Managing the Bleeding Patient

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The Fritsma Factor, Your Interactive Hemostasis Resource
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Bleeding Patient Overview

- Managing trauma and massive transfusion
- Acquired multiple procoagulant deficiencies
- Von Willebrand disease
- Hemophilia: inherited single factor deficiency
- Coagulation factor inhibitors
- Disseminated intravascular coagulation

40 YO Af-Am Hemophilic

- Bleeding into ankle: midnight
  - Anatomic soft-tissue and joint bleeds
  - Tried RICE, DDAVP (Stimate®) inhaler
- Ran out of factor VIII (FVIII) concentrate
  - Provided free by Medicare through hemophilia center
  - National Hemophilia Foundation: www.hemophilia.org
- Clinical path resident on-call; night tech
  - Determine patient residual factor VIII activity
  - Order antihemophilic factor (AHF, FVIII) concentrate
    - Dispensed by transfusion service
  - Compute and prepare dosage
  - Reconstitute with sterile water, administer as IV push
  - Subsequently determine therapeutic factor VIII activity

Hemophilia

- Anatomic bleeding caused by congenital single-factor deficiencies
- 85% factor VIII deficiency (hemophilia A)
  - 1 in 10,000 male births
- 14% factor IX deficiency
  - Hemophilia B or Christmas disease
  - 1 in 30,000 male births
- 1% XI (autosomal, Rosenthal syndrome)
- Rare autosomal recessive single factor deficiencies
  - Prothrombin, V, VII, X, XIII

Factor VIII is a Glycoprotein Cofactor

- 285,000-D heterodimer
  - Translated from the X chromosome
- Cleaved by thrombin, leaving a Ca**+-dependent portion that detaches from VWF and binds factor IXa and phospholipid
- Stabilizes IXa in the “tenase” reaction
- Deficiency slows thrombin production
- In vitro, deteriorates 5%/hour at 18–24°C

Hemophilia A Inheritance

- Sex-linked recessive, 1/10,000 males
- Carrier mother, hemizygous son
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**Hemophilia A Genetics**
- 186 kb gene on X chromosome
  - Deletions, stop codons, missense and nonsense point mutations
  - 25–30% spontaneous mutation rate
  - Predominantly quantitative deficiency, a few qualitative

- Hemophilia A in females is rare
  - Acquired anti-factor VIII
  - Autosomal hemophilia or VWD type N (Normandy)
  - Random “excess Lyonization”
  - Hemophilic father with carrier mother

**Hemophilia A Symptoms**
- Spontaneous anatomic (soft-tissue) bleeds
  - Bleeding at umbilical stump, circumcision
  - Delayed bleeding following injury
    - Joints, muscles, body cavities, GI, soft tissue, tongue, kidney, testicles, CNS
  - Often spontaneous bleeds, especially joints
  - Inflammation, hematomas, hemarthroses

**Coagulation Pathway**
- Initiation: Exposed TF binds VIIa, activates IX→IXa and X→Xa
- Fibrinogen
- Fibrin polymer
- Crosslinked fibrin

**VIII/VWF-Platelets Interaction**
- PLT
- VWF binding site
  - GP Ia/IIa
  - CD 42a-d
  - SMC: Smooth muscle cell
  - FB: Fibroblast
  - Lines: Collagen

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**Other Complications**
- Lifestyle
- Economic
- Vocational
- Neurologic
- Psychological
- Lack of insurance
- Narcotics addiction

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Calculating AHF Dosage

- One unit of AHF = amount of activity in 1 mL normal plasma, = 100%
- Determine plasma volume based on weight
  - Blood volume (BV, mL) = weight (kg) x 70 mL/kg
  - Use 60 mL/kg for obese, BMI 25–30
  - Use 50 mL/kg for morbidly obese, BMI >30
  - Plasma volume (PV, mL) = BV x (100%−HCT%)
- Determine units of AHF required

