The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

Managing Hemostasis in Trauma-induced Coagulopathy

TIC-TIC
Timing is Everything

Hemorrhage and Thrombosis

George A. Fritsma, MS MLS www.fritsmafactor.com; george@fritsmafactor.com

PROUDLY SUPPORTED BY PrecisionBioLogic

1

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

Objectives in Question Form

Q1: What is the death rate in the US and in the world?

Q2: What is the most common cause of premature death in the US and in the world?

PROUDLY SUPPORTED BY PrecisionBioLogic 2

2

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

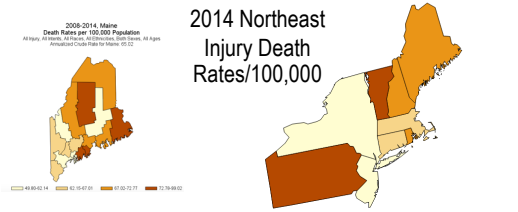
10 Leading Causes of US Death in 2020

3

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

Death Rates per 100,000 Population
All Injury, All Intents, All Races, All Ethnicities, Both Sexes, All Ages
Annualized Crude Rate for Northeast Region: 50.82

2014 Northeast Injury Death Rates/100,000



PROUDLY SUPPORTED BY PrecisionBioLogic 4

4

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

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

PROUDLY SUPPORTED BY PrecisionBioLogic 5

5

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

US Injury Incidence

- 27,000,000 injury-related provider visits
- 45,000 die before reaching hospital: neurologic displacement
- 1,700,000 injury-related hospital admissions
- 1,000,000 are transferred to trauma centers, 93,000 die.
- 150,000 receive transfusion of blood or blood products
- 10,000 require massive Tx—10 RBC units/24 h, 40% die
- Half in hospital die in 4–6 h of hemorrhage
- Another 40% develop thrombosis after 24 hours
- Extent of injury is determined by…
  - whole body CT scan
  - focused abdominal sonography for trauma [FAST]

Holcomb JB et al. Evidence based and clinically relevant outcomes for hemorrhage control trauma trials. Ann. Surg 2021, 273:395–401.

PROUDLY SUPPORTED BY PrecisionBioLogic 6

6

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

Objectives in Question Form

Q3: How did we manage TIC before 2006?
Q4: What happened in 2006 to change all this?

PROUDLY SUPPORTED BY PrecisionBioLogic 7

7

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

24-YO ♂, GSW in ED, 2006

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 concentrate unit, 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]

PROUDLY SUPPORTED BY PrecisionBioLogic 8

8

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

Injury Severity Score [ISS]

Region	Examples	1–6	Top 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		19	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; Gennarelli TA, Wodzin E. "AIS 2005: A contemporary injury scale". Injury 2006;37: 1083–91.*

PROUDLY SUPPORTED BY PrecisionBioLogic 9

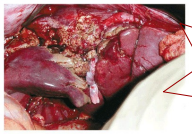
9

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

24-YO ♂, GSW in ED, 2006

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



Distended viscera due to crystalloids/colloids

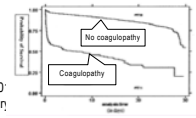
PROUDLY SUPPORTED BY PrecisionBioLogic 10

10

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

PT and PTT Predict Mortality [2003]

- 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
  - Mortality incidence increase 35%; OR, 3.6; p <0.000
  - Controlled for age, ISS, BP, HCT, pH, and head injur
- 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.

PROUDLY SUPPORTED BY PrecisionBioLogic 11

11

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

2006 TIC Management

No coagulopathy suspected…

- Ligate and treat with crystalloids and RBCs
- In Viet Nam [1970], 5–10 units of crystalloids = "Da Nang lung"
  - Acute respiratory distress syndrome [ARDS]
- Discouraged plasma and PLT concentrate, few resources
  - Risk of hepatitis [HIV not identified before 1983]

Coagulopathy suspected…

- PT >1.5X "normal" or PTT >2X "normal"
  - Plasma to replenish multiple factors
- Coagulation factor concentrates: VIII, IX
- Replenish FG with CRYO
- Tx RBCs if HGB <6 g/dL
- Tx PLTs if <50,000/uL
- Recombinant activated factor VII [rFVIIa]
- Activated PCC [FEIBA]
- PCC [unactivated]

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.

