Hematology Consultation on Bleeding of Indeterminate Cause in Hospitalized Patients

NCOA & SCOS Joint Membership Conference
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The Ballantyne, Charlotte, NC
Jenny Petkova, MD
Disclosures

• I do intend to discuss an off-label use of a product during this activity.

• I have not had any relevant financial relations during the past 12 months to disclose.
Bleeding of Undetermined Cause

• Unequivocal bleeds in whom all current diagnostic tests are repeatedly within normal ranges, precluding diagnosis of any known hematologic disorder.

• Patients with unexpected bleeding.
Presentation Focus

Patients with no prior bleeding history who present with unrelenting bleeding, unusual sites of bleeding, or life-threatening hemorrhage.
Case Presentation 1

• 85-year-old man presents with bleeding after removal of basocellular carcinoma from his left eyelid.

• He also has extensive bruising, encompassing palmar and dorsal aspects of both hands and spreading to forearms.

• No aches in joints or muscles.
Case Presentation 1 (cont)

• His medical history includes prostate carcinoma with metastases to bone; glaucoma, hypertension

• Surgical history - hernia repair, appendectomy

• Medications - goselerin, amlodipine
Lab Results

- Normal CBC
- Normal kidney and liver function
- Normal PT and INR
- aPTT of 92 sec (ref <35 sec)
- 1:1 mixing assay corrected partially to aPTT 55 sec, however, time-delayed 1:1 mix failed to correct aPTT
- FVIII <1 %
- Bethesda assay >100 BU
Acquired Hemophilia A (Acquired Inhibitor to FVIII)

- Incidence 1 in 1,000,000
- Median age at presentation 60-67 years
- Mucocutaneous bleeding pattern
  - Gastrointestinal bleeding
  - Hematuria
  - Ecchymosis
  - Intramuscular hematomas
  - Postsurgical bleeding
  - Intracranial hemorrhage
Associated Conditions

• 50 % are idiopathic
• The other 50%:
  – Autoimmune disorders – systemic lupus erythematosus, rheumatoid arthritis, Sjogren’s syndrome
  – Malignancies – lymphoproliferative disorders, solid tumors
  – Drugs – antibiotics, immunomodulatory agents, psychiatric drugs
  – Postpartum and postsurgical state

Diagnosis

• Screening tests – prolonged aPTT, normal PT
• Mixing study (repeating a PTT after mixing the patient’s plasma with normal plasma in 1:1 ratio)
  – Fails to fully correct
  – Prolongs after incubation (1-2 hours at 37°C)
• Factor VIII is low
• Other factor assays may have inhibitory pattern
• Bethesda assay
Management

• Goals
  – Treat the bleeding
    • Increase FVIII levels
    • Use bypassing agent to achieve hemostasis
  – Eradicate the inhibitor
Increasing FVIII Levels

• Desmopressin
  – For weak inhibitors (<3BU)
  – Minor bleeding

• Factor VIII concentrates
  – If the inhibitor is <5 BU
  – B domain-deleted recombinant FVIII

• Bypassing agents if inhibitor > 5 BU
Bypassing Agents

- Recombinant activated factor VII (rFVIIa)
  - FDA-approved for this indication
  - 70-90 mcg/kg every 2-3 hours until hemostasis is achieved
  - Risk of thrombosis

- Activated prothrombin complex concentrate (aPCC)
  - Off label use
  - 50-100 units/kg every 8-12 hours until bleeding is controlled
  - Doses >200 units/kg/day increase the risk for disseminated intravascular coagulation or thrombosis

NovoSeven RT [prescribing information]. Bagsvaerd, Denmark: Novo Nordisk; December 2012;
FEIBA [prescribing information]. Deerfield Park, IL: Baxter International Inc; May 2012
Inhibitor Eradication

• Prednisone
  – 1mg/kg daily
  – leads to eradication in 32% of the patients

• Adding cyclophosphamide
  – 50-100 mg/day by mouth
  – increases the response to 60-70%
  – Most patients respond within 3-6 weeks

• Rituximab
  – 375 mg/m² weekly x 4
  – In combination with prednisone if inhibitor 5-30 BU
  – With prednisone and cyclophosphamide if inhibitor >30 BU

