**COAGULOPATHY IN LIVER DISEASE**

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Faculty discussant Siobhan Keel

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**Case presentation**

62 year-old gentleman with a history of liver transplant in 2004 and recurrent hepatitis C with moderate grade fibrosis presented with worsening hepatic encephalopathy, jaundice, and ascites.

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**Laboratory abnormalities**

<table>
<thead>
<tr>
<th>Test</th>
<th>February 2009</th>
<th>March 2013</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST</td>
<td>67</td>
<td>120</td>
<td>15-40</td>
</tr>
<tr>
<td>ALT</td>
<td>69</td>
<td>57</td>
<td>10-48</td>
</tr>
<tr>
<td>ALP</td>
<td>142</td>
<td>316</td>
<td>25-99</td>
</tr>
<tr>
<td>T4</td>
<td>0.7</td>
<td>3.4</td>
<td>3.5-3.5</td>
</tr>
<tr>
<td>A2H</td>
<td>3.5</td>
<td>1.9</td>
<td>3.5-3.5</td>
</tr>
<tr>
<td>TP</td>
<td>6.9</td>
<td>6.4</td>
<td>6.0-8.2</td>
</tr>
<tr>
<td>INR</td>
<td>1.1</td>
<td>1.7</td>
<td>0.6-1.3</td>
</tr>
<tr>
<td>PTT</td>
<td>28</td>
<td>54</td>
<td>22-35</td>
</tr>
<tr>
<td>WBC</td>
<td>7.6</td>
<td>7.8</td>
<td>4.3-10</td>
</tr>
<tr>
<td>HCT</td>
<td>36</td>
<td>30</td>
<td>38-50</td>
</tr>
<tr>
<td>MCV</td>
<td>100</td>
<td>97</td>
<td>81-98</td>
</tr>
<tr>
<td>PLT</td>
<td>238</td>
<td>156</td>
<td>150-400</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.1</td>
<td>1.5</td>
<td>0.2-1.1</td>
</tr>
</tbody>
</table>

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**Imaging findings**

CT revealed hepatic vein thrombosis associated with two liver masses measuring a 7.1 cm and 4.9 cm.

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**Budd-Chiari syndrome**

- Budd-Chiari is defined as hepatic venous outflow obstruction at the level of the hepatic veins, the inferior vena cava, or the right atrium.
- Obstruction of the hepatic venous outflow leads to increased hepatic sinusoidal pressure and portal hypertension.
- The ensuing venous stasis and congestion causes hypoxic injury to adjacent hepatocytes.

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**Causes of Budd-Chiari Syndrome**

**Common causes**

- Acquired hypercoagulable states
  - Myeloproliferative disorders
  - Paroxysmal nocturnal hemoglobinuria
  - Antiphospholipid syndrome
  - Cancer
  - Pregnancy
  - Oral contraceptives
- Inherited hypercoagulable states
  - Antithrombin III deficiency
  - Protein C deficiency
  - Protein S deficiency
  - Factor V Leiden mutation
  - Prothrombin mutation

**Uncommon causes**

- Tumoral invasion
- Hepatocellular carcinoma
- Renal-cell carcinoma
- Adrenal carcinoma
- Miscellaneous
- Aspergillosis
- Behcet’s syndrome
- Inferior vena caval webs
- Trauma
- Inflammatory bowel disease
- Dacarbazine therapy
Additional laboratory testing
- JAK2 V617F mutation analysis negative
- Alpha-fetoprotein level 23.2 (normal 0-8.5)

Treatment

VTE is increased in liver disease
In a Danish case-control study, the relative risk of DVT or PE in patients with liver disease was compared to population controls.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Provoked DVT or PE</th>
<th>Unprovoked DVT or PE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative risk</td>
<td>95% CI</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>1.87</td>
<td>1.73 - 2.03</td>
</tr>
<tr>
<td>Non-cirrhotic liver disease</td>
<td>1.74</td>
<td>1.54 - 1.95</td>
</tr>
</tbody>
</table>

n = 95,644 patients with DVT or PE and 496,872 age and sex matched controls.
Unprovoked was defined as no recent diagnosis of cancer, fracture, trauma, surgery, or pregnancy.


High INR is not protective of VTE
In a retrospective study, 190 adult patients admitted to a university hospital with a primary diagnosis of chronic liver disease were evaluated for the development of VTE during their hospital stay.

Our standard measures of anticoagulation are not be reliable in liver disease.
INR does not correlate with bleeding

- Liver bleeding time was measured under direct laprospic visualization in 200 patients following percutaneous liver biopsy.
- There was no correlation between the liver bleeding time and INR, platelet count, whole blood clot time, length of biopsy core, or liver histopathology.


INR does not correlate with bleeding

- Normal hemostasis is a balance of the procoagulant and anticoagulant system.
- The INR and PTT measure in-vitro thrombin generation but do not take into account in-vivo thrombin inhibition.

Clotting and bleeding in patients with liver disease may be due to an imbalance in the procoagulant and anticoagulant systems.
**Coagulation**

**Decreased** II, V, VII, IX, X, and XI
- Vitamin K deficiency

**Increased** VIII
- Decreased protein C and S, antithrombin, and heparin cofactor II

**Bleeding**
- Liver Disease

**Fibrinolysis**

**Decreased** α2-antiplasmin and TAFI

**Increased** t-PA

**Decreased** plasminogen

**Bleeding**
- Liver Disease

**Liver Disease**

NEJM 2011;365(2):147-156.

