CHALLENGING CASES OF ACQUIRED COAGULOPATHY ENCOUNTERED IN THE EMERGENCY DEPARTMENT
CME Information

Learning Objectives

• Review the prevalence, pathophysiology, causes, clinical assessment, and risk factors of acquired coagulopathy in emergency and trauma patients

• Implement appropriate monitoring strategies using the interpretation of commonly available coagulation laboratory assays, key biomarkers, and transfusion algorithms for emergency and trauma patients

• Review guidelines and expert recommendations for managing perioperative bleeding in surgical and trauma patients, including strategies for blood conservation, transfusion, and clinical effects of newer antithrombotic, anticoagulant, and antiplatelet drugs

• Distinguish clinical issues in managing anticoagulant-associated intracerebral hemorrhage (AAICH), acute traumatic coagulopathy, and transfusion-related postoperative surgical complications

• Incorporate new clinical data into perioperative strategies for reversing and managing acquired coagulopathy and restoring perioperative hemostasis in emergency, trauma, and surgical patients
Overview of Acquired Coagulopathy in the Emergency Department

Joshua N. Goldstein, MD, PhD
Overview of Acquired Coagulopathy in the Emergency Department

- There are multiple causes of acquired coagulopathy, including medications and acute trauma.
- The increasing use of anticoagulants and antiplatelet agents to treat patients with conditions such as atrial fibrillation (AF), deep vein thrombosis (DVT), pulmonary embolism (PE), transient ischemic attack (TIA), myocardial infarction (MI), and artificial heart valves has complicated the treatment of trauma cases and increased the risk of ICH and other life-threatening hemorrhage.

Overview of Acquired Coagulopathy (cont)

- Newer anticoagulants, with no known antidotes, may make acute care of these patients even more complex.¹-³
  - Dabigatran (Pradaxa), a direct thrombin inhibitor
  - Rivaroxaban (Xarelto), a direct factor Xa inhibitor ¹-³
  - Apixaban (Eliquis), another direct factor Xa inhibitor, is approved for use in Europe and may soon be approved in the United States⁴

The Coagulation Cascade, Pathophysiology of Coagulopathy, and Fibrinolysis

- Effective hemostasis depends on procoagulant reactions as well as fibrinolytic process
- 2-fold purpose of fibrinolysis
  - Removal of clots during the process of wound healing
  - Removal of intravascular clots that might otherwise be manifested as thrombosis
Anticoagulants in Clinical Use

• Warfarin

• Heparins
  ▪ Unfractionated heparin (UFH)
  ▪ Low-molecular-weight heparin (LMWH)

• Newer anticoagulants
  ▪ Dabigatran
  ▪ Rivaroxaban

Warfarin: Mechanism of Action

Vitamin K-dependent carboxylation

CYP450

Slight genetic variation can produce significant differences in dose response

Image courtesy of David Garcia, MD.
Warfarin: Mechanism of Action (cont)

Decarboxylated zymogen

Carboxylated zymogen

Vitamin KH$_2$

Vitamin K reductase

Vitamin K epoxide

Vitamin K epoxide reductase

Image courtesy of David Garcia, MD.
Hemostasis as a Stepwise Process

**Initiation Phase**

- The extrinsic pathway acts on the initiating cell.

**Amplification Phase**

- The intrinsic pathway acts on the platelet surface.

**Propagation Phase**

Sites of Action of New Anticoagulant Agents

Intrinsic activation
- Surface contact
  - Factor XII
  - Factor XI
  - Factor VIII
  - Factor IXa
  - Factor X

Extrinsic activation
- Vessel injury
  - Factor VII

Prothrombin → Factor Xa → Thrombin → Fibrinogen → Fibrin

- Rivaroxaban
- Dabigatran etexilate

Challenging Case 1:
Patient with AAICH

David A. Garcia, MD
Case Study—AAICH

- A 68-year-old retired school teacher, Helen F, is undergoing warfarin treatment for a pulmonary embolism. She was doing relatively well, but 5 days into treatment she developed a severe headache and then lost consciousness. She arrives at the ED
- Patient is awake but has a significant right-sided facial droop and some dysarthria
- Vitals
  - Temperature = 98.9°F
  - Blood pressure (BP) = 180/80
  - Heart rate = 55
  - Respiratory rate (RR) = 27
  - Glasgow Coma Scale (GSC) = 9
In addition to the prothrombin time (PT), which of the following assays would be most important for this patient?

A. Platelet count
B. Partial thromboplastin time (PTT)
C. Thrombin time (TT)
D. Ecarin clotting time (ECT)
Case Study—AAICH (cont)

- A PT/INR is ordered
- Patient’s platelet count is normal
- Patient’s INR is 3.6
- CT scan shows intracerebral hemorrhage

Image courtesy of Joshua Goldstein, MD.
What would your initial course of action be?

