The Staging of Trauma-Induced Coagulopathy: Monitoring & Therapeutic Implications

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The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.
Although I have published original research, review articles and even a chapter in Dr. Moore's textbook on Trauma-Induced Coagulopathy, and rendered "expert" consultative care to patients with TIC, I must disclose that I am completely mystified by this clinical entity. I am sure of only one thing: like trauma itself, TIC is not good.
Overview

**Staging TIC?:** ATC, hyperfibrinolysis vs. “shutdown,” hypercoagulability, DIC, “bloody vicious circle,” clinical staging?

**Limitations of monitoring:** no good answers, not sure what any of the results really mean

**Therapeutic implications:** goal-directed therapy? Empiric therapy? No therapy? **First, do no harm: don’t overdo it.**

**RDCR considerations:** pre-hospital/POI care, prolonged field care
**Terminology & Up Front Issues**

**ATC:** acute traumatic coagulopathy  
-- pre-intervention, early coagulation disturbance (PT, INR, aPTT)

**TIC:** trauma-induced coagulopathy  
-- broadly, the coagulation changes including ATC and continuing through first few days post-trauma

**Problems:** no baseline, admission studies, missing data over time, plasma samples, dilution effects ignored, clot-based assays → **WE’RE GOING TO GET THIS WRONG!**
Why we care about TIC

Having TIC, as defined by admission INR >1.5, is associated with bad outcomes (US combat trauma patients). Mean INR was 1.5 in transfused patients.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>INR &lt; 1.5</th>
<th>INR &gt; 1.5</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>1,224</td>
<td>592</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>INR, mean (SD)</td>
<td>1.2 (0.2)</td>
<td>2.2 (1.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nonsurvivors, %</td>
<td>6</td>
<td>30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood use, U per patient</td>
<td>6</td>
<td>10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IQR</td>
<td>2–12</td>
<td>4–23</td>
<td></td>
</tr>
</tbody>
</table>

• You are anticoagulated!
  – Protein C as the driver
• Fibrinolysis is THE problem!
  – Followers of CRASH
• CRASH is EVIL!
  – TEG says, “No TXA for you!”
  – Shutdown vs. lysis vs. normal
• All you need is love… er, I mean FIBRINOGEN!
  – And maybe PCCs
• It’s really all just DIC of either thrombotic or fibrinolytic phenotype…
  – Just have some sake and thrombomodulin, ATIII, TXA…relax

Resistance is futile…
You will be assimilated!
Lighting the fire…
Stage 1: normal early response

- Hemorrhage causes: Shock & Coagulopathy
  - Decreased perfusion → hypoxia, cell injury, ↓metabolism → hypothermia
  - Release reactions: Catecholamines, tPA, vWF, TF/PDI, DAMPs, PAMPs, PS/MPs, cytokines, ROS/RNS, EC glycocalyx
  - Protease activation: coagulation & complement proteases
  - Cellular activation: platelets, neutrophils, endothelium, etc. → proteins & cells stick
  - Low BP → movement of interstitial fluid into vascular compartment (dilution: by 1/3 if HCT 45→30)

Net effect: thrombin↑, fibrinogen↓, DDimer↑, cells & proteases activated, blood diluted

Normal response

Loss of auto-regulation?
Acute Traumatic Coagulopathy?
Animal Models

**tPA**

**Plasmin**

**D-Dimer**

**Thrombin**

**Fibrinogen**

**Platelets**

**Thrombin Anti-Thrombin**
What about Protein C anticoagulation?

### “xigris” dose

<table>
<thead>
<tr>
<th>Reported doses in Howard et al. (ng/ml)</th>
<th>Converted doses in Howard et al. (nM)</th>
<th>Potential doses* in Howard et al. (nM)</th>
<th>Reported doses in Campbell et al. (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.001</td>
</tr>
<tr>
<td>75</td>
<td>1.33</td>
<td>2.67</td>
<td>1.00</td>
</tr>
<tr>
<td>300</td>
<td>5.34</td>
<td>10.68</td>
<td>33.00</td>
</tr>
<tr>
<td>2000</td>
<td>35.59</td>
<td>71.18</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Fig 1. Characteristic ROTEM EXTEM tracings from a study subject. In every single one of the 20 subjects, as depicted here, increasing concentration of aPC produced ROTEM tracings consistent with worsening acute traumatic coagulopathy.

doi:10.1371/journal.pone.0150930.g001
What about Protein C anticoagulation?

