THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

Managing Hemostasis in Trauma-induced Coagulopathy

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US Injury Incidence

- In the USA, 36,000,000/y (1/7) suffer significant injury
- 27,000,000 injury-related doctor or hospital visits
- 1,700,000 injury-related hospital admissions
- 1,000,000 are transferred to trauma centers
- 10,000 require massive transfusion
- Extent of injury is determined by *whole body CT scan* or *focused abdominal sonography for trauma* (FAST)

Zimrin AB, Bai Y, Holcomb JB, Hess JR. Hemorrhage control and thrombosis following severe injury. In Kitchens CS, Kessler CM, Konkle BA. Consultative Hemostasis and Thrombosis. Elsevier, 2013

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Death by Trauma

- Unintended or intentional injury is the most common cause of death in N Americans age 1–45
  - 93,000/y in the USA, up 20% since 2005
  - 3,000,000/y worldwide, exceeded only by AIDS deaths
- 50% of trauma deaths are caused by neurological displacement and occur before reaching hospital
- 20,000 die in hospital of *exsanguination* in 48 h
  - 30–35% with blood loss & uncompensated shock expire
  - 3–4,000 of US hemorrhage deaths are preventable
  - Coagulopathy, failure to achieve hemostasis

Rhee P, Joseph B, Pandit V, et al. Increasing trauma deaths in the United States. Ann Surg 2014;260: 13–21.

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Years of Potential Life Lost (YPLL) Before Age 65

Cause of Death	YPLL	Percent	
All Causes	948,426	100.0%	
Unintentional Injury	199,903	21.1%	31.7%
Suicide	52,265	5.5%	
Homicide	48,190	5.1%	
Malignant Neoplasms	137,221	14.5%	
Heart Disease	107,009	11.3%	
Perinatal Period	75,496	8.0%	
Congenital Anomalies	43,615	4.6%	
Cerebrovascular	21,817	2.3%	
HIV	21,508	2.3%	
Liver Disease	21,352	2.3%	
All Others	220,050	23.2%	

Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. Web-based Injury Statistics Query and Reporting System (WISQARS) accessed 5-19-14. www.cdc.gov/injury/wisqars

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	Age Groups										
Rank	<1	1-4	5-9	10-14	15-24	25-34	35-44	45-54	55-64	65+	All Ages
1	Congenital Anomalies 4,758	Unintentional Injury 1,316	Unintentional Injury 746	Unintentional Injury 775	Unintentional Injury 11,619	Unintentional Injury 16,209	Unintentional Injury 15,354	Malignant Neoplasms 46,185	Malignant Neoplasms 113,324	Heart Disease 488,156	Heart Disease 611,105
2	Short Gestation 4,202	Congenital Anomalies 476	Malignant Neoplasms 447	Malignant Neoplasms 448	Suicide 4,878	Suicide 6,348	Malignant Neoplasms 11,349	Heart Disease 35,167	Heart Disease 72,568	Malignant Neoplasms 407,558	Malignant Neoplasms 584,881
3	Maternal Pregnancy Comp. 1,595	Homicide 337	Congenital Anomalies 179	Suicide 386	Homicide 4,329	Homicide 4,236	Heart Disease 10,341	Unintentional Injury 20,357	Unintentional Injury 17,857	Chronic Low. Respiratory Disease 127,194	Chronic Low. Respiratory Disease 149,205
4	SIDS 1,563	Malignant Neoplasms 328	Homicide 125	Congenital Anomalies 161	Malignant Neoplasms 1,496	Malignant Neoplasms 3,673	Suicide 6,551	Liver Disease 8,785	Chronic Low. Respiratory Disease 15,942	Cerebro-vascular 109,602	Unintentional Injury 130,557
5	Unintentional Injury 1,156	Heart Disease 169	Chronic Low. Respiratory Disease 75	Homicide 152	Heart Disease 941	Heart Disease 3,258	Homicide 2,581	Suicide 8,621	Diabetes Mellitus 13,061	Alzheimer's Disease 83,786	Cerebro-vascular 128,978
6	Placenta Cord Membranes 953	Influenza & Pneumonia 102	Heart Disease 73	Heart Disease 100	Congenital Anomalies 362	Diabetes Mellitus 684	Liver Disease 2,491	Diabetes Mellitus 5,899	Liver Disease 11,951	Diabetes Mellitus 53,751	Alzheimer's Disease 84,767
7	Bacterial Sepsis 578	Chronic Low. Respiratory Disease 64	Influenza & Pneumonia 67	Chronic Low. Respiratory Disease 80	Influenza & Pneumonia 197	Liver Disease 676	Diabetes Mellitus 1,952	Cerebro-vascular 5,425	Cerebro-vascular 11,364	Influenza & Pneumonia 48,031	Diabetes Mellitus 75,578
8	Respiratory Distress 522	Septicemia 53	Cerebro-vascular 41	Influenza & Pneumonia 61	Diabetes Mellitus 193	HIV 631	Cerebro-vascular 1,687	Chronic Low. Respiratory Disease 4,619	Suicide 7,135	Unintentional Injury 45,942	Influenza & Pneumonia 56,979
9	Circulatory System Disease 458	Benign Neoplasms 47	Septicemia 35	Cerebro-vascular 48	Complicated Pregnancy 178	Cerebro-vascular 508	HIV 1,246	Septicemia 2,445	Septicemia 5,345	Nephritis 39,080	Nephritis 47,112
10	Neonatal Hemorrhage 389	Perinatal Period 45	Benign Neoplasms 34	Benign Neoplasms 31	Chronic Low. Respiratory Disease 155	Influenza & Pneumonia 449	Influenza & Pneumonia 881	HIV 2,378	Nephritis 4,947	Septicemia 28,815	Suicide 41,149

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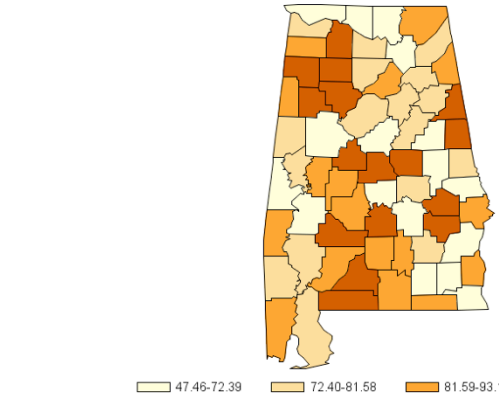

Reports for All Ages include those of unknown age.
* Rates based on 20 or fewer deaths may be unstable. These rates are suppressed for counties (see legend above); such rates in the title have an asterisk.

Produced by: the Statistics, Programming & Economics Branch, National Center for Injury Prevention & Control, CDC
Data Sources: NCES National Vital Statistics System for numbers of deaths; US Census Bureau for population estimates.