A. Oral vitamin K and fresh frozen plasma (FFP)
B. Intravenous (IV) vitamin K and FFP
C. IV vitamin K and PCC
D. IV vitamin K and rFVIIa
Case Study—AAICH (cont)

• The patient receives IV vitamin K and FFP
• The patient is admitted to the intensive care unit (ICU)
Ideal Coagulation Assay

• The ideal test to guide transfusion therapy\(^1\)
  - Rapid
  - Accurate
  - Allowing quick clinical assessment and prompt implementation of appropriate therapy
  - Empiric or delayed clinical decisions may result in undertreatment or overtreatment and poor outcomes
• Interpretation of coagulation assays requires knowledge of principal clotting pathways\(^2,3\)

Available Coagulation Assays

• Widely available blood tests with rapid turnaround would include\textsuperscript{1,2}
  
  ‣ Platelet count
  ‣ PT
  ‣ PTT

Introduction of Novel Anticoagulants Affects Assays

- Dabigatran$^1$
  - Oral, direct thrombin inhibitor
  - Inhibits both free and fibrin-bound forms of thrombin plus thrombin-induced platelet aggregation
- Rivaroxaban$^2$
  - FDA approval July 1, 2011
  - Oral, direct factor Xa inhibitor
  - Inhibits prothrombinase complex-bound and clot-associated factor Xa
- Traditional coagulation assays not always helpful for newer anticoagulants$^1$
- No standardized tests for the newer agents$^{1,2}$

Assessing Anticoagulant Activity in a Patient Taking Newer Anticoagulant Agents

- LMWH: anti-Xa activity\(^1\)
- Fondaparinux: anti-Xa activity (must be specially set up for this agent)\(^1\)
- Dabigatran\(^1\)
  - **NORMAL** activated partial thromboplastin time (aPTT) indicates little or no drug in the plasma
  - Elevated aPTT = dabigatran present, otherwise uninterpretable
  - Selected TTs and ECTs correlate well with drug levels, but can be assay-specific
- Rivaroxaban\(^2\)
  - Normal prothrombin time (PT) indicates little or no drug present\(^3\)
  - Anti-Xa activity can correlate with plasma concentration – may be assay-specific\(^3\)

Management of AAICH
Which of the following statements regarding anticoagulants and ICH is NOT true?

A. The annual risk of warfarin-associated AAICH is 0.3% to 1.0%
B. The risk of ICH with dabigatran is less than that associated with warfarin
C. ICH has not been associated with rivaroxaban
Annual Risk of AAICH

- ICH accounts for \( \approx 90\% \) of the deaths from warfarin-associated hemorrhage\(^1\)
- Among users of warfarin for AF, annual risk of AAICH is 0.3\% to 1.0\%\(^2\)
- ICH rate among users of new anticoagulants lower than among warfarin users\(^3-5\)

Major Hemorrhage in the ED

• ED visits for hemorrhage-related events from anticoagulants\(^1\)
  ▪ 60,575 ED visits per year for warfarin
• Most events occur at an INR between 2.0 and 3.5 (ie, within the conventional therapeutic range)\(^2\)

Management of AAICH

- The acute phase is usually managed in the ED\(^1\)
  - Thus, proper management at this point is crucial
- Predictors of outcome (7-day mortality)\(^2\)
  - Initial ICH volume
  - Level of consciousness at presentation

AAICH Management Issues

• Reversal of anticoagulation is essential and should be performed without delay
• Vitamin K and FFP are standard therapies that have limitations
  ▪ Time intensive
  ▪ Large volume challenge required
  ▪ Exposure to blood supply
• No general consensus about optimal short-term treatment

Warfarin-Associated Coagulopathy: Treatment Choices

• IV vitamin K **PLUS**
  - FFP *or*
  - PCC *or*
  - rFVIIa

## Reversal Management Options

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Volume</th>
<th>Time to administer</th>
<th>Ability to increase activity of individual clotting factors</th>
<th>Can “bypass” usual clotting pathways</th>
<th>Potential to cause thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh-frozen Plasma (FFP)</td>
<td>++++</td>
<td>++++</td>
<td>+</td>
<td>No</td>
<td>-</td>
</tr>
<tr>
<td>Prothrombin Complex Concentrate (PCC or aPCC*)</td>
<td>+</td>
<td>+</td>
<td>++++</td>
<td>Yes*</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(+ if aPCC)</td>
<td></td>
</tr>
<tr>
<td>Recombinant activated FVII</td>
<td>+</td>
<td>+</td>
<td>N/A</td>
<td>Yes</td>
<td>++</td>
</tr>
</tbody>
</table>

*activated PCC, eg = FEIBA
# PCCs: Activated vs Nonactivated

<table>
<thead>
<tr>
<th>Product</th>
<th>Characteristics</th>
</tr>
</thead>
</table>
| Activated PCCs     | • Includes activated coagulation factors to allow for bypassing FVII inhibitor<sup>1</sup>  
• For treatment of hemophilia with inhibitors<sup>1</sup>  
• FEIBA<sup>®</sup> NF (anti-inhibitor coagulant complex, Baxter) is the only activated PCC available in the US<sup>1,2</sup>  
• May have greater risk of thrombotic complications than nonactivated PCCs<sup>1</sup>                                                                 |
| Nonactivated PCCs  | • Categorized based on presence or absence of sufficient levels of FVII<sup>1</sup>  
• 3-factor PCCs (II, IX, X) available in the US  
• 4-factor PCCs (II, IX, X, and VII) available in Europe and under investigation in US  
• Two clinical trials currently under way in US to assess effects of 4-factor PCCs as rapid reversal agents in presence of anticoagulant-associated coagulopathy or in anticoagulated patients requiring urgent surgery or invasive procedures<sup>3,4</sup>  
• Case series and retrospective analyses indicate rapid correction of INR with both 3-factor and 4-factor PCCs in setting of urgent anticoagulant reversal<sup>5-8</sup>  
• To date, no demonstrable differences in clinical outcome when PCC compared to FFP<sup>5,8</sup> |

FEIBA is a registered trademark of Baxter International Inc.