PROUDLY SUPPORTED BY PrecisionBioLogic 12

12

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

Q5: What happened to change all this?

PROUDLY SUPPORTED BY PrecisionBioLogic 13

13

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

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 always keep 4 units of thawed AB plasma available
- 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 Guidelines
- 2012: Joint Trauma System Clinical Practice Guidelines

- 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.
- Holcomb JB, Jenkins D, Rhee P, et al. Damage control resuscitation: directly addressing the early coagulopathy of trauma. J Trauma 2007;62: 307–10.
- Duchesne JC, Holcomb JB. Damage control resuscitation: addressing trauma-induced coagulopathy. Br J Hosp Med (Lond) 2009; 70: 22–5.

PROUDLY SUPPORTED BY PrecisionBioLogic 14

14

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

Q5: What Causes TIC?

Hemorrhage: 3–6 h		Thrombosis 24 h	
Hyperfibrinolysis	PLT Dysfunction	Hypofibrinolysis	PLT Activation
Hypofibrinogenemia	Decreased Thrombin	Hyperfibrinogenemia	Increased Thrombin

From: Lining up for low titer O whole blood in trauma care: CAP Today, June, 2023

PROUDLY SUPPORTED BY PrecisionBioLogic 15

15

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

TIC Initial Management

Record hypothermia, hypotension, acidosis [base deficit], hemorrhage ↔ **Lab**: PT, PTT, CBC w/ PLTs, FG, D-D, ABG, Lytes, Viscoelastometry [VET]

Surgery: use warmed room, warmed plasma, PLTs and RBCs, close large vessels

Coagulopathy Rx: RBC, PLT, plasma 1:1:1; FG, FVIII, FIX; FEIBA, PCC, rFVIIa; tranexamic acid [TXA]

Hypothermia: remove wet clothing, cover with blanket, peritoneal lavage, extracorporeal arteriovenous warming ↔ **Acidosis**: shock resuscitation, normal saline, correct base deficit, maintain moderate target BP: systolic >70

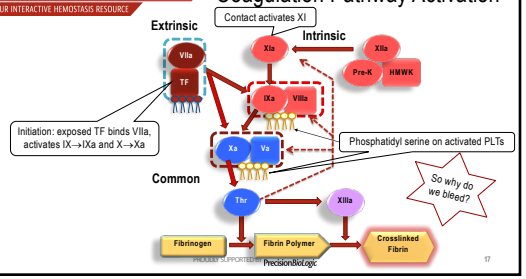
Modified from: Tieu BH, Holcomb JB, Schreiber MA. Coagulopathy: Its pathophysiology and treatment in the injured patient .World J Surg 2007 31: 1055–64.
Larson CR, White ED, Spinella PC, et al. Association of shock, coagulopathy, and initial vital signs with massive transfusion in combat casualties.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

PROUDLY SUPPORTED BY PrecisionBioLogic 16

16

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

Coagulation Pathway Activation



PROUDLY SUPPORTED BY PrecisionBioLogic 17

17

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

Lost Procoagulants: Exsanguination

- Half of FG and PLT pools are lost in massive hematoma or hemorrhage
  - A 70 kg male has 10 g FG, 15 mL PLTs
- Factor VII is consumed by exposed and secreted tissue factor
- Massive VWF release from endothelial cells consumes ADAMTS13
  - Results in ULVWF triggering platelet activation
- Factor V and VIII are depleted by activated protein C
- Nerve tissue emboli from injured brain, fat emboli from broken bones, and amniotic fluid emboli in pregnancy cause progression to DIC with defibrination
  - Especially thromboplastin-rich brain microvesicles and phospholipids

Zhang J, Zhang F & Dong JF Coagulopathy induced by traumatic brain injury: systemic manifestation of a localized injury. Blood 2018; 131: 2001–6