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24-YO ♂, GSW in ED

A 24-YO male arrived in the ED with a shotgun wound causing massive abdominal trauma. He had received three units of Dextran® balanced 5% glucose-electrolyte crystalloid 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, she ordered 1 more plasma and 1 more platelet, but the patient was still bleeding. Labs:

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

FG: 130 mg/dL (RI 225–498); PLTs: 70,000/uL (RI 150–450,000)

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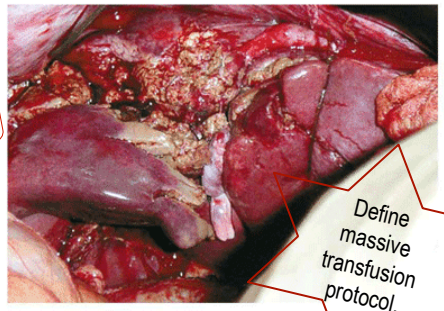
24-YO ♂, GSW in ED

Patient BP was 70/40, temp 32°C, pH 7.30. In surgery, major vessels were tied, but the field was obscured by microvascular bleeds. The patient survived surgery but expired in the recovery room.

Thanks to Margaret Fritsma, Mary Anne Krupsky, Michelle Brown, Birmingham, AL and Jose De Jesus, Tuscaloosa, AL for information on which this case is based.



Define massive transfusion protocol.

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Traditional TIC Management

- If no coagulopathy is suspected
  - Ligate and treat with crystalloids and RBCs
  - Discourage plasma and platelets
- If coagulopathy is suspected
  - Plasma to replenish multiple coagulation factors
  - Platelet concentrate for thrombocytopenia
  - Coagulation factor concentrates: VIII, IX
  - Replenish FG with CRYO or RiaSTAP
  - Activated PCC (FEIBA)
  - Four-factor PCC (KCentra)
  - NovoSeven® recombinant activated factor VII

Off-label

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American Society of Anesthesiologists 2006 Practice Guidelines

- Use no plasma to augment volume, use colloid or crystalloid expanders (5% dextrose: Dextran®)
  - Plasma only if microvascular bleeding…
  - And PT >1.5X "normal" or PTT >2X "normal"
- Use RBCs when HGB <6 g/dL
- "Usually" give platelets if <50,000/uL, unless…
  - Limited blood loss is anticipated based on type of surgery
  - Thrombocytopenia is associated with HIT, ITP, or TTP, where platelets may be ineffective

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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2004 Baghdad Case

- An IED-injured US soldier received 18 RBC units and died of dilutional coagulopathy before plasma could be thawed
- Surgeons and BB director agreed to keep 4 units of thawed AB plasma available at all times
- Initiated 1:1 plasma/RBC Rx; improved resuscitation, reduced hemorrhage, added PLT concentrate 2006
- Reduced crystalloids (Dextran, 5% glucose), reduced lung and tissue edema
- 2006: Joint Theatre Trauma System guideline

Holcomb JB, Jenkins D, Rhee P, et al. Damage control resuscitation: directly addressing the early coagulopathy of trauma. J Trauma 2007;62: 307–10.

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Bottom Line At the Start (BLATS)

- Crystalloid (Dextran®) resuscitation raises blood loss, transfusion requirements, edema, and mortality
- Balanced blood product (BBP) resuscitation reduces blood loss, Tx requirements, and improves survival
- Thawed plasma in the ER (or EMT), time is critical

Holcomb JB, Pati S. Optimal trauma resuscitation with plasma as the primary resuscitative fluid: the surgeon's perspective. Am Soc Hematol Educ Program. 2013; 2013:656–9.
Duchesne JC, Holcomb JB. Damage control resuscitation: addressing trauma-induced coagulopathy. Br J Hosp Med (Lond) 2009; 70: 22–5.

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TIC: Massive Trauma Hematoma or Hemorrhage

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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TIC Initial Management

Record hypothermia, hypotension, acidosis (base deficit), coagulopathy ↔ **Lab**: PT, PTT, PLTs, FG, D-D, ABG, Lytes, TEG, TEM, PAI-1

Surgery: use warmed room, warmed fluids & RBCs, close large vessels, control for microvascular bleeding

Coagulopathy Rx: RBC, PLT, plasma 1:1:1; FG, FEIBA or PCC, TXA, factors, rFVIIa

Hypothermia: remove wet clothing, cover with blanket, peritoneal lavage, extracorporeal arteriovenous warming ↔ **Acidosis**: shock resuscitation, normal saline, correct base deficit, maintain low target BP

Modified from: Tieu BH, Holcomb JB, Schreiber MA. Coagulopathy: Its pathophysiology and treatment in the injured patient .World J Surg 2007 31: 1055–64
Larson CR, White ED, Spinella PC, et al. Association of shock, coagulopathy, and initial vital signs with massive transfusion in combat casualties. J Trauma 2010;69:S75–80.

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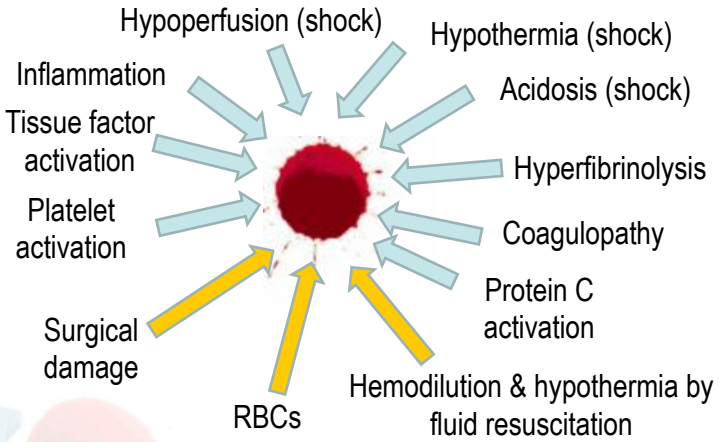
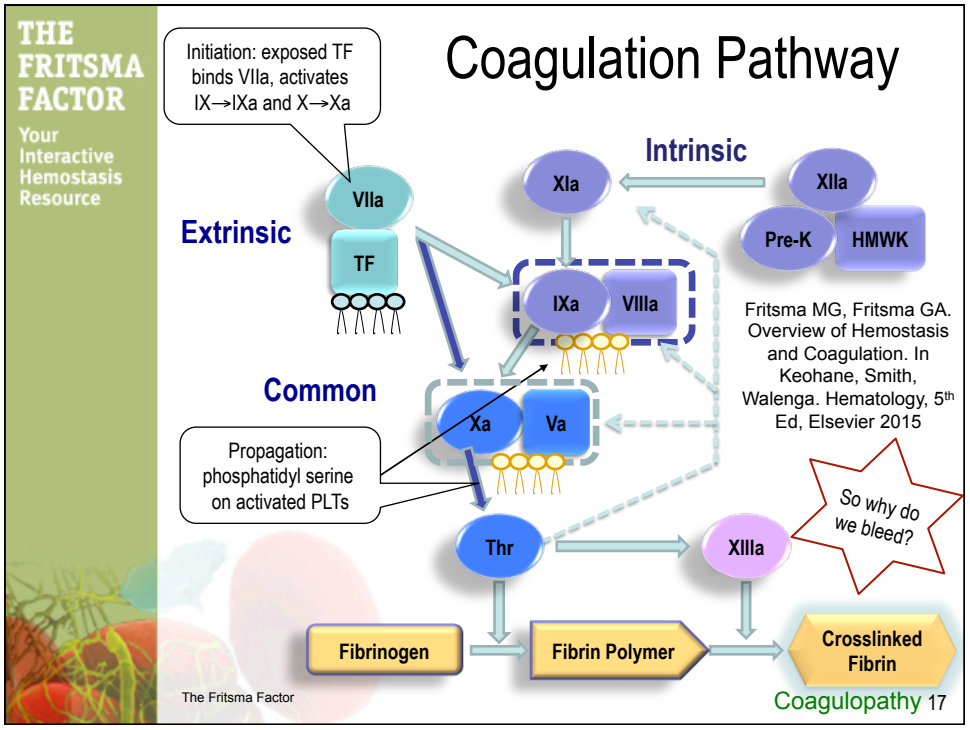
TIC Mechanisms



