

## Thromboelastography (TEG) Based Reversal of Coagulopathy and the TXA Controversy

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### What We Know...

- Trauma is the leading cause of death and morbidity for children in US
- Trauma Induced Coagulopathy (TIC)
  - Dysfunction of hemostatic and inflammatory systems in response to injury
  - Defined as INR > 1.3
  - Induced by hemorrhage
  - Associated with increased morbidity and mortality

### Pediatric Massive Transfusion

- Ratio of blood products that simulates the components of whole blood
- Designed to deliver blood product to the bedside as rapidly as possible with minimal product waste

Product Type and Weight	Blood Product Released with Pediatric Massive Transfusion Pack (PMPPT)
Age: 0-10 years Weight: 2 kg - 12 kg "Pediatric PMP"	1 unit PRBC (100 mL) 1 unit PPF (100 mL) 50 mL Platelets
Age: 10 - 19 years Weight: 12 kg - 35 kg "Pediatric PMP"	2 units PRBC (200 mL) 2 units PPF (200 mL) 100 mL Platelets
Age: 20 years to Adolescence Weight: 40 kg - 60 kg "Pediatric PMP"	3 units PRBC (300 mL) 3 units PPF (300 mL) 150 mL Platelets
Age: Adult Weight: 60 kg "Adult PMP"	4 units PRBC (400 mL) 4 units PPF (400 mL) 200 mL Platelets (100 mL)

Cryoprecipitate  
 Consider every other  
 round of blood  
 product or fibrinogen  
 < 150-300.  
 - dose 5ml/kg

*Massive resuscitation protocols are great...but what about this concern for coagulopathy?*

**Coagulation Studies**

- Bleeding time
- Activated Partial Thromboplastin Time (aPTT)
- Prothrombin Time (PT)
- Thrombin Time

**Coagulation Cascade**



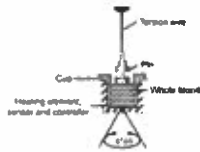
**Trauma Induced Coagulopathy**

- Traditionally defined as elevated INR but inadequate as treatment target
- Viscoelastic hemostatic assays (TEG and ROTEM)
  - Monitors all phases of coagulation
  - Depicts real-time component activity rather than static values
  - Also provides information if hypercoagulability
  - Elevated INR DOES NOT NECESSARILY INDICATE a true bleeding coagulopathy

**TEG-Directed Resuscitation<sup>1</sup>**

- Improved survival compared to MTP guided by conventional tests of coagulation cascade
- Better than traditional ratio-driven algorithms
- Utilize less plasma and platelet transfusions during resuscitation process
- When is TEG most useful?
  - Admission, OR, or ICU

### What is a TEG?



Whole picture of coagulation cascade

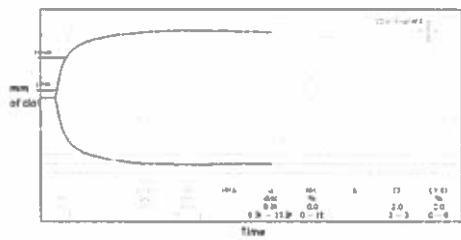
- Clot Initiation
- Clot Kinetics
- Clot Strength
- Clot lysis

### TEG 5100 System

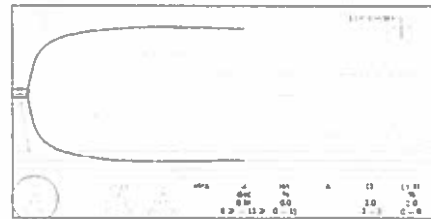


Index	Reagent	Transmittance	Product	Clot
TEG 5100	20-113	1.000	Plasma	0.00
TEG 5100	20-113	1.000	Clot	1.00
TEG 5100	20-113	1.000	Clot	1.00
TEG 5100	20-113	1.000	Clot	1.00

### Normal TEG Tracing



### Clot time (R)

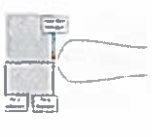


- Time from start of sample until 1 mm of clot amplitude formed
- Reaction time, important for assessing activation of clotting cascade
- A sign of the thrombin burst (Thrombin Critical Mass) required for clot starting
- Normally 6-8 minutes

### Clot Time Irregularities

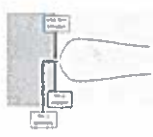
#### Long Clot Time (R) > 8min

- Possible etiologies
  - Factor deficiencies/fibrinolysis
  - Essential heparin
- Common treatments
  - FFP
  - Protamine

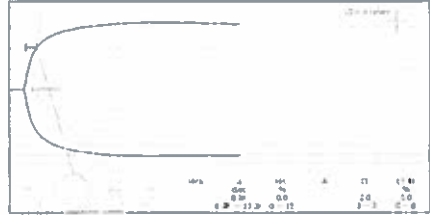


#### Short Clot Time (R) < 4min

- Possible etiologies
  - Extrinsic hypercoagulability
- Common treatments
  - Anticoagulant