Franchini M. Crit Rev Oncol Hematol 2007
Case Presentation 2

• A 62-year-old man is transferred from an outside institution for uncontrolled bleeding after cholecystectomy.
• He has developed perihepatic hematoma and has required 5 units of red blood cells over the two days before transfer.
• He denies any bruising, but has had recurrent nose bleeds in the weeks preceding his surgery.
Case Presentation 2 (cont)

- His past medical history includes CAD, hypercholesterolemia, MGUS and hypothyroidism.
- He reports significant bleeding after dental extraction 2 years ago, but has had uneventful hernia repair 8 years prior.
- He denies any new medications.
Case Presentation 2 (cont)

- aPTT is prolonged at 57 sec, PT is WNL
- Mixing studies corrected the aPTT to 28 sec
- von Willebrand antigen is 8%, activity <4%
- Factor VIII level is 12%
- 12 hours after receiving Humate P his VWF:Ag is 13%, VWF:Rco – 6%
- VWF propetide antigen 217 IU/dL
Acquired Von Willebrand Disease

• Associated with a number of different diseases:
  – Malignancies - plasma cell dyscrasias, lymphomas, myeloproliferative neoplasms, CML, Willms tumor
  – Immunologic disorders – systemic lupus erythematosus
  – States of high vascular flow - ventricular septal defect, aortic stenosis, ventricular assist device
  – Others – hypothyroidism, gastrointestinal angiodyplasia, uremia
  – Drugs - valproic acid, hydroxyethyl starch, griseofulvin, ciprofloxacin

Acquired Von Willebrand Disease

• Caused by several different pathophysiologic mechanisms:
  – Antibodies – inhibitory or causing increased clearance
  – Nonimmune mechanisms
    • Adsorption of VWF onto cells (Wilms' tumor, multiple myeloma and Waldenstrom macroglobulinemia, MPN’s)
    • Proteolysis of VWF (accelerated fibrinolysis in decompensated cirrhosis, pancreatitis, and disseminated intravascular coagulation)
    • High intravascular shear forces (ventricular septal defect, aortic stenosis, ventricular assist devices)
    • Reduced VWF synthesis (hypothyroidism)
Therapy

• Goals:
  – control acute bleeds
    • desmopressin
    • plasma-derived concentrates containing VWF
    • recombinant factor VIIa
    • antifibrinolytics
    • IVIG
    • plasmapheresis
  – obtain long-term remission
    • treat the underlying disorder

Case Presentation 3

• A 52 y/o female patient is admitted for hematemesis.
• She has a history of end stage liver disease due to HASH
• Three weeks prior to the admission she was diagnosed with lower extremity deep vein thrombosis at an outside institution and is currently on oral anticoagulation.
• At the time of the admission her INR is 11.
Case Presentation 3 (cont)

• The patent relates that when she was first diagnosed with DVT she was first treated with IV heparin followed by warfarin.

• Two days after discharge she was found to have INR of 7.

• Warfarin was discontinued and she was started on rivaroxaban on the following day.
Case Presentation 3 (cont)

• On review of her records her baseline INR prior to anticoagulation was 1.8-2.
• Her renal function has been normal.
• Her medications are combivent, bumetanide, lactulose, nadolol, spironolactone and omeprazole.
Goals of Care

- Reversal of anticoagulation
- Recommendations for future anticoagulation
# Novel Oral Anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T max</strong></td>
<td>1.5-3 hrs</td>
<td>2-4 hrs</td>
<td>1-3 hrs</td>
</tr>
<tr>
<td><strong>Half life</strong></td>
<td>12-14 hrs</td>
<td>9-13 hrs</td>
<td>8-15 hrs</td>
</tr>
<tr>
<td><strong>Renal excretion</strong></td>
<td>80%</td>
<td>33%</td>
<td>25%</td>
</tr>
<tr>
<td><strong>FDA approval</strong></td>
<td>Atrial fibrillation</td>
<td>Atrial fibrillation, VTE prophylaxis, VTE therapy</td>
<td>Atrial fibrillation</td>
</tr>
</tbody>
</table>
Stroke Prevention in Atrial Fibrillation

