THE FRITSMA FACTOR

Your Interactive Hemostasis Resource

Managing Hemostasis in Trauma-induced Coagulopathy

TIC-TIC

Timing is Everything

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Overview

- Pathophysiology of trauma and shock
- Traditional trauma management
- Current trauma management
- Massive transfusion protocol
- Balanced blood product therapy
- Antifibrinolytics and components

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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%
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%

31.7% (Unintentional Injury, Suicide, Homicide)

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

10 Leading Causes of Death by Age Group, United States – 2014

	Age Groups										
Rank	<1	1-4	5-9	10-14	15-24	25-34	35-44	45-54	55-64	65+	Total
1	Congenital Anomalies 4,746	Unintentional Injury 1,216	Unintentional Injury 730	Unintentional Injury 750	Unintentional Injury 11,836	Unintentional Injury 17,357	Unintentional Injury 16,048	Malignant Neoplasms 44,834	Malignant Neoplasms 115,282	Heart Disease 489,722	Heart Disease 614,348
2	Short Gestation 4,173	Congenital Anomalies 399	Malignant Neoplasms 436	Suicide 425	Suicide 5,079	Suicide 6,569	Malignant Neoplasms 11,267	Heart Disease 34,791	Heart Disease 74,473	Malignant Neoplasms 413,885	Malignant Neoplasms 591,699
3	Maternal Pregnancy Comp. 1,574	Homicide 364	Congenital Anomalies 192	Malignant Neoplasms 416	Homicide 4,144	Homicide 4,159	Heart Disease 10,368	Unintentional Injury 20,610	Unintentional Injury 18,030	Chronic Low. Respiratory Disease 124,693	Chronic Low. Respiratory Disease 147,101
4	SIDS 1,545	Malignant Neoplasms 321	Homicide 123	Congenital Anomalies 156	Malignant Neoplasms 1,569	Malignant Neoplasms 3,624	Suicide 6,706	Suicide 8,767	Chronic Low. Respiratory Disease 16,492	Cerebro-vascular 113,308	Unintentional Injury 136,053
5	Unintentional Injury 1,161	Heart Disease 149	Heart Disease 69	Homicide 156	Heart Disease 953	Heart Disease 3,341	Homicide 2,588	Liver Disease 8,627	Diabetes Mellitus 13,342	Alzheimer's Disease 92,604	Cerebro-vascular 133,103
6	Placenta Cord. Membranes 965	Influenza & Pneumonia 109	Chronic Low. Respiratory Disease 68	Heart Disease 122	Congenital Anomalies 377	Liver Disease 725	Liver Disease 2,582	Diabetes Mellitus 6,062	Liver Disease 12,792	Diabetes Mellitus 54,161	Alzheimer's Disease 93,541
7	Bacterial Sepsis 544	Chronic Low Respiratory Disease 53	Influenza & Pneumonia 57	Chronic Low Respiratory Disease 71	Influenza & Pneumonia 199	Diabetes Mellitus 709	Diabetes Mellitus 1,999	Cerebro-vascular 5,349	Cerebro-vascular 11,727	Unintentional Injury 48,295	Diabetes Mellitus 76,488
8	Respiratory Distress 460	Septicemia 53	Cerebro-vascular 45	Cerebro-vascular 43	Diabetes Mellitus 181	HIV 583	Cerebro-vascular 1,745	Chronic Low. Respiratory Disease 4,402	Suicide 7,527	Influenza & Pneumonia 44,836	Influenza & Pneumonia 55,227
9	Circulatory System Disease 444	Benign Neoplasms 38	Benign Neoplasms 36	Influenza & Pneumonia 41	Chronic Low Respiratory Disease 178	Cerebro-vascular 579	HIV 1,174	Influenza & Pneumonia 2,731	Septicemia 5,709	Nephritis 39,957	Nephritis 48,146
10	Neonatal Hemorrhage 441	Perinatal Period 38	Septicemia 33	Benign Neoplasms 38	Cerebro-vascular 177	Influenza & Pneumonia 549	Influenza & Pneumonia 1,125	Septicemia 2,514	Influenza & Pneumonia 5,390	Septicemia 29,124	Suicide 42,773

Data Source: National Vital Statistics System, National Center for Health Statistics, CDC.
Produced by: National Center for Injury Prevention and Control, CDC using WISQARS™.

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National Center for Injury Prevention and Control

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10 Leading Causes of Injury Deaths by Age Group Highlighting Unintentional Injury Deaths, United States – 2014

	Age Groups										
Rank	<1	1-4	5-9	10-14	15-24	25-34	35-44	45-54	55-64	65+	Total
1	Unintentional Suffocation 991	Unintentional Drowning 388	Unintentional MV Traffic 345	Unintentional MV Traffic 384	Unintentional MV Traffic 6,531	Unintentional Poisoning 9,334	Unintentional Poisoning 9,116	Unintentional Poisoning 11,009	Unintentional Poisoning 7,013	Unintentional Fall 27,044	Unintentional Poisoning 42,032
2	Homicide Unspecified 119	Unintentional MV Traffic 293	Unintentional Drowning 125	Suicide Suffocation 225	Homicide Firearm 3,587	Unintentional MV Traffic 5,856	Unintentional MV Traffic 4,308	Unintentional MV Traffic 5,024	Unintentional MV Traffic 4,554	Unintentional MV Traffic 6,373	Unintentional MV Traffic 33,736
3	Homicide Other Spec., Classifiable 83	Homicide Unspecified 149	Unintentional Fire/Burn 68	Suicide Firearm 174	Unintentional Poisoning 3,492	Homicide Firearm 3,260	Suicide Firearm 2,830	Suicide Firearm 3,953	Suicide Firearm 3,910	Suicide Firearm 5,367	Unintentional Fall 31,959
4	Unintentional MV Traffic 61	Unintentional Suffocation 120	Homicide Firearm 58	Homicide Firearm 115	Suicide Firearm 2,270	Suicide Firearm 2,829	Suicide Suffocation 2,057	Suicide Suffocation 2,321	Unintentional Fall 2,558	Unintentional Unspecified 4,590	Suicide Firearm 21,334
5	Undetermined Suffocation 40	Unintentional Fire/Burn 117	Unintentional Other Land Transport 36	Unintentional Drowning 105	Suicide Suffocation 2,010	Suicide Suffocation 2,402	Homicide Firearm 1,835	Suicide Poisoning 1,795	Suicide Poisoning 1,529	Unintentional Suffocation 3,692	Suicide Suffocation 11,407
6	Unintentional Drowning 29	Unintentional Pedestrian, Other 107	Unintentional Suffocation 34	Unintentional Fire/Burn 49	Unintentional Drowning 507	Suicide Poisoning 800	Suicide Poisoning 1,274	Unintentional Fall 1,340	Suicide Suffocation 1,509	Unintentional Poisoning 1,993	Homicide Firearm 10,945
7	Homicide Suffocation 26	Homicide Other Spec., Classifiable 73	Unintentional Natural/ Environment 22	Unintentional Other Land Transport 49	Suicide Poisoning 363	Undetermined Poisoning 575	Undetermined Poisoning 637	Homicide Firearm 1,132	Unintentional Suffocation 698	Adverse Effects 1,554	Suicide Poisoning 6,808
8	Unintentional Natural/ Environment 17	Homicide Firearm 47	Unintentional Pedestrian, Other 18	Unintentional Suffocation 33	Homicide Cut/Pierce 314	Homicide Cut/Pierce 430	Unintentional Fall 504	Undetermined Poisoning 820	Undetermined Poisoning 539	Unintentional Fire/Burn 1,151	Unintentional Suffocation 6,580
9	Undetermined Unspecified 16	Unintentional Struck by or Against 38	Unintentional Struck by or Against 16	Unintentional Poisoning 22	Undetermined Poisoning 229	Unintentional Drowning 399	Unintentional Drowning 363	Unintentional Suffocation 452	Homicide Firearm 538	Suicide Poisoning 1,028	Unintentional Unspecified 5,848
10	Unintentional Fire/Burn 15	Unintentional Natural/ Environment 35	Unintentional Firearm (Tied) 14	Homicide Cut/Pierce 19	Unintentional Other Land Transport 177	Unintentional Fall 285	Homicide Cut/Pierce 313	Unintentional Drowning 442	Unintentional Unspecified 530	Suicide Suffocation 880	Unintentional Drowning 3,406

Data Source: National Center for Health Statistics (NCHS), National Vital Statistics System.
Produced by: National Center for Injury Prevention and Control, CDC using WISQARS™.

Centers for Disease Control and Prevention
National Center for Injury Prevention and Control

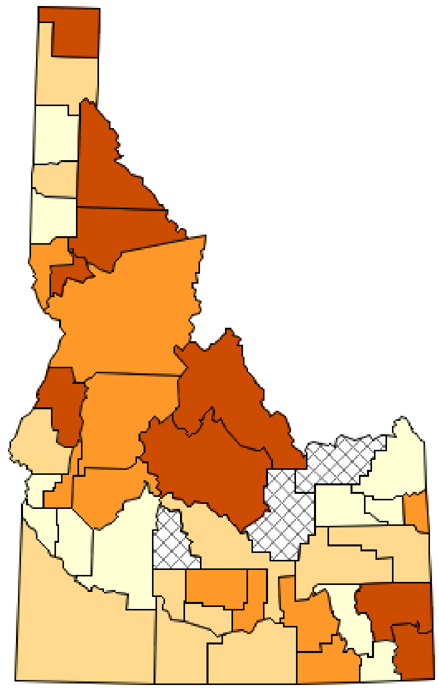
Idaho Injury Death Rates/100,000

2004-2010, Idaho

Death Rates per 100,000 Population

All Injury, All Intents, All Races, All Ethnicities, Both Sexes, All Ages

Annualized Crude Rate for Idaho: 64.23



Suppressed/Unstable/Undefined	31.48-65.25	65.26-78.48
78.49-93.93	93.94-125.00	

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: NCHS National Vital Statistics System for numbers of deaths; US Census Bureau for population estimates.