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
Initiation: exposed TF binds VIIa, activates IX→IXa and X→Xa
Intrinsic
Extrinsic
Common
VIIa
TF
XIa
XIIa
Pre-K
HMWK
IXa
VIIIa
Xa
Va
Thr
XIIIa
Fibrinogen
Fibrin Polymer
Crosslinked Fibrin
Propagation: phosphatidyl serine on activated PLTs
So why do we bleed?
Fritsma MG, Fritsma GA. Overview of Hemostasis and Coagulation. In Keohane, Smith, Walenga. Hematology, 5th Ed, Elsevier 2015
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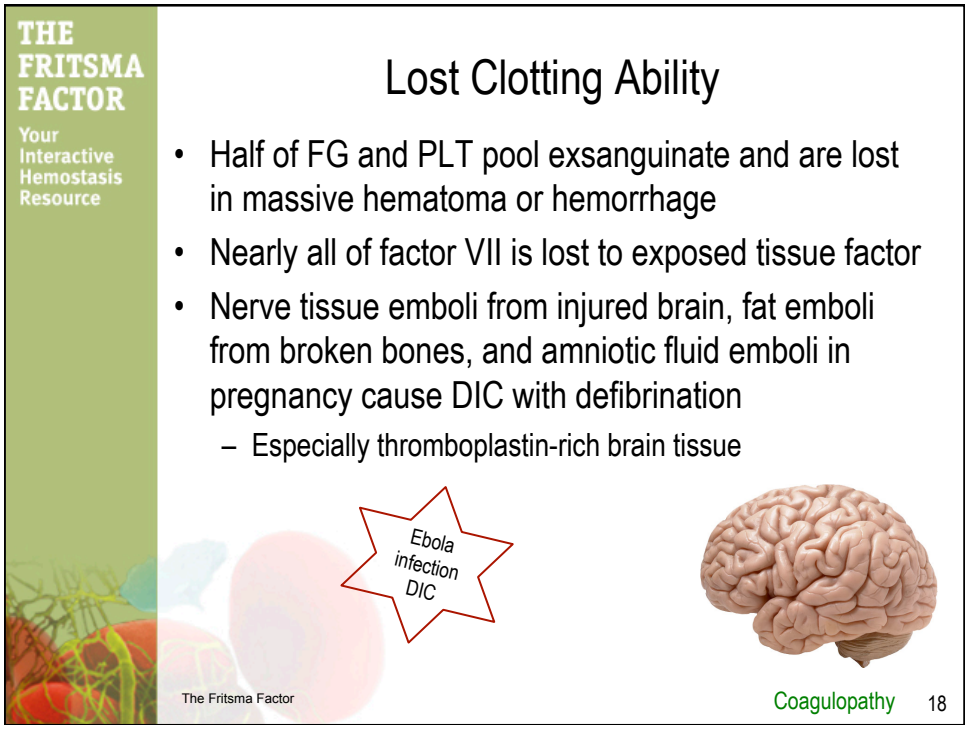
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Lost Clotting Ability
• Half of FG and PLT pool exsanguinate and are lost in massive hematoma or hemorrhage
• Nearly all of factor VII is lost to exposed tissue factor
• Nerve tissue emboli from injured brain, fat emboli from broken bones, and amniotic fluid emboli in pregnancy cause DIC with defibrination
– Especially thromboplastin-rich brain tissue
Ebola infection DIC
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Clotting Factor Dilution

- Hypotension leaves plasma colloid osmotic pressure unopposed. Protein-poor fluid seeps into vasculature, diluting coagulation factors and PLTs
- Crystalloids like 5% dextrose further dilute blood
- Combination of RBCs, plasma, and PLTs at 1:1:1…
  - Donor whole blood is diluted with 67 mL A/C per 450 mL TV
  - Whole blood theoretical best HCT is 28%
  - Coagulation factor activity is diminished to 60%
  - PLT count averages 90,000/uL

Bolliger D, Gorlinger K, Tanaka KA. Pathophysiology and treatment of coagulopathy in massive hemorrhage and hemodilution. Anesthesiology 2010;113:1205–19.

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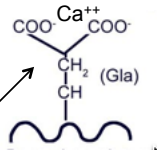
Hypothermia, Acidosis, Fibrinolysis

- All enzyme activity slows at <37°C
- PLT activation slows at 32–34°C
- Platelets cease to bind VWF at 30°C
- Vitamin K-dependent factors II, VII, IX, and X fail to bind phospholipid in acidosis



- Thrombomodulin exposure activates & consumes protein C
- α_2-antiplasmin loss prolongs free plasmin life
- Decreased plasminogen activator inhibitor (PAI-1) prolongs tissue plasminogen activator (TPA) life
- Thrombin consumption lowers TAFI activation
  - Thrombin-activatable fibrinolysis inhibitor
- Factor XIII dilution causes inadequate fibrin crosslinking
  - Fibrin strands are thin, easily digested

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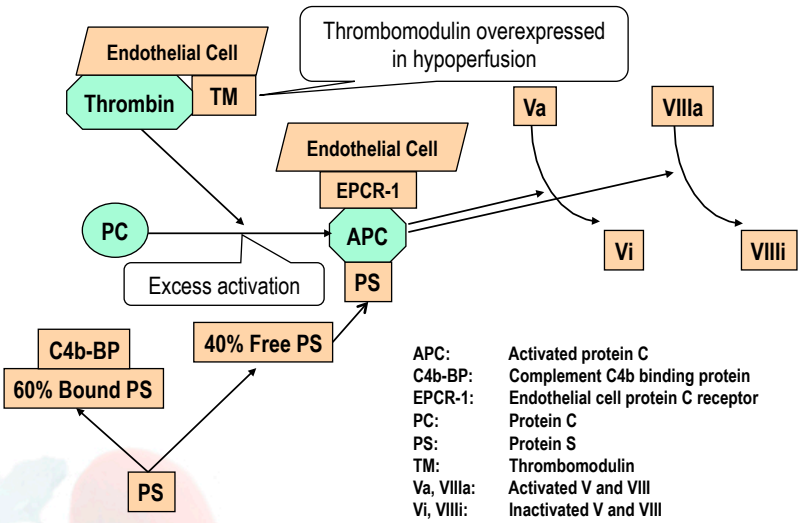
The Protein C Control Pathway



APC:	Activated protein C
C4b-BP:	Complement C4b binding protein
EPCR-1:	Endothelial cell protein C receptor
PC:	Protein C
PS:	Protein S
TM:	Thrombomodulin
Va, VIIIa:	Activated V and VIII
Vi, VIIIi:	Inactivated V and VIII

Brohi K, Cohen MJ, Ganter MT, et al. Acute traumatic coagulopathy: initiated by hypoperfusion: modulated through the protein C pathway? Ann Surg 2007; 245:812–8.