Units of AHF required =
(desired AHF in units/mL - initial units/mL) x PV (mL)

40 YO Af-Am Hemophilic

- 80 kg, HCT 40%, factor level <1%
- Determine plasma volume
  - Blood volume (mL) = 80 kg x 70 mL/kg = 5600 mL
  - Plasma volume (mL) = blood volume (5600 mL) x (100%−40%) = 60% x 5600 = 3360 mL
- Determine units of factor required:
  - Wish to reach 80% factor level (0.8 U/mL), therefore...
  - Units of factor required = (0.8 U/mL − 0) x 3360 mL = 2688 (2700) U
  - Typical FVIII concentrate vial provides ~1000 U, use 3
- Avoid overdose: thrombotic and wasteful

If Factor Assay not Available

- When factor assay is not available and timing is critical, assume 0 activity or...
- Estimate factor VIII from PTT

<table>
<thead>
<tr>
<th>Factor VIII</th>
<th>PTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>40%</td>
<td>35 s</td>
</tr>
<tr>
<td>30%</td>
<td>50 s</td>
</tr>
<tr>
<td>20%</td>
<td>65 s</td>
</tr>
<tr>
<td>10%</td>
<td>90 s</td>
</tr>
<tr>
<td>1%</td>
<td>120 s</td>
</tr>
</tbody>
</table>

- Collect baseline plasma
  - Assay or freeze and confirm with assay next day shift
- Maintain patient database

Plasma-derived FVIII Concentrates

- Risk of HBV, HCV, HIV transmission
  - Human and animal plasma matrix
  - Hemofil-M®, Monarc-M®, Monoclate-P®
  - Purification: immunoaffinity column, solvent-detergent, Pasteurization, viral filtration, combinations
  - $0.35–0.60/AHF unit
- Seroconversions per CDC surveillance: 0
  - Predicted risk, 1:60,000

Recombinant FVIII Concentrates

- Serum in culture medium
  - Helixate®, Kogenate®, Recombinate®
  - $0.68–1.05/AHF unit: some select for only previously untreated patients (PUPs)
  - No HBV, HCV, HIV seroconversions
- No protein in culture or prep
  - Calculated viral risk=0, actual=0: Advate®
- B-domain-deleted FVIII concentrate
  - Human albumin: ReFacto®, Xyntha®
- Can’t assay using clot-based factor VIII assay, use chromogenic

Factor VIII Assay

- Dilute plasma 1:10, add factor VIII-depleted reagent plasma 1:1
- Add PTT reagent, incubate 3 minutes
- Add CaCl₂, record interval to clot formation
- Compare result in seconds to dilution curve

Factor VIII Assay Reference Curve
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**Factor VIII Assay Dilutions**

Parallelism Indicates No Inhibitor

<table>
<thead>
<tr>
<th>Plasma Dilution</th>
<th>Seconds</th>
<th>Raw Factor VIII Activity</th>
<th>Computed Factor VIII Activity (× dilution)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:10 “undiluted”</td>
<td>90 s</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>1:20</td>
<td>104 s</td>
<td>10%</td>
<td>20% (parallel)*</td>
</tr>
<tr>
<td>1:40</td>
<td>107 s</td>
<td>5%</td>
<td>20% (parallel)</td>
</tr>
<tr>
<td>1:80</td>
<td>110 s</td>
<td>2.5%</td>
<td>20% (parallel)</td>
</tr>
</tbody>
</table>

* >10% difference from undiluted indicates parallelism, no inhibitor

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**FVIII Assay Dilutions**

non-Parallelism Indicates Inhibitor

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<th>Raw Factor VIII Activity</th>
<th>Computed Factor VIII Activity (× dilution)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:10 (undiluted)</td>
<td>80 s</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>1:20</td>
<td>93 s</td>
<td>8%</td>
<td>16%</td>
</tr>
<tr>
<td>1:40</td>
<td>107 s</td>
<td>5%</td>
<td>20%</td>
</tr>
<tr>
<td>1:80</td>
<td>108 s</td>
<td>4%</td>
<td>32%</td>
</tr>
</tbody>
</table>