Nonactivated PCCs for Reversal of Warfarin-Associated Coagulopathy

<table>
<thead>
<tr>
<th>Product</th>
<th>II</th>
<th>VII</th>
<th>IX</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Available in the US: 3-Factor PCCs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Profilnine® SD (Grifols)*</td>
<td>≤150</td>
<td>≤35</td>
<td>≤100</td>
<td>≤100</td>
</tr>
<tr>
<td>Bebulin® VH (Baxter)*</td>
<td>24-38 IU/mL</td>
<td>&lt;5 IU/mL</td>
<td>24-38 IU/mL</td>
<td>24-38 IU/mL</td>
</tr>
<tr>
<td><strong>Available outside US: 4-factor PCCs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beriplex® (CSL Behring)a</td>
<td>20-48 IU/mL</td>
<td>10-25 IU/mL</td>
<td>20-31 IU/mL</td>
<td>22-60 IU/mL</td>
</tr>
<tr>
<td>Octaplex® (Octapharma)b</td>
<td>14-38 IU/mL</td>
<td>9-24 IU/mL</td>
<td>25 IU/mL</td>
<td>18-30 IU/mL</td>
</tr>
<tr>
<td>Cofact (Sanquin)c</td>
<td>14-35 IU/mL</td>
<td>7-20 IU/mL</td>
<td>25 IU/mL</td>
<td>14-35 IU/mL</td>
</tr>
<tr>
<td>Prothromplex T (Baxter)d</td>
<td>30 IU/mL</td>
<td>25 IU/mL</td>
<td>30 IU/mL</td>
<td>30 IU/mL</td>
</tr>
<tr>
<td>PPPSB-HTe</td>
<td>20 IU/mL</td>
<td>20 IU/mL</td>
<td>20 IU/mL</td>
<td>20 IU/mL</td>
</tr>
<tr>
<td><strong>Available outside US: 3-factor PCCs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prothromplex HT (Baxter)f</td>
<td>30 IU/mL</td>
<td>---</td>
<td>30 IU/mL</td>
<td>130 IU/mL</td>
</tr>
</tbody>
</table>


a United Kingdom (UK), European Union (EU); b UK, Canada, EU; c Austria; d Japan; e Australia. Blood: Journal of the American Society of Hematology by American Society of Hematology. Copyright 2011. Reproduced with permission of American Society of Hematology (ASH) in the format “presentation” via Copyright Clearance Center. Profilnine is a registered trademark of GrifolsBiologics Inc.; Bebulin is a registered trademark of BaxterInternational Inc.; Beriplex is a registered trademark of CSL Behring; Octaplex is a registered trademark of Octapharma; Cofact is a registered trademark of Sanquin; Prothromplex T is a trademark of Immuno Productos Biologicos e Quimicos.
rFVIIa: Advantages and Disadvantages

• Procoagulant agent approved for bleeding complications of hemophilia and congenital FVII deficiency\(^1\)

• Use in ICH and other bleeding events not associated with hemophilia and congenital FVII deficiency is off-label\(^2\)

**Advantage\(^2,3\)**

• Rapid reversal of INR

**Disadvantages\(^3,4\)**

• Small risk of thrombotic events

• Risk-benefit tradeoffs uncertain

• Ineffective if pH<7.25

• Correlation between INR reduction and correction of coagulopathy not well established\(^5\)

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Guidelines for Management of Nontherapeutic INRs

- ED physicians often refer to the guidelines in *Rosen’s Emergency Medicine: Concepts and Clinical Practice*
- These are similar to the 9th American College of Chest Physicians (ACCP) guidelines for the management of nontherapeutic INRs below

<table>
<thead>
<tr>
<th>INR</th>
<th>Bleeding</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥4.5-≤10.0</td>
<td>No bleeding</td>
<td>Recommend against routine use of vitamin K (2B)</td>
</tr>
<tr>
<td>&gt;10.0</td>
<td>No bleeding</td>
<td>Recommend that oral vitamin K be administered (2C)</td>
</tr>
<tr>
<td>Any</td>
<td>Major bleeding</td>
<td>Recommend rapid reversal of anticoagulation with 4-factor PCC rather than plasma (2C); suggest the additional use of 10 mg IV vitamin K (slow injection) rather than reversal with coagulation factors alone (2C)</td>
</tr>
</tbody>
</table>

Adapted from Holbrook A et al; for the American College of Chest Physicians. *Chest.* 2012;141(2)(suppl):e152S-e184S.
# Published Guidelines for Warfarin Anticoagulation Reversal in Patients With ICH

<table>
<thead>
<tr>
<th>Society (year)</th>
<th>Vitamin K (mg)</th>
<th>Plasma (mL/kg)</th>
<th>PCC (U/kg)</th>
<th>rFVII</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australian (2004)</td>
<td>IV (5-10)</td>
<td>Yes (NS)</td>
<td>AND</td>
<td>Yes (NS)*</td>
</tr>
<tr>
<td>British Standards (2005)</td>
<td>IV (5-10)</td>
<td>Yes (15)</td>
<td>OR</td>
<td>Preferred (50)</td>
</tr>
<tr>
<td>EU Stroke (2006)</td>
<td>IV (5-10)</td>
<td>Yes (10-40)</td>
<td>OR</td>
<td>Yes (10-50)</td>
</tr>
<tr>
<td>ACCP (2012)</td>
<td>IV (10)</td>
<td>Not recommended for rapid reversal</td>
<td>4-factor PCC Preferred (NS)</td>
<td>Yes†</td>
</tr>
<tr>
<td>AHA (2010)</td>
<td>IV (NS)</td>
<td>Yes (10-15)</td>
<td>OR</td>
<td>Yes (NS)</td>
</tr>
<tr>
<td>French (2010)</td>
<td>Oral or IV (10)</td>
<td>Yes (NS)‡</td>
<td>OR</td>
<td>Preferred (25-50)</td>
</tr>
</tbody>
</table>

Abbreviations: ACCP, American College of Chest Physicians; AHA, American Heart Association; EU, European Union; IV, intravenous; NS, not specified; PCC, prothrombin complex concentrates; rFVII, recombinant factor VII.

