Standard
Lab Test Targets

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MCWBD

Multidisciplinary Clinic for Women with Bleeding Disorders

Medicine
UNIVERSITY OF TORONTO

St. Michael's

Inspired Care. Inspiring Science.

Disclaimer

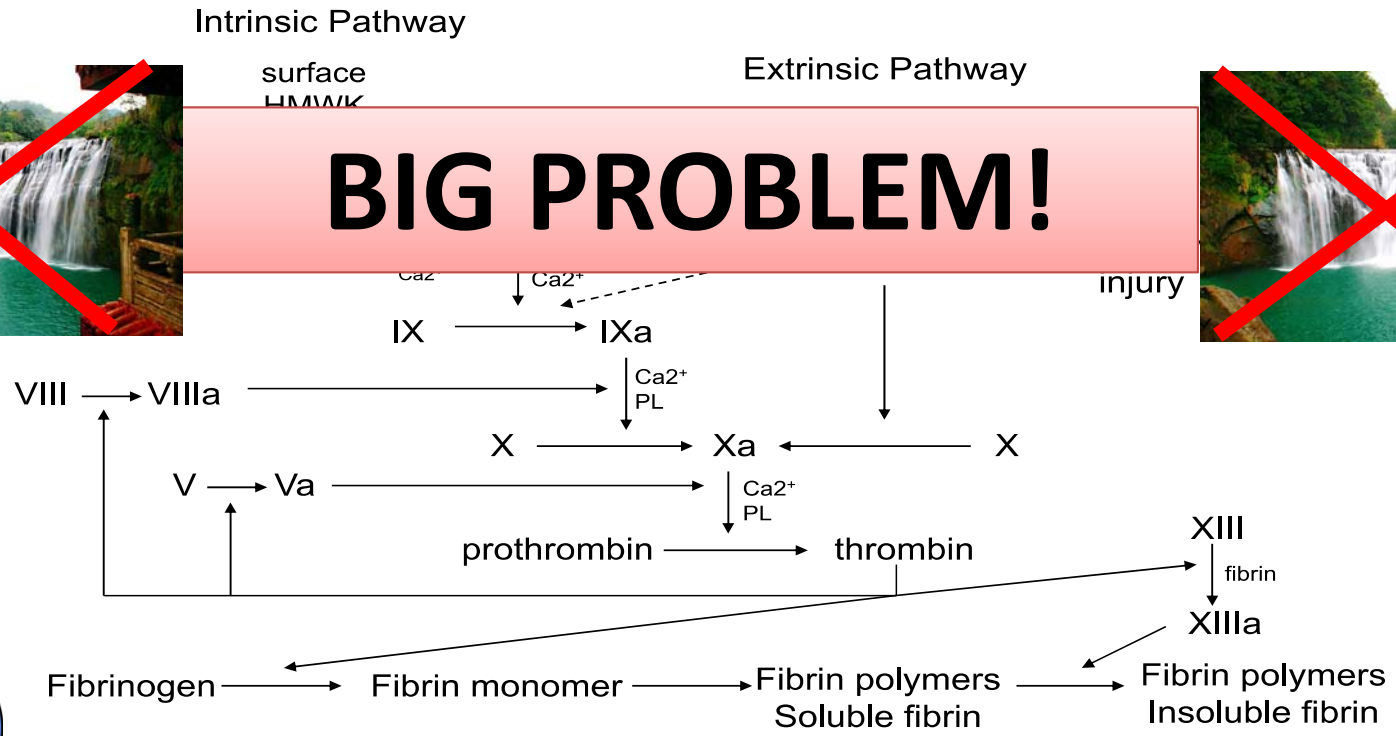
- No relevant financial conflicts of interest

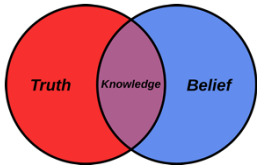
Objectives

- Brief review of hemostasis
- Brief review of acute coagulopathy of trauma
- Review of testing limitations for standard lab tests
- Review lab triggers for transfusion of RBCs and components in setting of MH

Updated Coagulation Cascade

BIG PROBLEM!