24-YO ♂, GSW in ED, 2008

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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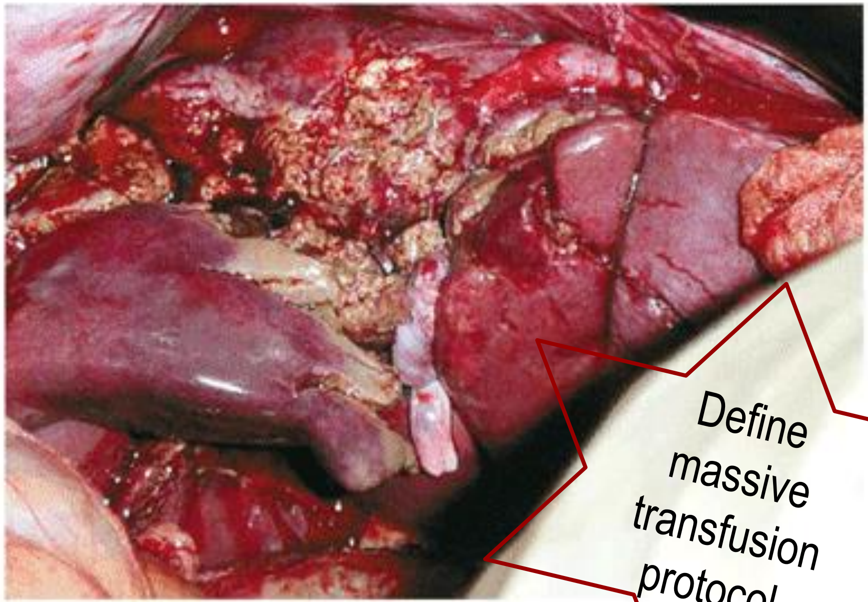
24-YO ♂, GSW in ED, 2008

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.

Previous Massive Tx 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 (2009)
  - Activated PCC (FEIBA)
  - Four-factor PCC (KCentra)
  - NovoSeven® recombinant activated factor VII

Off-label

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 Guidelines
- 2012: Joint Trauma System Clinical Practice Guidelines

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

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, CBC w/ PLTs, FG, D-D, ABG, Lytes, TEG, TEM

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 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.

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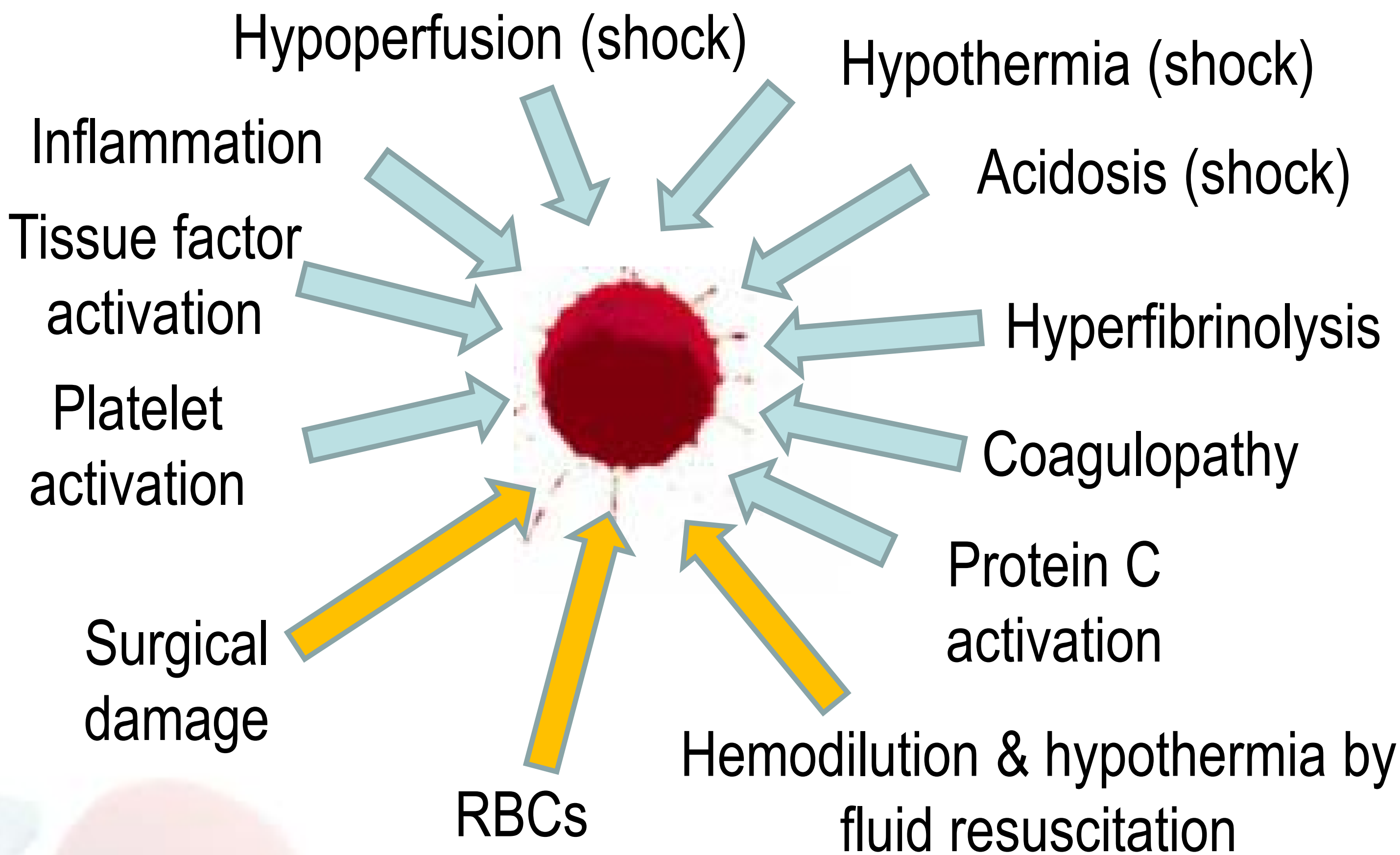
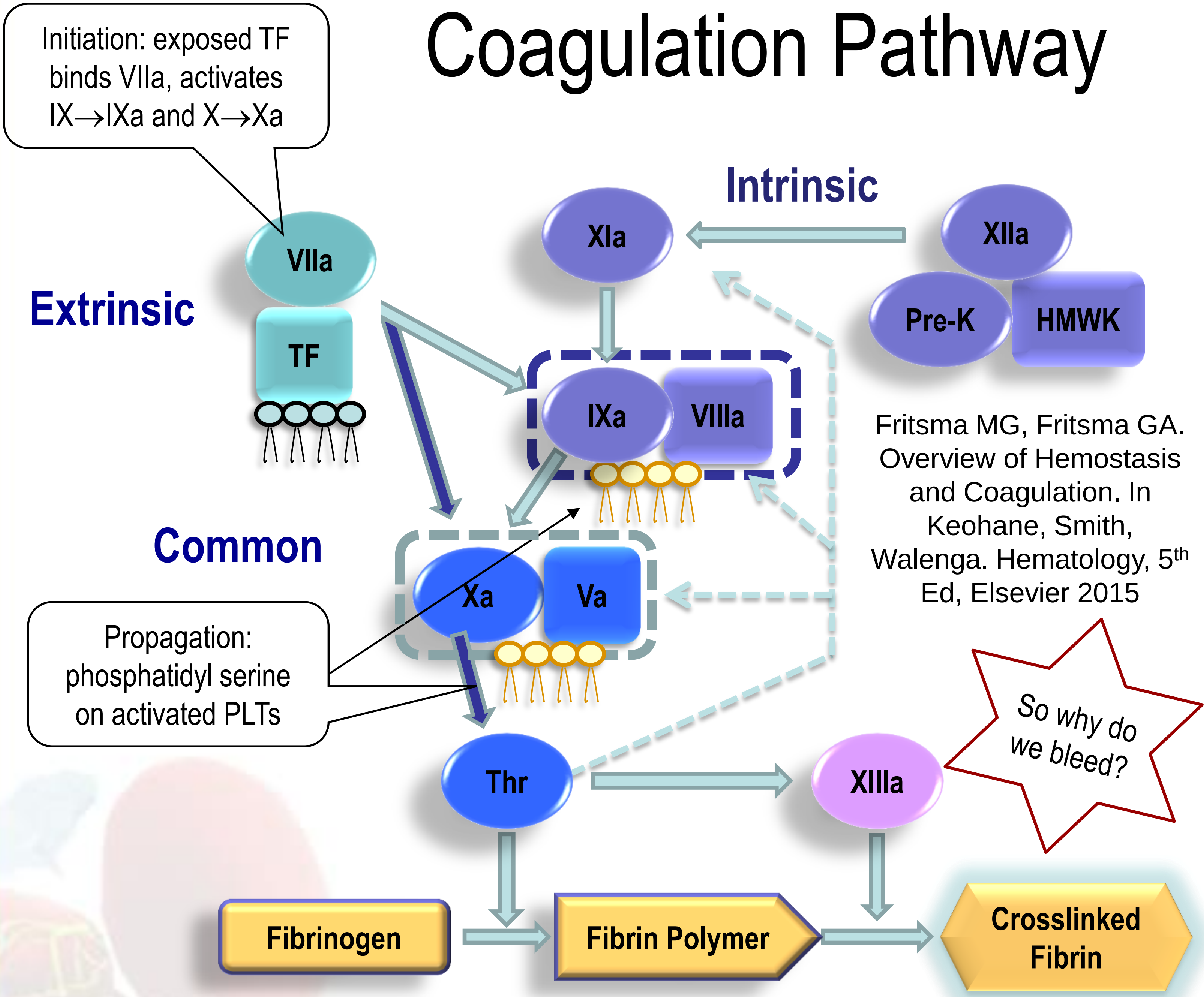
TIC Mechanisms



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

Coagulation Pathway



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

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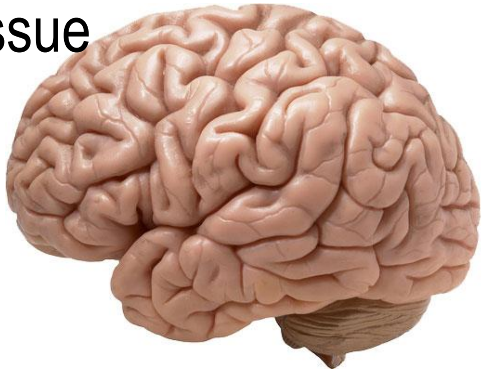
Lost Clotting Ability

- Half of FG and PLT pools exsanguinate and are lost in massive hematoma or hemorrhage
- Factor VII is lost to exposed tissue factor
- Factor V and VIII depletion
- 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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Coagulant Deficit Upon Arrival Injury Severity Score >16

Clotting factors	Critical deficit ≤30% clotting factor activity 22 patients
Factor II (n=105)	2 (9.1%)
Factor V (n=105)	22 (100%)
Factor VII (n=108)	1 (4.5%)
Factor VIII (n=110)	4 (18.2%)
Factor IX (n=105)	2 (10%)
Factor X (n=96)	2 (10%)
Factor XI (n=99)	3 (15%)
Factor XII (n=97)	2 (10%)

Rizoli SB, Scarpelini S, Callum J, et al. Clotting factor deficiency in early trauma-associated coagulopathy. J Trauma. 2011; 71: S427–S434

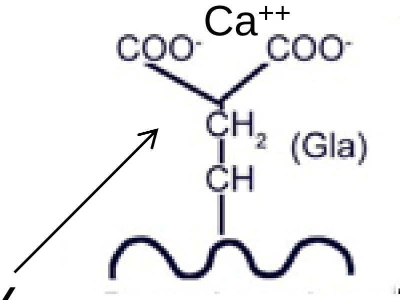
Clotting Factor Dilution

- 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
- Whole blood?
  - Donor whole blood is diluted with 67 mL A/C per 450 mL TV
  - Whole blood theoretical best HCT is 28%
- Red cells?
  - 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.