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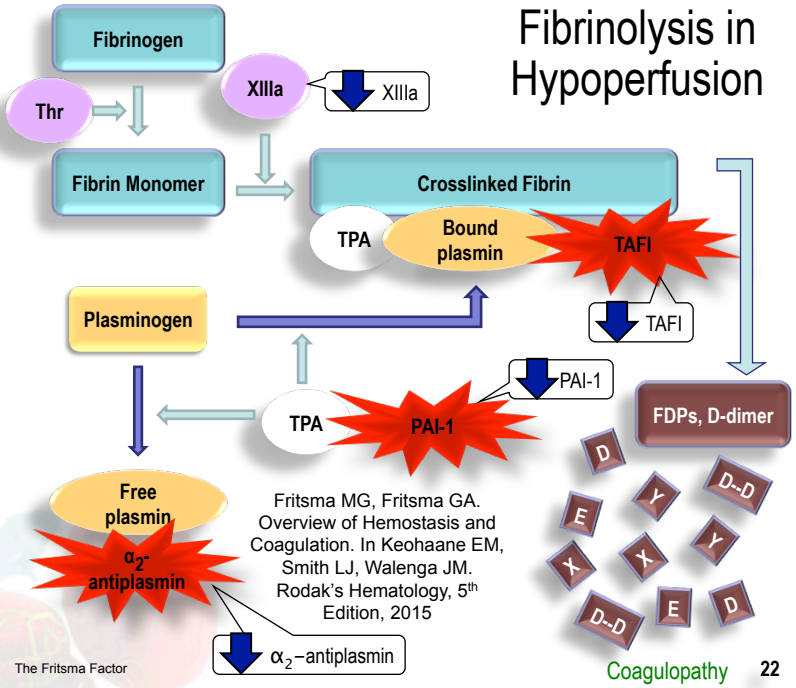
Fibrinolysis in Hypoperfusion



Fritsma MG, Fritsma GA. Overview of Hemostasis and Coagulation. In Keohaane EM, Smith LJ, Walenga JM. Rodak's Hematology, 5th Edition, 2015

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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		1 (Minor)	1
Sum		ISS:	50

Maximum is 75. If injury is assigned a score of 6 (unsurvivable), the ISS is automatically 75. ISS correlates linearly with mortality, morbidity and hospital stay. See also automated revised ISS, TRISS, which incorporates respiration and BP.

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 in Trauma

n = 58, received >10 RBCs Condition:	% Coagulopathy*
Injury severity score (ISS) >25 alone	10%
ISS >25 & systolic BP <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 arbitrarily 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;42:857–62.

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Coagulopathy in Trauma

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

*Coagulopathy defined independent of fluid replacement as: PT >18s,16.3%; PTT >60s, 24.4%; or thrombin time >15s, 14.2%

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

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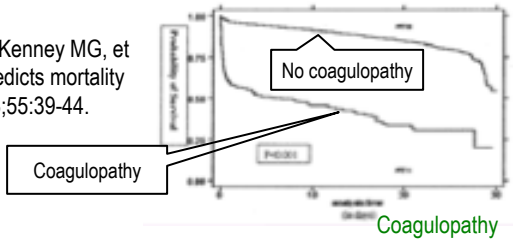
PT and PTT Predict Mortality

- 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
    - Controlled 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.



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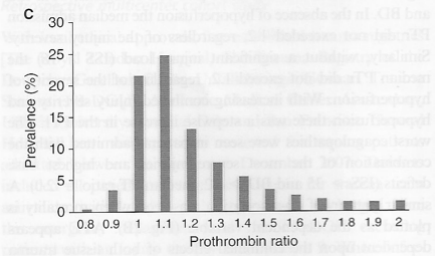
Definition and "Drivers" of TIC

- Retrospective cohort study
  - 3646 trauma patients at 5 international trauma centers
  - TIC = PTR >1.2; correlates with ISS and shock
- Prothrombin time ratio (PTR) >1.2
  - Mortality 22.7% Vs. 7.0%, p <0.001
  - RBC use 3.5 versus 1.2 units, p <0.001
  - Plasma use 2.1 versus 0.8 units, p <0.001



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.

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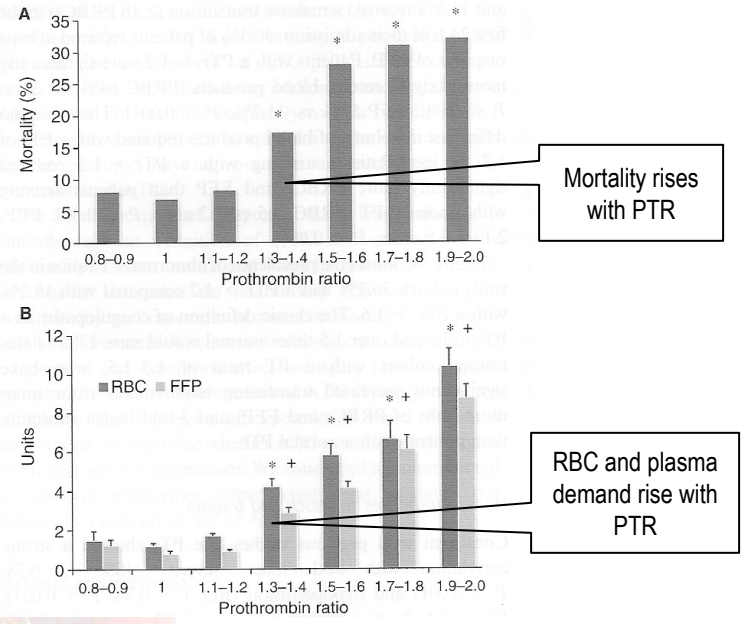

Mortality rises with PTR

RBC and plasma demand rise with PTR

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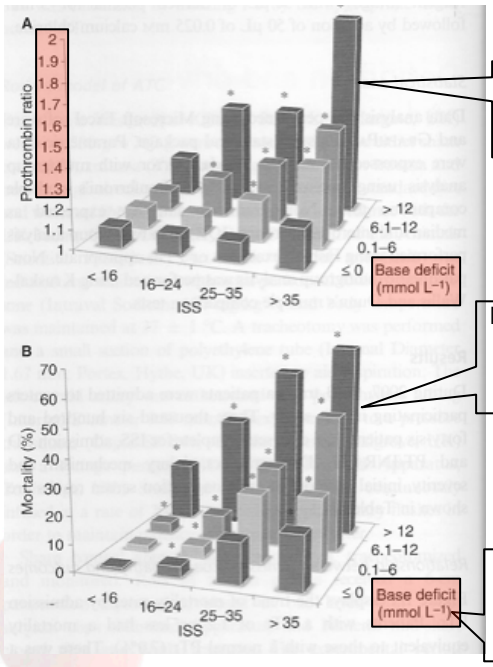

PTR rise depends upon both ISS and acidosis (base deficit)

Mortality mirrors PTR as it also depends upon both ISS and hypoperfusion

Base deficit (mmol/L) mirrors shock

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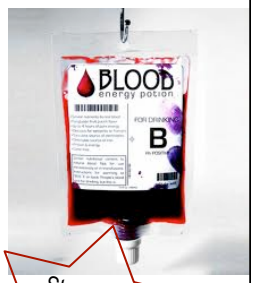
Massive Transfusion Protocol (MTP)

- Major hemorrhage defined by blood loss
- Retrospective: ≥ 10 RBC units in 24h
  - Or ≥ 50 total component units in 24h
  - 1 blood volume replaced in 70 kg patient
- Ongoing: 3 units RBCs/h; 5 units/3h
- Why give RBCs first?
  - Patient loses "red stuff," needs "red stuff."
  - But HCT unchanged, though volume lost



Start MTP if blood loss >150 mL/m

Burtelow M, Riley E, Druzin M, et al. How we treat: Management of life-threatening primary postpartum hemorrhage with a standardized massive transfusion protocol. Transfusion 2007; 47:1564-72. .