**Other causes of bleeding in liver disease**

- Other factors which contribute to bleeding tendency in cirrhosis:
  - Portal hypertension
  - Endothelial dysfunction
  - Bacterial infections causing increased production of heparin-like substances
  - Renal failure (uremic platelets)

**Case presentation continued**

- The day after the patient was discharged, his INR had increased from 2.4 to 3.3 with a single dose of warfarin 1 mg. His primary care physician discontinues the warfarin.

- A week later, his encephalopathy and jaundice worsens and his family brings him back to the hospital.

**Laboratory abnormalities**

<table>
<thead>
<tr>
<th>Test</th>
<th>March 16</th>
<th>April 2</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST</td>
<td>120</td>
<td>110</td>
<td>15-40</td>
</tr>
<tr>
<td>ALT</td>
<td>57</td>
<td>44</td>
<td>10-48</td>
</tr>
<tr>
<td>ALP</td>
<td>216</td>
<td>167</td>
<td>37-59</td>
</tr>
<tr>
<td>TB</td>
<td>3.4</td>
<td>20</td>
<td>3.5-3.5</td>
</tr>
<tr>
<td>Alb</td>
<td>1.9</td>
<td>2.4</td>
<td>3.5-3.5</td>
</tr>
<tr>
<td>TP</td>
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<td>0.8-1.3</td>
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<tr>
<td>PTT</td>
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<td>52</td>
<td>22-33</td>
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<td>245</td>
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<tr>
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<td>1.5</td>
<td>1.9</td>
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</tr>
</tbody>
</table>

**Imaging findings**

- Abdominal ultrasound showed persistent hepatic vein thrombosis as well as mild interval increase in liver masses.
Additional laboratory tests

<table>
<thead>
<tr>
<th>Lab</th>
<th>Result</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT 1:1 Mix</td>
<td>15.2</td>
<td>(11-16)</td>
</tr>
<tr>
<td>PTT 1:1 Mix</td>
<td>35</td>
<td>(22-35)</td>
</tr>
<tr>
<td>Thrombin time</td>
<td>22</td>
<td>(18-26)</td>
</tr>
<tr>
<td>Factor V assay</td>
<td>31</td>
<td>(50-150)</td>
</tr>
<tr>
<td>Factor VII assay</td>
<td>12</td>
<td>(50-150)</td>
</tr>
<tr>
<td>Factor VIII assay</td>
<td>383</td>
<td>(50-234)</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>192</td>
<td>(150-400)</td>
</tr>
<tr>
<td>D-dimer</td>
<td>3.1</td>
<td>(0-0.6)</td>
</tr>
</tbody>
</table>

Liver biopsy

- Heparin drip was recommended monitored by anti-Xa with a goal anti-Xa level < 0.3 units/ml (usual therapeutic range 0.3-0.7 units/ml).
- Interventional radiology requested INR to be ≤ 2.0 for a percutaneous biopsy of the liver masses.
- The patient was given vitamin K 5 mg IV daily X 3 doses which improved his INR from 4.1 to 2.3.
- Two units FFP before and 2 units FFP during liver biopsy was recommended. After the first 2 units of FFP, his INR corrected to 2.0.

The complication

- Following the uneventful biopsy, the heparin drip was restarted 4 hours later at the pre-procedural rate.
- Twelve hours after the biopsy, the patient became hypotensive and was found to have a HCT drop from 25 to 16%. Anti-Xa level was 0.2, INR 2.1, and PTT 54.
- Heparin drip was stopped and the patient was transfused 4 units of PRBC and 2 units of FFP. dDAVP recommended.

The results

- The biopsy showed DLBCL.
- The patient’s family declined further aggressive care and the patient was treated with comfort measures only and died peacefully the following day.

FFP to correct coagulopathy

- The use of FFP and rFVIIa to reduce bleeding in patients with liver disease is not well supported.
FFP rarely corrects INR to normal

- In a prospective trial of 121 patients receiving FFP for mild coagulopathy (INR 1.1-1.85), the pre- and post-transfusion INR was compared.
- Transfusion of FFP resulted in normalization of INR (<1.1) in 0.8% of patients and decreased the INR halfway to normal in 15% of patients.
- Median decrease in INR was 0.07.

Transfusion 2006;46:1279-1285.

The effect of FFP on blood loss

RBC loss = (Hctpre-FFP transfusion – Hctpost-FFP transfusion)/3 + number of units of RBCs transfused

Recombinant activated human factor VII (rFVIIa)

- Produced by transfection of the human factor VII gene into cultured hamster cells.
- FDA approved indications:
  - Treatment of patients with hemophilia A or B who have inhibitors to factors VIII or IX
  - Treatment of patients with acquired hemophilia
  - Treatment of patients with congenital factor VII deficiency
- A single dose costs $4,500

rFVIIa does not control variceal bleeding

- In a placebo controlled trial of 265 patients with Child-Pugh B or C cirrhosis with active variceal bleeding, patients were randomized to placebo, rFVIIa 300 µg/kg, or rFVIIa 600 µg/kg in addition to standard treatment.
- There was no significant difference in the primary endpoint defined as failure to control acute bleeding within 24 hours, failure to prevent clinically significant rebleeding, or death within 5 days.
- The number number of adverse events was similar across all groups.

Summary

- The notion that cirrhotic are “autoanticoagulated” is not true and may in fact be at a higher risk for thrombosis.

- Conventional clotting assays do not accurately assess bleeding risk in patients with liver disease.

- The use of FFP and rFVIIa to reduce bleeding in patients with liver disease is not well supported.