Hypothermia, Acidosis, Fibrinolysis

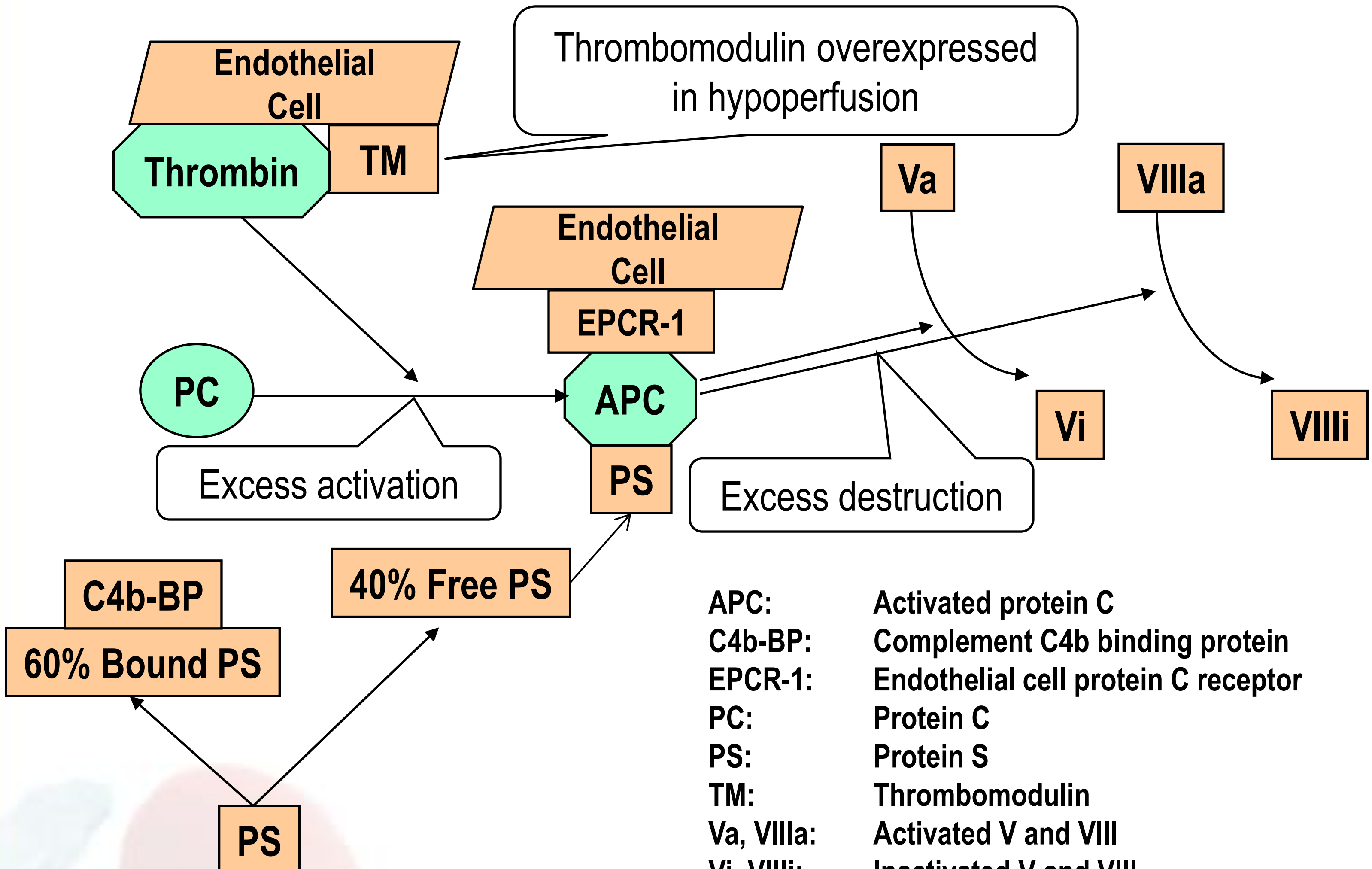
- All enzyme activity slows at <37°C
- PLT activation slows at 32–34°C (?)
- Platelets cease to bind VWF at 30°C
- Vitamin K-dependent factors II, VII, IX, and X fail to bind phospholipid in acidosis



- 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

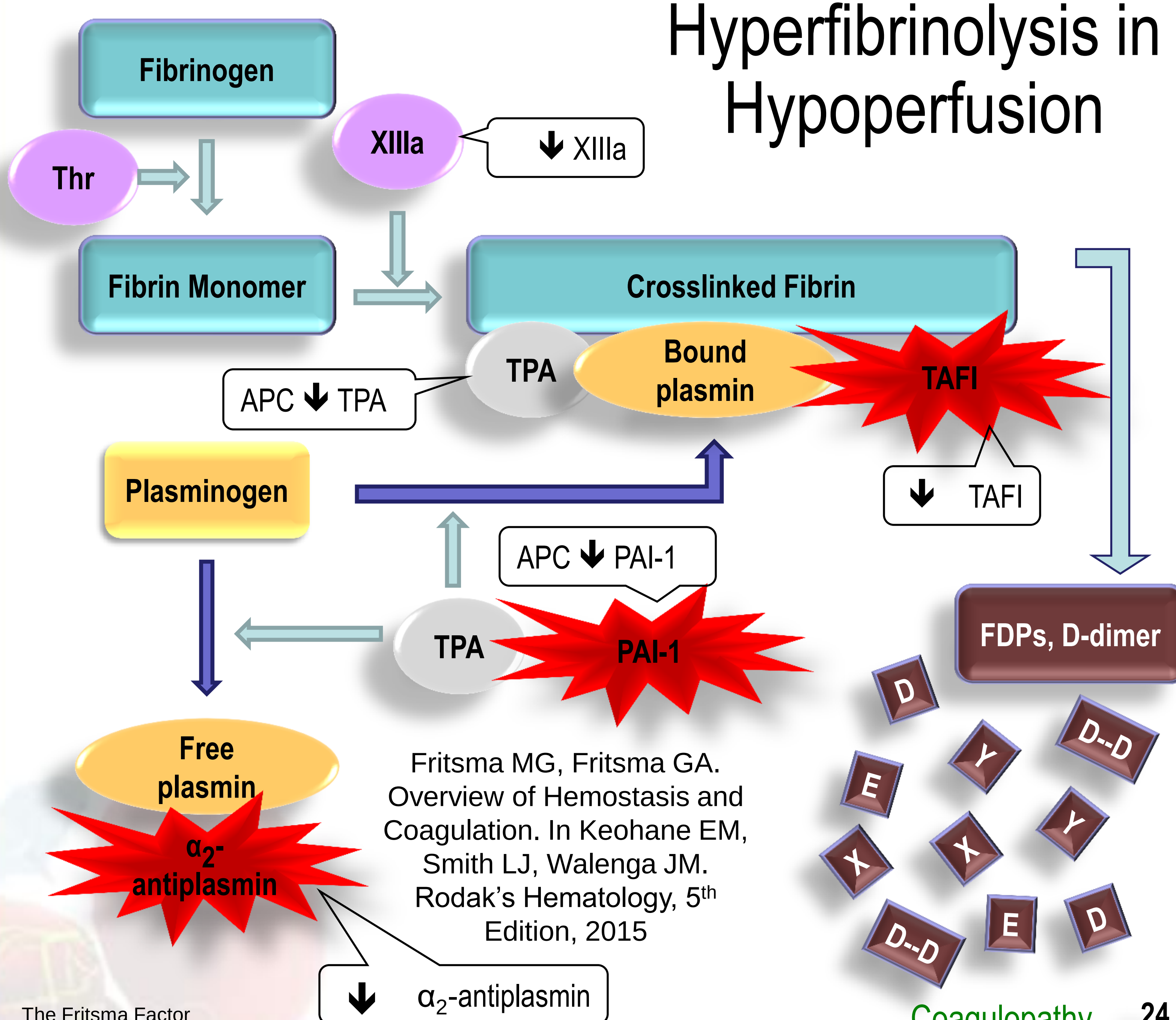
The Protein C Control Pathway



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.

