

THE FRITSMFACTOR
Your Interactive Hemostasis Resource

Managing Hemostasis in Trauma-induced Coagulopathy

TIC-TIC


Timing is Everything

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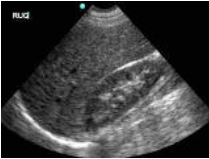
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US Injury Incidence

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

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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Rank	Age Groups											All Ages
	<1	1-4	5-9	10-14	15-24	25-34	35-44	45-54	55-64	65+	All Ages	
1	Congenital Anomalies 2,763	Unintentional Injury 2,512	Unintentional Injury 2,512	Unintentional Injury 2,512	Unintentional Injury 2,512	Unintentional Injury 2,512	Unintentional Injury 2,512	Unintentional Injury 2,512	Unintentional Injury 2,512	Unintentional Injury 2,512	Unintentional Injury 2,512	Unintentional Injury 2,512
2	Open Wound 2,292	Congenital Anomalies 1,476	Malignant Neoplasms 1,476	Malignant Neoplasms 1,476	Malignant Neoplasms 1,476	Malignant Neoplasms 1,476	Malignant Neoplasms 1,476	Malignant Neoplasms 1,476	Malignant Neoplasms 1,476	Malignant Neoplasms 1,476	Malignant Neoplasms 1,476	Malignant Neoplasms 1,476
3	Invasive Prostate Canc 1,893	Heart Disease 1,179	Cerebral Hemorrhage 1,179	Stroke 1,179	Stroke 1,179	Stroke 1,179	Stroke 1,179	Stroke 1,179	Stroke 1,179	Stroke 1,179	Stroke 1,179	Stroke 1,179
4	EBIS 1,863	Malignant Neoplasms 1,218	Stroke 1,218	Congenital Anomalies 1,218	Malignant Neoplasms 1,218	Malignant Neoplasms 1,218	Malignant Neoplasms 1,218	Malignant Neoplasms 1,218	Malignant Neoplasms 1,218	Malignant Neoplasms 1,218	Malignant Neoplasms 1,218	Malignant Neoplasms 1,218
5	Unintentional Injury 1,152	Heart Disease 1,152	Chronic Liver Disease 1,152	Stroke 1,152	Heart Disease 1,152	Heart Disease 1,152	Stroke 1,152	Stroke 1,152	Stroke 1,152	Stroke 1,152	Stroke 1,152	Stroke 1,152
6	Alcohol Use Disorders 863	Influenza & Pneumonia 863	Joint Disease 863	Joint Disease 863	Congenital Anomalies 863	Congenital Anomalies 863	Liver Disease 863	Diabetes Mellitus 863	Liver Disease 863	Diabetes Mellitus 863	Diabetes Mellitus 863	Alzheimer's Disease 863
7	Bacterial Sex 818	Controlled Subst Abuse 818	Influenza & Pneumonia 818	Chronic Liver Disease 818	Chronic Liver Disease 818	Liver Disease 818	Liver Disease 818	Diabetes Mellitus 818	Diabetes Mellitus 818	Diabetes Mellitus 818	Diabetes Mellitus 818	Diabetes Mellitus 818
8	Respiratory Disease 812	Sepsis 812	Controlled Subst Abuse 812	Influenza & Pneumonia 812	Diabetes Mellitus 812	Diabetes Mellitus 812	Diabetes Mellitus 812	Diabetes Mellitus 812	Diabetes Mellitus 812	Diabetes Mellitus 812	Diabetes Mellitus 812	Influenza & Pneumonia 812
9	Chronic Liver Disease 812	Beign Neoplasms 812	Sepsis 812	Cerebral Hemorrhage 812	Congenital Anomalies 812	Congenital Anomalies 812	July 1,2012	Sepsis 812	Sepsis 812	Sepsis 812	Sepsis 812	Sepsis 812
10	Neural Hemorrhage 812	Parital 812	Beign Neoplasms 812	Beign Neoplasms 812	Chronic Liver Disease 812	Influenza & Pneumonia 812	Influenza & Pneumonia 812	Influenza & Pneumonia 812	Influenza & Pneumonia 812	Influenza & Pneumonia 812	Influenza & Pneumonia 812	Stroke 812

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2004-2010, Alabama
Death Rates per 100,000 Population
All Injury, All Races, All Ethnicities, Both Sexes, All Ages
Annualized Crude Rate for Alabama: 76.07

Reports for All Ages include those of unknown age.
* Rates based on 25 or fewer deaths may be unstable. These rates are suppressed for counties (see legend above); such rates in the file have an asterisk.