*If a 3-factor PCC is administered, FFP is also recommended as a source of FVII.
† Use of PCCs or rFVIIa may vary, depending on availability.
‡ Use of plasma only when PCCs are not available.

Warfarin Reversal with 3-Factor PCC and rFVIIa for ICH

INR Following Trauma Coumadin Protocol in 49 Patients

INR Following TCP (PCC + rFVIIa)

Mean time from blood bank dispense to post-TCP 179 mins (range: 26-637)

Dabigatran Reversal

• Specific antidote lacking for dabigatran\(^1\)
  ▪ Vitamin K administration has no role to play\(^2\)
• Dabigatran has shorter half-life than warfarin\(^2\)
  ▪ 12 to 17 hours vs 38 to 42 hours
  ▪ Renal impairment can prolong this\(^3\)
• Limited evidence to support use of reversal agents\(^4\)

Dabigatran Reversal (cont)

- FFP
  - No clinical evidence demonstrating reversal of dabigatran’s anticoagulant effects\(^1,2\)

- PCCs
  - Data are mixed\(^3\)
    - Reduction of bleeding time prolongation in rat tail model of template bleeding with \textit{activated} PCC\(^3\)
    - Nonactivated PCC did not reduce aPTT or increase thrombin generation in healthy volunteers\(^4\)
  - FEIBA corrected altered lag-time of thrombin generation in healthy volunteers\(^5\)

- rFVIIa
  - Normal volunteer and ex vivo data suggest antagonism of anticoagulant effects\(^1\)

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Dabigatran Reversal—Expert Opinion

- Oral activated charcoal
  - May be effective after recent ingestion
- Hemodialysis or hemoperfusion
  - Dialysis removed 62% of dabigatran at 2 hours and 68% at 4 hours
  - Hemoperfusion with activated charcoal may be effective
- FFP
  - May be effective in limiting dabigatran-associated serious bleeding, but evidence is from animal trials and applicability to humans is uncertain
- rFVII
  - Animal models suggest it may be effective
  - Although bleeding time was completely corrected, thrombin time, aPTT, and ECT were not normalized, only PT returned to normal
- PCC
  - Animal models suggest that bleeding time is normalized and PT shortened, but prolongations in aPTT, thrombin time, dilute thrombin time, and ECT not reversed
  - Trials in humans also showed no reversal of thrombin time and ECT, but bleeding times were not measured

Rivaroxaban Reversal

- No specific antidote to reverse effects\(^1,2\)
  - Shorter half-life than warfarin\(^3\)
    - 7 to 11 hours vs 38 to 42 hours
    - Renal impairment can prolong this

- Preclinical studies suggest that rFVIIa or PCCs may reverse anticoagulant effects of the agent\(^3\)

- 4-factor nonactivated PCC corrected in vitro measures of coagulopathy and restored thrombin generation\(^4\)

- In healthy volunteers, PCC strongly corrected ETP-AUC and FEIBA corrected all parameters; rFVIIa only modified kinetic parameters\(^5\)

Abbreviations: AUC, area under the curve; ETP, endogenous thrombin potential.

Rivaroxaban Reversal—Expert Opinion

• Oral activated charcoal
  - There is no evidence to support its use

• Hemodialysis or hemoperfusion
  - Rivaroxaban is highly protein-bound and unlikely to be removed by dialysis

• FFP
  - There is no evidence to support its use

• rFVIIa
  - Modest effects have been observed in primate models

• PCC
  - Nonactivated 4-factor PCC can reverse prolongation of PT, but it is uncertain whether this would reverse the bleeding tendency

Suggestions for Emergent Reversal of New Oral Anticoagulants

• Supportive care with fluid resuscitation, red blood cell (RBC) transfusions, maintenance of renal perfusion, identification of bleeding source and surgical intervention as needed

• Discontinue the anticoagulant
  ▪ Given their short half-lives, this may be sufficient in many patients, particularly those with normal renal function

• Consider hemodialysis and hemoperfusion for dabigatran ONLY

• FFP is not likely to be effective

• 3-factor or 4-factor PCCs have the potential to increase risk of thrombosis, but may be a reasonable approach in dire situations

### Suggestions for Reversal of New Oral Anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral activated charcoal</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Hemoperfusion with activated charcoal</td>
<td>Possible</td>
<td>Yes</td>
<td>Possible</td>
</tr>
<tr>
<td>FFP</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>rFVIIa</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>3-factor PCC</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>4-factor PCC</td>
<td>Possible</td>
<td>Possible</td>
<td>Possible</td>
</tr>
</tbody>
</table>

Challenging Case 2:
Acute Traumatic Coagulopathy

Mark Walsh, MD, FACEP
Predicting Need for Massive Transfusion Protocol (MTP) in Trauma

- Identification of shock
- Triggers for MTP
- Imperfection of common coagulation tests based on “cascade”
- Utility of Viscoelastic Hemostatic Assays (VHA) based on “cell-based theory”
- Focus on TEG
Assessment of Blood Consumption (ABC)

Penetrating mechanism
ER systolic blood pressure ≤ 90 mm Hg
ER heart rate ≥ 120 bpm
FAST positiv

Identification and Resuscitation of the Trauma Patient in Shock

Michael N. Cocchi, MD\textsuperscript{a}, Edward Kimlin, MD\textsuperscript{a}, Mark Walsh, MD\textsuperscript{b}, Michael W. Donnino, MD\textsuperscript{c,d,e,*}

\textsuperscript{a}Department of Emergency Medicine, Harvard Affiliated Emergency Medicine Residency,
Lactate Clearance and Base Deficit

- In addition to lactate clearance, base deficit may provide yet another metabolic end point of resuscitation.

