Critical and Point-of-Care Testing: Real World and Emerging Applications for Improved Clinical Outcomes

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Clinical Overview of Coagulation Testing Issues

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Disclosure

I have no relevant financial or nonfinancial relationships to disclose

(I’m a surgeon)
Learning Objective

• Describe the controversies surrounding coagulation testing and monitoring in clinical medicine:
  – Trauma
  – Extracorporeal life support
Overview

• Hemostasis and coagulopathy
• “Clinical Issues”
• Trauma
• Extracorporeal life support
• Summary
Hemostasis and Coagulopathy
The “Cascade” Model

The “Cell-Based” Model

Multiple Players – Virchow’s Triad

“Balance”

Healthy individual

## Developmental Hemostasis

Reference values for coagulation tests in healthy full-term infants during the first 6 months


<table>
<thead>
<tr>
<th>Tests</th>
<th>Day 1 (n)</th>
<th>Day 5 (n)</th>
<th>Day 30 (n)</th>
<th>Day 90 (n)</th>
<th>Day 180 (n)</th>
<th>Adult (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT (s)</td>
<td>13.0 ± 1.43 (61)*</td>
<td>12.4 ± 1.46 (77)**†</td>
<td>11.8 ± 1.25 (67)**†</td>
<td>11.9 ± 1.15 (62)*</td>
<td>12.3 ± 0.79 (47)*</td>
<td>12.4 ± 0.78 (29)</td>
</tr>
<tr>
<td>APTT (s)</td>
<td>42.9 ± 5.80 (61)</td>
<td>42.6 ± 8.62 (76)</td>
<td>40.4 ± 7.42 (67)</td>
<td>37.1 ± 6.52 (62)*</td>
<td>35.5 ± 3.71 (47)*</td>
<td>33.5 ± 3.44 (29)</td>
</tr>
<tr>
<td>TCT (s)</td>
<td>23.5 ± 2.38 (58)*</td>
<td>23.1 ± 3.07 (64)†</td>
<td>24.3 ± 2.44 (53)*</td>
<td>25.1 ± 2.32 (52)*</td>
<td>25.5 ± 2.86 (41)*</td>
<td>25.0 ± 2.66 (19)</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>1.83 ± 0.58 (61)*</td>
<td>3.12 ± 0.75 (77)*</td>
<td>2.70 ± 0.54 (67)*</td>
<td>2.43 ± 0.68 (60)**†</td>
<td>2.51 ± 0.68 (47)**†</td>
<td>2.78 ± 0.61 (29)</td>
</tr>
<tr>
<td>II (U/mL)</td>
<td>0.48 ± 0.11 (61)</td>
<td>0.63 ± 0.15 (76)</td>
<td>0.68 ± 0.17 (67)</td>
<td>0.75 ± 0.15 (62)</td>
<td>0.88 ± 0.14 (47)</td>
<td>1.08 ± 0.19 (29)</td>
</tr>
<tr>
<td>V (U/mL)</td>
<td>0.72 ± 0.18 (61)</td>
<td>0.95 ± 0.25 (76)</td>
<td>0.98 ± 0.18 (67)</td>
<td>0.90 ± 0.21 (62)</td>
<td>0.91 ± 0.18 (47)</td>
<td>1.06 ± 0.22 (29)</td>
</tr>
<tr>
<td>VII (U/mL)</td>
<td>0.66 ± 0.19 (60)</td>
<td>0.89 ± 0.27 (75)</td>
<td>0.90 ± 0.24 (67)</td>
<td>0.91 ± 0.26 (62)</td>
<td>0.87 ± 0.20 (47)</td>
<td>1.05 ± 0.19 (29)</td>
</tr>
<tr>
<td>VIII (U/mL)</td>
<td>1.00 ± 0.39 (60)**†</td>
<td>0.88 ± 0.33 (75)**†</td>
<td>0.91 ± 0.33 (67)**†</td>
<td>0.79 ± 0.23 (62)**†</td>
<td>0.73 ± 0.18 (47)**†</td>
<td>0.99 ± 0.25 (29)</td>
</tr>
<tr>
<td>vWF (U/mL)</td>
<td>1.53 ± 0.67 (40)**†</td>
<td>1.40 ± 0.57 (43)**†</td>
<td>1.28 ± 0.59 (40)**†</td>
<td>1.18 ± 0.44 (40)**†</td>
<td>1.07 ± 0.45 (46)**†</td>
<td>0.92 ± 0.33 (29)**†</td>
</tr>
<tr>
<td>IX (U/mL)</td>
<td>0.53 ± 0.19 (59)</td>
<td>0.53 ± 0.19 (75)</td>
<td>0.51 ± 0.15 (67)</td>
<td>0.67 ± 0.23 (62)</td>
<td>0.86 ± 0.25 (47)</td>
<td>1.09 ± 0.27 (29)</td>
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<td>X (U/mL)</td>
<td>0.40 ± 0.14 (60)</td>
<td>0.49 ± 0.15 (75)</td>
<td>0.59 ± 0.14 (67)</td>
<td>0.71 ± 0.18 (62)</td>
<td>0.78 ± 0.20 (47)</td>
<td>1.06 ± 0.23 (29)</td>
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<td>XI (U/mL)</td>
<td>0.38 ± 0.14 (60)</td>
<td>0.55 ± 0.16 (74)</td>
<td>0.53 ± 0.13 (67)</td>
<td>0.69 ± 0.14 (62)</td>
<td>0.86 ± 0.24 (47)</td>
<td>0.97 ± 0.15 (29)</td>
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<td>XII (U/mL)</td>
<td>0.53 ± 0.20 (60)</td>
<td>0.47 ± 0.18 (75)</td>
<td>0.49 ± 0.16 (67)</td>
<td>0.67 ± 0.21 (62)</td>
<td>0.77 ± 0.19 (47)</td>
<td>1.08 ± 0.28 (29)</td>
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<tr>
<td>PK (U/mL)</td>
<td>0.37 ± 0.16 (45)**†</td>
<td>0.48 ± 0.14 (51)</td>
<td>0.57 ± 0.17 (48)</td>
<td>0.73 ± 0.16 (46)</td>
<td>0.86 ± 0.15 (43)</td>
<td>1.12 ± 0.25 (29)</td>
</tr>
<tr>
<td>HMW-K (U/mL)</td>
<td>0.54 ± 0.24 (47)</td>
<td>0.74 ± 0.28 (63)</td>
<td>0.77 ± 0.22 (50)*</td>
<td>0.82 ± 0.32 (46)*</td>
<td>0.82 ± 0.23 (48)*</td>
<td>0.92 ± 0.22 (29)</td>
</tr>
<tr>
<td>XIIIa (U/mL)</td>
<td>0.79 ± 0.26 (44)</td>
<td>0.94 ± 0.25 (49)*</td>
<td>0.93 ± 0.25 (44)*</td>
<td>1.04 ± 0.34 (44)*</td>
<td>1.04 ± 0.29 (41)*</td>
<td>1.05 ± 0.25 (29)</td>
</tr>
<tr>
<td>XIIIb (U/mL)</td>
<td>0.76 ± 0.23 (44)</td>
<td>1.06 ± 0.37 (47)*</td>
<td>1.11 ± 0.36 (45)*</td>
<td>1.16 ± 0.37 (44)*</td>
<td>1.10 ± 0.40 (41)*</td>
<td>0.97 ± 0.20 (29)</td>
</tr>
<tr>
<td>Plasminogen (CTA, U/mL)</td>
<td>1.95 ± 0.35 (44)</td>
<td>2.17 ± 0.38 (60)</td>
<td>1.98 ± 0.36 (52)</td>
<td>2.48 ± 0.37 (44)</td>
<td>3.01 ± 0.40 (47)</td>
<td>3.36 ± 0.44 (29)</td>
</tr>
</tbody>
</table>
“Clinical Challenges”