Bleeding Risk

Major bleeding

Intracranial bleeding

Gastrointestinal bleeding

Relative Risk for Recurrent Venothromboembolism

<table>
<thead>
<tr>
<th>Study</th>
<th>Events/total</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Novel oral anticoagulants</td>
<td>Vitamin K antagonists</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td></td>
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<tr>
<td>EINSTEIN-DVT</td>
<td>36/1731</td>
<td>51/1718</td>
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<tr>
<td>EINSTEIN-PE</td>
<td>50/2419</td>
<td>44/2413</td>
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<td>EINSTEIN-DOSE</td>
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<td>7/101</td>
</tr>
<tr>
<td>OXIda</td>
<td>2/100</td>
<td>1/112</td>
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<tr>
<td>Random effects model</td>
<td>91/4365</td>
<td>103/4344</td>
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<tr>
<td></td>
<td>Heterogeneity $I^2=38%$, $P=0.185$</td>
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<tr>
<td>Apixaban</td>
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<tr>
<td>Botticelli-DVT</td>
<td>3/130</td>
<td>3/128</td>
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<tr>
<td>Random effects model</td>
<td>3/130</td>
<td>3/128</td>
</tr>
<tr>
<td></td>
<td>Heterogeneity $I^2=NA$, $P=1$</td>
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<tr>
<td>Dabigatran</td>
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<tr>
<td>RECOVER</td>
<td>30/1274</td>
<td>27/1265</td>
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<tr>
<td>RECOVER II</td>
<td>30/1279</td>
<td>28/1289</td>
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<td>Random effects model</td>
<td>60/2553</td>
<td>55/2554</td>
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<tr>
<td></td>
<td>Heterogeneity $I^2=0%$, $P=0.954$</td>
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<td>Ximelagatran</td>
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<tr>
<td>THRIVE II/V</td>
<td>26/1240</td>
<td>24/1249</td>
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<td>THRIVE I</td>
<td>1/65</td>
<td>2/73</td>
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<tr>
<td>Random effects model</td>
<td>27/1305</td>
<td>26/1322</td>
</tr>
<tr>
<td></td>
<td>Heterogeneity $I^2=0%$, $P=0.594$</td>
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</tbody>
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Fox B D et al. BMJ 2012;345:bmj.e7498
**Relative Risk for Major Bleeding**

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<tr>
<td><strong>Rivaroxaban</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>EINSTEIN-DVT¹³</td>
<td>14/1718</td>
<td>20/1711</td>
<td>0.70 (0.35 to 1.38)</td>
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<tr>
<td>EINSTEIN-PE¹⁴</td>
<td>26/2412</td>
<td>52/2405</td>
<td>0.50 (0.31 to 0.80)</td>
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<tr>
<td>EINSTEIN-DOSE¹¹</td>
<td>1/135</td>
<td>2/137</td>
<td>0.51 (0.05 to 5.53)</td>
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</tr>
<tr>
<td>OXIDa¹²</td>
<td>2/117</td>
<td>0/126</td>
<td>5.38 (0.26 to 110.96)</td>
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<td>Random effects model</td>
<td>43/4382</td>
<td>74/4379</td>
<td>0.57 (0.39 to 0.84)</td>
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<tr>
<td>Heterogeneity</td>
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<td></td>
<td>I²=0%, P=0.426</td>
<td></td>
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<tr>
<td><strong>Apixaban</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Botticelli-DVT¹⁵</td>
<td>1/128</td>
<td>0/126</td>
<td>2.95 (0.12 to 71.82)</td>
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<tr>
<td>Random effects model</td>
<td>1/128</td>
<td>0/126</td>
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<tr>
<td>Heterogeneity</td>
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<td></td>
<td>I²=NA, P=1</td>
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<tr>
<td><strong>Dabigatran</strong></td>
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<tr>
<td>RECOVER I¹⁶</td>
<td>20/1274</td>
<td>24/1265</td>
<td>0.83 (0.46 to 1.49)</td>
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<tr>
<td>RECOVER II¹⁷</td>
<td>15/1279</td>
<td>22/1289</td>
<td>0.69 (0.36 to 1.32)</td>
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<tr>
<td>Random effects model</td>
<td>35/2553</td>
<td>46/2554</td>
<td>0.76 (0.49 to 1.18)</td>
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<td>THRIVE II/V¹⁹</td>
<td>14/1240</td>
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<td>0.54 (0.28 to 1.03)</td>
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<tr>
<td>THRIVE I¹⁸</td>
<td>0/62</td>
<td>0/73</td>
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<td>I²=NA, P=1</td>
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When NOT to use New Oral Anticoagulants