Walsh PN. Biochemistry 2007,Nov 6; 46(44): 12886-12887

Hemostasis Simplified

Trauma to the endothelium = TRIGGER

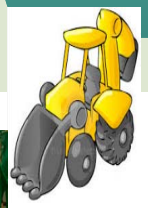
-Platelets 1st on the scene

-VWF glues platelets to the endothelium

Coagulation factors assemble to make a clot

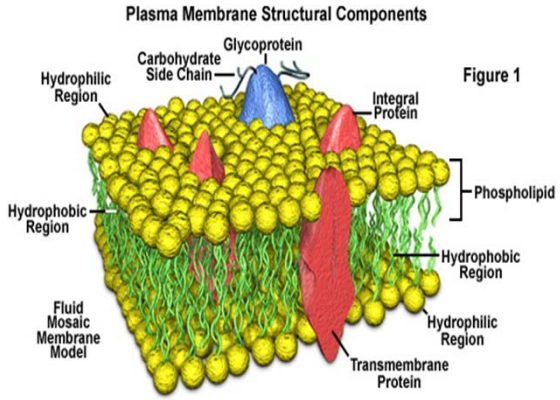
Additional factors stabilize clot

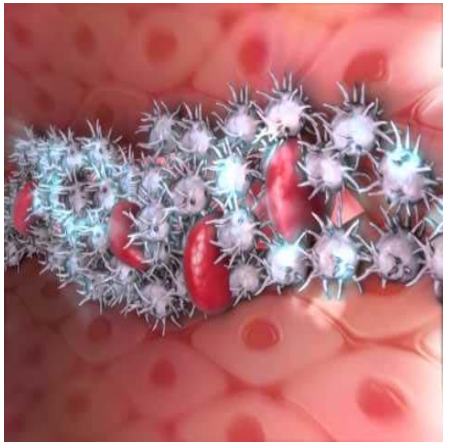
Fibrinolytic system breaks down clot



Coagulation is Localized to the Cellular Surface

- Occurs on membranes with <u>exposed</u> phospholipids
  - Phosphatidyl serine
  - Phosphatidyl ethanolamine
- Exposed phospholipids are not found on resting cells





Hoffman, M. & Monroe, D.M. *Thrombosis and haemostasis* **85**, 958-965 (2001).

Coagulopathy of Trauma Simplified

BLEEDING

-Trauma -Diffuse endothelial damage -Inflammation -Shock	-Platelet consumption & dysfunction	-Coagulation consumption -Auto-Heparinization -Upregulated Thrombomodulin → Activation of protein C	-Diminished Stabilization -Uncontrolled tPA	-Hyperfibrinolysis