- Davis and colleagues found the base deficit calculated on admission for trauma patients was predictive of need for early transfusion of blood products, as well as increased complications.
How do I know shock? It’s like pornography:

• I shall not today attempt further to define the kinds of material I understand to be embraced within that shorthand description ["hard-core pornography"]; and perhaps I could never succeed in intelligibly doing so. But I know it when I see it, and the motion picture involved in this case is not that.

Definition of Shock

• “A rude unhinging of the machinery of life.”
  - Samuel Gross, 1862

Serial Base Deficits and TEGs

Stay by the side of the patient and orchestrate MTP
Endpoints of Resuscitation

Traditional
- Improved level of consciousness
- Improved skin perfusion
- Return of VS to baseline
- Improved urine output
- Normalization of lab values

Current
- Normal TEG
- Normal pH
“Visco-elastic” Hemostatic Assay

- Thromboelastogram provides an analysis of hemostatic competence from a sample of whole blood as it clots in a small crucible (0.36cc). The test is a true reflection of the ability of the blood to clot

- PT, PTT test only the fluid phase not including cells

TEG® Movie

TEG is a registered trademark of Haemoscope Corporation, Niles, IL
Admission Rapid Thrombelastography Can Replace Conventional Coagulation Tests in the Emergency Department: Experience With 1974 Consecutive Trauma Patients

John B. Holcomb, MD, Kristin M. Minei, BS, Michelle L. Scerbo, BS, Zayde A. Radwan, BS, Charles E. Wade, PhD, Rosemary A. Kozar, MD, PhD, Brijesh S. Gill, MD, Rondel Albarado, MD, Michelle K. McNutt, MD, Saleem Khan, MD, Phillip R. Adams, MD, James J. McCarthy, MD, and Bryan A. Cotton, MD, MPH
Well Entrenched in History

• 1967 Hardaway Vietnam Conflict
• 1997 Kaufman cheaper and better than CCT
• 1997-2012 Many papers to confirm the above
• Central importance of thrombin generation

• “PT, INR, PPT never intended for screening of coagulopathy in surgery or trauma, but rather to guide Rx for hemophilia, heparin, and warfarin”
“Initially during the 18 months of our study, few of our residents and faculty were guiding clinical care based on the r-TEG values. However, as the clinicians have become more comfortable with the information, most are now using the r-TEG to guide therapy. Table 7 reflects our current approach (next slide).
# Current Memorial Hermann Hospital Transfusion Recommendations Based on Abnormal r-TEG Values in Bleeding Patients

<table>
<thead>
<tr>
<th>Laboratory Values</th>
<th>Blood Product Transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT &gt; 128</td>
<td>Plasma and RBC’s</td>
</tr>
<tr>
<td>r-value &gt; 1.1</td>
<td>Plasma and RBC’s</td>
</tr>
<tr>
<td>k-time &gt; 2.5</td>
<td>Cryoprecipitate / fibrinogen / plasma</td>
</tr>
<tr>
<td>α - angle &lt; 56</td>
<td>Cryoprecipitate / fibrinogen / platelets</td>
</tr>
<tr>
<td>MA &lt; 55</td>
<td>Platelets / cryoprecipitate / fibrinogen</td>
</tr>
<tr>
<td>LY30 &gt; 3%</td>
<td>Tranexamic acid</td>
</tr>
<tr>
<td>PT &gt; 18.0</td>
<td>Plasma</td>
</tr>
<tr>
<td>aPTT &gt; 35</td>
<td>Plasma</td>
</tr>
<tr>
<td>INR &gt; 1.5</td>
<td>Plasma</td>
</tr>
<tr>
<td>Platelet count &lt; 150 x 10⁹ /L</td>
<td>Platelets</td>
</tr>
<tr>
<td>Fibrinogen &lt; 180 g/L</td>
<td>Cryoprecipitate / fibrinogen</td>
</tr>
</tbody>
</table>
“Therefore, we have recently stopped obtaining admission CCTs on our trauma patients and instead rely on r-TEG to help guide blood products administration.”

