APPROACH TO COAGULOPATHY IN THE ICU
DIC AND THROMBOTIC EMERGENCIES

NEIL KUMAR, MD
UNIVERSITY OF ROCHESTER MEDICAL CENTER
Disclosures

- I have no financial disclosures
- I am NOT A HEMATOLOGIST
Review of hemostasis and coagulopathy
Discuss laboratory markers for coagulopathy
Discuss an approach to a few specific coagulopathies and thrombotic emergencies
Outline

- Review of hemostasis and coagulopathy
- Discuss laboratory markers for coagulopathy
- Discuss an approach to a few specific coagulopathies and thrombotic emergencies
**Coagulation**

- Coagulation is the process in which blood clots.
- Fibrinolysis is the process in which clot dissolves.
- Hemostasis is the stopping of bleeding or hemorrhage.
- Ideally, hemostasis is a balance between coagulation and fibrinolysis.

![Diagram of Coagulation and Fibrinolysis](image-url)
Coagulation (classic pathways)

Michael G. Crooks  
Simon P. Hart  
Eur Respir Rev  
2015;24:392-399
Coagulation (another view)

Gando, S. et al. (2016) Disseminated intravascular coagulation
Coagulation (yet another view)

- Inflammation and coagulation intersect with platelets in the middle
- An example of this is Disseminated Intravascular Coagulation.
Outline

- Review of hemostasis and coagulopathy
- Discuss laboratory markers for coagulopathy
- Discuss an approach to a few specific coagulopathies and thrombotic emergencies
PT / INR

- Prothrombin Time
- Test of Extrinsic Pathway
- Take plasma (blood without cells) and re-add calcium
  - Calcium was removed with citrate in tube
- Add tissue factor
- See how long it takes to clot and normalize PT to get INR
PT / INR

- Causes for elevated INR
  - Warfarin or other vitamin K antagonist
  - Liver disease
    - Hepatocellular disease
    - Cholestatic disease
  - DIC
Activated Partial Thromboplastin Time
Test of Intrinsic Pathway
Take plasma (blood without cells) and re-add calcium
  Calcium was removed with citrate in tube
Add “partial thromboplastin”
  Thromboplastin is a lab surrogate for tissue factor. It Is actually phospholipid and tissue factor. Partial thromboplastin is just the phospholipid
Add negative charged particle (usually kaolin or silica)
  Negative charged particle in the vessel is collagen exposed by vessel injury
See how long it takes to clot
Coagulation (classic pathways)

Michael G. Crooks
Simon P. Hart
Eur Respir Rev
2015;24:392-399
Causes for elevated INR

- Anticoagulant use such as heparin, bivalirudin
- Mildly elevated in warfarin use
- Liver disease
- DIC
Activated Clotting Time

- Test of entire coagulation cascade, except fibrinolysis
- Take whole blood and mix with glass beads or kaolin
- See how long clot will take to form

- Most commonly used in cardiac bypass due to extreme amounts of heparin used
ACT will thus be elevated in a wide range of circumstances; a short list could resemble the following:

- Thrombocytopenia, or platelet dysfunction
- Clotting factor deficiency, or factor inhibitors
- Low fibrinogen
- Hypothermia
Thrombin Time

Measures conversion of fibrinogen to fibrin.

Take plasma and add thrombin
Causes of an unusually prolonged thrombin time:

- Heparin therapy
- Low fibrinogen levels
- Dysfunctional fibrinogen (e.g., foetal fibrinogen)
- Direct thrombin inhibitors (e.g., hirudin, argatroban, dabigatran)
- High levels of abnormal proteins, e.g., paraproteins and fibrin degradation byproducts can lead to abnormal TT by interfering with the cleavage of fibrinogen by thrombin.