1245 patients, 10 trauma centers (PROMMSTT)
In 69 patients, PC activity drops 30%
aPC 37ng/ml

<table>
<thead>
<tr>
<th></th>
<th>INR-Based</th>
<th>PTT-Based</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coagulopathic (n = 69)</td>
<td>Noncoagulopathic (n = 87)</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>p</td>
</tr>
<tr>
<td>PT</td>
<td>18.5 (16.5–24.0)</td>
<td>14.9 (13.8–16.6)</td>
</tr>
<tr>
<td>PTT</td>
<td>32.6 (27.5–38.0)</td>
<td>26.9 (23.4–30.5)</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>279 ± 34</td>
<td>209 ± 11</td>
</tr>
<tr>
<td>Factor II</td>
<td>61.9 ± 24.0</td>
<td>74.5 ± 26.1</td>
</tr>
<tr>
<td>Factor V</td>
<td>35.1 ± 23.0</td>
<td>57.6 ± 30.4</td>
</tr>
<tr>
<td>Factor VII</td>
<td>74.0 ± 29.9</td>
<td>91.5 ± 37.6</td>
</tr>
<tr>
<td>Factor VIII</td>
<td>302.0 ± 237.4</td>
<td>405.6 ± 237.4</td>
</tr>
<tr>
<td>Factor IX</td>
<td>108.4 ± 78.1</td>
<td>125.4 ± 102.2</td>
</tr>
<tr>
<td>Factor X</td>
<td>60.3 ± 25.0</td>
<td>72.5 ± 32.6</td>
</tr>
<tr>
<td>Antithrombin III</td>
<td>70.7 ± 24.8</td>
<td>80.6 ± 27.0</td>
</tr>
<tr>
<td>d-dimer</td>
<td>4.0 (1.4–20.0)</td>
<td>3.8 (0.0–14.8)</td>
</tr>
<tr>
<td>Protein C</td>
<td>71.3 ± 24.9</td>
<td>87.9 ± 32.2</td>
</tr>
<tr>
<td>aPC</td>
<td>37.2 (13.5–64.6)</td>
<td>8.1 (1.1–16.5)</td>
</tr>
</tbody>
</table>
What about Protein C?

Reported clinical aPC range

“xigris” dose is 75ng/ml

Total PC in humans 4000ng/ml

No “de-repression” of lysis

Fig 3. Changes in standard coagulation measures and factor activity assays by aPC concentration. Findings were confirmed in conventional plasma tests, with significantly increased PT and PTT at higher levels of APC. Corresponding decreases in Factors V and VIII are consistent with the primary anticoagulant mechanism of APC. * indicates p-value < 0.05 by mixed effects model by-group analysis, compared to control. PT, prothrombin time, PTT partial thromboplastin time.
Is thrombin really a limiting factor?
Is it all about the fibrinogen?

The sicker you are, the lower your fibrinogen…

So give fibrinogen?
## CRASH-2 Summary

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>TXA 10,060</th>
<th>Placebo 10,067</th>
<th>Risk of death</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding</td>
<td>489</td>
<td>574</td>
<td><strong>0.85 (0.76–0.96)</strong></td>
<td>0.0077</td>
</tr>
<tr>
<td>Vascular occlusion</td>
<td>33</td>
<td>48</td>
<td>0.69 (0.44–1.07)</td>
<td>0.096</td>
</tr>
<tr>
<td>Multi-organ failure</td>
<td>209</td>
<td>233</td>
<td>0.90 (0.75–1.08)</td>
<td>0.25</td>
</tr>
<tr>
<td>Head injury</td>
<td>603</td>
<td>621</td>
<td>0.97 (0.87–1.08)</td>
<td>0.60</td>
</tr>
<tr>
<td>Other</td>
<td>129</td>
<td>137</td>
<td>0.94 (0.74–1.20)</td>
<td>0.63</td>
</tr>
<tr>
<td>Any death</td>
<td>1463</td>
<td>1613</td>
<td><strong>0.91 (0.85–0.97)</strong></td>
<td>0.0035</td>
</tr>
</tbody>
</table>
Give TXA EARLY!