PROUDLY SUPPORTED BY PrecisionBioLogic 18

18

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

Diluted Procoagulants

- Hypotension leaves plasma colloid osmotic pressure unopposed.
  - Protein-poor fluid seeps into vasculature, diluting procoagulants and PLTs
- Crystalloids and colloid Rx
- Whole blood
  - Donor whole blood is diluted with 67 mL A/C per 450 mL total volume
  - Whole blood theoretical best HCT is 35-40%, procoagulants 60 U/dL, PLTs 90,000/uL
- Packed red cells
  - Procoagulants absent, PLTs 90,000/uL

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

PROUDLY SUPPORTED BY PrecisionBioLogic 19

19

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

Hypothermia, Acidosis, Fibrinolysis

- 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 membrane phospholipids in acidosis

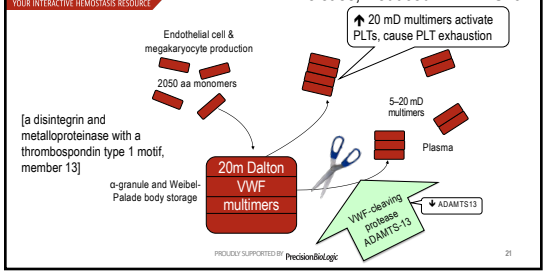
- Thrombomodulin exposure activates protein C
- α_2-antiplasmin loss prolongs free plasmin life, hyperfibrinolysis
- Decreased PLT PAI-1 prolongs tissue plasminogen activator [TPA] life
- Thrombin consumption lowers TAFI activation
  - Thrombin-activatable fibrinolysis inhibitor
- Factor XIII dilution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

PROUDLY SUPPORTED BY PrecisionBioLogic 20

20

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

VWF Release, Reduced ADAMTS13

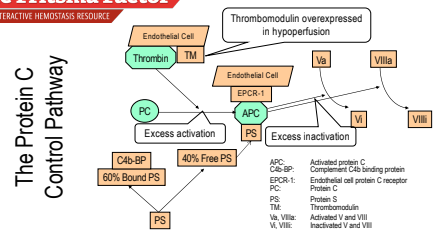


PROUDLY SUPPORTED BY PrecisionBioLogic 21

21

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

The Protein C Control Pathway



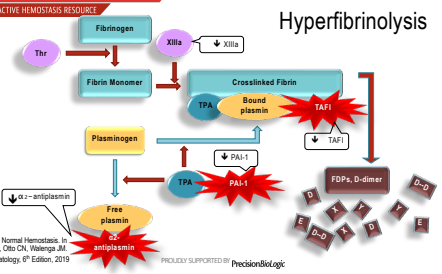
Brohi K, Cohen MJ, Ganter MT, et al. Acute traumatic coagulopathy: initiated by hypoperfusion: modulated through the protein C pathway? Ann Surg 2007; 245:812–8.

PROUDLY SUPPORTED BY PrecisionBioLogic 22

22

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

Hyperfibrinolysis



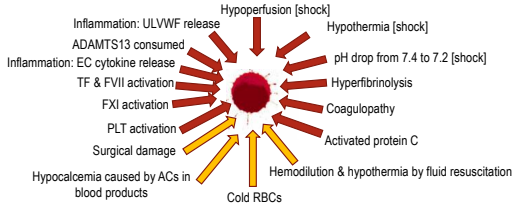
Walenga JM. Normal Hemostasis. In Kechane EM, Otto CN, Walenga JM. Rodak's Hematology, 6th Edition, 2019

PROUDLY SUPPORTED BY PrecisionBioLogic 23

23

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

TIC Mechanisms



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

PROUDLY SUPPORTED BY PrecisionBioLogic 24

24

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

How to Measure?

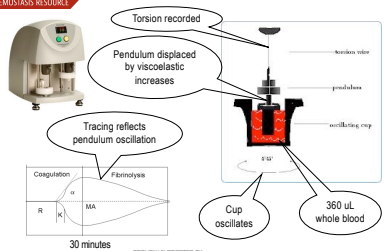
- Q6: Besides PT, PTT, fibrinogen, and D-dimer, how can we measure TIC? Especially, how do we tell when the patient is flipping from hemorrhage to thrombosis?