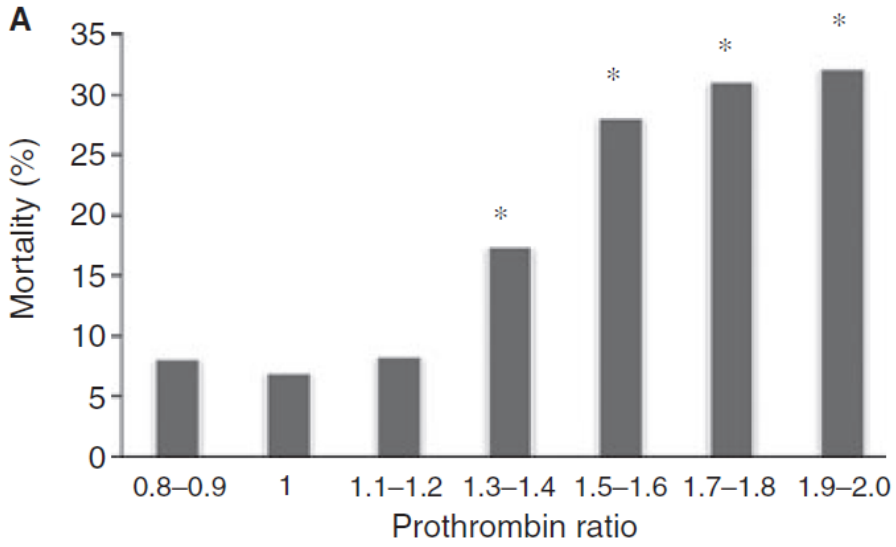
Acute Coagulopathy of Trauma is Bad

Retrospective cohort study of 1088 trauma patients

- Coagulopathy defined as: PT>18 s, aPTT>60 s, or TT>15 s
  - 24% met this definition on arrival before resuscitation
  - 46% mortality rate with coagulopathy vs. 11% mortality rate without (p<0.001)

Retrospective cohort study of 3646 trauma patients

- Those with a prothrombin time ratio (PTr) > 1.2 had higher mortality and transfusion requirements than patients with a normal PTr
  - Mortality: 22.7% vs. 7.0% (p< 0.001)
  - Packed red blood cells: 3.5 vs. 1.2 units (p< 0.001)



Brohi K, et al. Acute traumatic coagulopathy. *J Trauma.* 2003;54(6):1127-1130; Firth D, et al. J H and T 2010; 8: 1919-25.

What is the role of the Hematology (Routine & Coagulation) Lab in a MHP?

- For effective management, it is necessary to understand ***why*** the patient is currently bleeding

- **Is the bleeding coagulopathic or surgical in nature?**

- **If the patient has coagulopathic bleeding – is this due to:**
  - Platelet deficiency or dysfunction?
  - Reduced thrombin generation?
  - Clot instability?
  - Hyperfibrinolysis?
  - Acidosis?
  - Hypothermia?

The Ideal Coagulation Laboratory Test

- The ideal laboratory test in the face of a MH would provide an **accurate**, **reliable** and **rapid** assessment of the patient's **in vivo hemostatic capacity**

- **The ability of our contemporary coagulation tests to comply with these requirements must be questioned**

- **Important to understand what a test was originally designed to measure and what it has been validated to measure**

Categories of Lab Tests

- Two broad categories of laboratory tests that are useful in the assessment of massive hemorrhage