### Clot Kinetics




**Clot formation time (K)**

- Time from 2min to 20min post to 4min
- Alpha Angle 90° means strong blood clot
- Angle of time lagged to curve from 2min to 20min
- Dependent to plasma rate and efficacy of clotting system to generate thrombin and conversion of fibrinogen to fibrin

### Clot Kinetic Irregularities

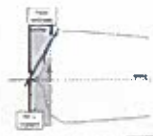
#### Prolonged Kinetics (K > 4min; alpha < 43°)

- Possible etiologies
  - Low fibrinogen levels or function
  - Insufficient rate/amount of thrombin generation
  - Purified fibrinogen/fibrinolysis
- Common Treatments
  - FFP
  - Cryoprecipitate

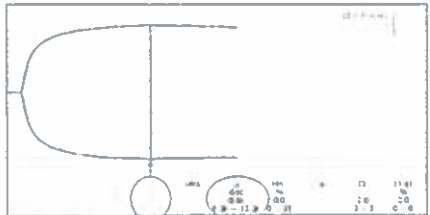


#### Shortened Kinetics (K < 1min; alpha > 74°)

- Possible etiologies
  - Plasma hypercoagulability
  - Fast rate of thrombin generation
- Common treatments
  - None



### Clot Strength



**Max Amplitude (M)**

- High amplitude of peak production
- Clot strength = 80% plasmin + 20% fibrinogen
- Clot mass (M)
- Calculated from M & C =  $\frac{M \times C}{M + C}$

### Clot Strength Irregularities

#### High MA

**Possible etiologies**

- Platelet hyperreactivity

**Common treatments**

- Antiplatelet agents

#### Low MA

**Possible etiologies**

- Poor platelet function
- Low platelet count
- Low fibrinogen levels or function

**Common treatments**

- Platelet transfusion

### Clot Lysis

APL	APL	APL	APL	APL	APL
0.9	11.2	0	11	2.0	2.0
0.9	11.2	0	11	2.0	2.0

**LY30**

- \*Percent decrease in the amplitude of an occlusion 30 minutes after MA is obtained
- \*Estimated percent lysis value (EPL)
- \*Estimates the rate of change in amplitude after MA is reached
- \*Assessment of the rate of overall clot breakdown
- \*Coagulation index (CI)
- \*Calculated factor from MA, R, R, and a slope to describe global hemostasis index

### Fibrinolysis

#### Primary Fibrinolysis

**LY30 >7.5% (or EPL >18%) with CI ≤1.0.**

**Possible etiologies**

- High levels of tPA

**Common treatments**

- Antifibrinolytic agent

#### Secondary Fibrinolysis

**LY30 >7.5% (or EPL >18%) with CI >3.0.**

**Possible etiologies**

- Microvascular hyperpermeability (e.g. DVT)

**Common treatments**

- Antifibrinolytic

**HERE COMES THE CONTROVERSY!**

### Tranexamic Acid (TXA)

- Lysine analog thought to bind plasmin and inhibit fibrinolysis but mechanism not fully known
- Administration within 3 hours of injury as bolus followed by drip infusion

#### DOSEING

##### ≥ 12 Years of Age

- Loading Dose: 1g in NS over 10 minutes
- Infusion: 1g in NS infused over 8 hours

##### Birth - 11 Years of Age

- Loading Dose: 15 mg/kg (Max 1g) in NS over 10 minutes
- Infusion: 2 mg/kg/hour (Max total over 8 hours of 1g) in NS for 8 hours

### Tranexamic Acid (TXA)

- Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage 2 Study (CRASH II) – Adult Patients
  - Small survival benefit in patients who received TXA within 3 hours of injury
- Pediatric Trauma and Tranexamic Acid (PED-TRAX)
  - Survival benefit for empiric TXA in children
  - Large percentage of penetrating and blast injuries
  - Does not necessarily mirror injuries in civilian population

### Hyperfibrinolysis vs. Shutdown

- Fibrinolysis – physiologic process of clot breakdown required for wound healing and remodeling
- Excessive fibrinolysis yields increased clot breakdown and can promote bleeding
  - Treated with TXA administration
- But deficiency of fibrinolysis (shutdown) may promote thrombotic complications of DVT
- Patients in hemorrhagic shock requiring massive transfusion most often in fibrinolysis shutdown at time of admission

### Why So Much Controversy?

- Mortality risk increased by odds ratio of 1.6 for shutdown and 3.3 for hyperfibrinolysis in adults<sup>2</sup>
  - Odds ratio of 6.2 in pediatric patients<sup>1</sup>
- Recent findings of increased mortality if TXA initiated > 3 hours after injury or no benefit from TXA<sup>4,5</sup>
- Hyperfibrinolysis is rare in children, especially with TBI and blunt injury, and appears to correct with hemostatic resuscitation<sup>6</sup>