Hyperfibrinolysis in Hypoperfusion



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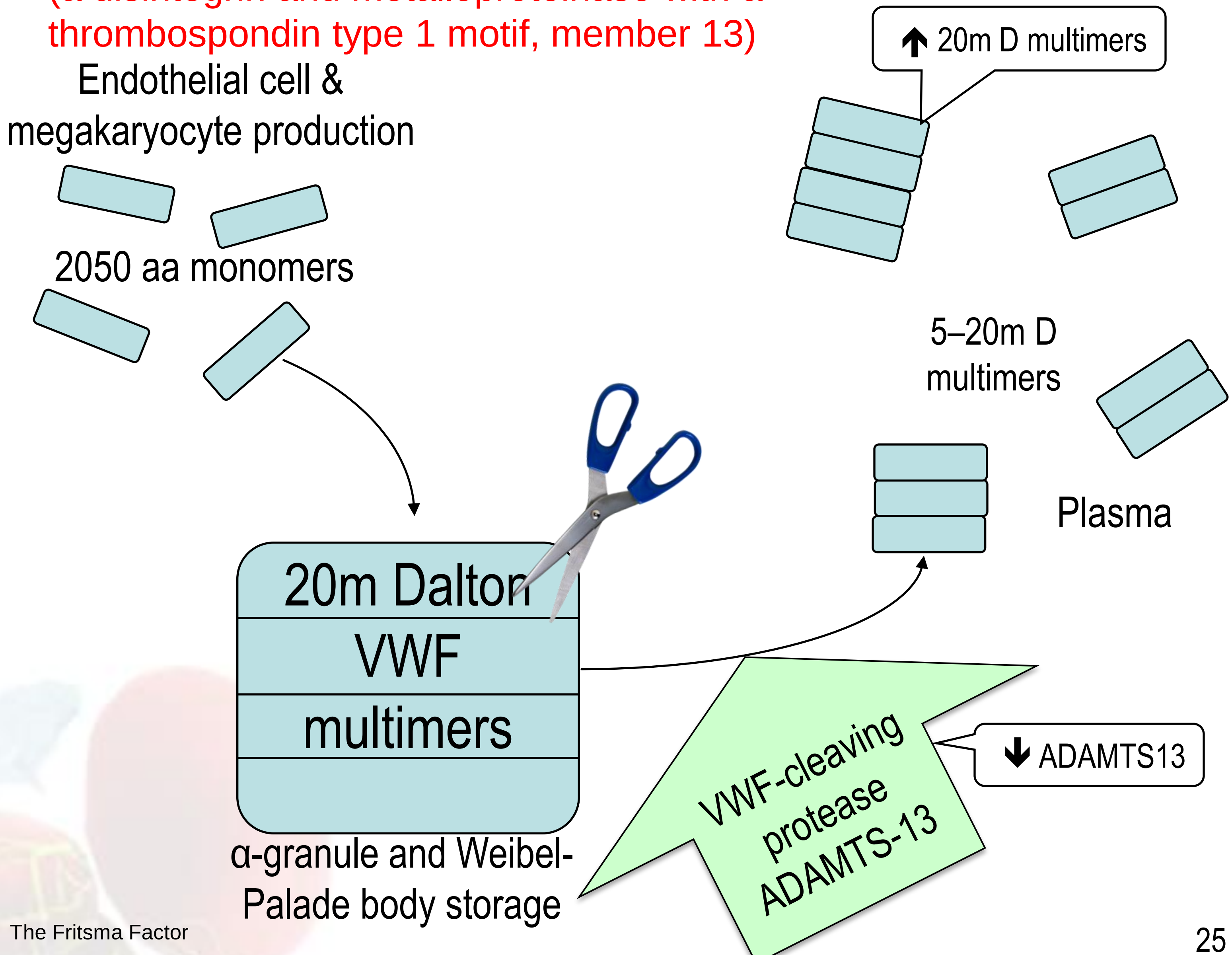
VWF Synthesis, Reduced ADAMTS13

(a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13)



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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:	% Coagulo-pathy*
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 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.

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%

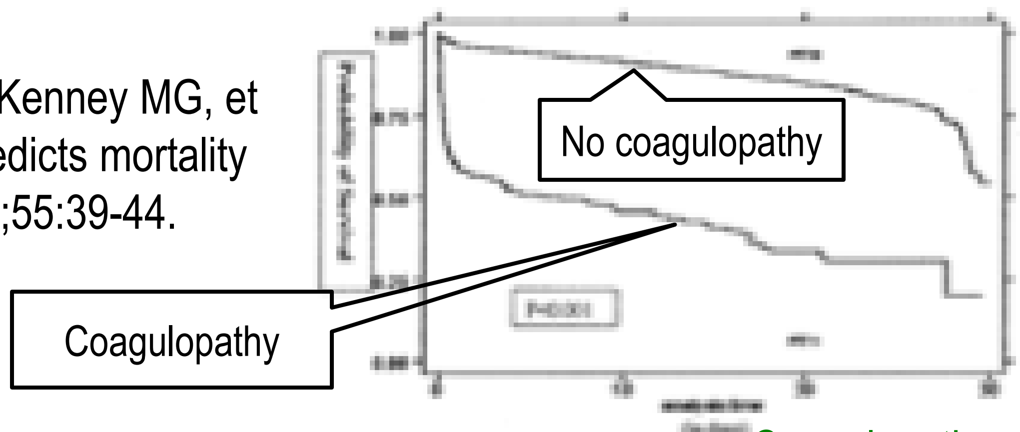
*Coagulopathy defined independent of fluid replacement as: PT ≥18s,16.3%; PTT ≥60s, 24.4%; or thrombin time ≥15s, 14.2%

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

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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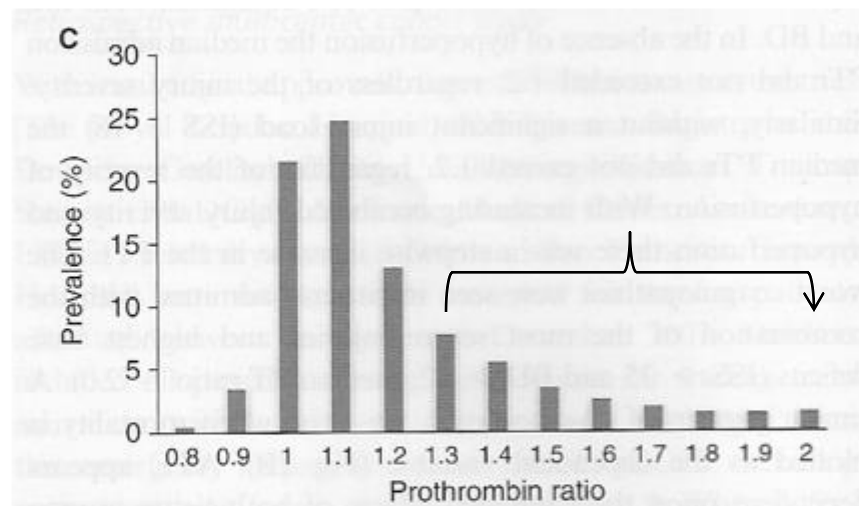
Definition and “Drivers” of TIC

- Retrospective cohort study
  - 3646 trauma patients at five 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, et al. Definition and drivers of acute traumatic coagulopathy: clinical and experimental investigations. J Thromb Haemost 2010;8:1919–25.

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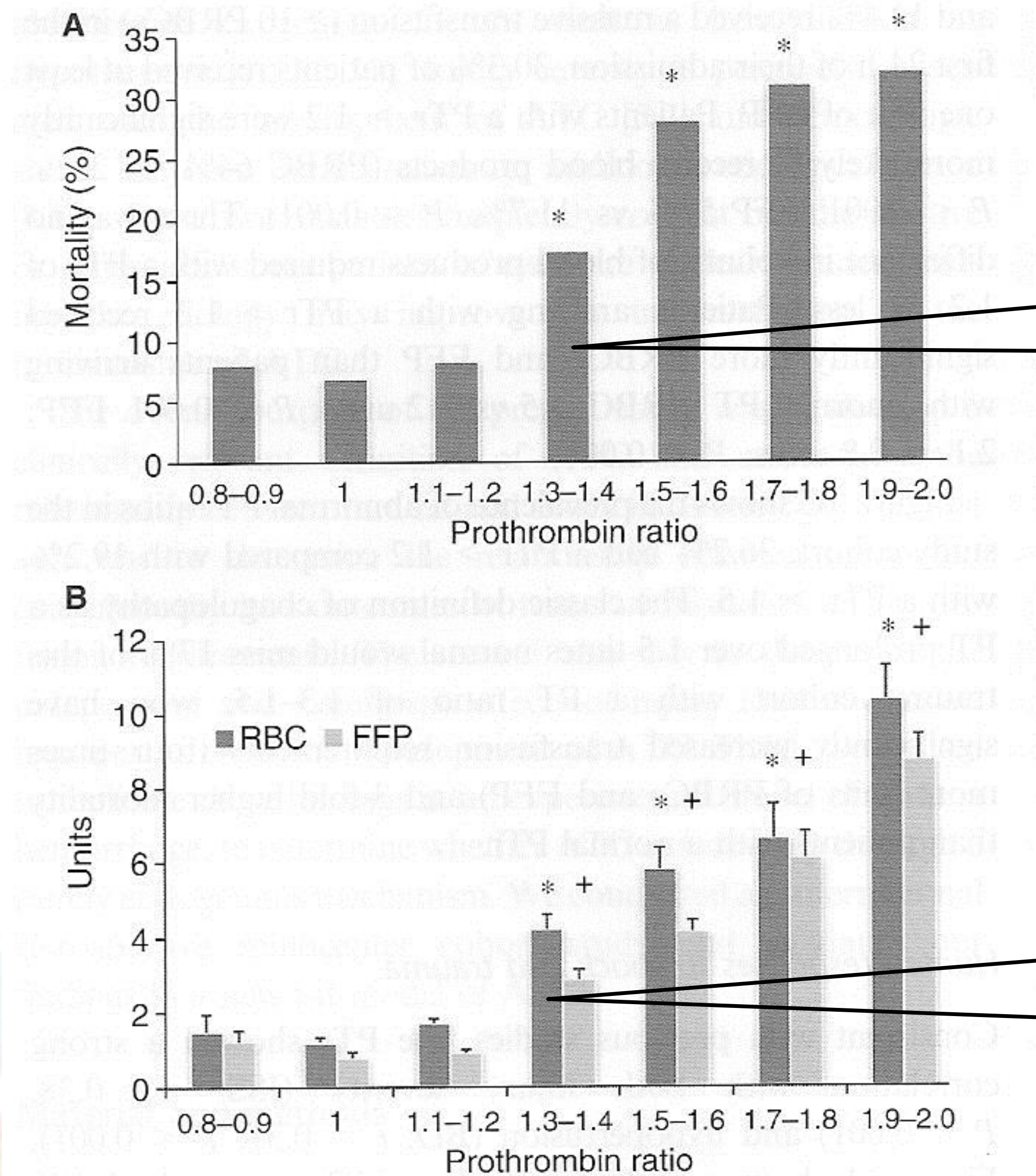
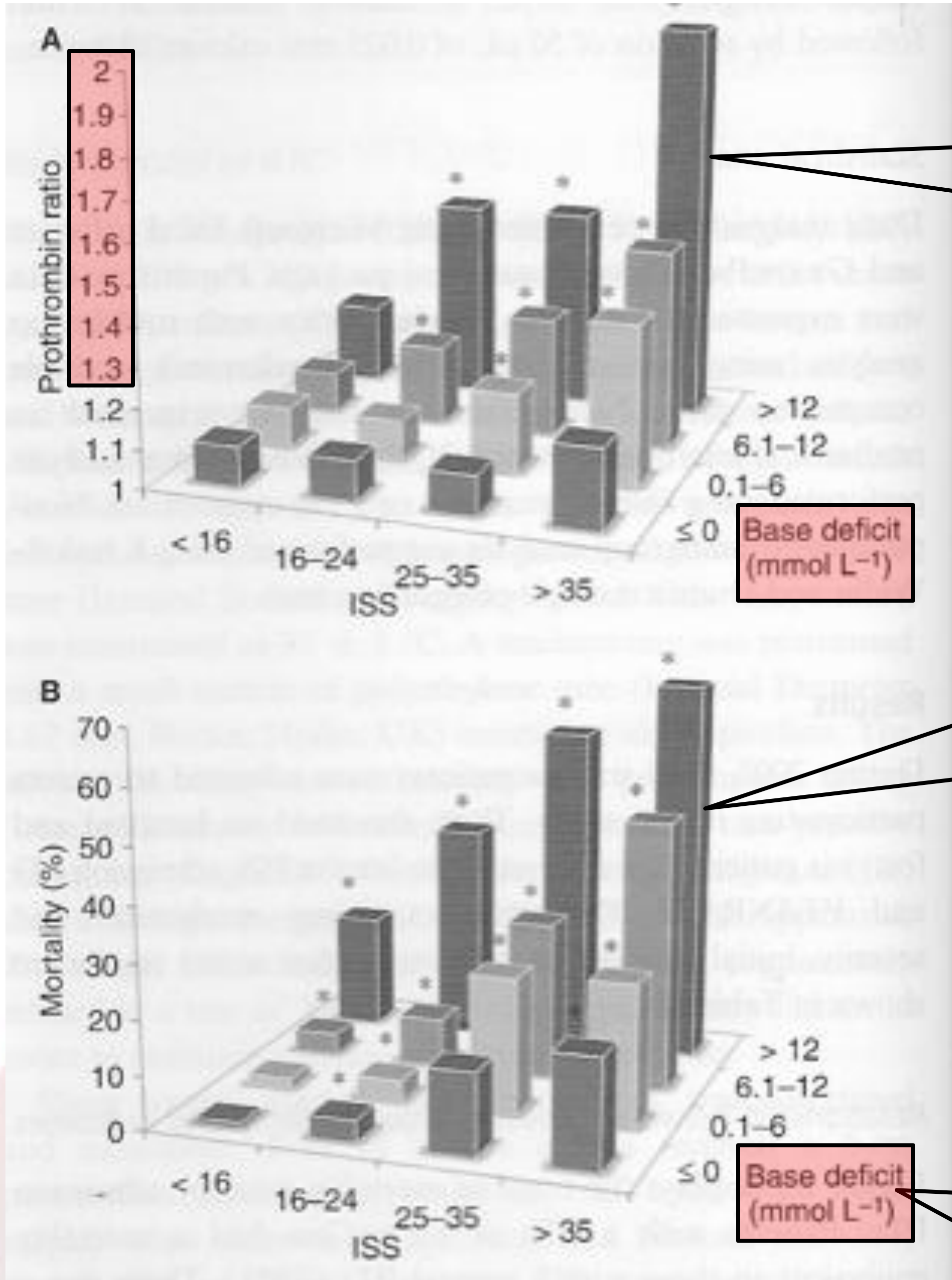