- Renal impairment (Cr Cl<30)
- Liver disease
- Increased bleeding risk
- Extremes of body weight
- Cancer-associated thrombosis
- Patient preference (no known reversal agents)
- Insurance carrier
- Drug interactions – HAART, antifungals, anticonvulsants, St. John’s wart.
## Monitoring

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<tr>
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<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT (INR)</td>
<td>- ↑</td>
<td>- ↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>aPTT</td>
<td>- ↑↑</td>
<td>- ↑</td>
<td>↑</td>
</tr>
<tr>
<td>Thrombin time</td>
<td>Very sensitive</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Ecarin time</td>
<td>Good, linear</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Anti-Xa activity</td>
<td>N/A</td>
<td>Good, linear</td>
<td>Good, linear</td>
</tr>
</tbody>
</table>

Hawes, E et al, JTH; ePup May 2013
Man, H et al, Thrombosis J 2013; 11;22
Francart S at al, Am J Hematology 2013
## Perioperative Management

<table>
<thead>
<tr>
<th>Renal function (CrCl mL/min)</th>
<th>Half life (hrs)</th>
<th>When to hold before surgery</th>
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<tr>
<td></td>
<td></td>
<td><strong>Standard bleeding risk</strong></td>
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<tr>
<td></td>
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<td><strong>High bleeding risk</strong></td>
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<tr>
<td>Dabigatran</td>
<td></td>
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<tr>
<td>&gt;80</td>
<td>13 (11-22)</td>
<td>24-36 hrs</td>
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<tr>
<td></td>
<td></td>
<td>2-3 days</td>
</tr>
<tr>
<td>50-80</td>
<td>15 (12-34)</td>
<td>1-2 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2-3 days</td>
</tr>
<tr>
<td>30-50</td>
<td>18 (13-23)</td>
<td>1.5-2 days</td>
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<tr>
<td></td>
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<td>3-4 days</td>
</tr>
<tr>
<td>&lt;30</td>
<td>27 (22-35)</td>
<td>2-3 days</td>
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<tr>
<td></td>
<td></td>
<td>4-5 days</td>
</tr>
<tr>
<td>Rivaroxaban</td>
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<td></td>
<td></td>
<td>2 days</td>
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<tr>
<td>&lt;30</td>
<td></td>
<td>2 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 days</td>
</tr>
</tbody>
</table>
Bleeding Management
Therapeutic Options

- Supportive care
- Activated charcoal
- Hemodialysis (for dabigatran only)
- Prothrombin complex concentrates (PCC)
- Activated PCC
- Recombinant factor VIIa
- FFP
- Anti-fibrinolytic drugs (aminocaproic acid, tranexamic acid)
Bleeding Suspected
Obtain baseline CBC, aPTT, PT, platelets, and fibrinogen

Patient taking APIXABAN AND aPTT ≥ 36 sec
Patient taking RIVAROXABAN AND PT ≥ 16 sec

Mild bleeding:
A drop in Hgb of < 2 gm/dL, OR
A decrease in HCT of < 10%

Administer blood products as needed; repeat CBC

Did patient respond?
Yes
Continue to monitor

No
Administer additional blood products as needed, consider
Factor IX Concentrate (Profilnine® SD) OR
Anti-Inhibitor Coagulant (FEIBA® NF)
25 units/kg

Moderate-to-Severe bleeding:
A drop in Hgb of 2 – < 5 gm/dL, OR
A decrease in HCT of 10-15%

Administer blood products as needed. (additional supportive care with fluids if needed)

Life-threatening bleeding:
A drop in Hgb of ≥ 5 gm/dL, OR
A decrease in HCT of >15%, OR
Urgent surgical intervention required, OR
Bleeding at a critical site*

Administer blood products as needed

Administer
Factor IX Concentrate (Profilnine® SD) OR
Anti-Inhibitor Coagulant (FEIBA® NF)
50 units/kg

Repeat doses require hematology consult
Thank you!