**So...What's the Verdict?**

- In general, empiric administration of TXA in children remains controversial with no clear consensus
- However, many support TEG-directed TXA administration according to hemorrhage and hyperfibrinolysis as indicated by LY30 value

**Product Class of Fibrinolytic (PLI) for use of Tissue Plasminogen Activator (tPA) in Pediatric Trauma Patients**

• Indicated for emergency multi-trauma or subarachnoid hemorrhage in trauma patients who meet criteria below

- INDICATION CRITERIA**
- Age  $\geq 18$  years of age
  - Trauma patient (blast or penetrating)
  - Imaging (computed tomography or MRI) Class I/II/III
  - Alert conditions of the Modified Rankin Scale
  - Exposed and/or PPHC, transfused with oxygenated blood, bleeding disorders
  - Clinical criteria by consensus in the attending trauma patient (2 of 3 items of the following):
    - If maximum KAP  $\geq 40$  appropriate (15-5.0 pt in trauma)
    - Fibrinogen  $\leq 1.50$  g/L (fresh appropriate)
    - LY30  $\geq 10\%$  (initial bleeding)
    - Fibrin  $\geq 4.0$  g/L
    - Observed actual bleeding
    - Prior blood product exposure in  $\geq 10$  mL

**EXCLUSION CRITERIA**

- Evidence of subarachnoid hemorrhage or CT/CTA PE, vascular anatomy

- DOSE**
- 10-15 mg/kg of tPA
  - Loading Dose: 10 mg/kg over 10 minutes
  - Infusion: 1 mg/kg (0.5 mg/kg over 1 hour)
  - Weight 1 (Type of Age)
    - Loading Dose: 1 mg/kg (0.5 mg/kg over 10 minutes)
    - Infusion: 2 mg/kg over 1 hour (0.5 mg/kg over 1 hour of 1 mg/kg over 1 hour)
- With start adjustment to the European Department of base product  
 • Administration within 3 hours of injury  
 • Informative dose may need repeated for most severe or remote hemorrhage

**Quick Review**

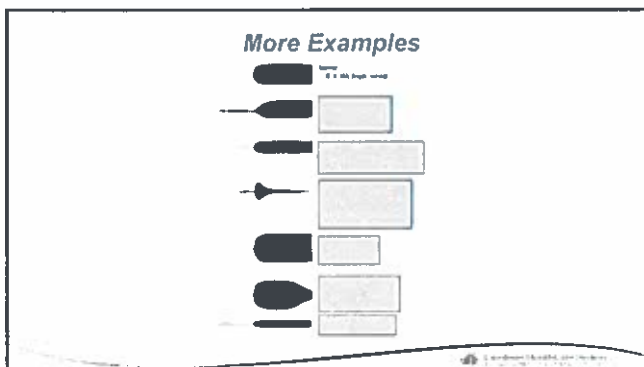
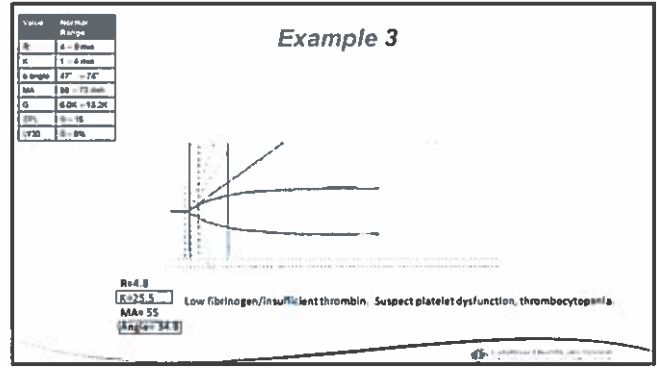
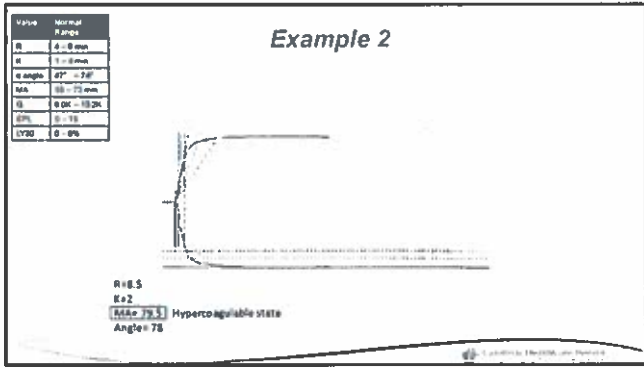
Parameter	Symbol	Definition
Clotting Time	R	Time from start to 2mm of clot amplitude (initial fibrin formation)
Clot Kinetics	K	Speed to reach 20mm clot amplitude (clot kinetics)
	$\alpha$ Angle	Measure of rapidity of fibrin build up and cross linking (fibrinogen level)
Clot Strength	MA	Direct function of max dynamic properties of fibrin and platelet bonding (Max platelet function)
	G	Conversion of MA to dynes/cm <sup>2</sup>
Coagulation Index	CI	Global hemostatic index
Clot Stability	LY30	Rate of amplitude reduction 30 min after MA
	EPL	Estimates % lysis on amplitude reduction after MA