Mortality rises with PTR >1.2

RBC and plasma demand rise with PTR >1.2



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

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

Base deficit (mmol/L) mirrors shock

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Massive Transfusion Protocol (MTP)

- 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. .

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Massive Transfusion in Young, Healthy Combat Casualties

Start MTP if any two are present

- 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)

- 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

MTP in ER: Civilian Casualties

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

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 but the last two significant at $p < 0.05$		

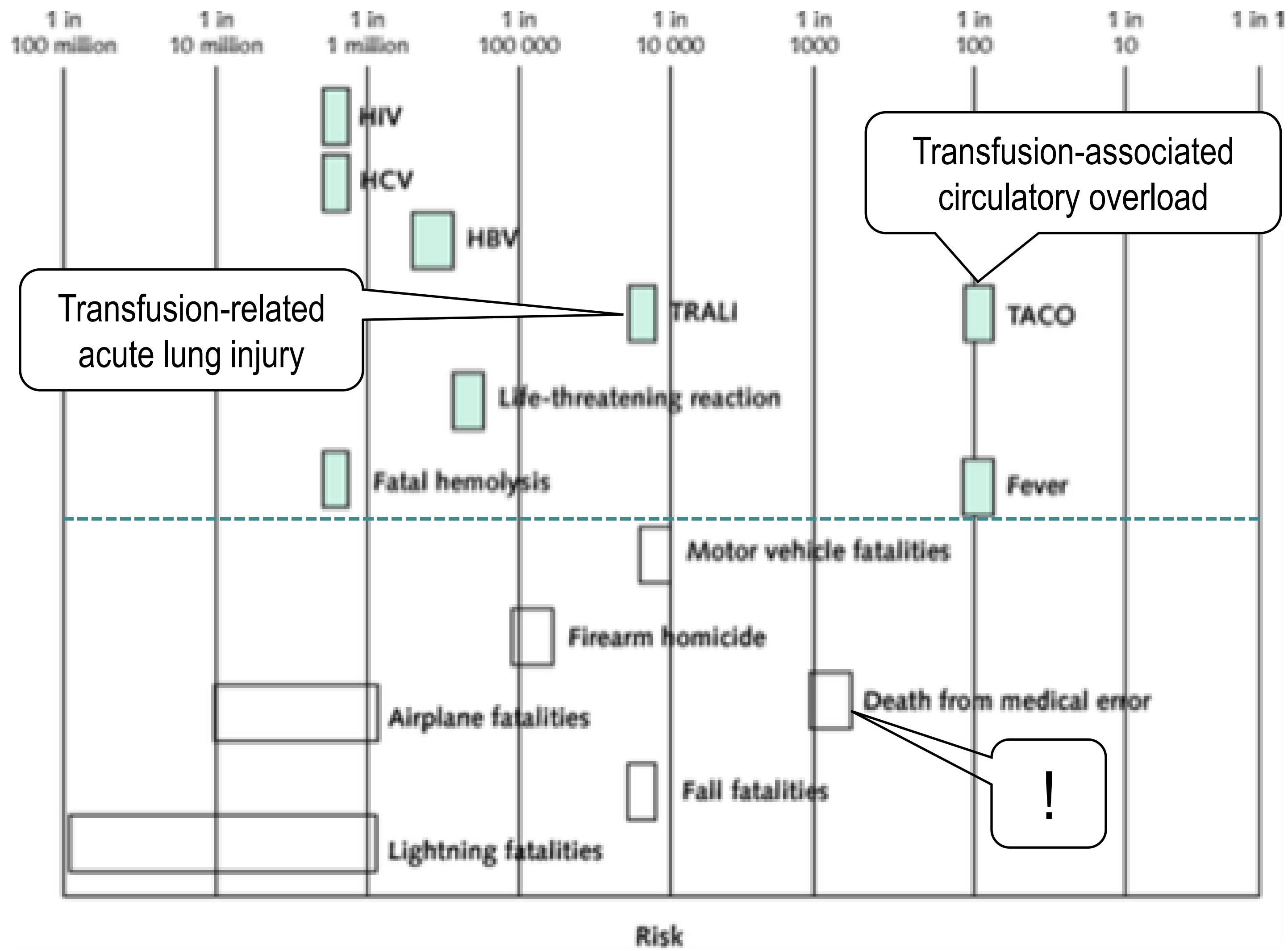
Glance LG, Dick AW, Mukamel DB, et al. Association between intraoperative blood transfusions and mortality and morbidity in patients undergoing noncardiac surgery. Anesthesiology 2011;114:283–92.

RBC Transfusion Risks in Trauma

- Tx predicts MOF when victim survives >24 h
- Transfusion-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
- 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.

RBC Transfusion Risks in Context



Ann Intern Med. 2012;157:49–58

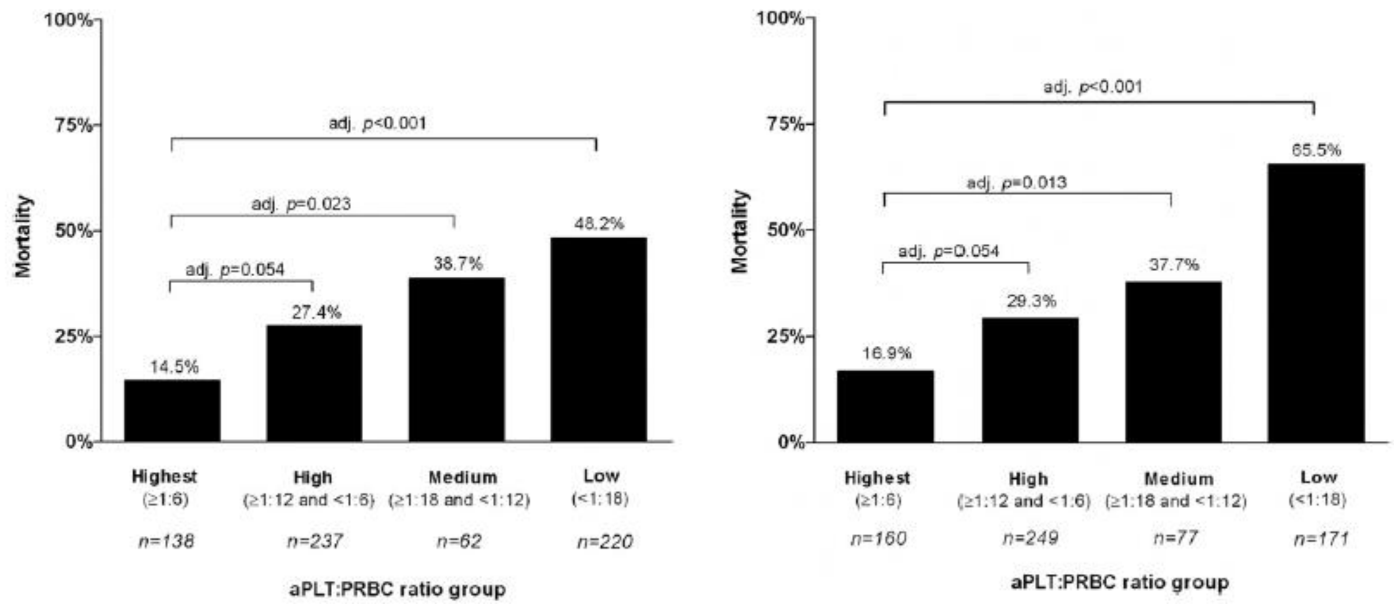
RBC Risks and Indications

Risk	Indication
ABO Incompatibility*	Fever, hemoglobinuria, hemoglobinemia
TRALI* or TACO	Respiratory distress, hypoxemia
Bacterial contamination	Fever, hypotension
Allergic reaction	Urticaria
Citrate toxicity	Hypocalcemia

*Observe for delayed TRALI and Tx reaction; terminate Tx and start diagnostic tests

Platelet Concentrate

- Clinicians discouraged from giving platelets
  - Why? "Platelets are a precious commodity."
- Use early anyway, they stabilize the coagulopathy
  - PLT concentrate has 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.

