Interesting Coagulation Cases

Nancy Rosenthal, MD
University of Iowa Carver College of Medicine
Objectives

- Describe complications of some anticoagulant drugs
- Assess the bleeding disorder associated with liver disease
- Describe the laboratory testing for the diagnosis of disseminated intravascular coagulation
Case 1

- 23 year old female with pancreatitis due to hypertriglyceridemia. Now with renal failure on dialysis. Developed clots in IV lines.
- Put on heparin but continued to clot. Heparin resistant?
- Switched to argatroban
- Elevated PT, PTT and thrombin time which continued despite stopping argatroban.
- Worried about starting coumadin with prolonged clotting studies but also worried about clotting.
Coagulation parameters

- First week PTT ran in 26-32 sec. range
- Antithrombin 60% (nl 83-118%)
- PT/INR – 29 sec/3.0, Mix PT 19 sec.
- PTT 71 sec. Mix PTT 50 sec.
- Thrombin time >150 sec.
- Fibrinogen 309 mg/dL
Topics of interest

- Monitoring heparin
- Use of antithrombin testing
- Monitoring argatroban
Heparin-Antithrombin System
Monitoring heparin

- Heparin level for patients with deep venous thrombosis should be 0.3-0.7 U/mL.
- Our Hemostasis/Thrombosis laboratory selects a reagent which has an appropriate sensitivity to heparin (1.5 to 2.5 times the mean of the reference range).
- To determine heparin sensitivity a lab can simultaneously measure PTT and the heparin concentrations or a lab can use comparisons with existing validated PTT reagent.
### Cumulative Summation of Reagent Mean Differences

<table>
<thead>
<tr>
<th>#</th>
<th>Mean old lot</th>
<th>Mean new lot</th>
<th>Diff. New-old</th>
<th>Cum sum</th>
<th>action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(2001)</td>
<td>76.6</td>
<td>73.9</td>
<td>-4.7</td>
<td>-4.7</td>
<td>Accept</td>
</tr>
<tr>
<td>2a (2002)</td>
<td>48.3</td>
<td>41.7</td>
<td>-6.6</td>
<td>-11.3</td>
<td>Reject</td>
</tr>
<tr>
<td>2b (2002)</td>
<td>47.6</td>
<td>53.6</td>
<td>+6.0</td>
<td>+1.3</td>
<td>Accept</td>
</tr>
<tr>
<td>3 (2003)</td>
<td>71.9</td>
<td>72.3</td>
<td>+0.4</td>
<td>+1.7</td>
<td>Accept</td>
</tr>
<tr>
<td>4a (2004)</td>
<td>62.0</td>
<td>71.2</td>
<td>+9.2</td>
<td>+10.9</td>
<td>Reject</td>
</tr>
</tbody>
</table>
Confusion in test names

- Anti Xa activity – heparin level
- Chromogenic X – often used in monitoring warfarin anticoagulation in patients with lupus anticoagulant
- Factor X level - measured by clot detection, determination of factor X deficiency
- Often mis-ordered by the clinicians!
Heparin level
Chromogenic X

1. Factor X in plasma
2. Reagent RVV
3. Active Xa
4. Chromogenic Xa substrate
5. Oligopeptide
6. Color for detection
**Interpretation of Test Result**

The diagram illustrates a reference curve for APTT (seconds) against Percent Factor Activity. The curve is defined by the equation:
\[ y = -8.1803 \ln(x) + 79.324 \]
with an R² value of 0.9964. The table provides dilution factors, % FVIII, and seconds for various dilutions:

<table>
<thead>
<tr>
<th>Reference Dilution</th>
<th>% FVIII</th>
<th>Seconds</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:10</td>
<td>92</td>
<td>41.4</td>
</tr>
<tr>
<td>1:20</td>
<td>46</td>
<td>48.1</td>
</tr>
<tr>
<td>1:40</td>
<td>23</td>
<td>53.8</td>
</tr>
<tr>
<td>1:80</td>
<td>11.5</td>
<td>60.5</td>
</tr>
<tr>
<td>1:160</td>
<td>5.7</td>
<td>65.7</td>
</tr>
<tr>
<td>1:320</td>
<td>2.9</td>
<td>71.0</td>
</tr>
<tr>
<td>1:640</td>
<td>1.4</td>
<td>76.2</td>
</tr>
</tbody>
</table>

**Example**

Patient value is determined by interpolating time, 50.1 seconds using a 1:10 dilution, from the reference curve to yield a FVIII activity of 38%. This indicates that the patient’s FVIII activity level is only 38% that of normal activity.
Argatroban

- Direct thrombin inhibitor
- Monitored similar to heparin
  - PTT prolonged 1.5-3 X normal
- Will cause prolongation of PT
- Protocol for changing over to coumadin
Transitioning to warfarin therapy

If argatroban dose is ≤2 mcg/kg/min
1. Stop argatroban when INR on combined argatroban and warfarin is >4
2. Repeat INR in 4-6 hours
3. If INR is <2, restart argatroban
4. Repeat procedure daily until INR ≥2 is achieved

