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Acute Traumatic Coagulopathy
Plan

1. Description of the coagulation system
2. Post-traumatic coagulopathy: mechanisms
3. Mouse model of trauma-hemorrhage
4. Therapeutic approach of post-traumatic coagulopathy
1. Coagulation in the perfect world...
Initiation phase

Trauma, induces the initiation of coagulation

Tissue factor (TF) is exposed and binds to FVIIa or FVII which is subsequently converted to FVIIa

The complex between TF and FVIIa activates FIX and FX

FXa binds to FVa on the cell surface
The FXa/FVa complex converts small amounts of prothrombin into thrombin.

The small amount of thrombin generated activates FVIII, FV, FXI and platelets locally.

FXIa converts FIX to FIXa.

Activated platelets bind FVa, FVIIIa and FIXa.
The FVIIIa/FIXa complex activates FX on the surfaces of activated platelets.

FXa in association with FVa converts large amounts of prothrombin into thrombin creating a "thrombin burst".

The "thrombin burst" leads to the formation of a stable fibrin clot.
2. Coagulopathy in the wild…
Mechanisms of Acute Traumatic Coagulopathy
The Lethal Triad
Bloody Vicious Cycle

Severe Trauma → Bleeding → Tissue Hypoxia → Acidosis → Coagulopathy

 Fluid Replacement → Dilution → Hypothermia → RBC Transfusion
The Lethal Triad
Bloody Vicious Cycle

Severe Trauma

Bleeding

Tissue Hypoxia

Fluid Replacement

RBC Transfusion

Acidosis

Dilution

Hypothermia

Coagulopathy

Occurs at pH < 7.1
Not reversed with pH neutralization

Seen only at <33°C??
in only 9% pts

IV Fluids
Acute Traumatic Coagulopathy

• Study at Royal London Hospital
• Brohi et al J Trauma 54:1127–1130, 2003

• 1088 trauma patients admitted over 6-year period
• Median time Incident – Hospital Admission: 72 minutes

• 24.4% arrived to the Hospital coagulopathic

• No coagulopathy: 10.9% mortality
• Coagulopathy: 46% mortality
Posttraumatic Coagulopathy

- Injury Hemorrhage
  - EAC (endogenous acute coag.)
  - SAC (systemic acquired coag.)
    - Death MODS
    - Recover

- Ø Coag
  - Recover

- SAC (systemic acquired coag.)
  - Recovery
  - Death MODS

Time after Injury
Possible Mechanisms for EAC

Impaired thrombin formation?

Coagulation factor deficiency?

Activation of the natural anticoagulant pathways (Protein C, Tissue Factor Pathway Inhibitor and antithrombin)?
Acute Traumatic Coagulopathy: Initiated by Hypoperfusion
Modulated Through the Protein C Pathway?

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Michael A. Matthay, MD,‡ Robert C. Mackersie, MD,* and Jean-François Pittet, MD†‡

• Study at San Francisco General Hospital

• 209 severely traumatized patients admitted to SFGH
• Median time injury – hospital admission: 28 minutes
• 18% of the patients had a systolic BP < 100 mm Hg
• 27% of the patients had an arterial base deficit > 6
Acute Traumatic Coagulopathy: Role of Hypoperfusion

A. PTT (s)

B. PT (s)

C. PTT (s)

D. PT (s)

Prothrombin fragments 1+2

Prothrombin fragments 1+2 (nM)
Acute Traumatic Coagulopathy: Role of Protein C Pathway

A  PTT (s)

B  PT (s)

C  aPC (ng/ml)

D  Factor V (%)
Acute Traumatic Coagulopathy: Effect on Fibrinolysis

A  PAI-1 (AU/ml)

B  D-Dimers (ng/ml)

Protein C (%)
Activated protein C pathway

Thrombin binds Thrombomodulin

The complex Thrombin-Thrombomodulin activates Protein C

APC decreases FVIIIa and FVYa and induces D-dimers production

HYPOPERFUSION

Thrombin

Fibrin

VIIIa

Va

D-Dimers

Activated protein C (APC)

Thrombomodulin
Acute Traumatic Coagulopathy (EAC)

Early coagulopathy after trauma and shock:

- Independent of ‘traditional’ iatrogenic causes.
- Associated with tissue hypoperfusion.
- Secondary to the activation of the Protein C pathway.
- Associated with a derepression of fibrinolysis.
- Hypoperfusion is necessary for TBI patients to be coagulopathic early after trauma.
3. Mouse Model of Trauma-Hemorrhage
Animal Model of Trauma/Hemorrhage

Soft-Tissue Trauma

Hemorrhagic shock:
- Non-ventilated, fixed-pressure.
- Blood withdrawn via vascular line.
- MAP 35 +/- 5mmHg x 60 min.

Fluid Resuscitation:
- LR @ 2x shed blood volume
  + shed blood
Acute Traumatic Coagulopathy in Mice

A. APTT (seconds)

B. Activated Protein C (ng/mL)
Acute Traumatic Coagulopathy is Mediated by aPC Anticoagulant Function

![Graph showing aPTT (seconds) with mAb 1761 and mAb 1591]

- mAb 1591
- aPC
- cytoprotective
- mAb 1761

* **

C TH C TH
Inhibition of the Cytoprotective Domain of Protein C Causes Diffuse Intravascular Coagulation Lung Injury

A. Control mAb

B. mAb 1609

- Perivascular Hemorrhage
- Pulm. Artery with Thrombus

Diagram:
- mAb 1609
- aPC
- anticoagulant
- cytoprotective
Acute Traumatic Coagulopathy in Mice:

mAb 1609 - anticoagulant
aPC - cytoprotective
Summary

* **First Animal Model of Acute Traumatic Coagulopathy**
  - Mimics human response to trauma/hypoperfusion

* **Role of Activated Protein C in Trauma/Hypoperfusion**

<table>
<thead>
<tr>
<th>aPC function</th>
<th>Acute Traumatic Coagulopathy</th>
<th>SURVIVAL/Prevention of DIC</th>
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<tbody>
<tr>
<td><strong>REQUIRED for</strong></td>
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<tr>
<td>Anticoagulant</td>
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<tr>
<td>Cytoprotective</td>
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Clinical Implications

1. Inhibition of anticoagulant function of Protein C could become a NEW, mechanistic treatment for Acute Traumatic Coagulopathy in trauma patients.

2. Role of protein C in organ dysfunction in traumatic shock: recombinant mutant non-anticoagulant protein C…potential treatment in humans?
4. But what should we do?
Focus on Coagulopathy

- Early use of blood products
- Massive blood loss:
  - Give products in a ratio of PRBC:FFP:platelets 1:1:1?
Massive Transfusion

Traditionally, FFP & platelet concentrates are given as “needed”

--->

However:

1. The coagulation lab is slow!
2. Patients already have a coagulopathy, why wait?
Prevent the Lethal Triad

1. Keep warm:
   - All fluids through warmers
   - Keep the OR warm

2. Minimalize crystalloid:
   - Continue a 1:1:1 resus.

3. Reduce Shock:
   - *Damage control surgery*

4. Break the cycle:
   - Consider other components

- Hypothermia
- Dilution
- Acidosis
- Bleeding
- Coagulopathy
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