Produced by the Statistics, Programming & Economic Branch, National Center for Injury Prevention & Control, CDC
Data Sources: NCEI 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

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

Hypothermia: remove wet clothing, cover with blanket, peritoneal lavage, extracorporeal arteriovenous warming

Lab: PT, PTT, PLTs, FG, D-D, ABG, Lytes, TEG, TEM, PAI-1

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

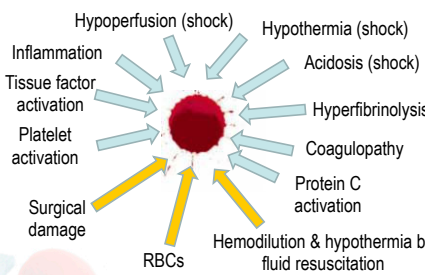
Acidosis: shock resuscitation, normal saline, correct base deficit, maintain low target BP

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

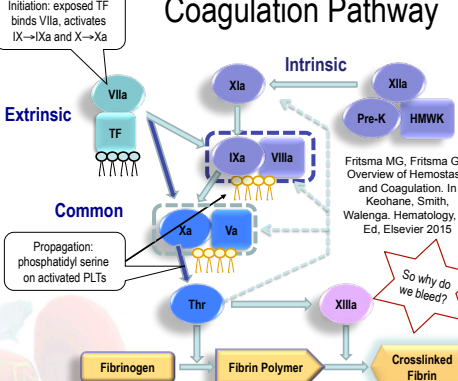


Duchesne JC, Holcomb JB. Damage control resuscitation: addressing trauma-induced coagulopathy. Br J Hosp Med (Lond) 2009; 70: 22-5.

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Coagulation Pathway



Initiation: exposed TF binds VIIa, activates IX→IXa and X→Xa

Propagation: phosphatidyl serine on activated PLTs

Fritsma MG, Fritsma GA. Overview of Hemostasis and Coagulation. In Keohane, Smith, Walenga. Hematology, 5th Ed, Elsevier 2015

So why do we bleed?


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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

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

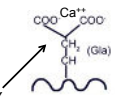



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Hypothermia, Acidosis, Fibrinolysis

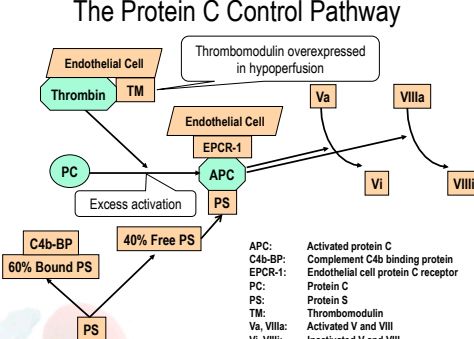
- All enzyme activity slows at <37°C
- PLT activation slows at 32-34°C
- Platelets cease to bind VWF at 30°C
- Vitamin K-dependent factors II, VII, IX, and X fail to bind phospholipid in acidosis
- Thrombomodulin exposure activates & consumes protein C
- α_2 -antiplasmin loss prolongs free plasmin life
- 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

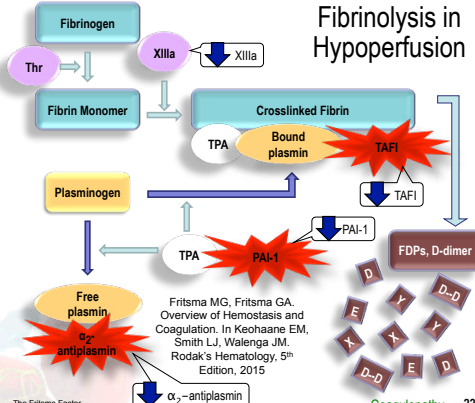


Brohi K, Cohen MJ, Ganter MT, et al. Acute traumatic coagulopathy: initiated by hypoperfusion: modulated through the protein C pathway? *Ann Surg* 2007; 245:812-8.

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Fibrinolysis in Hypoperfusion



Fritsma MG, Fritsma GA. Overview of Hemostasis and Coagulation. In Keochaane 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	2 (Moderate)	25
	Spleen rupture	5 (Critical)	
Extremity	Fractured femur	3 (Serious)	
External		1 (Minor)	1
Sum		ISS: 50	

Maximum is 75. If injury is assigned a score of 6 (un survivable), 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

Condition:	% Coagulopathy*
n = 58, received >10 RBCs	
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	
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 **Coagulopathy 25**

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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.

Coagulopathy 26

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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. **Coagulopathy 27**

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Mortality rises with PTR

RBC and plasma demand rise with PTR

Coagulopathy 28

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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

Coagulopathy 29

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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

Burtelov 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. **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 \leq -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.

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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

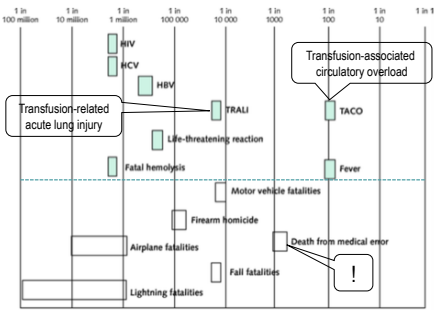


Robinson WP, Ahn J, Stiller A, et al. Blood transfusion is an independent predictor of increased mortality in non-operatively managed blunt hepatic and splenic injuries. J Trauma 2005;58:437-44.

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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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What Does "Plasma" Mean?

- Fresh frozen plasma (FFP)
 - Plasma processed and placed at $\leq -18C$ 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 \rightarrow 1-6C ≤ 16 h \rightarrow processed \rightarrow -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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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.

The Fritsma Factor Plasma 40

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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.

