whistleblowers to settle a lawsuit that alleged it improperly paid military doctors to use and promote an expensive hemophilia drug to slow bleeding in wounded soldiers.

The lawsuit, which was joined by Justice Department lawyers, claimed Novo Nordisk, a Danish company with global operations, targeted influential military doctors and researchers at the Army Institute of Surgical Research at Fort Sam Houston.

Their published studies and presentations led to its use in combat and also influenced civilian doctors to use the drug for off-label purposes despite a lack of evidence for its effectiveness.

The Fritsma Factor 50

THE FRITSMA FACTOR
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Suit Over Drug Used on GIs Settled

June 11, 2011

The lawsuit was particularly critical of Dr. John Holcomb, who served as head of the ISR at the time and now is director of the Center for Translational Injury Research at the University of Texas Health Science Center at Houston.

He did not reply to a request for comment, but in the past has defended his aggressive approach in pushing Factor VIIa in the field.

"You have a drug you know is safe from the prospective randomized controlled clinical trials," he told the New York Times in 2006. "And you have to make a decision. It's not something you can decide to talk about. It's really yes or no. You have a lot of people bleeding to death in Iraq."

The Fritsma Factor 51

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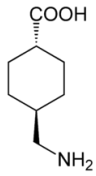
Tranexamic Acid (Cyclokapron) Rx

- Synthetic lysine blocks plasminogen binding sites
  - Cyclohexane carboxylic acid
- Reduces Tx requirements in surgery without raising mortality
- Aprotinin (trypsin inhibitor, anti-fibrinolytic) ineffective, withdrawn in 2008



CRASH-2 trial collaborators (570). Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. The Lancet 2010; 376: 23-32

TXA

The Fritsma Factor 52

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Tranexamic Acid Death by Cause

CRASH-2	TXA	Placebo	RR	p
	n = 10060	n = 10067		
Any cause of death	1463 (14.5%)	1613 (16%)	0.91	0.0035
Bleeding death	489 (4.9%)	574 (5.7%)	0.85	0.0077
Vascular occlusion death	33 (0.3%)	48 (0.5%)	0.69	0.096
No dependency symptoms	1483 (14.7%)	1334 (13.3%)	1.11	0.0023

- No significant differences:
  - MI, stroke, PE, DVT, blood products, surgery

TXA

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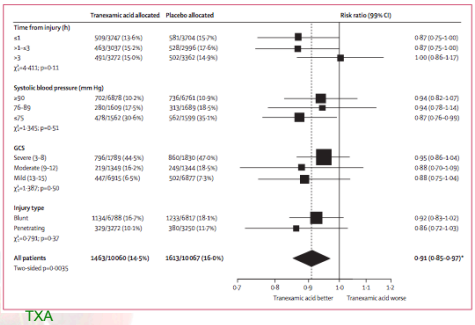
All-cause Mortality by Subgroups



TXA

The Fritsma Factor 54

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

Combat Tourniquets in Baghdad

- Prospective survey over 7 months in 2006
  - Military and civilian casualties: 2838
  - Major limb trauma requiring tourniquets: 232 (8%)
  - 428 tourniquets were applied on 309 injured limbs
  - Shock based on weak/absent radial pulse, base deficit

Tourniquet Applied:	Shock Absent	Shock Present	Sum
Pre-hospital	171/17 (91%)	1/5 (17%)	171/22
In ED	29/5 (85%)	0/4 (0%)	29/9
Sum	200/22	1/9	201/31

Alive/Dead; tourniquet use in absence of shock Vs not, $p=0.4x10^{-8}$; pre-hospital Vs ED tourniquet, p=0.06

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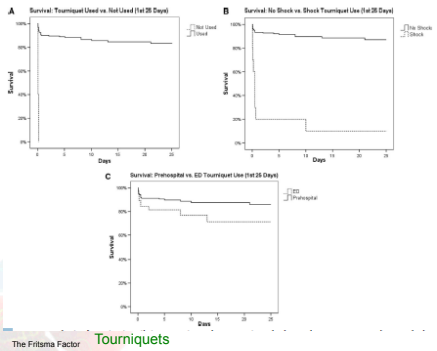
Combat Tourniquets in Baghdad



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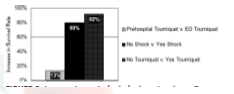
Combat Tourniquets in Baghdad

- Five casualties with tourniquet indication who had none used all died
- Four casualties (1.7%) sustained transient nerve palsy at site of tourniquet
- No amputations solely as a result of tourniquet use.



Kragh JF, Walters TJ, Baer DG, et al. Survival with emergency tourniquet: use to stop bleeding in major limb trauma. Ann Surg 2009; 249: 1-7)

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Survival in Afghanistan

The New York Times

- January 7, 2011
- Speedy evacuation
- Tourniquets
- Cyclokapron (tranexamic acid)
- NovoSeven (rVIIa)

	Total Casualties	Death Rate
2010	5,500	7.9%
2009	2415	11%
2008	402	14.3%