PROUDLY SUPPORTED BY PrecisionBioLogic 25

25

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

Thromboelastograph [TEG 5000]



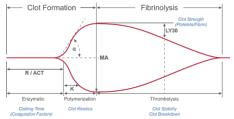
PROUDLY SUPPORTED BY PrecisionBioLogic 26

26

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

TEG 5000 Parameters

Parameter	Symbol	Definition	RI
Clot rate	R	Period from 0–2 mm amplitude	4–8 m
Clot kinetics	K	Period from 2–22 mm amplitude	0–4 m
Clot strengthening angle	α	slope of tangent at 2–22 mm amplitude	47–74°
Maximum clot strength	MA	Maximum amplitude	54–72 mm
Clot lysis	LY30	MA at 30 minutes	0–8%

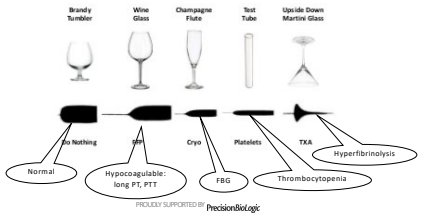


PROUDLY SUPPORTED BY PrecisionBioLogic 27

27

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

TEG 5000 Results For Oenophiles



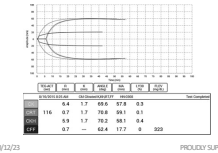
PROUDLY SUPPORTED BY PrecisionBioLogic 28

28

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

TEG 6s

Cartridges W/ four rgts. *Citrated WB* transferred to selected cartridge, mixed with respective rgts and exposed to vibration. Detector monitors vertical motion of the meniscus, converts to a clot-strength proportional resonance frequency tracing.



- ACT: activated clotting time
- CFF: activated by the functional FBG test [FLEV]
- CKH: activated with kaolin and heparinase
- CK: activated with kaolin
- CM: multichannel cartridge
- CRT: activated with rapid TEG
- FLEV: FBG level
- K: coagulation time
- MA: maximum amplitude
- R: reaction time

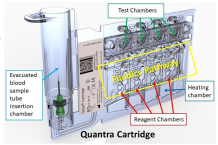
10/12/23 PROUDLY SUPPORTED BY PrecisionBioLogic

29

Hemosonics Quantra

QStat CARTRIDGE
- Trauma
- Liver transplant

QPlus CARTRIDGE
- Cardiac surgery
- Major orthopedic surgery



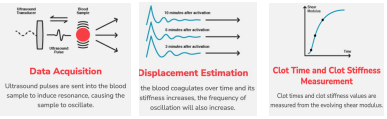
Thanks to **Todd Allen**, Clinical Development Director, Hemosonics, Inc.

Requires ~3 mL citrated WB

30

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

Hemosonics Quantra



Sonorheometry [SEER]

- CTH: heparinase clot time
- CT: clot time
- CTR: clot time ratio
- CS: Clot stiffness
- PCS: platelets contribution
- FCS: fibrinogen contribution

PROUDLY SUPPORTED BY PrecisionBioLogic 31

31

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

Quantra Qplus for Cardiac and Ortho Normal Result Numeric Screen

Thanks to Todd Allen, Clinical Development Director, Hemosonics, Inc.

PROUDLY SUPPORTED BY PrecisionBioLogic 32

32

Hemosonics Quantra Qplus Cartridge

Parameter [Units]	Measurement
CT [s]	Intrinsic system clot time
CTH [s]	Intrinsic system clot time with heparinase neutralizer
CS [hPa]	Clot stiffness of WB, extrinsic activation [maximum amplitude]
FCS [hPa]	FBG contribution to clot stiffness
PCS [hPa, calculated]	PLT contribution to clot stiffness
CTR [ratio, calculated]	Clotting time ratio [CT/CTH]: Indicates intrinsic pathway function or UFH influence
Citrated WB; CTH, CS, FCS, and PCS are measurable while on bypass	

The QPlus Cartridge evaluates coagulation function in adults undergoing cardiovascular or major orthopedic surgeries before, during, and after the procedure.