If argatroban dose is >2 mcg/kg/min
1. Reduce argatroban dose to 2 mcg/kg/min
2. Repeat INR in 4-6 hours
3. Stop argatroban when INR on combined argatroban and warfarin is >4
4. Repeat INR in 4-6 hours
5. If INR is <2, restart argatroban
6. Repeat procedure daily until INR ≥2 is achieved
Heparin-Antithrombin System
Antithrombin Assay
Chromogenic Anti-Xa Method

Patient Plasma

- AT + Heparin
- Excess Factor Xa

Test

AT/Heparin/Factor Xa

Residual Factor Xa

Chromogenic Substrate

- pNA
- pNA

Amount of color released (para-nitroaniline[pNA]) is inversely proportional to the amount of Antithrombin
Causes of antithrombin deficiency

- Inherited
- Acquired
  - Nephrotic syndrome
  - Hepatic failure
  - DIC
  - Heparin administration
  - L-asparaginase therapy (chemotherapy)
Heparin resistance

- **Definition:** Use of >35,000U/24hrs with a sub-therapeutic PTT
- **Causes**
  - Antithrombin deficiency (rare)
  - Increased heparin binding proteins
  - Increased clearance
  - Increased factor VIII and fibrinogen levels
- **Not done in this case but measuring a heparin level is often helpful.**
Why did the coagulation parameters continue to be prolonged?

- Additional coagulation studies

  - Factor VII 10%
  - Factor VIII 43%
  - Factor V 72%
  - Factor X <5%
Vitamin K deficiency

- Hemorrhagic disease of the newborn
- Chronic illness
- Malnutrition
- Alcoholism
- Multiple abdominal surgeries
- Long-term parenteral nutrition
- Malabsorption
- Cholestatic disease
- Parenchymal liver disease
- Cystic fibrosis
- Inflammatory bowel disease
- Drugs - Antibiotics (cephalosporin), cholestyramines, warfarin, salicylates, anticonvulsants, and certain sulfa drugs) are some of the common causes of VK deficiency
- Massive transfusion
- Disseminated intravascular coagulation (DIC) - Severe
- Chronic kidney disease/hemodialysis\cite{15}
Outcome

- Patient given Vitamin K and coagulation parameters normalized
- Started on warfarin for a short period of time
- Kidney function normalized
- Was discharged from the hospital
Case history

- 59 year old male with end-stage liver disease due to hepatitis C and hepatorenal syndrome on dialysis.
- Recently taken off the liver transplant list due to development of heparin induced thrombocytopenia
- Admitted with hypotension
Pertinent laboratory studies

- PT/INR 44 sec/4.4
- PTT 49 sec
- Platelets 73 x 10⁹/L
- Chromogenic X 53%
- No fibrinogen was done
Changes in hemostasis in liver disease

A. Decreased clotting factor synthesis
B. Decreased levels of inhibitors of coagulation
C. Dysfibrinogenemia
D. Decreased platelet counts
   1. decreased thrombopoietin
   2. splenic sequestration of platelets
E. Increased levels of von Willebrand factors and Factor VIII due to endothelial cell activation
F. Elevated levels of tPA, PAI-1, nitric oxide and prostacyclin also due to endothelial cell activation
Causes of the hemostatic changes in patients with liver disease.

- Elevated levels of VWF (and factor VIII)
- Elevated levels of tPA, PAI-1, nitric oxide and prostacyclin

- Low levels of coagulation factors and inhibitors
- Low levels of plasminogen and inhibitors of fibrinolysis
- Decreased levels of ADAMTS13
- Dysfibrinogenemia
- Thrombocytopenia and platelet function defects

Lisman T, Porte R J Blood 2010;116:878-885
Hemostasis in Hepatic Failure and Renal Disease.

The concept of rebalanced hemostasis in patients with liver disease.

A

Healthy individual

B

Patient with liver disease

<table>
<thead>
<tr>
<th>Hemostatic changes promoting bleeding</th>
<th>Hemostatic changes promoting thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Thrombocytopenia</td>
<td>- Elevated levels of VWF</td>
</tr>
<tr>
<td>- Platelet function defects</td>
<td>- Decreased levels of ADAMTS-13</td>
</tr>
<tr>
<td>- Enhanced production of nitric oxide and prostacyclin</td>
<td></td>
</tr>
<tr>
<td>- Low levels of coagulation factors II, V, VII, IX, X, and XI</td>
<td></td>
</tr>
<tr>
<td>- Vitamin K deficiency</td>
<td>- Elevated levels of FVIII</td>
</tr>
<tr>
<td>- Dysfibrinogenemia</td>
<td>- Decreased levels of protein C, Protein S, antithrombin, α2-macroglobulin, and heparin cofactor II</td>
</tr>
<tr>
<td>- Low levels of α2-antiplasmin, factor XIII, and TAF</td>
<td></td>
</tr>
<tr>
<td>- Elevated IPA levels</td>
<td>- Low levels of plasminogen</td>
</tr>
</tbody>
</table>

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Laboratory abnormalities in liver disease