RR (99% CI)  p=0.000008

- ≤1 hour: 0.68 (0.54–0.86)
- >1 to ≤ 3 hours: 0.79 (0.60–1.04)
- >3 hours: 1.44 (1.04–1.99)

0.85 (0.76–0.96)
No TXA for you! (haters of CRASH-2)

Fibrinolysis can be a problem, but it is also a normal part of homeostasis.

Use TEG to guide appropriate TXA use.

Thromboelastometry underestimates fibrinolysis

All about lysis?
Patients with fibrinolysis also had high thrombin activation.

This is looking like loss of autoregulation: the sicker you are the more everything is activated/consumed...
Stage 2: ATC, 20-120 min?

• Overwhelming shock/coagulopathy → loss of autoregulation
  – Excess fibrinolysis?
  – Auto-anticoagulation by Protein C?
  – De-activation of platelets?
  – Auto-anticoagulation by shedding endothelial glycocalyx?
  – How about too much thrombin too fast?
  – Depletion of antithrombin?
  – Dysfunctional fibrin polymerization?

Net effect: PT or aPTT prolonged, PLT not working, but...

IS THERE COAGULOPATHIC or ANATOMIC BLEEDING??
So what’s really happening?

• First response: **STOP THE BLEED!**

• Last line of defense: **REVERSE GEARS; KEEP THE PIPES OPEN?** (“Hail Mary pass”)
  
  – Fibrinolysis
  
  – Protein C pathway?
  
  – Platelet inhibition

*(i.e., ATC is the last ditch attempt to maintain perfusion.)*

• **OR**, does maximum effort to stop the bleed led to consumption, dilution, loss of autoregulation → **ATC is BLOOD FAILURE?**
Nature’s response vs. organ failure

• When we say “coagulopathy,” are we referring to PATHOLOGY or ADAPTIVE RESPONSE?

• We know that ATC means worse outcomes, but…

• Is the patient bleeding because of ATC or does the patient have ATC because of bleeding (shock)?

• Is a lytic response an attempt to avoid MOF?

Lytics for ARDS?

Treatment of severe acute respiratory distress syndrome: a final report on a phase I study.
Hardaway RM, Harke H, Tyroch AH, Williams CH, Vazquez Y, Krause GF.
PMID:11308009

Linear Evolution or Branching Path?

normal

or

ATC
Limitations of monitoring

• PT, aPTT: current standard but what do they mean?
  – Deficient thrombin?
  – Slow clot polymerization?
  – Plasma-based (lose RBC, PLT effects)

• ROTEM or TEG?
  – At least measuring whole blood!
  – Low shear
  – Insensitive to PLT defects and lysis

• PLT assays? Is this an elephant?
  – Aggregation
  – Adhesion
  – Release
  – catalysis
• Speaking of platelet function in TIC… what do we do with this?

![Graph showing platelet aggregation over time](image-url)
Therapeutic targets?

• What the heck are we treating?

• Fix a dysfunctional coagulation system in order to decrease bleeding? (deliberate coagulation management)
  – Increase thrombin?
  – Increase fibrinogen?
  – Shut off fibrinolysis?
  – Shut off Protein C?

• Fix bleeding and resuscitate shock without making coagulopathy worse? (target overall homeostasis)
  – Repay oxygen debt
  – Rebalance plasma
  – Rescue endothelium
  – Reinforce platelets
  – Don’t dilute!
EVALUATION OF PREHOSPITAL BLOOD PRODUCTS TO ATTENUATE ACUTE COAGULOPATHY OF TRAUMA IN A MODEL OF SEVERE INJURY AND SHOCK IN ANESTHETIZED PIGS

Sarah Watts, Giles Nordmann, Karim Brohi, Mark Midwinter, Tom Woolley, Robert Gwyther, Callie Wilson, Henrietta Poon, and Emrys Kirkman

*CBR Division, Defence Science and Technology Laboratory, Defence Science and Technology Laboratory, Porton Down, Salisbury; †Centre for Trauma Sciences, Bizard Institute, Queen Mary University of London, London; and ‡University of Birmingham, Birmingham, United Kingdom

Give blood, prevent TIC

CRISTALLOID IS BAD!