* >10% difference from undiluted, rising = non-parallel, implies inhibitor

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**FVIII Inhibitor Therapy**

- Plasma-derived factor IX complex
  - Activated prothrombin complex concentrate (PCC)
  - Prepared by BaSO₄ extraction
  - Available since 1980
  - FEIBA®, Autoplex ®
- FEIBA dosage
  - 50 units/kg/12 h standard
  - 70 units/kg/8 h in hemorrhage
  - Limit 200 units/kg/24 h to avoid DIC risk: fatal
  - Cannot monitor: only general evaluation with PTT
  - $0.78/unit, about $4300/dose for our 80 kg patient

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**Recombinant FVIIa Concentrate**

- Dose: 90 µg/kg
  - Repeat every 3–6 h
  - 6 h FVII half-life
  - $0.83/µg
  - For our 80-kg patient, one dose = $6000
- Cannot monitor
  - General evaluation using PTT
  - No risk of DIC

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**40 YO Af-Am**

FVIII Concentrate Therapy

- Peak: 15 m after administration: 0.3 units/mL
  - Should have been 0.8 units/mL, what happened?
  - Suspect anti-factor VIII inhibitor
  - If peak reaches expected value, go to next administration
- Nadir (trough): 12 h after administration
  - Reflects half-life, should reach 50% of desired activity
  - Administer new AHF, use half the dosage second time

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**40 YO Af-Am, FVIII Inhibitor**

- Inhibitor: alloantibody to FVIII inhibitor
  - 30% incidence
  - Dose and severity response: mostly severe hemophilia
- Factor VIII assay
  - If non-parallel, reflex to Bethesda titer
  - The "poor man's" Bethesda titer substitute
    - Dilute plasma 1:20 in normal plasma, perform PTT
    - If prolonged, presume >5 BU, treat as high-titer inhibitor
    - If normal, presume <5 BU, treat as low-titer inhibitor
- Rx with corticosteroids and FEIBA® or NovoSeven® (VIIa)
- If normal, presume <5 BU, treat as low-titer inhibitor
  - Rx with factor VIII concentrate
    - Confirm with full Bethesda titer

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Larry D. Brace, PhD, Edward Hospital, Naperville, Il
Patient Database

- Maintain a database of VWD and hemophilia patients, needs seldom vary
  - Factor level and inhibitor, if present
  - If HBV, HCV, HIV pos; use plasma-derived
- Product patient takes at home
- Monitor usage as factor concentrates tend to be overdosed at considerable expense

Disseminated Intravascular Coagulation (DIC)

- Generalized hemostasis activation
  - Generalized microthrombosis
  - Generalized hemorrhage
- Synonyms
  - Consumption coagulopathy
  - Defibrination syndrome
- Chronic or acute

35 YO Woman With Pancreatitis Admitted to NICU

- Two injuries at two instances resulted in pancreatitis
- Vascular non-malignant abdominal mass
- Admission for severe right-side headache
  - Subdural hematoma

Initial Laboratory Results

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>RI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGB</td>
<td>9.1 mg/dL</td>
<td>11.3–15.3 mg/dL</td>
</tr>
<tr>
<td>HCT</td>
<td>27%</td>
<td>33–45%</td>
</tr>
<tr>
<td>PLT</td>
<td>120,000/µL</td>
<td>150–450,000/µL</td>
</tr>
<tr>
<td>RBC</td>
<td>MOD schistocytes</td>
<td></td>
</tr>
<tr>
<td>PT</td>
<td>15.8 s</td>
<td>12.3–14.2 s</td>
</tr>
<tr>
<td>PTT</td>
<td>39 s</td>
<td>25–34 s</td>
</tr>
<tr>
<td>Fg</td>
<td>185 mg/dL</td>
<td>224–467 mg/dL</td>
</tr>
<tr>
<td>D-D</td>
<td>&gt;20,000 ng/mL</td>
<td>&lt;240 ng/mL</td>
</tr>
</tbody>
</table>