The Fritsma Factor Plasma 41

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Plasma Reduces EC Permeability

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

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

The Fritsma Factor Plasma 42

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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
 - WHAT?

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.

The Fritsma Factor Plasma 43

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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 emergency release transfusion? Transfusion 2014; 54: 1751-5.

The Fritsma Factor Plasma 44

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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 O₂ 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;74:69-74; discussion 74-5.

The Fritsma Factor Plasma 45

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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.

The Fritsma Factor PROMMT 46

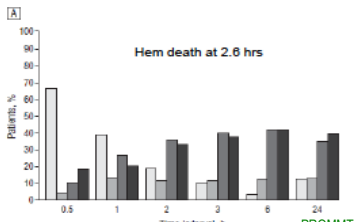
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PROMMT Plasma:RBC Ratio

PROMMT
PROSPECTIVE OBSERVATIONAL MULTICENTER MASSIVE TRANSFUSION STUDY

UTHealth
The University of Texas Health Science Center at Houston

Plasma:RBC ratio
0 <1:2 ≥1:2 to <1:1 ≥1:1



Hem death at 2.6 hrs

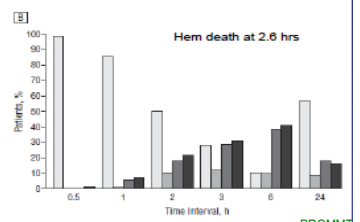
The Fritsma Factor PROMMT 47

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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

Platelet:RBC ratio
0 <1:2 ≥1:2 to <1:1 ≥1:1



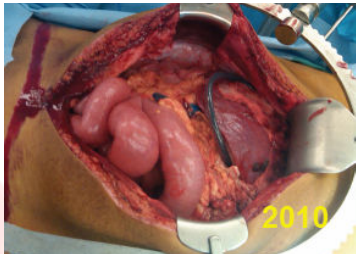
Hem death at 2.6 hrs

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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




2010

The Fritsma Factor PROMMT 49

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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)?



2004

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

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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 Current Massive Tx Protocol 51

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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

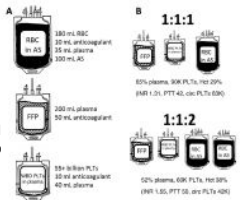
Novak DJ, Bai Y, Cooke RK, Marques MB, et al. Making thawed universal donor plasma available rapidly for massively bleeding trauma patients: experience from the Pragmatic, Randomized Optimal Platelets and Plasma Ratios (PROPPR) trial. Transfusion 2015

The Fritsma Factor Plasma 52

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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.

The Fritsma Factor PROPPR 53

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Tranexamic Acid (Cyclokapron) Rx

Cyclohexane carboxylic acid

NC1CCCCC1C(=O)O

- 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



The Fritsma Factor TXA 54

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Tranexamic Acid Death by Cause

CRASH-2	TXA n = 10060	Placebo n = 10067	RR	p
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.

The Fritsma Factor TXA 55

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All-cause Mortality by Subgroup Tranexamic Acid Versus Placebo

Subgroup	Tranexamic acid-allocated (n)	Placebo-allocated (n)	Risk ratio (95% CI)
Time from injury (h)			
<4	509 (327 (13.6%))	582 (104 (15.7%))	0.87 (0.75-1.00)
4-3	493 (327 (15.0%))	549 (296 (17.6%))	0.87 (0.70-1.09)
>3	493 (327 (15.0%))	502 (362 (14.9%))	1.00 (0.86-1.17)
Specific blood pressure (mm Hg)			
<90	762 (488 (20.2%))	756 (161 (10.9%))	0.94 (0.81-1.07)
76-89	280 (169 (17.5%))	313 (168 (18.5%))	0.94 (0.78-1.14)
>89	428 (152 (10.6%))	582 (299 (19.7%))	0.87 (0.73-1.03)
GCS			
Score (3-8)	756 (128 (64.5%))	860 (139 (47.0%))	0.95 (0.86-1.04)
Moderate (9-12)	219 (149 (18.2%))	249 (144 (18.5%))	0.88 (0.75-1.03)
Severe (13-15)	467 (162 (16.9%))	500 (67 (7.3%))	0.88 (0.73-1.04)
Injury type			
Blunt	1134 (528 (16.7%))	133 (88 (18.3%))	0.92 (0.85-1.00)
Penetrating	329 (327 (10.3%))	380 (250 (13.7%))	0.86 (0.72-1.03)
All patients	1463 (10060 (14.5%))	1613 (10067 (16.0%))	0.91 (0.85-0.97)

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Thromboelastograph

1946

Pen displacement by viscoelastic changes

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Rotational Thromboelastometry

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Thromboelastograph

Normal R & MA

Hypocoagulable

Hyperfibrinolysis

Thrombocytopenia

The Fritsma Factor TEG and TEM 59

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Thromboelastometry

Maximum Clot Firmness (MCF) [mm]

Maximal Lysis (ML) [%]

Clotting time (CT / r) [sec]

Clot formation time (CFT / k) [sec]

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: 104–113.

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.

The Fritsma Factor 63

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The Fritsma Factor 64