33

Hemosonics Quantra Qstat Cartridge

Parameter [Units]	Measurement
CT [s]	Intrinsic system clot time
CTH [s]	Intrinsic system clot time with heparinase neutralizer
CS [hPa]	Clot stiffness of WB, extrinsic activation [maximum amplitude]
FCS [hPa]	Fibrinogen contribution to clot stiffness
PCS [hPa, calculated]	PLT contribution to clot stiffness
CSL %	Clot Stiffness to Lysis : difference of the CS in the absence of TXA and the corresponding CS in the presence of TXA
Samples with CSL <90% indicate reduced CS due to hyperfibrinolysis.	

The QStat cartridge evaluates coagulation and fibrinolytic function in adult trauma and liver transplant.

But fibrinolysis is a cell-localized function!

34

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

How to Treat?

- Q6: How do you manage TIC?
- A: MTP?

PROUDLY SUPPORTED BY PrecisionBioLogic 35

35

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

2007: 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, 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.

PROUDLY SUPPORTED BY PrecisionBioLogic 36

36

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

Massive Tx Protocol [MTP] in Young, Healthy Combat Casualties

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

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

PROUDLY SUPPORTED BY PrecisionBioLogic 37

37

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

MTP Defined by RBC Volumes

- Major hemorrhage defined by blood usage
- 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. .

PROUDLY SUPPORTED BY PrecisionBioLogic 38

38

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

MTP in ER: Civilian Casualties

Start MTP if any two are present

- Penetrating Vs. blunt mechanism
- focused abdominal sonography for trauma [FAST]
  - Peritoneal fluid, organ rupture, internal bleeding
- Arrival systolic BP <90 mmHg, pulse >120

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.

PROUDLY SUPPORTED BY PrecisionBioLogic 39

39

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

How to Treat?

- Q7: RBCs?

PROUDLY SUPPORTED BY PrecisionBioLogic 40

40

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

RBC Tx Risks in Trauma

- ABO incompatibility 1:80,000, allergic reaction, citrate toxicity
- Tx predicts thrombosis and MOF when victim survives >24 h
- Tx-associated circulatory overload [TACO]
- Tx correlates with 4X rise in ICU admission
- Mortality rises with each RBC unit
- No patient >75 who gets >12 RBC units survives
- Tx infection odds ratio 5.26 versus no Tx, febrile reaction
- Composite risk of TRALI* and ARDS* 1:5000
  - *Transfusion-related acute lung injury
  - *Acute respiratory distress syndrome

Robinson WP, Ahn J, Stiffler 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.

PROUDLY SUPPORTED BY PrecisionBioLogic 41

41

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

Intraoperative RBC Tx 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% NS
Cardiac complications	2.1%	1.4% NS

- 30-day outcomes, all but the last two significant at p <0.05
- Most RBCs used are near the end of their life span.

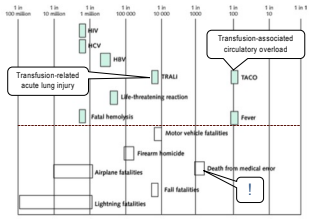
Glance LG, Dick AW, Mukamel DB, et al. Association between intraoperative blood transfusions and mortality and morbidity in patients undergoing noncardiac surgery. Anesthesiology 2011;114:283–92.

PROUDLY SUPPORTED BY PrecisionBioLogic 42

42

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

RBC Tx Risks in Context



Ann Intern Med. 2012;157:49–58

43

How to Treat?

- Q8: Plasma?

PROUDLY SUPPORTED BY PrecisionBioLogic

44

What Does "Plasma" Mean?

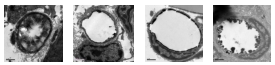
- Fresh frozen plasma (FFP)
  - Plasma processed and placed at ≤ –18ºC within 8 h of collection
  - Plasma from males or nulligravida females to avoid TRALI
  - Largely discontinued 2000–2010, though name lives on
- 24-h plasma (PF24)
  - WB ambient ≤8 h/1–6ºC ≤16 h; processed ≤ –18ºC in 24 h
  - Most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

PROUDLY SUPPORTED BY PrecisionBioLogic

45

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



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

PROUDLY SUPPORTED BY PrecisionBioLogic

46

Mean Factor V, VIII and Protein S Levels

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%

Use supplements in FV or FVIII deficiency

- 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.