- Very high fibrinogen levels can paradoxically interfere with TT.
Reptilase Time

- Reptilase is secreted by vipers and catalyzes fibrinogen to fibrin
  - Related to Thrombin Time
  - Except, since it not mammalian, it doesn’t adhere to normal human homeostatic feedback mechanisms
Reptilase Time

- Thus, reptilase time will not be affected by antithrombin III (and thus, by heparin)
- It will not be affected by direct thrombin inhibitors such as argatroban or hirudin
- It will only react to abnormalities of fibrinogen.

Thus, reptilase time will be abnormally increased in the following circumstances:
- Low fibrinogen levels
- Dysfunctional fibrinogen (e.g. foetal fibrinogen)
- High levels of abnormal proteins, e.g. paraproteins and fibrin degradation byproducts
- Very high fibrinogen levels
Ecarin Clotting Time

- Ecarin is from venom and activates prothrombin
- Bypasses extrinsic and intrinsic pathways
- ECT will be abnormal in the presence of any direct thrombin inhibitors.
Both are commercial types of viscoelastic tests.

- TEG, the cup moves. ROTEM, the pin moves.
- It shows interaction of platelets with the coagulation cascade.
TEG / ROTEM

Gregory Semon, Michael Cheatham. TEG in Trauma
http://www.surgicalcriticalcare.net/Guidelines/TEG%202014.pdf
# Thromboelastogram (TEG)

<table>
<thead>
<tr>
<th>Components</th>
<th>Definition</th>
<th>Normal Values</th>
<th>Problem with...</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>R Time</td>
<td>Time to start forming clot</td>
<td>5 – 10 minutes</td>
<td>Coagulation Factors</td>
<td>FFP</td>
</tr>
<tr>
<td>K Time</td>
<td>Time until clot reaches a fixed strength</td>
<td>1 – 3 minutes</td>
<td>Fibrinogen</td>
<td>Cryoprecipitate</td>
</tr>
<tr>
<td>Alpha angle</td>
<td>Speed of fibrin accumulation</td>
<td>53 – 72 degrees</td>
<td>Fibrinogen</td>
<td>Cryoprecipitate</td>
</tr>
<tr>
<td>Maximum Amplitude (MA)</td>
<td>Highest vertical amplitude of the TEG</td>
<td>50 – 70 mm</td>
<td>Platelets</td>
<td>Platelets and/or DDAVP</td>
</tr>
<tr>
<td>Lysis at 30 Minutes (LY30)</td>
<td>Percentage of amplitude reduction 30 minutes after maximum amplitude</td>
<td>0 – 8%</td>
<td>Excess Fibrinolysis</td>
<td>Tranexamic Acid and/or Aminocaproic Acid</td>
</tr>
<tr>
<td>Haemostatic therapy</td>
<td>ROTEM/TEG trace</td>
<td>ROTEM triggers</td>
<td>TEG/rTEG triggers</td>
<td></td>
</tr>
<tr>
<td>---------------------</td>
<td>----------------</td>
<td>----------------</td>
<td>-------------------</td>
<td></td>
</tr>
<tr>
<td>Consider administering fibrinogen concentrate or cryoprecipitate (FFP*)</td>
<td>Angle 20 mm A5/10, MCF MA</td>
<td>EXTEM A10&lt;45 mm (A5&lt;35 mm) or MCF&lt;55 mm and FIBTEM A10&lt;10 mm (A5&lt;9 mm) or MCF &lt;12 mm</td>
<td>TEG: FF MA&lt;14 mm, cryoprecipitate/fibrinogen/FFP rTEG: K&gt;2.5 min or angle &lt;56° (&lt;65°); cryoprecipitate/fibrinogen/FFP</td>
<td></td>
</tr>
<tr>
<td>Consider administering FFP or PCC</td>
<td>Angle CT, R, ACT A5/10, MCF MA</td>
<td>EXTEM CT&lt;80 s and A1045 mm (A5&gt;35 mm) or MCF&gt;55 mm and normal FIBTEM A10 (A5&gt;9 mm) or normal MCF</td>
<td>TEG: R&gt;10 min, angle &lt;52°, or FF MA&lt;14 mm, FFP rTEG: R&gt;1.1 min, FFP and prRBCs; ACT&gt;128 s, FFP and prRBCs</td>
<td></td>
</tr>
<tr>
<td>Consider administering platelet concentrate (fibrinogen concentrate, cryoprecipitate*)</td>
<td>Angle A5/10, MCF MA</td>
<td>EXTEM A10&lt;45 mm (A5&lt;35 mm) or MCF&lt;55 mm and normal FIBTEM A10 (A5&lt;9 mm) or normal MCF</td>
<td>TEG: MA&lt;49 mm, platelet concentrate (in patients with normal FF MA) rTEG: MA&lt;55 mm, platelet concentrate/fibrinogen/cryoprecipitate</td>
<td></td>
</tr>
<tr>
<td>Consider administering antifibrinolytics</td>
<td>Ly30</td>
<td>Any evidence of hyperfibrinolysis on EXTEM or FIBTEM</td>
<td>TEG: Ly30&gt;4%, TXA (if &gt;4% and angle and/or MA1, TXA contraindicated as considered reactive hyperfibrinolysis) rTEG: Ly30&gt;3% (&gt;5%);1, TXA if time since injury &lt;3 h and patient is bleeding</td>
<td></td>
</tr>
<tr>
<td>Consider withholding haemostatic therapy and transfusions</td>
<td>Angle A5/10, MCF</td>
<td>Abnormally high A10 or MCF on EXTEM</td>
<td>Recommendation not available</td>
<td></td>
</tr>
</tbody>
</table>
Tests of Coagulation