Fig. 3. Effects of tissue injury, hemorrhagic shock, and resuscitation on TEG R time (clot initiation), K time (clot dynamics), and MA (clot strength) in three treatment groups. For more details, see legend to Figures 1 and 2. Mean values ± SEM.
Give plasma, prevent fibrinolysis

Plasma Is the Physiologic Buffer of Tissue Plasminogen Activator-Mediated Fibrinolysis:
Rationale for Plasma-First Resuscitation after Life-Threatening Hemorrhage

Hunter B Moore, MD, Ernest E Moore, MD, FACS, Eduardo Gonzalez, MD, Gregory Wiener, BA,
Michael P Chapman, MD, Monika Dzieciatkowska, PhD, Angela Saueria, MD, Anirban Banerjee, PhD,
Kirk C Hansen, PhD, Christopher Silliman, MD, PhD

Figure 2. Plasma dilution of whole blood does not alter sensitivity to tissue plasminogen activator (tPA)-mediated fibrinolysis. The y axis represents the percent fibrinolysis quantified by LY30 (amount of blood clot lysed 30 minutes after reaching maximum amplitude). The x axis represents progressive dilution of whole blood with platelet poor, with largest dilution on the right. Blue bar, whole blood with no tPA added. Green bar, whole blood mixed with tPA. PPP, platelet poor plasma.

Figure 1. Normal saline (NS) dilution of whole blood increases sensitivity to tissue plasminogen activator (tPA)-mediated fibrinolysis. The y axis represents the percent fibrinolysis quantified by LY30 (amount of blood clot lysed 30 minutes after reaching maximum amplitude). The x axis represents progressive dilution of whole blood with saline, with largest dilution on the right. Blue bar, whole blood with no tPA added. Green bar, whole blood mixed with tPA.
More plasma and platelets, more survival!

Transfusion Ratio Effect on Odds of Death

<table>
<thead>
<tr>
<th>Transfusion Ratio</th>
<th>Odds Ratio for Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low FFP &amp; Low PLT</td>
<td>High</td>
</tr>
<tr>
<td>High FFP &amp; High PLT</td>
<td>Low</td>
</tr>
<tr>
<td>Low FFP &amp; Low PLT</td>
<td>Low</td>
</tr>
<tr>
<td>High FFP &amp; High PLT</td>
<td>High</td>
</tr>
</tbody>
</table>

Enlightened TIC Therapy?

• Goal-directed? We’re not there yet…
  – How do you do this if you don’t know what you’re treating?

• First do no harm
  – When you’re flying blind, use tools that are forgiving.

• Don’t overdo it
  – Volume overload
  – Procoagulant overload
  – *Remember acute phase response and hypercoagulable state w/in 48-72 hours*
PCCs increase thrombin generation (not the problem)

PCC in dark grey, note elevated ETP through day 4!

VTE risk!!!
Give PCC, increase thrombogenicity

PCC in dark grey; low AT means decreased autoregulation!
Bleeding or thrombosis?

Between Scylla & Charybdis…
RDCR Considerations

• “Coagulopathy” can be assumed in badly injured patients.

• The good news: if you don’t know what you’re supposed to be monitoring, don’t bother with the monitors (not available anyway).

• First do no harm: go with Mother Nature (whole blood or at least blood products).

• Pretty good evidence that TXA and “fibrinogen” and/or plasma are reasonable adjuncts or bridges to whole blood.

• Respect physiology and do what makes sense.
Damage Control for Combat Trauma

• Stop the bleeding!
  – Don’t try to fix everything at once, just stabilize

• Treat shock!
  – Lack of tissue perfusion = death; need oxygen

• Don’t worsen coagulopathy!
  – Blood that doesn’t clot will leak out, but don’t overdo it…

How do you do this?

*Surgical control of hemorrhage + whole blood!*
Thank You.