• This strategy is unlikely to spread beyond Houston
Tell the surgeon: “It looks like a fish”
Surgeon: “Looks like a fish”
### Demographic, Injury, and Outcome Data (n=1974)

<table>
<thead>
<tr>
<th>Category</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (interquartile range), yrs</td>
<td>33 (23, 49)</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>75</td>
</tr>
<tr>
<td>White race %</td>
<td>54</td>
</tr>
<tr>
<td>Initial GCS, median (interquartile range)</td>
<td>12 (3, 15)</td>
</tr>
<tr>
<td>Initial SBP, median (interquartile range), mm Hg</td>
<td>129 (107, 148)</td>
</tr>
<tr>
<td>Initial pulse, median (interquartile range), bpm</td>
<td>97 (80, 117)</td>
</tr>
<tr>
<td>w-RTS, median (interquartile range)</td>
<td>5.97 (2.93, 7.84)</td>
</tr>
<tr>
<td>ISS, median (interquartile range)</td>
<td>17 (9, 26)</td>
</tr>
<tr>
<td>ISS &gt;25, %</td>
<td>38</td>
</tr>
<tr>
<td>Presence of shock (base ≤5), %</td>
<td>25</td>
</tr>
<tr>
<td>Any transfusion, %</td>
<td>29</td>
</tr>
<tr>
<td>Substantial bleeding rate, %</td>
<td>12</td>
</tr>
<tr>
<td>Massive transfusion rate, %</td>
<td>5</td>
</tr>
<tr>
<td>24-h mortality, %</td>
<td>6</td>
</tr>
<tr>
<td>30-d mortality, %</td>
<td>11</td>
</tr>
</tbody>
</table>

Bpm, beats per minute; GCS, Glasgow Coma Scale; SBP, systolic blood pressure; w-RTS, weighted Revised Trauma Score; ISS, injury severity scale
Who does the TEG?

Algorithm for thromboelastographic-guided blood component therapy*

<table>
<thead>
<tr>
<th>TEG Abnormality</th>
<th>Blood Component Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged R</td>
<td>Fresh frozen plasma</td>
</tr>
<tr>
<td>Prolonged K and/or reduced α angle</td>
<td>Cryoprecipitate</td>
</tr>
<tr>
<td>Low MA</td>
<td>Platelets consider DDAVP</td>
</tr>
<tr>
<td>Elevated LY 30%</td>
<td>Consider antifibrinolytics</td>
</tr>
</tbody>
</table>

*Address other etiologies of coagulopathy; hypothermia, acidosis and continued hemorrhage, hypocalcemia, and dilution. Consider early surgery and 1:1:1 PRBC, FFP, platelets for damage control resuscitation and rFVIIa. Look for combined and occult causes of coagulopathy and primary fibrinolysis.

MA, maximum amplitude; LY, percent clot lysis at 30 minutes; DDAVP, 1-desamin-8-D-arginine vasopressin.

Perfusionists

Case 2: Scenario – Moped Crash Cardiac Arrest in ED

- 50-year-old male
- Unhelmeted mopedist
- Had been evading police after they attempted to pull him over
- Frontal impact with car at 45 mph
- Time of injury 07:51

Image courtesy of Mark Walsh, MD.
Case 2: Cardiac Arrest

- Chest compressions initiated
- Chest tube placed
- Pulse returned
- Arterial line placed
  - Systolic BP (SBP) in the 50s-60s
- MTP initiated (08:47)
Subxiphoid Window With Effusion

Image courtesy of Mark Walsh, MD.
Case 2: Pericardial Tamponade

- SBP remained in the 50s-60s
- Thoracotomy with pericardial window (09:10)
- Left atrial appendage injury
- BP improved with occlusion of injury
- To the operating room (OR) at 09:45
Case 2: Surgical Procedure

Image courtesy of Mark Walsh, MD.
Case 2: Surgical Procedure (cont)

Image courtesy of Mark Walsh, MD.
Case 2: Operative Course

- Repair of left atrial appendage injury
- Exploratory laparotomy
- Management of superficial liver lacerations
- Re-exploration of abdomen in ICU
Case 2: Massive Transfusion (24 hours)

- RBCs: 59 PRBC
- Plasma: 22 FFP
- Platelets: 8 apheresis plts
- Cryo: 1 (5 unit) “bag”
- rFVIIa: 90 μg/kg
- EACA
Case 2: Immediately in OR (TEG® Tracing) 09:38 – hyperfibrinolysis

TEG is a registered trademark of Haemoscope Corporation, Niles, IL.

Image courtesy of Mark Walsh, MD.
Case 2: Left Atrial Appendage Tear (TEG® Tracing) 10:43
– less lysis

TEG is a registered trademark of Haemoscope Corporation, Niles, IL.

Image courtesy of Mark Walsh, MD.
Early Platelet Dysfunction: An Unrecognized Role in the Acute Coagulopathy of Trauma

Max V. Wohlauer, MD, Ernest E. Moore, MD, FACS, Scott Thomas, MD, FACS, Angela Sauraia, MD, PhD, Ed Evans, BA, CCP, Jeffrey Harr, MD, MPH, Christopher Sullivan, MD, PhD, Victoria Ploplis, PhD, Francis J. Castellino, PhD, Mark Walsh, MD

Background: Our aim was to determine the prevalence of platelet dysfunction using an endpoint of assembly into a stable thrombus after severe injury. Although the current debate on acute traumatic coagulopathy has focused on the consumption or inhibition of coagulation factors, the question of early platelet dysfunction in this setting remains unclear.

Study Design: Prospective platelet function in assembly and stability of the thrombus was determined within 30 minutes of injury using whole blood samples from trauma patients at the point of care using thromboelastography-based platelet function analysis.

Results: There were 51 patients in the study. There were significant differences in the platelet response between trauma patients and healthy volunteers, such that there was impaired aggregation to the agonists. In trauma patients, the median ADP inhibition of platelet function was 86.1% (interquartile range [IQR] 38.6% to 97.7%) compared with 4.2% (IQR 0 to 18.2%) in healthy volunteers. After trauma, the impairment of platelet function in response to arachidonic acid was 44.9% (IQR 26.6 to 59.3%) compared with 0.5% (IQR 0 to 3.02%) in volunteers (Wilcoxon nonparametric test, P < 0.0001 for both tests).