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
  - Approved 4/1/2014 for replacement of non-labile coagulation factors
- All preparations stored frozen up to 12 months
- Thawed AB plasma: stored at 1–6C; 5 d if closed

Mean Factor V, VIII and Protein S Levels in FFP, PF24, 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
  - 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.

ASA 2015 Plasma Indications

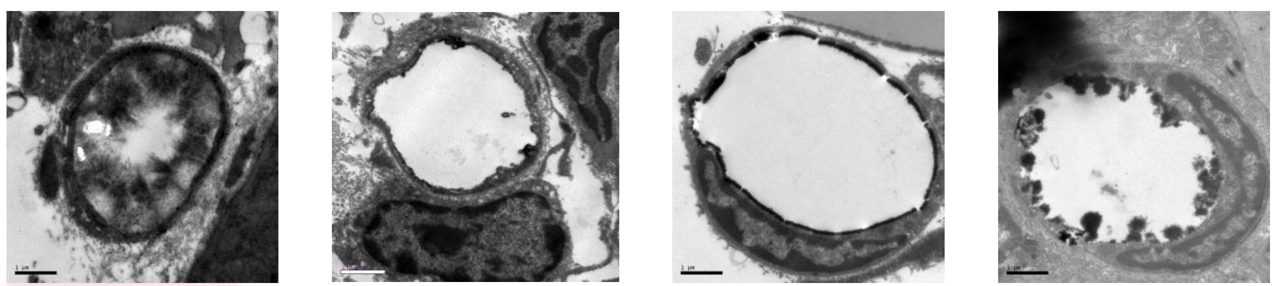
- Manage preoperative or bleeding pts who require replacement of multiple coagulation factors (eg, liver disease, DIC).
- Manage patients undergoing massive transfusion who have clinically significant coagulation deficiencies.
- Manage bleeding patients taking warfarin or who need an invasive procedure 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.

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
  - Pre-restrictions: 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.

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

Group AB 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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PROMMTT 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 (PROMMTT) study. JAMA Surg 2013; 148:127–36.

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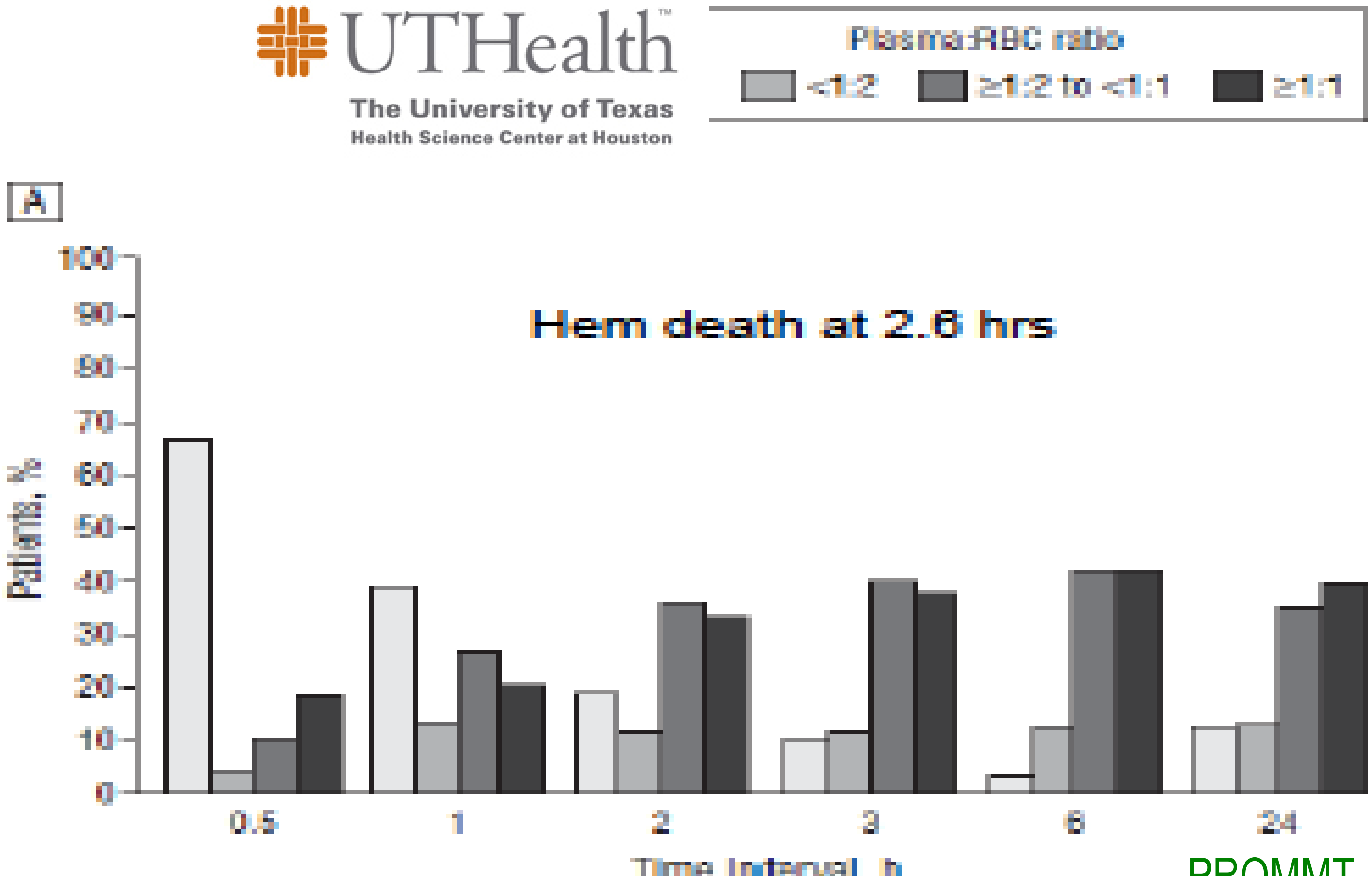
PROMMT Plasma:RBC Ratio

PROMMTT

PROSPECTIVE OBSERVATIONAL MULTICENTER MASSIVE TRANSFUSION STUDY

UTHealth

The University of Texas Health Science Center at Houston



PROMMT

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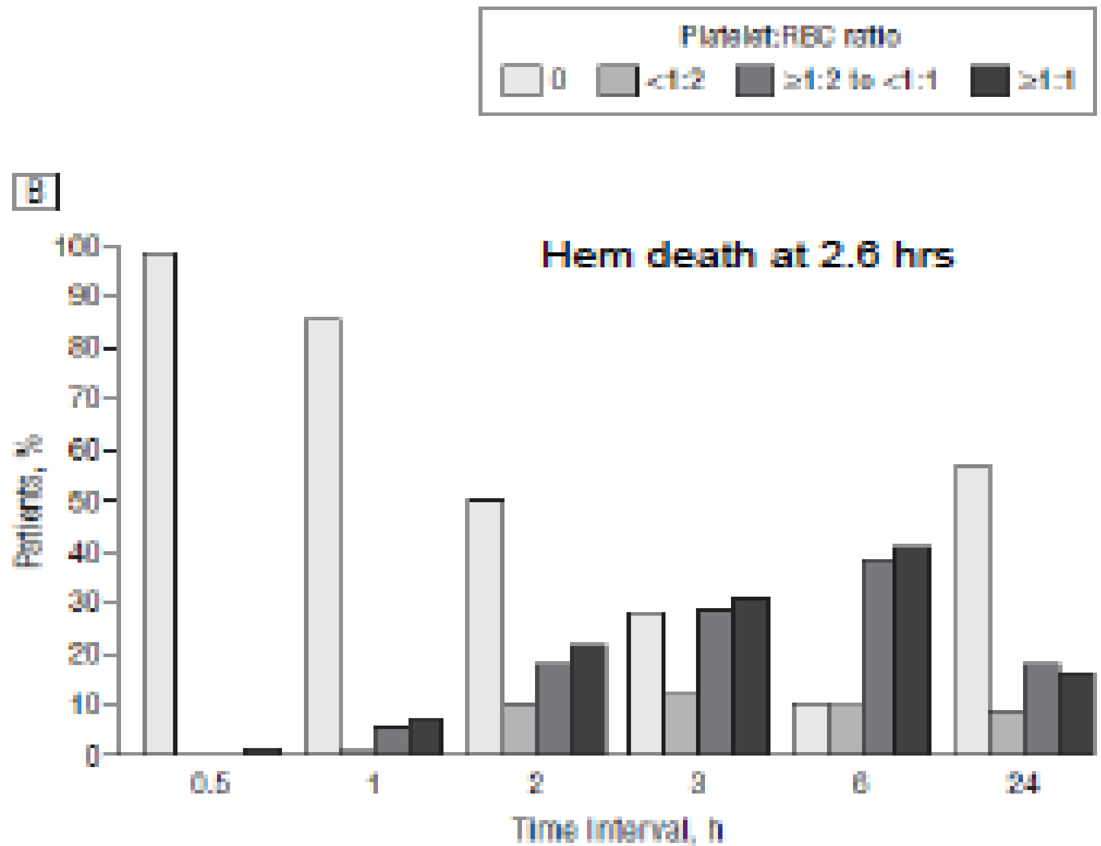
PROMMT Platelet:RBC Ratio

Earlier and higher ratios of plasma and platelets associated with decreased in-hospital mortality in the first 6 hours.



PROMMT

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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

TRALI Versus CRALI

- Crystalloid-related acute lung injury (CRALI)
- The amount of crystalloid versus 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.

PROMMT

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Updated TIC Rx

- Minimize crystalloids by targeting low BP
- Use thawed plasma in EMS, 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

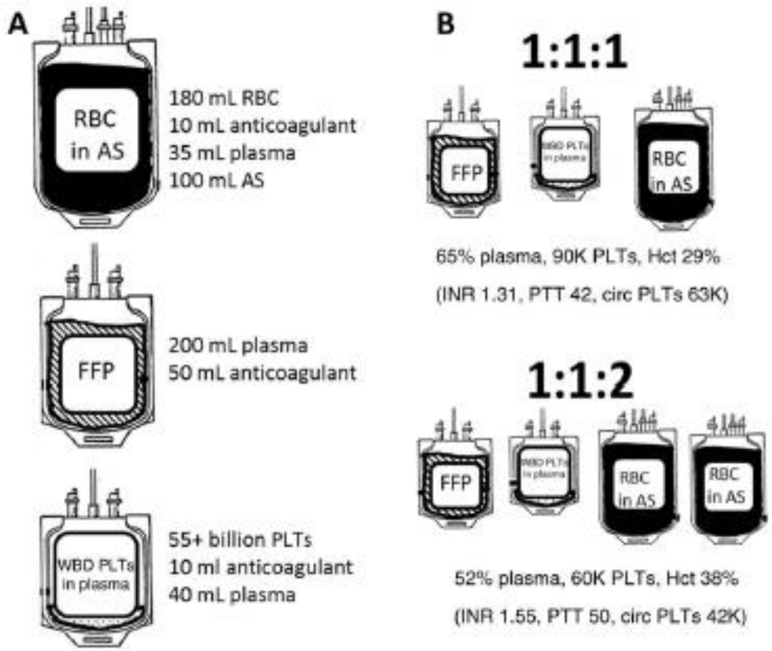
PROPPR Trial: Group A Plasma

- 12 level I trauma centers
- Balanced BPs randomized: 1:1:1 or 1:1:2
  - Plasma : platelet concentrate : red blood cells
- All but 1 center delivered 6 u universal donor 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; 55:1331–9.

