The Hemophilias

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DISCLOSURES

Off-Label Usage

• None

Interests

• Baxter
• Bayer Healthcare
• CSL Behring
• Genentech
• Novo Nordisk
## Prevalence of Inherited Factor Deficiency States

<table>
<thead>
<tr>
<th>Factor</th>
<th>Prevalence</th>
<th>Inheritance</th>
<th>Chromosome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td>1:1 million</td>
<td>Autosomal recessive</td>
<td>4</td>
</tr>
<tr>
<td>Prothrombin</td>
<td>1:2 million</td>
<td>Autosomal recessive</td>
<td>11</td>
</tr>
<tr>
<td>Factor V</td>
<td>1:1 million</td>
<td>Autosomal recessive</td>
<td>1</td>
</tr>
<tr>
<td>Factor VII</td>
<td>1:500,000</td>
<td>Autosomal recessive</td>
<td>13</td>
</tr>
<tr>
<td>Factor VIII</td>
<td>1:10,000</td>
<td>X-linked recessive</td>
<td>X</td>
</tr>
<tr>
<td>Factor IX</td>
<td>1:60,000</td>
<td>X-linked recessive</td>
<td>X</td>
</tr>
<tr>
<td>Factor X</td>
<td>1:1 million</td>
<td>Autosomal recessive</td>
<td>13</td>
</tr>
<tr>
<td>Factor XI</td>
<td>1:1 million</td>
<td>Autosomal recessive</td>
<td>4</td>
</tr>
<tr>
<td>Factor XIII</td>
<td>1:1 million</td>
<td>Autosomal recessive (2 subunits)</td>
<td>6 and 1</td>
</tr>
</tbody>
</table>
Hemophilia: A Defect In The Thrombin Propagation Phase of Coagulation

FXI is Activated by Thrombin; FXIa Provides “Over-drive” Thrombin Production That Activates TAFI

FXI Deficiency

- Homozygotes = 0–20% FXI; heterozygotes = 20–70% FXI
- Ashkenazi Jews (8% heterozygous)
- Spontaneous bleeding (including hemarthrosis) rare
- Post-operative bleeding at sites of high endogenous fibrinolytic activity (mouth, urinary tract), even in heterozygotes
- Target FXI of 30-45% for surgery. Anti-fibrinolytics useful.
X-Linked Hemophilias

• Hemophilia A and B are essentially indistinguishable on clinical grounds
Differential Diagnosis of Hemophilia A

Mild, Moderate, or Severe Forms (FVIII level: 0-30%)

• Acquired hemophilia

Mild or Moderate Forms (FVIII level: >3%)

• Von Willebrand disease (types 2N, 3)

• Combined V and VIII deficiency
  → autosomal recessive
  → FV:c and FVIII:c in 5-30% range

• Artifact (poor sample handling)

(Not liver disease -- FVIII levels usually elevated)
Laboratory Diagnosis of Hemophilia

- Bleeding Time: Normal
- PT: Normal
- APTT: Prolonged
- FVIII:c (or FIX:c): <1% = severe
- 1-5% = moderate
- 5-30% = mild
- vWF:Ag: Normal
- vWF:Rco: Normal
## Hemophilia

**Bleeding as a Function of Clinical Severity**

<table>
<thead>
<tr>
<th>Concentration of Coagulation Factor (%)</th>
<th>Bleeding Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 -100</td>
<td>None</td>
</tr>
<tr>
<td>25 - 50</td>
<td>Bleeding after severe trauma</td>
</tr>
<tr>
<td>5 - 25</td>
<td>Bleeding after surgery or moderate trauma</td>
</tr>
<tr>
<td>1 - 5</td>
<td>Bleeding even after slight trauma</td>
</tr>
<tr>
<td>&lt;1</td>
<td>Spontaneous bleeding predominantly in joints and muscles</td>
</tr>
</tbody>
</table>
Hemarthrosis: Clinical Features (1)

- **Hemarthrosis**
  - beginning first year of life
  - knees & elbows > ankles > shoulders > hips
  - early sensation of stiffness, "bubbling", or other aura
  - "target joints" (repeated hemarthrosis): indicative of synovitis
Progression of Hemophilic Arthropathy

Early Joint Bleed

Late Joint Bleed

Synovitis

Arthritis
Progression of Hemophilic Arthropathy
End Stage Hemophilic Arthropathy

A

B
Figure 8. Tsarevich Alexis.