Conclusions: In this study, we show that platelet dysfunction is manifest after major trauma and before substantial fluid or blood administration. These data suggest a potential role for early platelet transfusion in severley injured patients at risk for postinjury coagulopathy. (J Am Coll Surg 2012; 214: 739-746. © 2012 by the American College of Surgeons)
Case 2: First Platelet Mapping
– platelet dysfunction in AM

Image courtesy of Mark Walsh, MD.
Case 2: Platelet Mapping

- 3 days later, patient has platelet count of 42,000, but...

Image courtesy of Mark Walsh, MD.
Case 2: Second Platelet Mapping

- Platelets 42,000 but working well... fewer needed

Image courtesy of Mark Walsh, MD.
Case 2: ICU Day 4

Image courtesy of Mark Walsh, MD.
Case 2: ICU Day 4 (cont)

Image courtesy of Mark Walsh, MD.
Case 2: ICU Course

- Abdominal compartment syndrome
- Acute respiratory distress syndrome
- Acute renal failure
- Hepatic failure (hepatorenal syndrome)
Case 2: Day 48 with his FAST EM MD friend

AMBULATORY PATIENT THANKS HIS VERY SKILLED EMERGENCY PHYSICIAN 8 WEEKS LATER

Image courtesy of Mark Walsh, MD.
ATC Defined

• “An endogenous impairment of hemostasis that occurs early after injury”

Image courtesy of Mark Walsh, MD.

Impact of ATC

• Trauma accounts for 9% to 14% of deaths worldwide\(^1,2\)
• Traffic accidents (1.2 million deaths)\(^1\)
• In the United States: 3.7 million cases of injuries caused by transportation annually\(^3\)
• Among persons up to 19 years old, unintentional injury is the leading cause of death\(^4\)
  - Motor vehicle traffic-related deaths remain the leading cause of injury in this group\(^4\)

Impact of ATC (cont)

- Overall, 40% of trauma deaths are due to hemorrhage\(^1\)
- Hemorrhage accounts for almost 50% of deaths in the first 24 hours\(^2\)
  - Responsible for up to 56% of prehospital deaths
  - Cause of over 80% of OR deaths after trauma
  - Very few hemorrhagic trauma-related deaths occur after the first day

Acute Coagulopathy of Trauma (ACOT)

- Hemorrhage accounts for 40% of all trauma deaths
- An acute coagulopathy is identified in 1 in 4 trauma patients on admission
  - Four-fold increase in mortality

Risk Factors for ATC

• Extent of tissue damage\textsuperscript{1}
• Shock (SBP $\leq$ 90) 3-fold risk increase\textsuperscript{1}
• Prehospital IV fluids $\geq$ 3000 mL\textsuperscript{1}
• Hypothermia (temperature $\leq$ 35°C)\textsuperscript{1}
• Acidosis (base excess $\leq$ 10) 3-fold increase\textsuperscript{1,2}
• Inflammation\textsuperscript{1}

Preexisting Coagulopathic Comorbidities May Complicate Treatment

- Presence of cirrhosis
- Hemophilia, von Willebrand disease, and other bleeding disorders
- Preinjury anticoagulants or use of antiplatelet agents
  - Warfarin
  - Aspirin, nonsteroidal anti-inflammatory drugs, or clopidogrel
  - Warfarin and aspirin increase traumatic brain injury mortality 5-fold

Kauvar DS et al. J Trauma. 2006;60(suppl 6):S3-S11.
Coagulation Assays in the Setting of ATC

• Hess and colleagues found abnormal coagulation test results to be predictive of early death in trauma patients\(^1\)

• However, Schöchl and investigators found traditional tests to be unsuited for guiding treatment decisions in the ED\(^2\):
  - Need for point-of-care guidance over “blind” management of coagulation

• Traditional coagulation assays do not detect differences/effectiveness of newer agents\(^3,4\)

Management of ATC
In a patient experiencing massive hemorrhage, what is your primary concern?

A. Ensuring adequate fluid resuscitation
B. Ensuring return to normal levels of blood pressure
C. Managing hypothermia, metabolic acidosis, and coagulopathy
Overview

• Multimodal approach required
• Prevention of...
  ▪ Acidosis
  ▪ Hypothermia
  ▪ Progressive coagulopathy
Algorithm for Thromboelastographic-Guided Blood Component Therapy

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<tr>
<td>Elevated LY 30%</td>
<td>Consider antifibrinolytics</td>
</tr>
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</table>

Abbreviations: α, slope of the curve drawn as a tangent from the beginning of clot formation until 20 mm elevation; FFP, fresh frozen plasma; K, measure of time from beginning of clot formation until the curve reaches arbitrary amplitude of 20 mm; LY 30%, percent clot lysis at 30 minutes; MA, maximum amplitude; R, reflects initiation and the enzymatic phase of coagulation from the time of clot formation to the detection of initial fibrin strand formation.

TEG is a registered trademark of Haemoscope Corporation, Niles, IL.

Differences in Single System and Multiple Organ Failures*

<table>
<thead>
<tr>
<th></th>
<th>Pre-TEP (n=141)</th>
<th>TEP (n=125)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory failure (%)</td>
<td>62.4</td>
<td>56.0</td>
<td>.287</td>
</tr>
<tr>
<td>Cardiac failure (%)</td>
<td>39.0</td>
<td>12.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hepatic failure (%)</td>
<td>9.2</td>
<td>3.2</td>
<td>.045</td>
</tr>
<tr>
<td>Renal failure (%)</td>
<td>6.4</td>
<td>5.6</td>
<td>.801</td>
</tr>
<tr>
<td>Multiple organ failure</td>
<td>37.2</td>
<td>15.6</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviation: TEP, trauma exsanguination protocol.