- No one test can adequately give a good overview of coagulopathy
- Even a battery of tests cannot always give a good overview of coagulopathy

- Why?
Outline

- Review of hemostasis and coagulopathy
- Discuss laboratory markers for coagulopathy
- Discuss an approach to a few specific coagulopathies and thrombotic emergencies
Thrombocytopenia

- Extremely common in ICU patients – especially in the setting of surgery.
- Commonly used transfusion triggers
  - 10,000 / cubic millimeter for non-bleeding patients
    - If known myelodysplasia or aplastic anemia, can consider a lower trigger
  - 50,000 / cubic millimeter for bleeding patients
  - 100,000 / cubic millimeter for central nervous system bleeding
Thrombocytopenia

- Evaluation
  - Pseudothrombocytopenia?
    - Blood sample clotted? EDTA-dependent platelet antibodies
    - Large platelets that are missed by cell counters
  - Drug related?
    - Heparin
    - IIb/IIIa inhibitors
    - ADP receptor antagonists
    - Acute alcohol toxicity
  - Hematinic deficiency, such as folic acid?
Thrombocytopenia

- Other causes
  - Sepsis
  - Major blood loss and hemodilution
  - Mechanical fragmentation
    - Cardiopulmonary bypass
    - ECMO
    - IABP
    - Renal dialysis?
  - Immune mediated disorder
  - Hypersplenism
  - DIC
  - Microangiopathic hemolytic anemia
DIC

- Acquired syndrome
- Intravascular activation of coagulation
- Loss of localization arising from different causes.
DIC

- Usually presents as hemorrhage, only about 10% of cases presenting as microthrombi alone.
- Sepsis is most common underlying cause in critical care
DIC

- Early animal studies showed promise in the use of activated protein c, antithrombin, tissue factor pathway inhibitor.
- Studies in humans showed no survival benefit, but increased bleeding.
Consumption of coagulation proteins and platelets produces bleeding tendencies.