**Example 1**

Value	Normal Range
R	4 - 8 min
K	1 - 8 min
$\alpha$ angle	57 - 72°
MA	58 - 72 mm
G	600 - 1200
EPL	0 - 15
LY30	0 - 5%



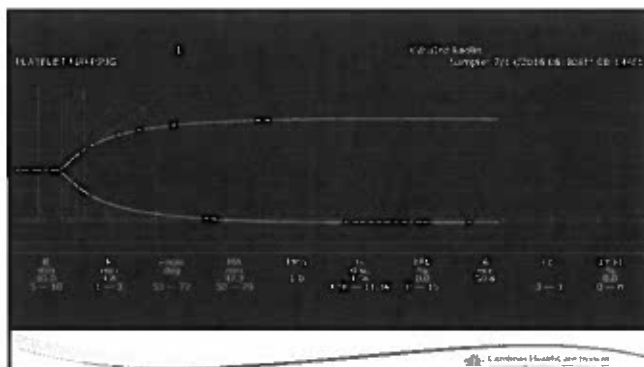
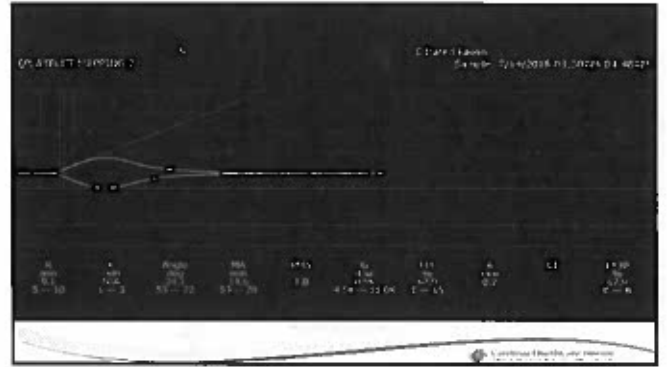
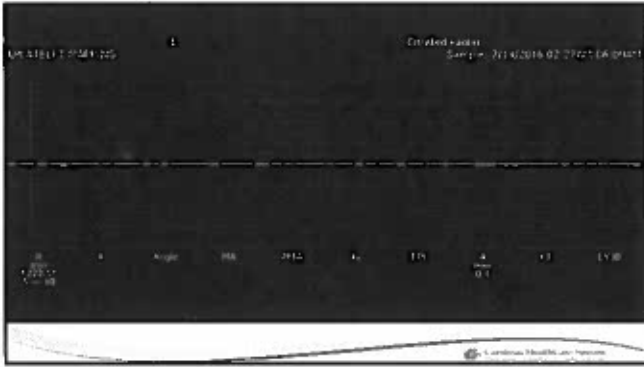
**[K11]** Delayed clot formation, suspect heparin or factor deficiency  
 K14  
 MA 55  
 Angle 54.5



### Case Study

- 61 year-old gentleman with hepatitis C, pulmonary stenosis, and HTN presents after 20 foot fall from ladder
- Left femur fracture
- CT Abdomen: Cirrhotic appearing liver. Recannulized periumbilical vein. Trace amount of ascites and findings of portal HTN.





**References**

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2. Moore HB, Moore EE, Liras IN, et al. Acute fibrinolyse shutdown after injury occurs frequently and increases mortality: a multicenter evaluation of 2540 severely injured patients. *J Am Coll Surg*. 2016; 222(4): 347-355
3. Liras IN, Cotton BA, Cardenas JC, Harling MT. Prevalence and impact of admission hyperfibrinolysis in severely injured pediatric trauma patients. *Surgery*. 2015; 158(3): 812-818
4. Roberts I, Shakur H, Afolabi A, et al. The importance of early treatment with Tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomized controlled trial. *Lancet*. 2011; 377: 1098-1101
5. Harvin JA, Mans MM, Hudson J, Podbielski J, et al. The impact of Tranexamic acid on mortality in injured patients with hyperfibrinolysis. *J Trauma Acute Care Surg*
6. Leeper CM, Neal MD, McKenna CJ, Gannoe BA. Trending fibrinolytic dysregulation, fibrinolysis shutdown in the days after injury is associated with poor outcome in severely injured children. *Ann Surg*. 2017; 266(3): 508-515