- Increased PT, PTT
- Increased D-dimers and FDP’s
- Decreased fibrinogen level
- Increased factor VIII level
- Decreased platelet count
- Treatment – fresh frozen plasma but don’t just treat the numbers
Acquired dysfibrinogenemia

- Liver disease
  - Abnormal increase in the number of sialic acid residues that impair fibrin monomer polymerization.
- Paraproteins
  - Interference with polymerization
- Hydroxyethyl starch and dextran
Liver disease

- Patients who bleed often have an anatomic reason – ulcer, esophageal varices
- Treat with fresh frozen plasma but need to avoid volume overload
- Should not just treat numbers
Thrombelastograph® (TEG®) Hemostasis Analyzer
A diagram showing a torsion wire connected to a cup containing a heating element, sensor, and controller. The cup holds 0.36 ml of whole blood (clotted). The angle is marked as 4°45'.
TEG Tracing

Coagulation

Clot kinetics

Fibrinolysis

Clotting time

Platelets (MA)

Clot stability Clot breakdown

Platelet function Clot strength (G)

Enzymatic (R)

Fibrinogen (K, \(\alpha\))

Thrombolysins (Ly30, EPL)

Time (min)

Amplitude (mm)
“Normal” TEG® Tracing

30 min
Teg on our patient

- R 9.2 mins. (5-10 mins.)
- K 2.2 mins. (1.0-3.0 mins)
- Angle 60.6 degrees (53-72 degrees)
- MA 48.4 MM (50-70 MM)
- LY30 2.6% (0-8%)
Outcome

- Patient had multiple hospitalizations for exacerbation of hypotension. Treated when possible with dialysis
- Hospice called in and patient died soon afterwards.
Case history

- 30 year old female with newly diagnosed Diffuse Large B cell Lymphoma treated with chemotherapy
- Developed a GI bleed
- Developed skin changes on her flank thought to be necrotizing fasciitis
- Underwent extensive debridement
Pertinent Lab Studies

- PT/INR 16 secs./1.6
- Fibrinogen 50 mg/dL
- Fibrin degradation products >80
- Platelet count 65,000/µL
- Hemoglobin in the 6-8 g/dL
- No schistocytes were ever reported on review of the peripheral blood smear
Causes of Bleeding among Patients in the ICU.

Disseminated Intravascular Coagulation

- Intravascular thrombin formation
- Deposition of fibrin in the microvasculature
- Thrombosis of vessels
- Inhibitors consumed (AT, Protein C and S) but fail to control the process
- Fibrinolysis initiated, fails to remove all the fibrin
- Platelet consumption
Disseminated Intravascular Coagulation

Systemic activation of coagulation

- Intravascular deposition of fibrin
- Depletion of plts. and coag. factors

- Thrombosis of vessels
- And organ failure
- Bleeding
Pathogenesis of Disseminated Intravascular Coagulation in Sepsis.

Causes of DIC

- Sepsis
- Trauma
  - Serious tissue injury, head injury
- Cancer
  - Acute myeloid leukemia, solid tumors
- Obstetrical complications
- Vascular disorders
- Toxins
  - Snake venom, drugs
- Immunologic disorders
Laboratory Abnormalities in DIC

- Increased PT, PTT, thrombin time – consumption
- Decreased fibrinogen
- Increased FDPs and D- dimer
- Decreased platelet count
- Fragmented red blood cells on peripheral blood smear
### Table 2. Diagnostic Scoring System for Disseminated Intravascular Coagulation (DIC). *

<table>
<thead>
<tr>
<th>Risk assessment: Does the patient have an underlying disorder known to be associated with overt DIC?</th>
</tr>
</thead>
<tbody>
<tr>
<td>If yes, proceed with this algorithm</td>
</tr>
<tr>
<td>If no, do not use this algorithm</td>
</tr>
</tbody>
</table>

Order global coagulation tests (prothrombin time, platelet count, fibrinogen, fibrin-related marker)

Score the test results as follows:
- Platelet count: 50,000 to 100,000 per mm$^3$, 1 point; <50,000 per mm$^3$, 2 points
- Elevated fibrin-related marker (e.g., D-dimer, fibrin degradation products): no increase, 0 points; moderate increase, 2 points; strong increase, 3 points
- Prolonged prothrombin time: <3 sec, 0 points; ≥3 sec but <6 sec, 1 point; ≥6 sec, 2 points
- Fibrinogen level: ≥1 g per liter, 0 points; <1 g per liter, 1 point

Calculate the score as follows:
- ≥5 points: compatible with overt DIC; repeat scoring daily
- <5 points: suggestive of nonovert DIC; repeat scoring within next 1 to 2 days

* Data are adapted from Toh and Hoots$^{21}$ on the basis of the scoring system developed by the International Society on Thrombosis and Hemostasis.

Schistocytes
Treatment of DIC

- Treat the underlying disorder
- Blood product replacement in patients who are bleeding
Fibrinolysis – LY30

Secondary fibrinolysis
(LY30 > 7.5%, CI > 3.0)

Primary fibrinolysis
(LY30 > 7.5%, CI < 1.0)

Normal
Outcome

- Patient was taken to the operating room several times for debridement but developed multi-organ failure and died.