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 differences
  - 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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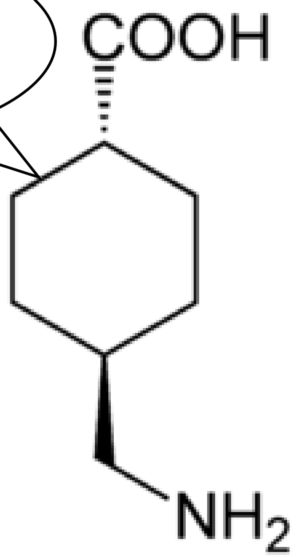
Fresh Whole Blood—Why Not?

- FWB provides plasma:RBC:PLTs in a 1:1:1 ratio
- FWB improvsd survival compared to stored components.
- FWB is available in austere conditions
- No cold storage loss of clotting factor or platelet function.
- No RBC storage lesion. Butt…
- Lack of screening: transfusion-transmitted infections
  - HBV, HCV, HIV, HTLV, syphilis
- Grouping error and hemolytic transfusion risk
  - Crossmatch required
- Bacterial contamination

Joint Theater Trauma System Clinical Practice Guideline: Fresh whole blood transfusion, 2012

Tranexamic Acid (Cyclokapron) Rx

Cyclohexane carboxylic acid



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

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	IV TXA	Placebo	RR	p
1 g TXA bolus + 1 g/8h	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 product volumes				

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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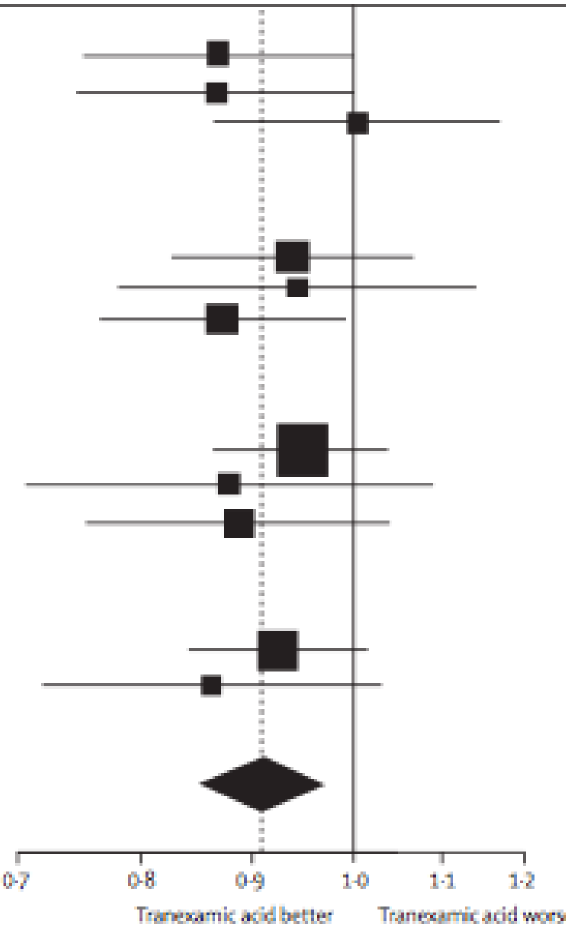
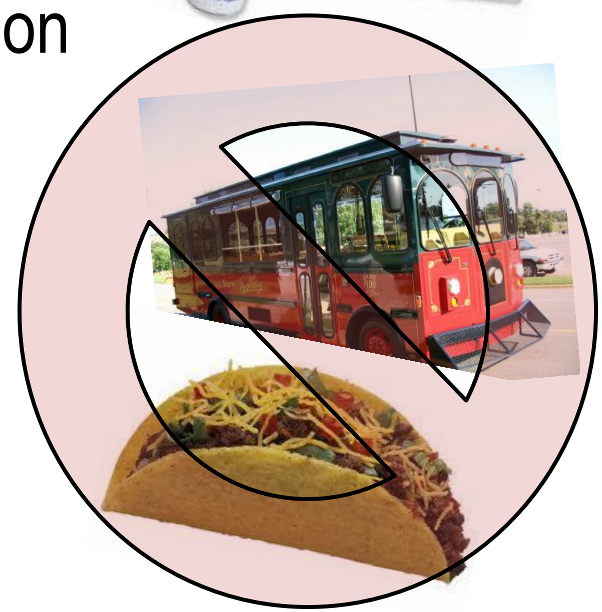
All-cause Mortality by Subgroup Tranexamic Acid Versus Placebo

	Tranexamic acid allocated	Placebo allocated	Risk ratio (99% CI)
Time from injury (h)			
≤1	509/3747 (13·6%)	581/3704 (15·7%)	0·87 (0·75–1·00)
>1–≤3	463/3037 (15·2%)	528/2996 (17·6%)	0·87 (0·75–1·00)
>3	491/3272 (15·0%)	502/3362 (14·9%)	1·00 (0·86–1·17)
χ^2_2=4·411; p=0·11			
Systolic blood pressure (mm Hg)			
≥90	702/6878 (10·2%)	736/6761 (10·9%)	0·94 (0·82–1·07)
76–89	280/1609 (17·5%)	313/1689 (18·5%)	0·94 (0·78–1·14)
≤75	478/1562 (30·6%)	562/1599 (35·1%)	0·87 (0·76–0·99)
χ^2_2=1·345; p=0·51			
GCS			
Severe (3–8)	796/1789 (44·5%)	860/1830 (47·0%)	0·95 (0·86–1·04)
Moderate (9–12)	219/1349 (16·2%)	249/1344 (18·5%)	0·88 (0·70–1·09)
Mild (13–15)	447/6915 (6·5%)	502/6877 (7·3%)	0·88 (0·75–1·04)
χ^2_2=1·387; p=0·50			
Injury type			
Blunt	1134/6788 (16·7%)	1233/6817 (18·1%)	0·92 (0·83–1·02)
Penetrating	329/3272 (10·1%)	380/3250 (11·7%)	0·86 (0·72–1·03)
χ^2_1=0·791; p=0·37			
All patients	**1463/10060 (14·5%)**	**1613/10067 (16·0%)**	**0·91 (0·85–0·97)***
Two-sided p=0·0035			



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"
- 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?



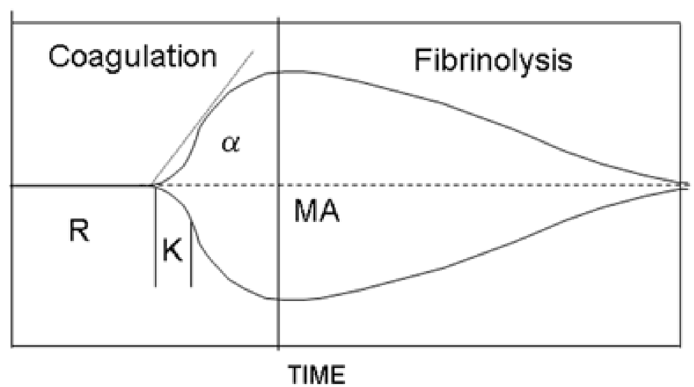
CRASH-2 Weaknesses

- Subject selection based upon "uncertainty" principle
- Most subjects in countries with austere trauma care
  - Benefits could be lost in mature facilities with BBP protocols
- No laboratory monitoring: TEG, TEM
- TXA antifibrinolytic mechanism poorly defined
- No effort to measure thrombosis except for death
  - Other studies report 13% DVT/PE prevalence in TXA Rx
- Small subject cohort who required blood
  - Blood product usage equivalent in TXA and control arm
- Several new trials in progress
- MATTER reported better outcomes than CRASH-2
  - Number needed to treat: 7 versus 67

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.