Fibrinolysis

- PT prolonged
  - Decreased VII, X, V, prothrombin
- PTT prolonged
  - Decreased XI, IX, VIII and common factors
- Both further prolonged by FDP interference
**Platelets and Fibrinogen**

- Platelet count <150,000/µL
  - Variable
  - May be normal but PLT function reduced by FDPs
- Fibrinogen <200 mg/dL
  - Acute phase reactant
  - Function reduced by FDPs
- Schistocytes
  - 70% of DIC cases

**35 YO Woman with DIC: HIT**

- UFH 400 U/h
- Plasma to replace factors
- Switched to Novastan® (argatroban)
  - Monitor with PTT results 1.5–2.5 x MRI

**Test** | **Result** | **RI**
--- | --- | ---
HCT | 24% | 33–45%
PLT | 82,700/µL | 150–450,000/µL
RBC | | |
PT | 17.6 s | 12.3–14.2 s
PTT | 43 s | 25–35 s
Fg | 96 mg/dL | 224–467 mg/dL
D-D | >20,000 ng/mL | <240 ng/mL

**35 YO Woman with DIC**

- Treat underlying cause
- Maintain hemodynamic stability and urine output to prevent acute tubular necrosis
- Replace fibrinogen with CRYO or FG concentrate
- No platelet concentrate
- Unfractionated heparin (sparingly) or...
  - Argatroban (Novastan®, 2000)
  - Hirudin (Lepirudin®, 1998, D/C 5/31/12)
- Monitor both with PTT
- Plasma or...
  - Antithrombin (Thrombate III®, 1988)
  - Activated protein C (Xigris®, 2001, D/C 2010)

**69-YO with Atrial Fibrillation**

- Bleeding in ED: What's he Got?

**Test** | **Result** | **RI**
--- | --- | ---
PT | 13.1 s | 8.3–10.8 s
INR | 1.3 | 0.9–1.2
PTT | 47 s | 25–35 s
TT | >200 s | 17–20 s
Reptilase time | 20 s | 16–22 s
PTT-LA | 77 s | 36–47 s
PTT-LA 1:1 Mix | 69 s | Control 45 s
StaClot | 7 s | >8 s
DRVVT confirm ratio | 1.3 | <1.2

**Dabigatran Risks: Meta-analysis**

- 256 Pradaxa-related deaths since 2009
- Two studies of stroke prophylaxis in AF
- Four studies in VTE
- One in acute coronary syndrome (ACS)

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<td>1.3</td>
<td>0.9–1.2</td>
</tr>
<tr>
<td>PTT</td>
<td>47 s</td>
<td>25–35 s</td>
</tr>
<tr>
<td>STA</td>
<td>&gt;200 s</td>
<td>17–20 s</td>
</tr>
<tr>
<td>RE-LY alone</td>
<td>OR 1.27, p=0.05*</td>
<td></td>
</tr>
</tbody>
</table>

*Significance not significant at P<0.01

**Monitoring DTIs Using Routine Assays**

- PT: flat response
- PTT: nonlinear @ >1 µg/mL
- TT: linear but too sensitive

**Two Cases of Rectal**

How to Monitor (All are RUO)

- Centerchem® Pefakit® Prothrombinase-induced clot time: direct anti-Xa and DTI
- BIOPHEN DiXal® chromogenic anti-Xa
- Stago chromogenic anti-Xa
  - Calibrators and controls
- Stago ecarin clotting and chromogenic assays: DTIs
- BIOPHEN thrombin inhibition assay: DTI
- Helena Cascade Abrazo DTM

Ecarin Clotting Time/Chromogenic

Stago Ecarin Chromogenic Assay®

Intensity at 405 nm is inversely proportional to DTI concentration.