1. **Static assays**

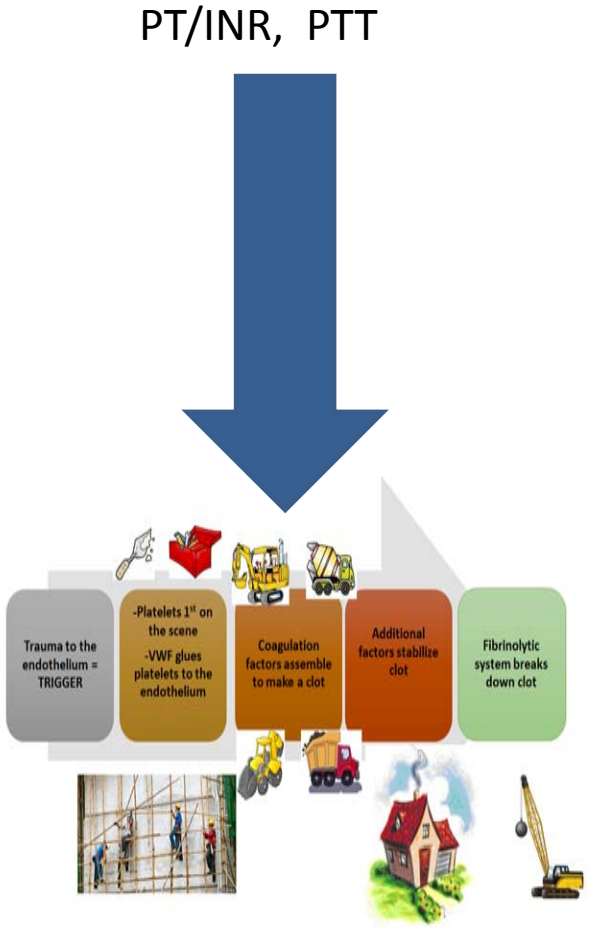
1. **Dynamic assays**

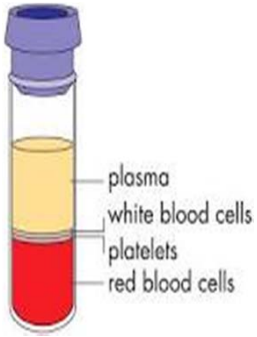
Static Assays

- Complete blood cell count (CBC)
- Prothrombin time (PT)
- Activated partial thromboplastin time (aPTT)
- Fibrinogen
- Thrombin time (TT)

Basic Clot Based Tests

- Prothrombin Time (PT)
  - International Normalized Ratio (INR)
- Activated Partial Thromboplastin Time (PTT)
- END RESULT = CLOT FORMATION

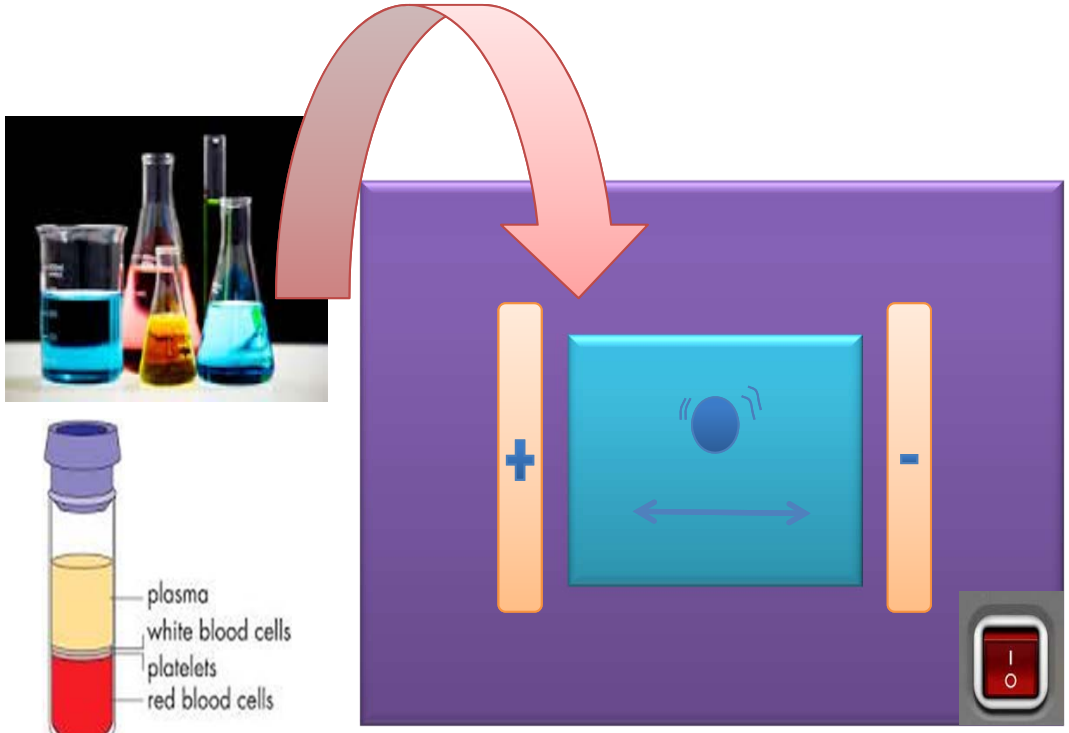




Throw out the Cell-Based Model!

- The PTT and PT measure the **<u>time to clot formation</u>** of the sample in a test tube in the presence of their respective clot-driving reagents
  - assess only a small component (<5%) of thrombin generation
- Both tests are automated and run on platelet poor patient plasma
- PPP acts as the in vitro representation of the patient's hemostatic capacity
- Therefore, there is a mechanistic disconnect between in vivo and in vitro hemostasis even **prior to placement of the sample on the analyzer**

What is the principle of Clot-Based Assays?