• Need to simplify a complex system
• Coagulation test mechanics
• In-vitro vs. In-vivo
• Different tests
• Different “flavors”
“Eye on the Prize”

• Focus on the patients = clinical outcomes

• Mortality/Survival

• Morbidity
  – Quality of life
  – Complications

• Costs
• Resource Utilization
Coagulopathy and Hemostasis

- OR, ER, ICU, IR, dialysis, outpatient clinics, etc.
- Cardiac surgery
- Transplantation
- Sepsis
- Liver failure
- Acute and chronic kidney injury
- Any really sick patient . . .
- Trauma
- Extracorporeal Life Support (ECLS)
The “Holy Grail”

• Accurate

• Precise

• Clinically meaningful
  – Tests improve outcomes

• I’d like the results 5 minutes ago please
Trauma
• 3287 patients, 391 patients transfused

• Acute coagulopathy ($\text{INR} > 1.5$) on arrival: 38%

• Mortality (+) coagulopathy 24% (vs. 4%)
The prevalence of abnormal results of conventional coagulation tests on admission to a trauma center

John R. Hess, Allison L. Lindell, Lynn G. Stansbury, Richard P. Dutton, and Thomas M. Scalea

TRANSFUSION 2009;49:34-39

- N=23,506
- 2000-2006

Interaction of ISS and admission PLT count with mortality

![Graph showing the interaction of ISS and admission PLT count with mortality.](image)
Pediatric Patients