*Patients treated according to an MTP were compared with patients who were not.

Damage Control Resuscitation (DCR): Addresses Lethal Triad

• Conventional resuscitation: rapid reversal of acidosis, prevention of hypothermia and hemorrhage, and contamination control but not coagulopathy

• DCR addresses the lethal triad of hypothermia, metabolic acidosis, and coagulopathy immediately upon admission to a trauma unit or hospital

DCR: Addresses Lethal Triad (cont)

• Early delivery of blood component therapy
  ▪ PRBCs, plasma, platelets
• Permissive hypotension
  ▪ Prevents renewed bleeding from clots
• Minimized crystalloid-based resuscitation
  ▪ Reduction of 50% compared with standard resuscitation
• Immediate control of hemorrhage with delayed definitive repair

4-Year Retrospective Study of DCR

• 4-year retrospective study of DCR and damage control laparotomy vs conventional resuscitation efforts (CRE)
  - DCR associated with survival advantage, shorter trauma ICU stay compared with CRE
    o Survival 73.6% vs 54.8%
    o Length of stay in ICU 11 days vs 20 days
  - Greater use of PRBC, FFP and platelets, less crystalloid solution used intraoperatively
    o Closer FFP to PRBC ratio
      ➢ 1 to 1.2 vs 1 to 4.2

Treatment Approaches

Initial volume resuscitation

**Advantages**
- Infusion of crystalloids and colloids in hypovolemia helps stabilize systemic circulation
- Intravascular volume sustained

**Disadvantages**
- Can result in dilute coagulation factors, platelets, and hemoglobin
- Reduction in viscosity, washing out previously formed clots and exacerbating hemorrhage

Treatment Approaches (cont)

**Plasma**

**Advantages**\(^1\)\(^-\)\(^3\)
- Less risk of thromboembolism vs other treatment options
- Contains all coagulation factors required for hemostasis
- Replaces volume lost from severe hemorrhage

**Disadvantages**\(^1\)\(^,\)\(^2\)\(^,\)\(^4\)
- Possible viral contamination, volume challenge potential for fluid overload
- Demonstrated inferiority when compared to PCC in correcting INR in animal models of dilutional coagulopathy and cardiac surgery

Treatment Approaches (cont)

Cryoprecipitate (*Fibrinogen Concentrate, FXIII Concentrate*)

**Advantages**
- Rich in fibrinogen, FXIII, von Willebrand factor, and FVIII
  - FXIII component can improve clot stability
- Rapidly increases the concentrations of fibrinogen and von Willebrand factor
- In the United States, cryoprecipitate is alternative to plasma for replacement of low plasma fibrinogen

**Disadvantages**
- Lack of data on safety and efficacy in setting of massive transfusion
- Must be transported and stored frozen
- Problematic viral inactivation

Treatment Approaches (cont)

**PCCs (off-label)**

**Advantages**¹,²

- Concentration of essential coagulation factors (II, VII, IX, X)
  - 3-factor PCCs lack VII
- Efficient, timely replacement of vitamin K–dependent factors
- Lower volume and infusion time needed with PCC to achieve target vitamin K–dependent factor levels compared with plasma
- Rapid onset of action

**Disadvantages**¹,²

- No evidence for administering PCC for management of massive bleeding
- Not able to correct blood volume; therefore, must be associated with (diluting) fluid therapy
- Prothrombotic risk of PCC may be increased in presence of antithrombin deficiency caused by hemodilution
- Potential for allergic reactions

Treatment Approaches (cont)

*rFVIIa (off-label) pH must be greater than 7.25*

**Advantages**
- Rapid reversal of coagulopathy, with significant improvement in laboratory measures
- Significant decrease in transfusion requirement following rFVIIa administration

**Disadvantages**
- No demonstrable survival benefit
- Potential for thrombotic complications

---

Summary

• Cells play a major role in controlling and directing coagulation reactions
• Rapid initiation of treatment is essential in patients presenting to the ED with conditions associated with acquired coagulopathy, including AAICH and ATC
• The ideal assays to guide transfusion therapy in patients on novel anticoagulants are not yet clear
• In patients with ATC, incorporating permissive hypotension and minimizing crystalloid use may reduce mortality and improve outcomes for trauma patients
• Establishment and use of an MTP may improve outcomes and blood utilization
• In patients with AAICH, several national guidelines are available to guide therapy
Faculty Panel

Question and Answer Session
In the future, how do you plan to incorporate coagulation factor replacement therapy guidelines into the management of coagulopathy in the ED?

A. I will continue to be adherent to national guidelines
B. I will use national guidelines to inform my clinical decisions in the future
C. I will use national guidelines and my own clinical experience in making decisions about the treatment of coagulopathy
D. I will rely on my own clinical experience in treating these patients
If your institution does not have an MTP now, do you intend to try to facilitate the development of one?

A. Yes
B. No
In the future, do you plan to use DCR in patients experiencing coagulopathy, hypothermia, and metabolic acidosis?

A. Yes
B. No
C. Undecided
How comfortable do you feel now about treating patients with coagulopathies associated with the use of dabigatran and rivaroxaban?

A. Not comfortable at all
B. Somewhat comfortable
C. Comfortable
D. Very comfortable
Thank you for participating. Please complete the post survey, posttest, and evaluation to receive CME credit.