PROUDLY SUPPORTED BY PrecisionBioLogic

47

Group AB Plasma When ABO is Unknown

- Restricted group AB plasma from males & nulligravida females
  - Odds of unrestricted AB plasma TRALI 14.5 X higher than restricted A, B, or O
  - TRALI restrictions applied 4/1/2014
  - AB = 2.6% of active donors before TRALI restriction, cut by 2/3
- AB plasma demand raised
  - New massive Tx protocols raise demand
  - Maintaining thawed plasma supply in ER or on EMI vans and copters
  - Thawed AB diverted to non-ABs on 5th day to avoid waste
- 3 sites provided 141 group A plasma to AB and B patients
  - 97 units of 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; 55:1331–9.
Zielinski 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.

PROUDLY SUPPORTED BY PrecisionBioLogic

48

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

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
- Patients 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
  - 12 exposed: 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.

PROUDLY SUPPORTED BY PrecisionBioLogic 49

49

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

How to Treat?

- Q9: PLTs?

PROUDLY SUPPORTED BY PrecisionBioLogic 50

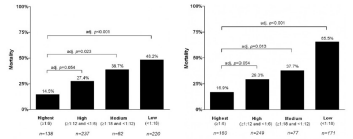
50

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

Platelet Concentrate

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

- Clinicians discouraged from giving platelets
  - Why? "Platelets are precious."
- Use anyway, they stabilize the coagulopathy
  - PLTs have all the "good stuff" that is in plasma



PROUDLY SUPPORTED BY PrecisionBioLogic 51

51

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

How to Treat?

- Q10: LTOWB?

PROUDLY SUPPORTED BY PrecisionBioLogic 52

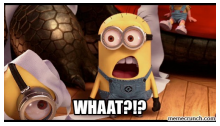
52

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

New [Old] Approaches

Cold-storage Low Titer Group O Whole Blood [LTOWB]
Cold Storage Platelet Concentrate

McCoy CC, Brenner M, Duchesne J, et al. Back to the future: whole blood resuscitation of the severely injured trauma patient. Shock. 2021;56:9-15



PROUDLY SUPPORTED BY PrecisionBioLogic 53

53

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

Cold Storage Low Titer Group O Whole Blood

- WB provides plasma:RBC:PLTs in a 1:1:1 ratio
- WB improves survival compared to stored components
- Better O_2 saturation, less hypoxia, superior platelet function
- No RBC storage lesion vs "reconstituted" whole blood

No Brainer?

Parameter	1:1:1	"Real" WB
Total volume	660 mL	570 mL
Hematocrit	29%	35–38%
Platelet count	90,000/μL	150–350,000/μL
Factor activity	65%	85%
Anticoagulant & preservative		Decreased

- Joint Theater Trauma System Clinical Practice Guideline: Fresh whole blood transfusion, 2012
- Shock 41 Supplement 1, p 62–9, 2014

PROUDLY SUPPORTED BY PrecisionBioLogic 54

54

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

Cold Storage LTOWB

- 1:1:1 ratio provides an estimated 38% loss of plasma coagulation factor activity and 56% loss of platelets compared to WB.
- Less decision-making, only one unit to hang
- Exposure to fewer blood donors
- When controlling for severity of injury, WB decreased the number of post-emergency room transfusions by 50% when compared to component therapy.
- But risk of exposure to "minor side" immune response to anti-A or anti-B
  - Study showed no laboratory evidence of reaction

Thanks to Sarah Bates, UCF Transfusion Svc.

Seheult JN, Bahr M, Anto V, et al. Safety profile of uncrossmatched, cold-stored, low-titer, group O+ whole blood in civilian trauma patients. Transfusion. 2018;58:2280-8.