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Massive Tx Protocol 30

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Massive Transfusion in Young, Healthy Combat Casualties

- Systolic <110 mm Hg
- Pulse >110 BPM
- Acidosis: pH <7.25 or base deficit ≤ −6
- HGB <11 g/dL
- PT >1.5 x mean of reference interval

Start MTP if any two are present

- 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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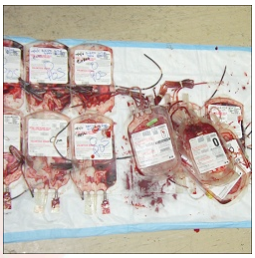
MTP in ER: Civilian Casualties

- Penetrating Vs. blunt mechanism
- focused abdominal sonography for trauma (FAST)
  - Peritoneal fluid, organ rupture, internal bleeding
- Arrival BP <90 mmHg, pulse >12

Start MTP if any two are present

ER use of uncrossmatched RBCs predicts 3X the incidence of MTP



Nunez TC, Dutton WD, May AK, et al. Emergency department blood transfusion predicts early massive transfusion and early blood component requirement. Transfusion 2010;50: 1914–20.

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Intraoperative RBC Transfusion Risks

Independent Outcome	RBCs	No RBCs
Sepsis	16.4%	9.8%
Pulmonary complication	12.6%	6.0%
Wound complications	9.2%	4.7%
Mortality	6.4%	4.4%
Thromboembolic disease	4.0%	1.9%
Renal complications	2.7%	1.9%
Cardiac complications	2.1%	1.4%
30-day outcomes, all significant at p <0.05		

Glance LG, Dick AW, Mukamel DB, et al. Association between intraoperative blood transfusions and mortality and morbidity in patients undergoing noncardiac surgery. Anesthesiology 2011;114:283–92.

The Fritsma Factor RBCs 33

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

RBC Transfusion Risks in Trauma

- Tx predicts MOF* when victim survives >24 h
  - *Multiple organ failure
- Tx correlates with 4X rise in ICU admission
- Mortality rises with each RBC unit
- No patient >75 who gets >12 RBC units survives
- Infection odds ratio 5.26 versus no Tx
- Composite risk of TRALI* and ARDS* 1:5000
  - *Transfusion-related acute lung injury
  - *Acute respiratory distress syndrome

Robinson WP, Ahn J, Stifler A, et al. Blood transfusion is an independent predictor of increased mortality in non-operatively managed blunt hepatic and splenic injuries. J Trauma 2005;58:437–44.

The Fritsma Factor RBCs 34

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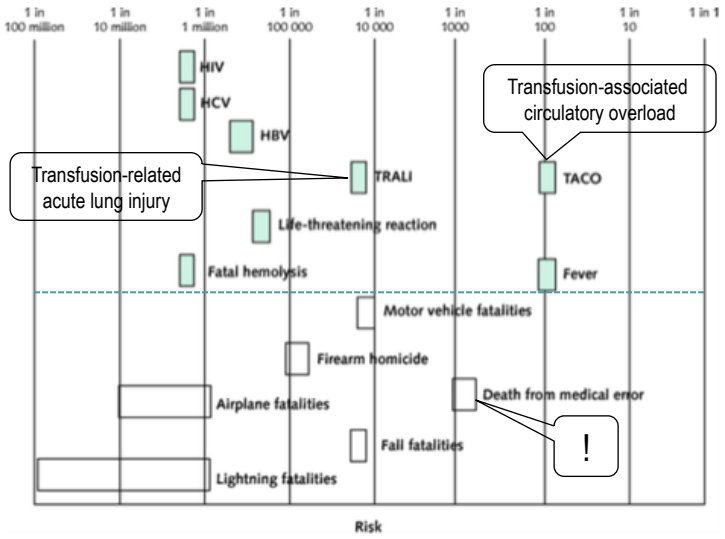
RBC Transfusion Risks in Context



Ann Intern Med. 2012;157:49–58

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RBC Risks and Indications

Risk	Indication
ABO Incompatibility*	Fever, hemoglobinuria, hemoglobinemia
TRALI* or TACO	Respiratory distress, hypoxemia
Bacterial contamination	Fever, hypotension
Allergic reaction	Urticaria
Citrate toxicity	Hypocalcemia
Terminate transfusion and start diagnostic tests	
*Observe for delayed TRALI and transfusion reaction	

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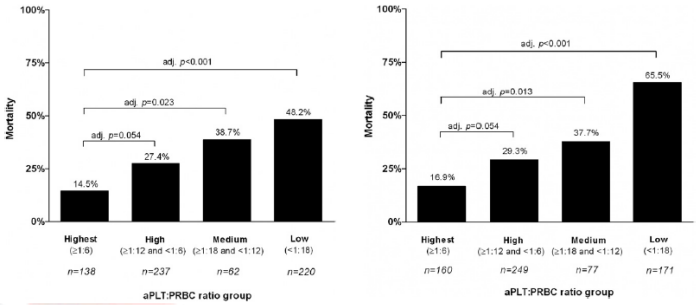
Platelet Concentrate

- Clinicians discouraged from giving platelets
  - Why? "Platelets are a precious commodity."
- Use early anyway, they stabilize the coagulopathy
  - They've got all the "good stuff" that is in plasma



Inaba K, Lustenberger T, Rhee P, et al. The impact of platelet transfusions in massively transfused trauma patients. JACS 2010.

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Your Interactive Hemostasis Resource

What Does "Plasma" Mean?

- Fresh frozen plasma (FFP)
  - Plasma processed and placed at ≤ –18C within 8 h of collection
  - Plasma from males or nulligravida females to avoid TRALI
  - Largely discontinued 2000–2010, though name lives on
- 24-h plasma (PF24)
  - WB ambient ≤8 h➔1–6C ≤16 h➔processed➔–18C in 24 h
  - Most common prep, mis-named FFP by most health care pros
- 24-h plasma (PF24RT24)
  - WB held ambient, processed and placed at –18C within 24 h
  - Released 4/1/2014 for replacement of non-labile coagulation factors
- All preparations stored frozen up to 12 months
- Thawed AB plasma: kept at 1–6C; 5 d if closed

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Mean Factor V, VIII and Protein S Levels in FFP, PF 24, and PF24RT24

Preparation	Factor V	Factor VIII	Protein S
FFP at thaw	85%	81%	97%
FFP 5d post-thaw	67%	43%	92%
PF24 at thaw	86%	66%	90%
PF24 5d post-thaw	59%	48%	78%
PF24RT24 at thaw	90%	86%	82%
PF24RT24 5d post-thaw	89%	86%	73%

- O'Neill EM, Rowley J, Hansson-Wicher M, et al. Effect of 24-hour whole-blood storage on plasma clotting factors. Transfusion 1999;39:488–91.
- Cardigan R, Lawrie AS, Mackie IJ, Williamson LM. The quality of fresh frozen plasma produced from whole blood stored at 4 C overnight. Transfusion 2005;45:1342–48.