- Prolonged prothrombin time
- Prolonged activated partial-thromboplastin time
- Hypofibrinogenemia
- Elevated levels of fibrinogen degradation products
- Thrombocytopenia
| Table 2. Diagnostic Scoring System for Disseminated Intravascular Coagulation (DIC). *
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk assessment: Does the patient have an underlying disorder known to be associated with overt DIC?</td>
</tr>
<tr>
<td>If yes, proceed with this algorithm</td>
</tr>
<tr>
<td>If no, do not use this algorithm</td>
</tr>
<tr>
<td>Order global coagulation tests (prothrombin time, platelet count, fibrinogen, fibrin-related marker)</td>
</tr>
<tr>
<td>Score the test results as follows:</td>
</tr>
<tr>
<td>- Platelet count: 50,000 to 100,000 per mm$^3$, 1 point; &lt;50,000 per mm$^3$, 2 points</td>
</tr>
<tr>
<td>- Elevated fibrin-related marker (e.g., D-dimer, fibrin degradation products): no increase, 0 points; moderate increase, 2 points; strong increase, 3 points</td>
</tr>
<tr>
<td>- Prolonged prothrombin time: &lt;3 sec, 0 points; ≥3 sec but &lt;6 sec, 1 point; ≥6 sec, 2 points</td>
</tr>
<tr>
<td>- Fibrinogen level: ≥1 g per liter, 0 points; &lt;1 g per liter, 1 point</td>
</tr>
<tr>
<td>Calculate the score as follows:</td>
</tr>
<tr>
<td>- ≥5 points: compatible with overt DIC; repeat scoring daily</td>
</tr>
<tr>
<td>- &lt;5 points: suggestive of nonovert DIC; repeat scoring within next 1 to 2 days</td>
</tr>
</tbody>
</table>

* Data are adapted from Toh and Hoots$^{21}$ on the basis of the scoring system developed by the International Society on Thrombosis and Hemostasis.
Management is based upon treating underlying cause

- Expert opinion suggests replacing coagulation proteins and platelets in setting of bleeding.

- Commonly used targets include
  - Platelet level of 50,000 / cubic millimeter
  - Prothrombin time less than 1.5 times normal control
  - Fibrinogen level of 1.5 gram / liter

- Antifibrinolytics avoided due to widespread fibrin deposition (fibrinolytic system necessary in recovery)

- Heparin in thrombotic phenotype is controversial.
Thrombotic Microangiopathies

- Characterized by profound thrombocytopenia and microangiopathic hemolytic anemia (red-cell fragmentation)
  - Examples include
    - Thrombotic thrombocytopenia purpura
    - Hemolytic uremia syndrome
    - HELLP syndrome
Acquired or hereditary

ADAMTS13 cleaves vWF. In its absence, large multimers of vWF are present, increasing risk for platelet thrombi in small vessels.

Acquired TTP diagnosis is supported by ADAMTS13 level less than 10% of normal activity.

Test not sufficiently sensitive nor specific to use in isolation.
Thrombotic thrombocytopenia purpura
ADAMTS13 deficiency-mediated TMA

- Initial presentation is varied. Weakness, gastrointestinal symptoms, purpura, and transient focal neurologic abnormalities are common.
- Most patients have normal or only slightly elevated creatinine levels.
- Treatment for hereditary is ADAMTS13 replacement.
- Survival for acquired is increased by plasma exchange. Initial management is ADAMTS13 replacement with plasma infusion.
- Glucocorticoids are standard treatment.
Complement mediated Thrombotic Microangiopathy

- Results from uncontrolled activation of alternative pathway of complement activation.
- Acute Kidney Injury in the setting of hypertension is common presentation.
- Diagnostic criteria include
  - Serum creatinine at or above upper limit of normal
  - Microangiopathic hemolytic anemia
  - Thrombocytopenia
  - ADAMTS13 activity of 5% or more.
  - Negative stool sample for Shiga-toxin producing infection.
- Treatment is with anti-complement agents. Eculizumab
Conclusion

- Hemostasis is the interplay between coagulation and fibrinolysis
- Laboratory evaluation is not perfect
- Management of coagulopathy and thrombotic emergencies requires a high degree of suspicion and vigilance.

References