PROUDLY SUPPORTED BY PrecisionBioLogic 55

55

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

Blood Center LTOWB Management

- Titer <256 [wisdom of the elders]: donor titers are consistent over time
- Leukoreduction: reduces TRALI, CMV, febrile reaction
  - Mostly components, if WB, must be with PLT-sparing filters
  - No difference in PLT count after 15d storage with non-LR
- Accept only nulligravida females
- Restrict rare units for multi-ab patients, observe Rh status
- Maintain adequate pheresis components
- Set up standing orders with transfusion service, avoid returns

CAP Today, June 2023

Remy KE, et al. J Trauma Acute Care Surg. 2018;84 [6S suppl 1] :S104–14
Pidcoke HE, McFaul SJ, Anand K, et al. Primary hemostatic capacity of whole blood: a comprehensive analysis of pathogen reduction and refrigeration effects over time. Transfusion 2013;53:137S–149S.

PROUDLY SUPPORTED BY PrecisionBioLogic 56

56

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

Cold-stored Pheresis Platelets

- Minimize bacteria contamination
- Provide crucial rapid, not prolonged hemostatic control
- Actin polymerization, disassembly of microtubules, increase in cytosolic Ca++, shape changes
- But: enhanced immediate adhesion, aggregation, clot strength
- Cleared in 2–3 days (RT 4–5 days)
- 18–24° C 5-day PLT concentrate not practical in transport
- Approved in 2015 by FDA for only 3-day storage, much wastage

Stubbs JB, Tran SA, Emery RL, et al. Cold platelets for trauma-associated bleeding: regulatory approval, accreditation approval, and practice implementation—just the "tip of the iceberg." Transfusion 2017; Cap AP, el al. Mil Med. 2018;183[suppl 2]:44–51

PROUDLY SUPPORTED BY PrecisionBioLogic 57

57

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

Transition to Venous Thromboembolism

- The worse the hemorrhage at 4–6 h, greater risk of VTE at 24 h
- Traumatic brain injury causes greater VTE risk
- Use of TXA early may reduce VTE risk late
- Anticoagulants? Too early, more bleeding, too late, VTE
- Use VET parameters to guide Rx, UFH or LMWH: clot strength, hypofibrinolysis

Hecht JP et al. Association of timing of initiation of pharmacologic venous thromboembolism prophylaxis with outcomes in trauma patients. J. Trauma Acute Care Surg 2021;90, 54–63

PROUDLY SUPPORTED BY PrecisionBioLogic 58

58

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

How to Treat?

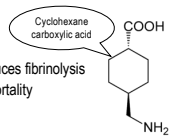
- Q11: TXA?

PROUDLY SUPPORTED BY PrecisionBioLogic 59

59

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

Tranexamic Acid [TXA, Cyclokapron] Rx



- Synthetic lysine blocks plasminogen binding sites, reduces fibrinolysis
- Reduces Tx requirements in surgery without raising mortality
- Around since 1968, cheap

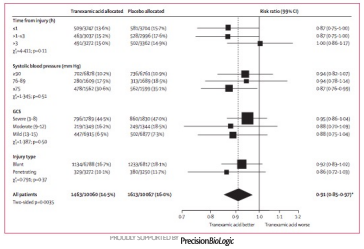
CRASH-2 trial collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage [CRASH-2]: a randomised, placebo-controlled trial. The Lancet 2010; 376: 23-32

PROUDLY SUPPORTED BY PrecisionBioLogic 60

60

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

All-cause Mortality by Subgroup TXA Versus Placebo



PROUDLY SUPPORTED BY PrecisionBioLogic 61

61

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

CRASH 2 on Public Media 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"
- Reduce RBC Tx by 8.4%
  - Smaller risk of incompatible Tx
- Reduce plasma demand by 90%
- Effective viral inactivation
- No risk of TRALI
- "Never" use rVIIa?