We conclude . . . coagulopathy is bad

Hemostatic Resuscitation
Assessment

• “Conventional coagulation” tests (CCT)
  – PT
  – INR (Measure Warfarin . . . Trauma?)
  – aPTT (Titrate Heparin . . . Trauma?)
  – Platelet count
  – Fibrinogen

• “Un-conventional” coagulation tests
  – TEG
  – ROTEM
• 20 patients
• rTEG, kTEG, CCT
• Time to results (MA)
  – rTEG: 19.2 ± 3.1 min
  – kTEG: 29.9 ± 4.3 min
  – CCT: 34.1 ± 14.5 min
• rTEG is the fastest
Timing: specimen “clocked-in” to results

- Early rTEG values (ACT, K,): 5 min
- Late rTEG values (α, MA): 15 min
- CCT: 48 min
- \( p < 0.001 \)

Transfusions

- ACT > 128 s (first to result) predicts PRBC, plasma, platelet, and MTP
- ACT < 105 s identifies patients who did not receive a transfusion
Prospective, 9/2009-2/2011

N=1974

Regression analysis controlling for age, gender, mechanism w-RTS, ISS, and base deficit
Can TEG replace CCTs?

• ACT predicted patients with substantial bleeding and RBC transfusion better than PT/PTT or INR ($p = 0.03$)

• $\alpha$-angle was superior to fibrinogen for predicting plasma transfusion ($p < 0.001$)

• mA was superior to platelet count for predicting platelet transfusion ($p < 0.001$)
Can TEG replace CCTs?

• These correlations improved for transfused, shocked or head injured patients

• The charge for r-TEG ($317) was similar to the five CCTs (>400)

• Admission conventional coagulation tests can be replaced with r-TEG
Prospective data collection
> 6 units PRBC within 6 hours of admission
Introduction of a rTEG transfusion algorithm
Pre-rTEG (N=34) and post-rTEG(N=34)

Trend towards fewer products in the post-rTEG
Improved FFP:PRBC in the post-rTEG
Improved mortality 65% to 29%
   – Small N, ISS differences
Trauma - Summary

• TEG/ROTEM probably the best modality to characterize acute traumatic coagulopathy
  – (my opinion . . . . I’m biased)

• Massive transfusion protocols
• Goal directed hemostatic resuscitation

• Adults and children(?)
• Outcome data
Extracorporeal Life Support (aka ECMO)
Systemic Anticoagulation

It’s Important

Anticoagulation Monitoring

- Accurate
- Precise
- Rapid results

- Delicate “Balance” between hypo and hyper coagulability
  - In REALLY sick patients!
Tests, tests, and more tests

- **Laboratory based**
  - PT, INR, aPTT
  - Anti-factor Xa
  - Thrombin time
  - Fibrinogen
  - Platelet count
  - AT III
  - Factor assays
  - TEG
  - ROTEM
  - Others

- **Point of Care**
  - ACT
  - aPTT
  - TEG
  - ROTEM
Systemic Anticoagulation

ECLS Coagulation Monitoring in US

139 responses from 97 institutions
Let's talk about coagulation tests (again . . . a surgeons perspective)
ACT

• Whole blood
• Primary use to titrate heparin in extracorporeal applications
  – Cardiac bypass

• Advantages
  – POC, rapid, available, “cheap”
  – We’ve using it forever . . .

• Disadvantages
  – Lack of standardization (devices, etc.)
    • Optical vs. mechanical
  – Impacted by other variables
ACT

The bigger issue. . .

ACT’s don’t really correlate to heparin dose !!
ACT

What about aPTT?

Anti-Factor Xa

Viscoelastic Monitoring

- Whole blood
- Coagulation (and fibrinolysis)
- Platelet Function
- Laboratory vs. POC
- Underlying hemostatic function
  - Heparinase
Summary
Common Themes in Trauma and ECLS

• Critically ill patients

• Dynamic clinical situation

• Importance of coagulopathy

• Need for monitoring
Guiding Principles

• “same thing, the same way, every time”
  – Every institution is unique
  – NO COMMON LANGUAGE

• Treat the patient NOT a number
  – A test is just a test . . .
  – Understand what you’re looking at
  – Take a step back and interpret all of the clinical data
Guiding Principles

• Clinical Outcomes

• I have no idea what the “right” answer is . . .
  – Any help would be greatly appreciated!

• Future clinical research
Self-Assessment Question

• The best coagulation test for monitoring and managing systemic anticoagulation on ECLS is:
  – ACT
  – INR
  – aPTT
  – TEG
  – Anti-factor Xa
  – Yes