Hemostasis Simplified: Static Assays

Trauma to the endothelium = TRIGGER

-Platelets 1st on the scene

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Coagulation factors assemble to make a clot

Additional factors stabilize clot

Fibrinolytic system breaks down clot

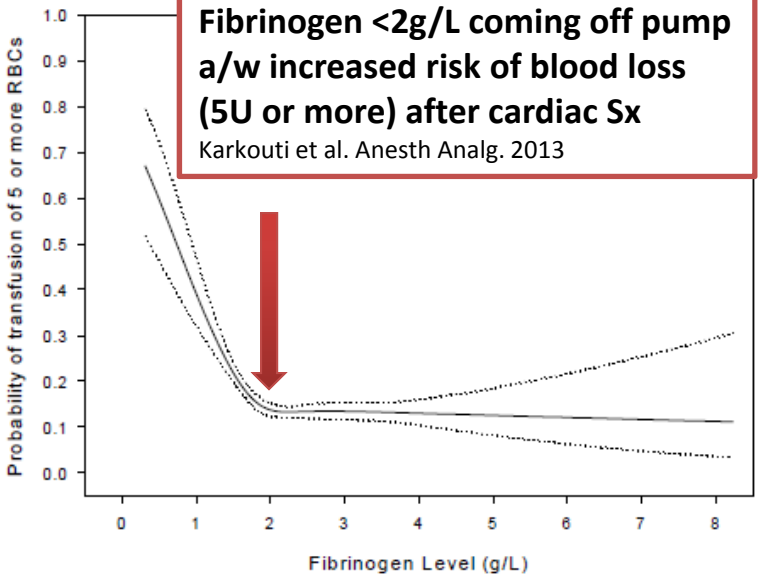
CBC

PTT
PT/INR
Fibrinogen

Origin & Evidence
Static Assays in setting of MH

- **PT/INR**
  - Effective at determining the amount of warfarin that is present in steady state
  - Was not designed to be a dynamic measure of the hemostatic system
  - INR>1.2 = BAD
- **aPTT**
  - Initially design operatively
  - Attuned to me less than 30-35%
  - May detect les
- **TT**
  - Nothing publis
- **Fibrinogen**
  - No quality stu stency of the Clauss fibrinogen detection method in setting of MH
  - Decreased fibrinogen on arrival at the ED = independent predictor of MT requirement and death in severely injured patients
  - Critically low threshold has not been well-established in trauma (?1, ?1.5, **?2**)

Fibrinogen <2g/L coming off pump a/w increased risk of blood loss (5U or more) after cardiac Sx
Karkouti et al. Anesth Analg. 2013



Chee Y et al. BJH 2008; Kitchens C. JTH 2005; Levy JH et al. Clinics in laboratory medicine 2014; Dzik WH et al. Crit Care, 2011;15(6):242; Hayakawa M et al. Semin Thromb Hemost. 2015; Schochl H et al. Crit Care.2011; Inaba K et al. J Am Coll Surg. 2013.

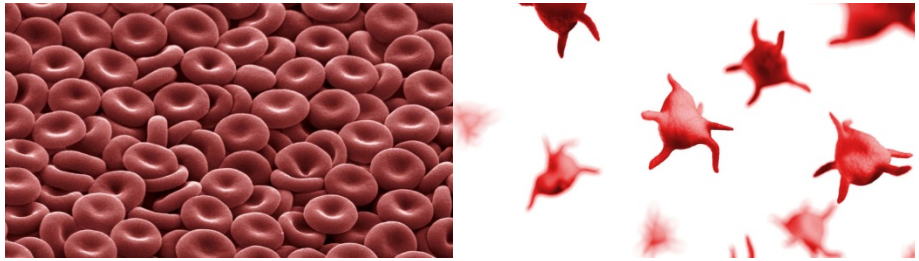
Based on the Evidence: Static Assays in setting of MH