PROUDLY SUPPORTED BY PrecisionBioLogic 62

62

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

TXA Comments

- "MATTER" study reported better outcomes than CRASH-2
  - Number needed to treat: 7 versus 67
- HALT-IT trial of TXA in patients with GI hemorrhage indicated a significant increase in VTE in those receiving TXA given over 24 hours.
- 13% DVT/PE prevalence attributed to 24h use causing hypofibrinolysis
- But CRASH-2 and CRASH-3 trials randomized tens of thousands of patients after injury to TXA or placebo, and neither study demonstrated an increase in VTE.
- Laboratory monitoring: VET only
- Europe uses TXA in field and hospital, in US, EMS units carry TXA but not used in hospital
- Military medics carry TXA, not rVIIa

Morrison JJ, Dubose JJ, Rasmussen TE, Midwinter MJ. Military application of tranexamic acid in trauma emergency resuscitation (MATTER) study. Arch Surg 2012;147: 113–19.

PROUDLY SUPPORTED BY PrecisionBioLogic 63

63

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

Mayo Transport Unit

- Cooler box with…
- 2 group O negative RBC units
- 2 group A thawed plasma units
- 1 cold-stored LTOWB Rh neg
- 1 group A cold-stored pheresis platelet unit

PROUDLY SUPPORTED BY PrecisionBioLogic 64

64

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

Duke Unit Transport

- Cooler box #1
  - 2 group O negative RBC units
  - 2 group A thawed plasma units
- Cooler box #2
  - 2 group O negative RBC units
  - 2 group A thawed plasma units
  - 1 group A pheresis platelet unit
- Step 3: consult w/ provider, get labs
  - Components, TXA, rVIIa, LTOWB as requested

PROUDLY SUPPORTED BY PrecisionBioLogic 65

65

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

Q12: What's Left?

- Progress
- Quality of life
- Match Rx to conditions

PROUDLY SUPPORTED BY PrecisionBioLogic 66

66

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

Any Progress?

A reduction in bleeding-related deaths was observed in one US urban trauma center from 36% to 25% after implementing a bleeding control bundle-of-care but since the 1990s, when bleeding caused over one third of trauma fatalities, we have made little progress, as currently hemorrhage accounts for 20–34% of trauma-related mortality.

Oyeniyi BT et al. Trends in 1029 trauma deaths at a level 1 trauma center: impact of a bleeding control bundle of care. Injury 2017: 48, 5–12.
Roberts DJ et al. One thousand consecutive in-hospital deaths following severe injury: has the etiology of traumatic inpatient death changed in Canada? Can. J. Surg 2018; 61 150–2.

PROUDLY SUPPORTED BY PrecisionBioLogic 67

67

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

Quality of Life [QOL]

- In Trauma Recovery Project post-injury functional limits in >75% at 12 and 18-months.
- Depression in 60% of patients at discharge and 31% at 6 months.
- Adolescents without TBI showed acute stress disorder in 40% upon discharge.
  - Large QOL deficits at 3, 6, 12 and 24 months and long-term PTSD rate 27%.
- In CONTROL report, over 70% report moderate or extreme difficulties in usual activities, pain or discomfort and mobility limitations.
  - Over half reported self-care problems and anxiety or depression.
- In Australia, Glasgow Outcome Score–Extended [GOSE] at 6 and 12 months in non-TBI adults with massive blood transfusion independently associated with unfavorable outcomes among survivors at 6 months after injury.

Holbrook TL, Anderson JP, Sieber WJ, eet al. Outcome after major trauma: 12-month and 18-month follow-up results from the Trauma Recovery Project. J. Trauma 1999; 46, 765–773.
Christensen MC, Banner C, Lefering R, et al. Quality of life after severe trauma: results from the global trauma trial with recombinant factor VII. J. Trauma 2011; 70 1524–31.

PROUDLY SUPPORTED BY PrecisionBioLogic 68

68

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

What's Left?

- Clinical TIC definition
  - Multiple TIC phenotypes exist; define to optimize Rx.
- How to distinguish early hemorrhagic from later thrombotic status.
- Massive transfusion definitions do not capture the effect of TIC on TBI.
- Too many hypotheses, too many mechanisms
  - Mechanisms vary with type of injury: blunt, penetrating, GSW, TBI
- How to match the right Rx with the right mechanism

PROUDLY SUPPORTED BY PrecisionBioLogic 69

69

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

PROUDLY SUPPORTED BY PrecisionBioLogic 70

70