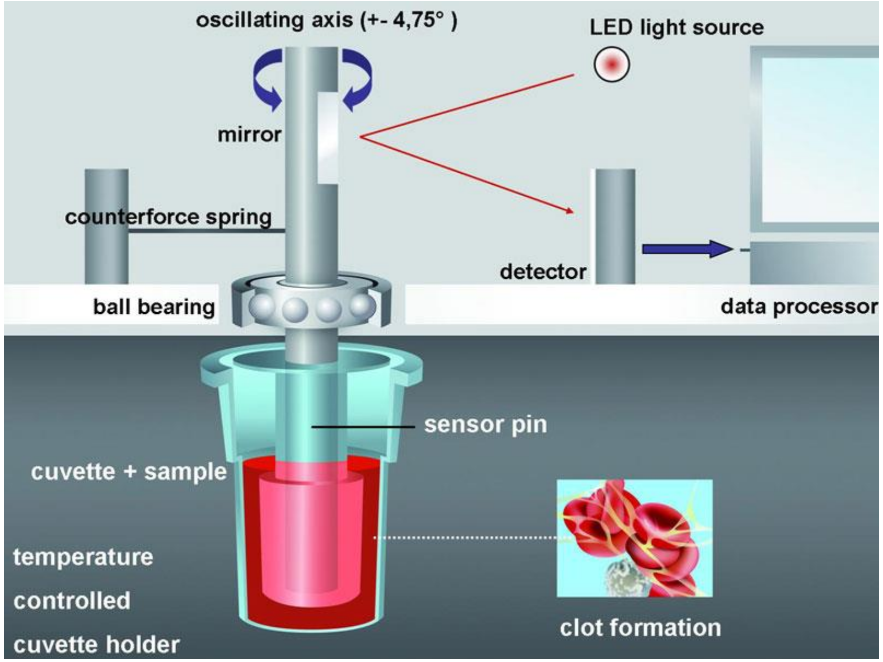
Thromboelastograph

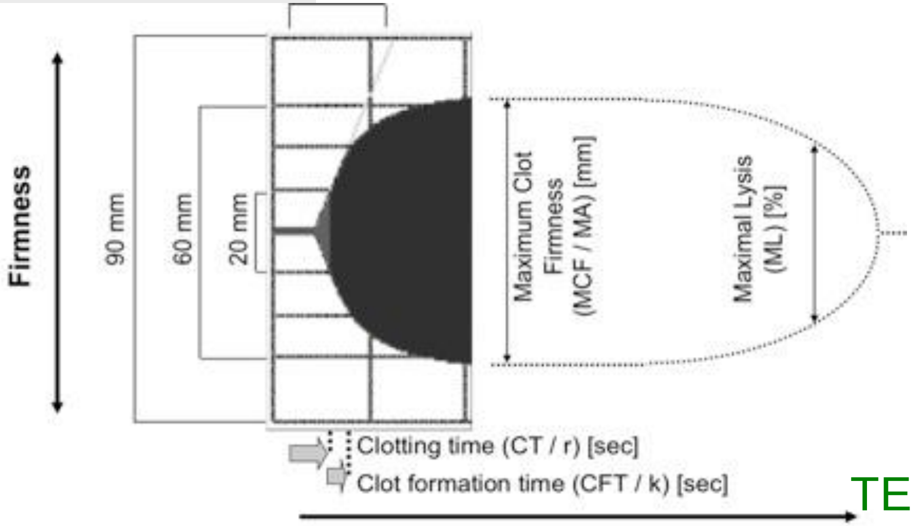
1946



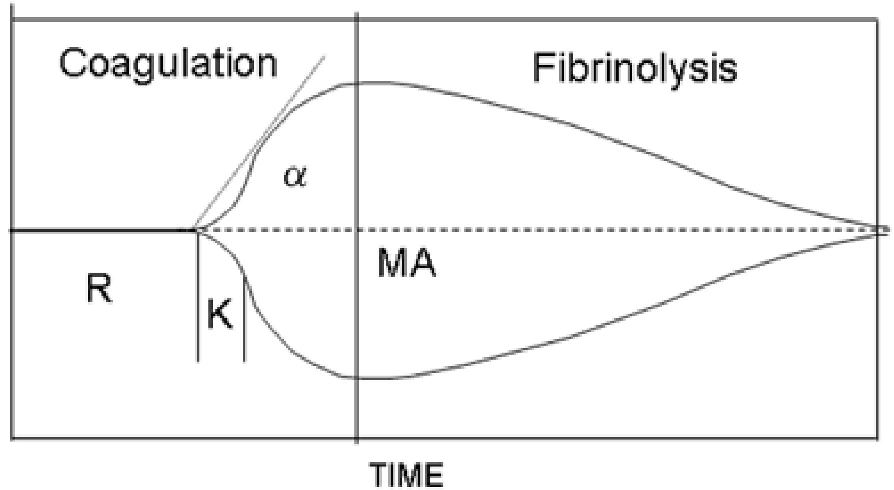
Pen displacement by viscoelastic changes

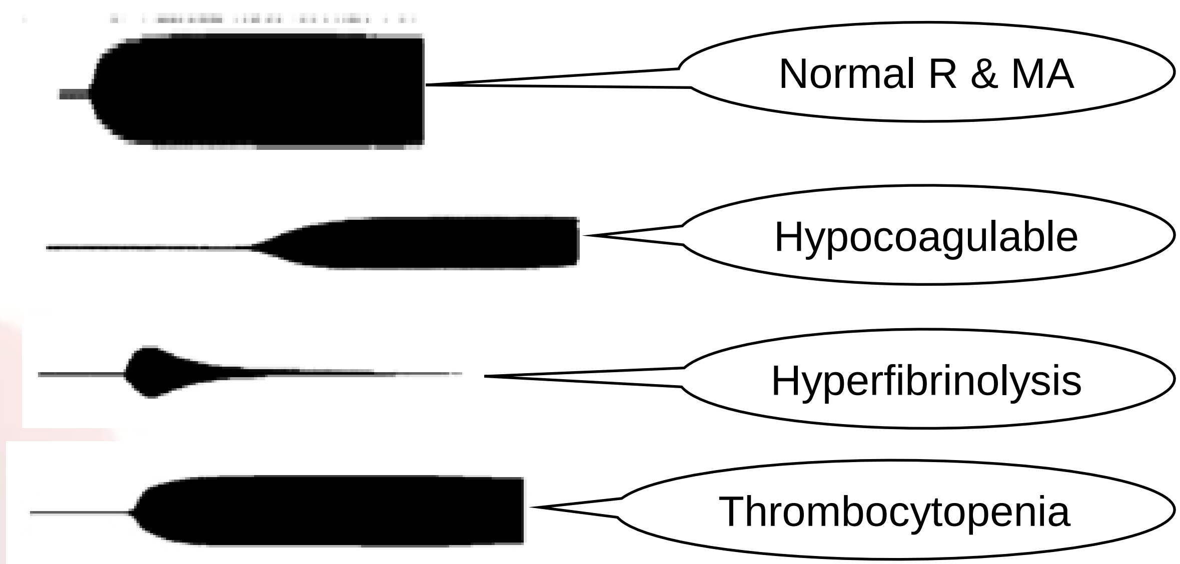
Rotational Thromboelastometry



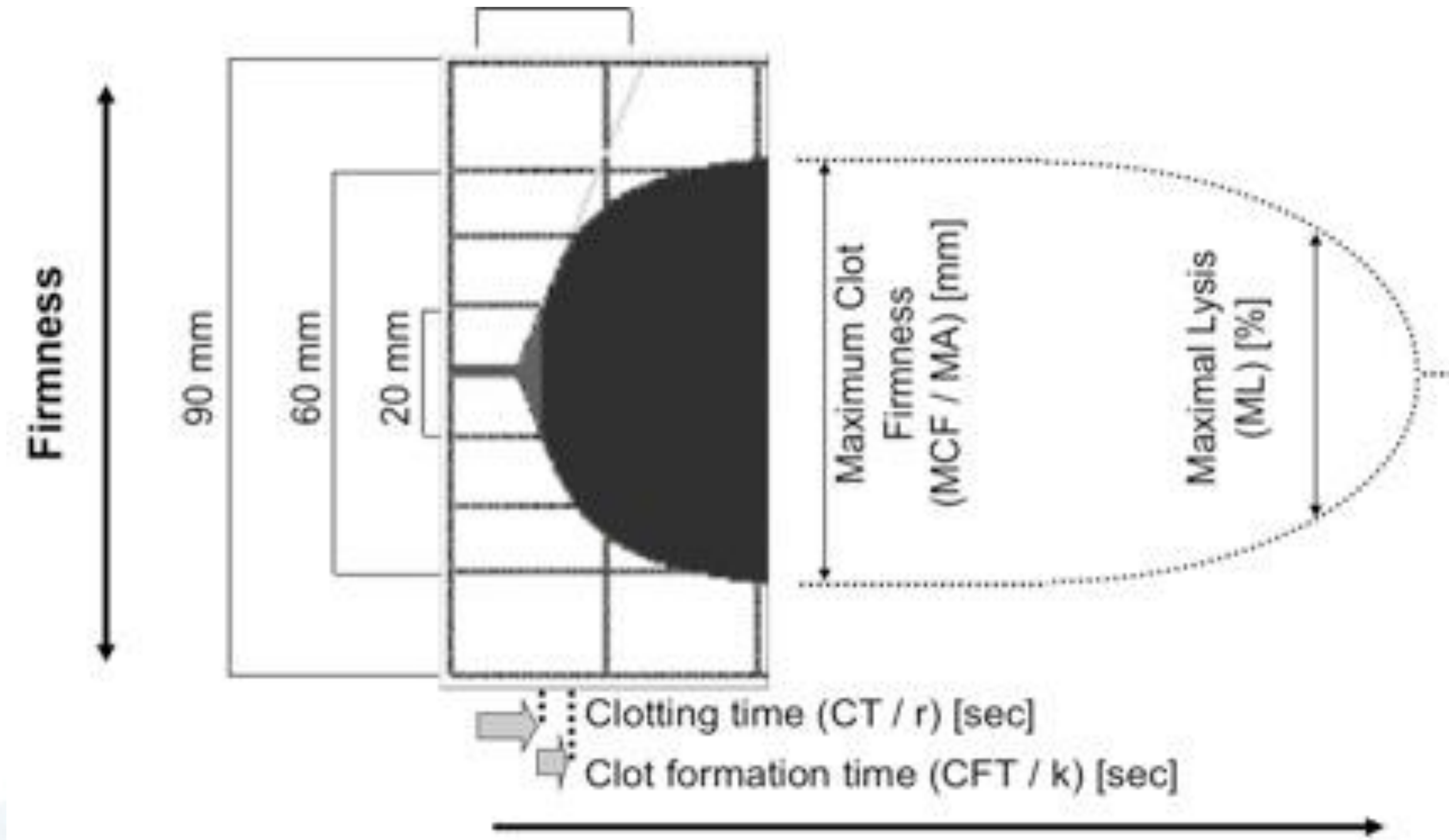


Thromboelastograph





Thromboelastometry



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

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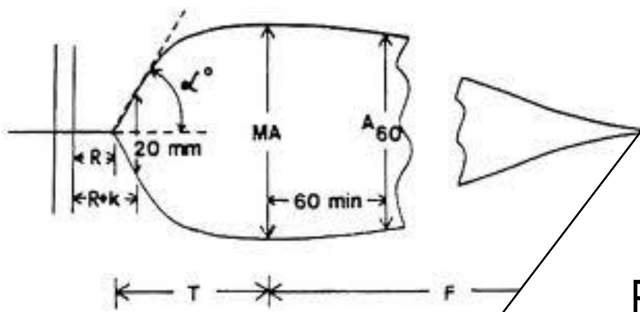
TEG 6s

- Small volume
- Cartridge
- Stable

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.

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Bottom Line At the End (BLATE)

- 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

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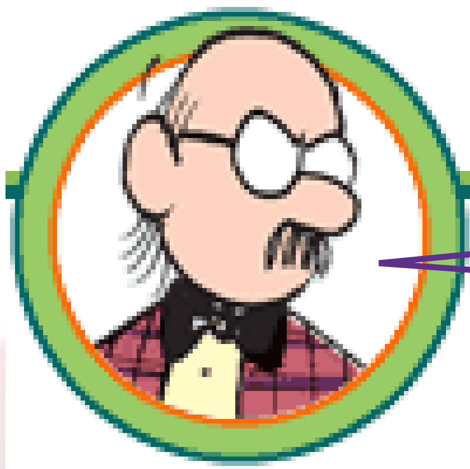

Questions?