- Fluctuations in the levels of the static studies may not correlate with in vivo bleeding diatheses
- Their proper interpretation is relatively unknown
- Their employment is entirely extrapolated from their use in other much more stable clinical environments
- Clot based assays are run on platelet poor plasma, which abrogates the setting of in vivo hemostasis
- There is a fixed delay in the performance of the tests that further negatively affect their clinical relevance in the acute setting

Toulon, P*., et al. Thrombosis and haemostasis* 101, 394-401 (2009).
Dzik WH et al. *Crit Care*,15(6):242 (2011).

The CBC

- **Hemoglobin**
  - Low hemoglobin is an **indicator of severe bleeding associated with coagulopathy**
  - Acute anemia ***may*** have a negative effect on **hemostasis rheology**
    - Possibly less platelet margination, activation, support of thrombin generation
  - RCTs that have evaluated Hb thresholds for transfusion in critically ill patients have consistently found that restrictive strategies (Hb 70-90) are **as safe or safer** than liberal strategies (Hb>90)
    - Not studied in MH patients



- **Platelet count**
  - No assessment of platelet function
  - Maintaining a platelet count >50-100 ***seems*** important to minimize risk of microvascular and diffuse bleeding in a variety of settings
  - Up front administration of platelets in patients who are not yet thrombocytopenic is controversial
  - The association between lower platelet counts and mortality applies to platelet counts within the normal range
  - Platelet count alone is a weak indicator of platelet transfusion need bc it ignores platelet function

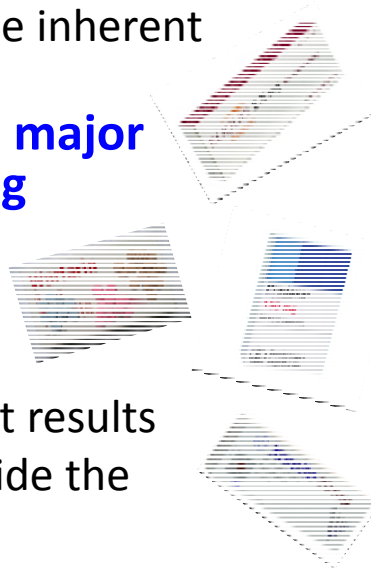
Rossaint et al. Crit Care 2016 Apr 12;20:100.

Conclusions:
Static Assays in setting of MH

- Paucity of good quality evidence supporting transfusion targets in the setting of MH
  - BUT coagulopathy IS associated with BAD things (INR>1.2, fibrinogen <2)

- **A few practical conclusions can be drawn:**

1. **We cannot rely on a single test result – test early and hourly**
   - A trend may be more clinically meaningful as this controls for the inherent variability
2. **A normal initial coagulation screen indicates that there is no major coagulation factor defect and possibly/probably no inhibiting anticoagulant present**
   - Small glimpse of thrombin generation; do not be fooled
3. **Decisions should be based on the clinical picture**
   - Acute events are likely to unfold prior to the achievement of test results
   - But that doesn't mean that you shouldn't order tests to help guide the direction of care



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Is there anything that we can do to make the Static Assays Better?

- Speed is critical in the case of MH
- Slow testing may be of no clinical benefit if the result arrives too late
- Accuracy is important, however the focus should be on **accuracy sufficient to make clinical decisions within the shortest possible time frame**

Chandler, W.L et al. *Transfusion* **50**, 2547-2552 (2010).