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Your Interactive Hemostasis Resource

RBC/Plasma 1:1

- USA hospital in Baghdad Green Zone
  - Tx >2000 wounded, massively Tx >600 wounded
  - Retrospective w/o controls but extensive, careful documentation
- Receiving ≤1 plasma per 4 RBCs: 65% mortality
  - Confounding data: soldiers who received >10 RBC units but died before plasma could thaw are counted in this arm
- Receiving 2 plasma for every 3 RBCs: 19% mortality
  - Confounded: survivors receive more plasma Vs. those who die
  - Requires ~15 h to resolve coagulopathy
  - Surgeons report less bleeding and edema
- Anticipated adverse effects
  - Plasma supply (yes)
  - Transfusion-associated circulatory overload (TACO, yes)
  - No TRALI, anaphylaxis, ARDS, MOF, or 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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ASA 2015 Plasma Indications

- Manage preoperative or bleeding pts who require replacement of multiple coagulation factors (eg, liver disease, DIC).
- Manage patients undergoing massive transfusion who have clinically significant coagulation deficiencies.
- Manage bleeding patients taking warfarin or who need an invasive procedure before vitamin K could reverse the warfarin effect (but 4-factor PCC is better).
- Transfusion or plasma exchange in patients with thrombotic thrombocytopenic purpura (TTP)
- Manage patients with congenital or acquired factor deficiencies for which there are no specific coagulation concentrates
  - FP24RT24 not indicated for factor VIII or protein S deficiency

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 2015;22:241–75.

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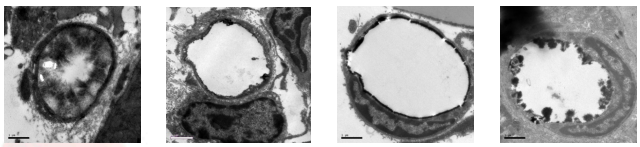
Plasma Reduces EC Permeability

Ebola causes vasodilation

- Barrier dysfunction, interstitial edema, tissue hypoxia, inflammatory cells
- Infiltration, detached pericytes, extracellular matrix breakdown, apoptosis, exposed subendothelium
- Stabilizes ECs through junction protein regulation



Normal Shock Crystalloids Plasma

Kozar R, Peng Z, Zhang R. Plasma restoration of endothelial glycocalyx in a rodent model of hemorrhagic shock. Anes & Analgesic 2011

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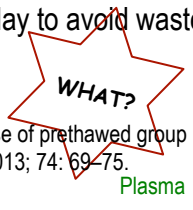
Group AB Plasma When ABO is Unknown

- Group AB from males & nulligravida females
  - Odds of AB plasma TRALI 14.5 X higher than A, B, or O
  - TRALI restrictions first applied 4/1/2014
  - AB = 2.6% of active donors before TRALI restriction
  - AB availability now cut by 33%
- AB demand raised
  - New massive Tx protocols raise plasma demand
  - Maintaining thawed plasma supply in ER
  - Thawed AB diverted to non-ABs on 5th day to avoid waste
- Solution: group A plasma



Zelinski MD, Johnson PM, Jenkins D, et al. Emergency use of prethawed group A plasma in trauma patients. J trauma Acute Care Surg 2013; 74: 69–75.

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Group A Plasma When ABO is Unknown

- Most recipients are A and O, compatible w/ A plasma
- Anti-B titers low in TRALI-restricted population
- B substance in secretors neutralizes anti-B
- Pts may be receiving massive O RBCs anyway
- U Mass, 2008–13 (similar data from Mayo)
  - Emergency release of 358 A plasmas
  - 84% of recipients turned out to be A or O, compatible
  - 23 recipients were B or AB, 11 of these received O RBCs
  - No acute hemolytic transfusion reactions
  - Three weak positive post-transfusion DATs
  - Reduced AB plasma usage 97%

Chhibber V, Green M, Vauthrin M, et al. Is group A plasma suitable as the first option for ememrgency release transfusion? Transfusion 2014; 54: 1751–5.

THE FRITSMA FACTOR
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Group A Plasma When ABO is Unknown

- 76 U of Cincinnati PTs received 76 gender-nonspecific group AB plasma transfusions, and compared to Mayo trial they had…
  - Lower ratios of arterial O_2 partial pressure to fractional inspired oxygen.
  - Higher rates of sepsis (p=0.024), acute renal failure (p = 0.003), DVT (p = 0.021), and PE (p = 0.013).
  - Longer ICU stays.

Postma K. Group A plasma: The new universal plasma for trauma patients. 2015 Clin Lab Sci—in process.
Zielinski M, Johnson P. Emergency use of prethawed Group A plasma in trauma patients. J Trauma Acute Care Surg 2013;741:69–74; discussion 74–5.

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PROMMT Study

- 34,362 trauma admissions, 10 centers 58 wks
- 10% transfused within 6 hours
- 7% received ≥ 3 RBCs
- Overall mortality 25%
  - 94% of hemorrhagic deaths occurred within 24 hours
  - Median time to hemorrhagic death 2.6 h, range, 1.7–5.4 h

Holcomb JB, Del Junco, DJ, Fox EE, et al. Prospective, observational, multicenter major trauma transfusion (PROMMT) study. JAMA Surg 2013; 148:127–36.

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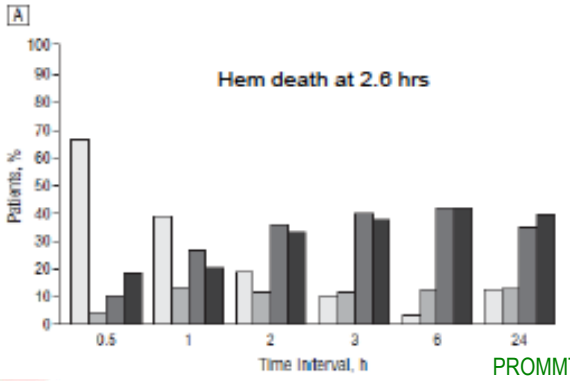
PROMMT Plasma:RBC Ratio