Improving Turn-Around Time

Pre-analytical Phase

Lab Panels

Education

- TM MLTs to inform Heme MLTs that MHP initiated → overhead announcement in lab

Prioritization

- Sample hand-delivered to lab

Analytical Phase

- **Rapid centrifugation**
  - Centrifuge setup to spin PPP in 5 (vs. 15) min
- **Run time**
  - PT/INR = 3 min
  - aPTT = 5 min
  - Fibinrogen = 4 min
  - All 3 tests = 6½ min
- **Fibrinogen reagent on board**
  - Switch to larger volume bottle (2mL to 5mL)
  - Auto-reflex to low fib calibration curve is <=1.5 g/L (+4 min) → verbal prelim

Post-Analytical Phase

- **Rapid reporting**
  - Setup auto-verification rules
    - abN results
    - LIS → EMR
    - Clarify who will accept critical results

<u>GOLD STANDARD:</u>

At Chandler's institution, to address the issue of speed, an emergency hemorrhage panel (EHP) was constructed

- **Reporting results within 10-20 minutes**
- **Median TAT of 88 mins in large prospective study**

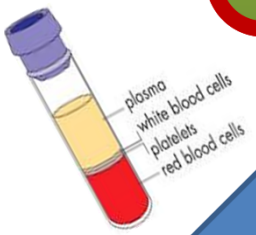
Chandler, W.L et al. *Transfusion* **50**, 2547-2552 (2010).
Toulon, P., *et al. Thrombosis and Haemostasis* 101, 394-401 (2009).

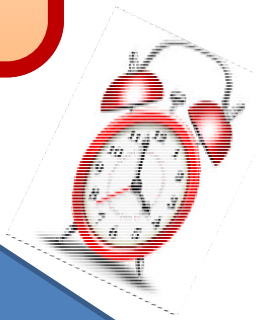
Take Home: Targets Simplified

TRUTH:
We know what test results are BAD.
We don't know what our transfusion targets should be.

BLEEDING

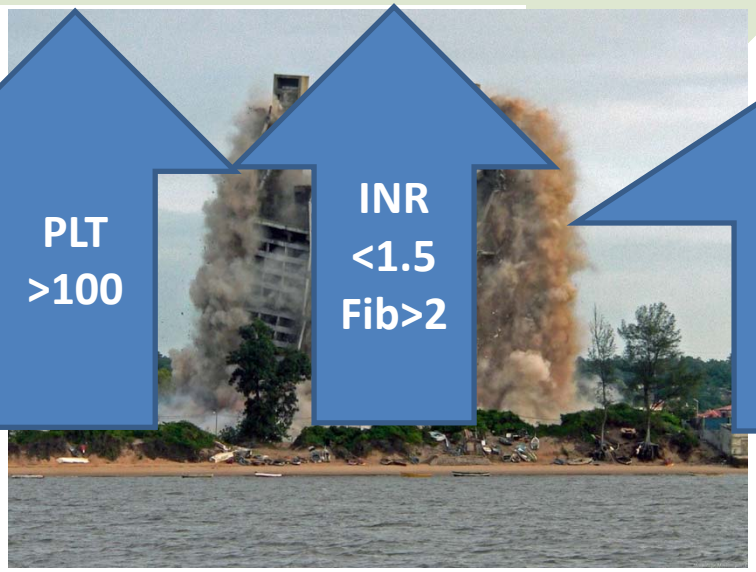
-Trauma -Diffuse endothelial damage -Inflammation -Shock	-Platelet consumption & dysfunction	-Coagulation consumption -Auto-Heparinization -Upregulated Thrombomodulin → Activation of protein C	-Diminished Stabilization -Uncontrolled tPA	-Hyperfibrinolysis





Hb >70

PLT >100



INR <1.5 Fib>2

TXA

Rossaint et al. Crit Care 2016 Apr 12;20:100.

Objectives Revisited

- Brief review of hemostasis
- Brief review of acute coagulopathy of trauma
- Review of testing limitations for standard lab tests
- Review lab triggers for transfusion of RBCs and components in setting of MH

Thank you

Questions?

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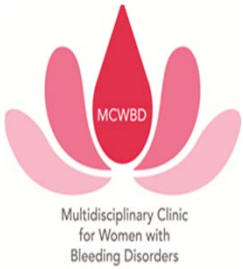

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