PROMMT
PROspective Observational Multicenter Massive Transfusion sTudy

UTHealth
The University of Texas Health Science Center at Houston



The Fritsma Factor PROMMT 47

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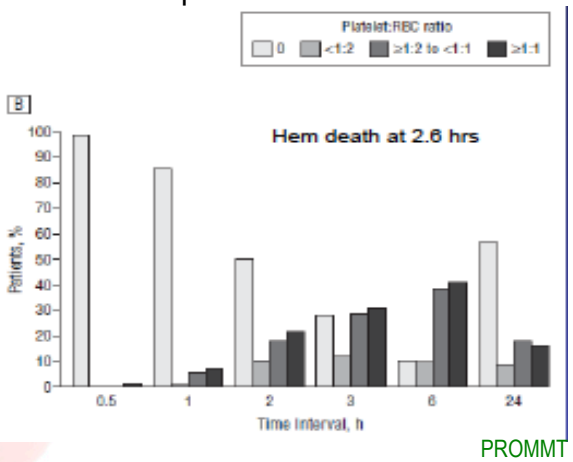
PROMMT Platelet:RBC Ratio

Earlier and higher ratios of plasma and platelets were associated with decreased in-hospital mortality in the first 6 hours. 1:1:1 is superior to 1:1:2



The Fritsma Factor PROMMT 48

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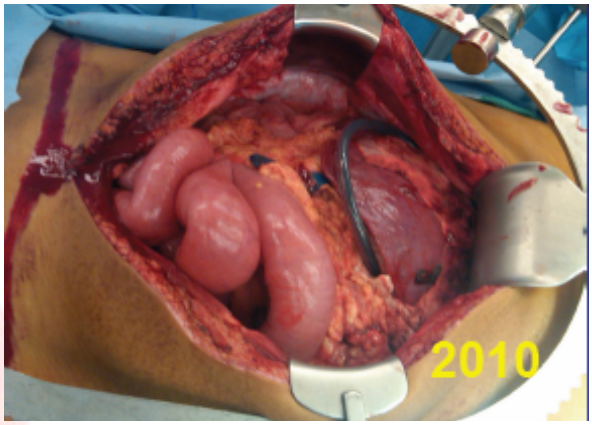
Reduced Crystalloids

- 17 YO GSW to liver, 60/30, base deficit 17
- 11 RBC, 10 plasma, 2 PLTs, 3 L crystalloid
- 3 surgeries, home in 10 days



The Fritsma Factor PROMMT 49

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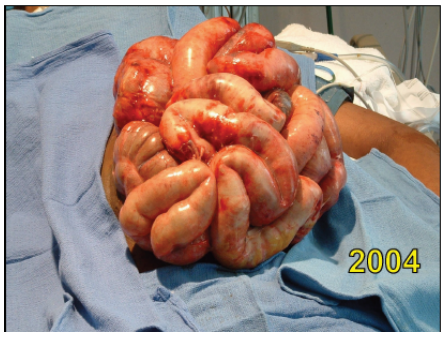
Your Interactive Hemostasis Resource

TRALI Versus CRALI

- Crystalloid-related acute lung injury
- The amount of crystalloid rather than blood products transfused during the first day of care seems to be the modifiable risk factor for lung injury
- TRALI (0) vs CRALI (505)?



Robinson BR, Cotton BA, Pritts TA, et al. Application of the Berlin definition in PROMMT patients. J Trauma Acute Care Surg 2013; 75 (1 Suppl 1):S61–7.

The Fritsma Factor PROMMT 50

THE FRITSMA FACTOR
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Updated TIC Rx

- Minimize crystalloids by targeting low BP
- Use plasma, not crystalloids
- Rewarm patient intensively, warm components
- In relatively stable patients, guide Rx w/ repeated CBCs, PTs, PTTs, TEG or TEM
- Rx: BBP: Plasma, PLTs, FG, RBCs 1:1:1:1
- Europe, 4-factor PCC, factor VIII, FG concentrate, rFVIIa (NovoSeven), tranexamic acid (TXA)

Off-label!

Holcomb JB, Wade CE, Michalek JE, et al. Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. Ann Surg 2008; 248: 447–58

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

PROPPR Trial: Group A Plasma

- 12 level I trauma centers
- Balanced blood products: 1:1:1 or 1:1:2
  - Plasma : platelet concentrate : red blood cells
- All but 1 delivered 6 u UD plasma and 6 of UD RBCs in 10 minutes
- 3 sites provided 141 group A plasma to AB and B patients, 97 units untitered anti-B
  - No transfusion reactions

Novak DJ, Bai Y, Cooke RK, Marques MB, et al. Making thawed universal donor plasma available rapidly for massively bleeding trauma patients: experience from the Pragmatic, Randomized Optimal Platelets and Plasma Ratios (PROPPR) trial. Transfusion 2015

THE FRITSMA FACTOR
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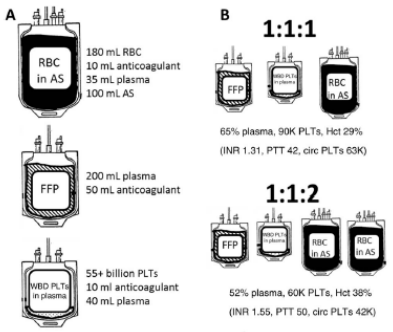
PROPPR Outcomes

- 1:1:1 vs 1:1:2 plasma/PLT concentrate/RBCs
  - 338 vs 342 severely injured patients in hemorrhagic shock
  - 12 sites, 9 used thawed AB, 3 added thawed A plasma
- FDA-required primary outcomes
  - 24-h and 30-d mortality no difference
  - Reduced 3-h mortality real measure of trauma resuscitation
  - 1:1:2 patients required "catch-up" products

Holcomb JB,Tilley BC, Baraniuk S, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma. JAMA 2015: 313: 471–82.



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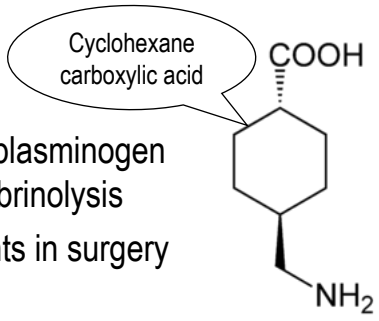
Tranexamic Acid (Cyclokapron) Rx



- Synthetic lysine blocks plasminogen binding sites, reduces fibrinolysis
- Reduces Tx requirements in surgery without raising mortality

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

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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
Thrombosis death	33 (0.3%)	48 (0.5%)	0.69	0.096
No significant differences in myocardial infarct, stroke, VTE, blood products				

Shakur H, Roberts I, Bautista R, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant hemorrhage (CRASH-2): a randomized, placebo-controlled trial. Lancet 2010; 376:23–32.

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TXA 55

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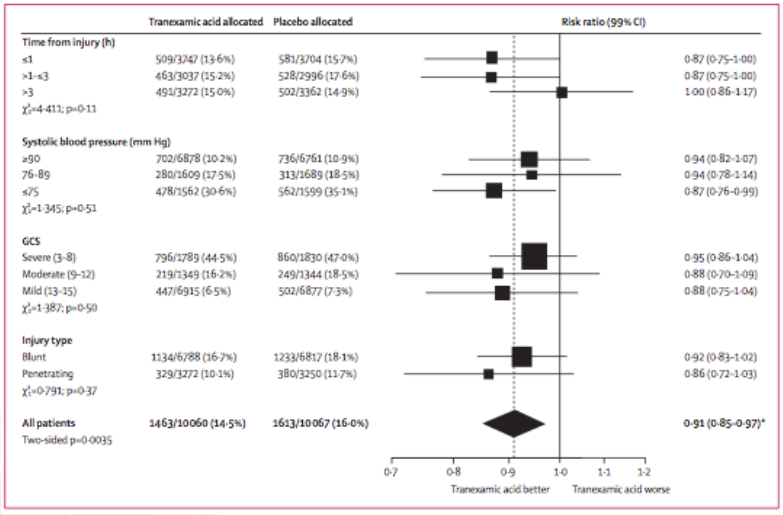
All-cause Mortality by Subgroup Tranexamic Acid Versus Placebo



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TXA 56

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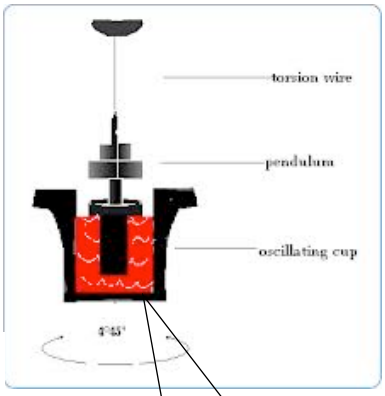
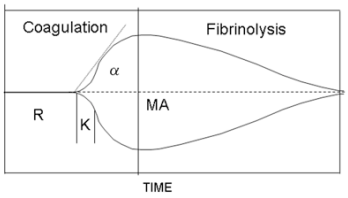
Thromboelastograph

1946





Pen displacement by viscoelastic changes

The Fritsma Factor

TEG and TEM 57

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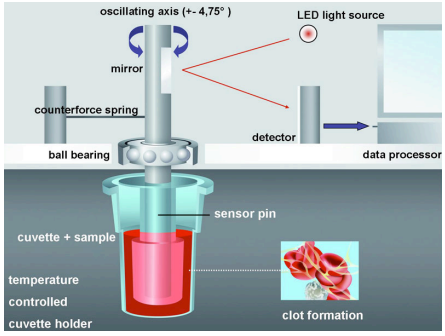
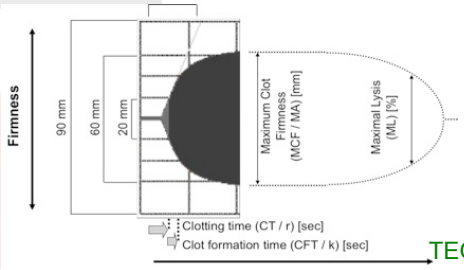
Rotational Thromboelastometry





The Fritsma Factor

TEG and TEM 58

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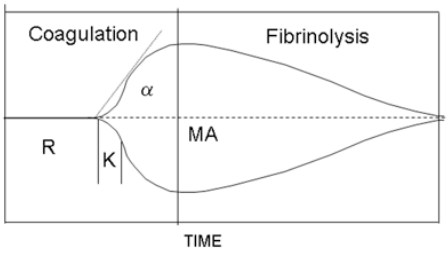
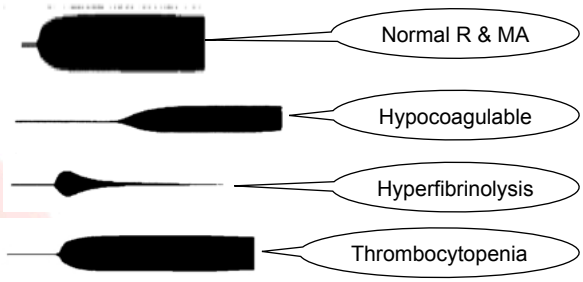
Thromboelastograph





The Fritsma Factor

TEG and TEM 59

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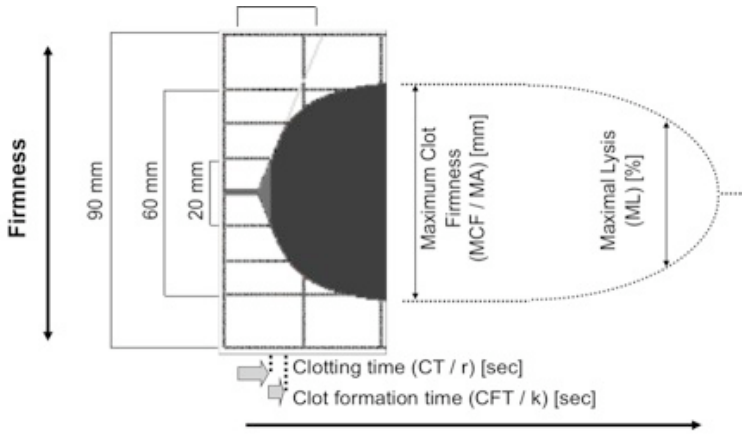
Thromboelastometry



Jackson GNB, Ashpole KJ, Yentis SM. The TEG® vs the ROTEM® thromboelastography/ thromboelastometry systems. Anaesthesia 2009;64:212–15.

The Fritsma Factor

TEG and TEM 60

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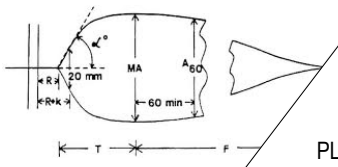
TEM Monitor, No Transfusion, No rFVIIa



rVIIa

plasma

PLTs, KCentra®

hypocoag: RiaSTAP®

hyperfibrinolysis: tranexamic acid

aspirin, clopidogrel, coumadin, heparin

T <37°C; pH <7.2; HGB <8 mg/dL, Ca^{++} <1 mmol/L

Surgical intervention: suture, divert, compress, and pack

Gorlinger K, Fries D, Dirkmann D, et al. Reduction of FFP requirements by perioperative POC coagulation management with early calculated goal-directed therapy. Transfus Med Hemother 2012; 29: 104–13.

The Fritsma Factor TXA 61

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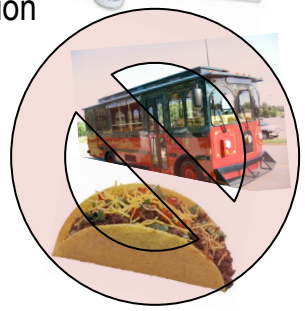
CRASH 2: Use TXA, CRYO, and PCC

- Rapid, effective, predictable rise in factor activity
- Activated PCC, 4-factor PCC; low volume vs. plasma
- RiaSTAP® FG; low volume vs. CRYO, no TACO
- Avoid 58% of massive transfusions
  - "Massive transfusion *avoidance* protocol"
- No risk of incompatible transfusion
- Reduce plasma Tx by 90%
- Effective viral inactivation
- Reduce RBC Tx by 8.4%
- No risk of TRALI
- Never use rVIIa?



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Bottom Line At the End

- Thawed A plasma on site, no crystalloids
- Treat shock: warm patient, pH
- BBP: 1:1:1:1 plasma, RBCs, FG, PLTs
- Factors VIII and IX when necessary
- Tranexamic acid, 4-factor PCC
- Monitor with ROTEM
  - PT and PTT if ROTEM not available
- New study: PROPPR

Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. JAMA 2015;313:471–82.

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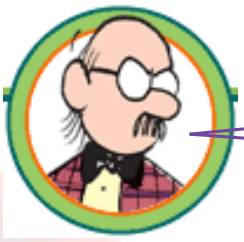

Questions?