Nilsson IM;
“Haemophilia”
Hemophilia: Clinical Features (2)

- **Muscle Bleeds**
  - flexors > extensors (ilio-psoas, quads, gastrocnemius)
  - may require prolonged therapy to prevent re-bleed
  - pseudotumor risk if neglected
HEMOPHILIC PSEUDOTUMOR
Hemophilia: Clinical Features (3)

- **Muco-cutaneous Bleeding**
  - bruising: "abused child" presentation
  - epistaxis, frenulum bleeds
  - hematuria: fluids and bed-rest. NOT anti-fibrinolytics.
Hemophilia: Clinical Features (4)

- **Intra-cranial bleeding**
  → high index of suspicion in neonatal period, after minor head trauma, unusual headache or vomiting

- **Post-dental bleeding**
  → anti-fibrinolytics useful

- **Post-surgical bleeding**
  → May be delayed several days

**NOT** excessive bleeding after minor cuts or abrasions
History of Clotting Factor Concentrates

Subfraction I-0
- Late 1950s
- Plasma fractionation

Cryoprecipitates
- Mid 1960s
- Donor/plasma screening for HBV

Low purity pdFVIII concentrates
- Early 1970s
- Heat treatment of pdFVIII

Intermediate-purity concentrates
- Late 1970s
- Heat-treated concentrates widely available

High-purity concentrates
- Early 1980s
- Immunoaffinity, treating with solvent or detergent, ion exchange

rFVIII available
- Mid 1980s
- HIV/HCV screening

rFIX available
- Late 1980s
- Qualification of donors, inventory hold, nucleic acid testing, nanofiltration

Early 1990s
- Late 1990s

Early 2000s

Key NS & Negrier C. Lancet 2007;370(9585):439
Technologies Employed to Prolong Half Life of Clotting Factor Concentrates

• Pegylation
  - varying size of PEG molecule (20kDa, 40 kDa, 60kDa)
  - varying site of PEG attachment

• Conjugation
  - Albumin
  - Fc portion of immunoglobulin
Experience with Long Acting Clotting Factor Concentrates

- **FIX**
  - dramatic prolongation of half-life (up to 5-fold)

- **FVIII**
  - half-life prolongation ‘capped’ at 1.4-1.7 fold (limited by half-life of vWF)
# Factor VIII Concentrates

## Plasma-derived

<table>
<thead>
<tr>
<th>Intermediate Purity</th>
<th>High Purity</th>
<th>Ultrapure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humate-P</td>
<td>Koate-HP</td>
<td>Hemofil-M</td>
</tr>
<tr>
<td>Alphanate</td>
<td>Monoclate</td>
<td></td>
</tr>
<tr>
<td>Wilate</td>
<td>Monarc-M</td>
<td></td>
</tr>
</tbody>
</table>

## Recombinant

<table>
<thead>
<tr>
<th>Standard (1st/2nd/3rd Gen)</th>
<th>Long acting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recombinate</td>
<td>Eloctate (FVIII-Fc)</td>
</tr>
<tr>
<td>Kogenate</td>
<td></td>
</tr>
<tr>
<td>Helixate</td>
<td>Advate</td>
</tr>
<tr>
<td>Xyntha</td>
<td></td>
</tr>
</tbody>
</table>
## Factor IX Concentrates

<table>
<thead>
<tr>
<th>Plasma-derived</th>
<th>Recombinant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate</td>
<td>Standard</td>
</tr>
<tr>
<td>Profilnine</td>
<td>Benefix</td>
</tr>
<tr>
<td>Bebulin</td>
<td>Rixubis</td>
</tr>
<tr>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Ultrapure</td>
<td></td>
</tr>
<tr>
<td>Mononine</td>
<td></td>
</tr>
</tbody>
</table>
Principles of Factor Dosing

- What’s the desired (peak) clotting factor level?

- 1 Unit = amount of factor present in 1 ml of normal plasma

- What’s the half-life of the factor?
  - FVIII = 8-12 hours
  - FIX = 18-24 hours
Factor Replacement Therapy

- **Bolus Dosing**
  - FVIII dose = 0.5 x (target-actual level) x wt in kg.
    Usually q.12 hours
  - FIX dose = 1.0 x (target-actual level) x wt in kg.
    Usually q.24 hours

- **Continuous infusion**
  - After a bolus to raise factor level to the desired target,
  - Infuse at 4U/Kg/hr (up to 6U/kg/hr may be needed in the presence of severe bleeding)
PK Profiles of rFVIIIIFc and rFIXFc

Powell, JS et al. Blood 2012:119;3031

Powell, JS et al. NEJM 2013:369;2313
Adjunctive Therapies (1)

- **Anti-fibrinolytics**
  - Epsilon amino caproic acid (Amicar™) or tranexamic acid (Lysteda™)
  - Inhibit fibrinolysis and increase clot stability
  - Useful especially in mucosal bleeding, after dental work
  - Contra-indicated in upper urinary tract bleeding
Adjunctive Therapies (2)

- **DDAVP (Desmopressin)**
  - Releases pre-formed stores of FVIII and VWF from endothelium
  - Typically increases FVIII and VWF 3-4 fold
  - Mild hemophilia A (>5% FVIII basal level), type 1 VWD, some 2A VWD
  - Efficacy must be tested beforehand
  - Can be given iv, sc, or as a nasal spray, 150 mcg (child)-300 (adult) mcg
  - Do not confuse with much lower dose used in nephrogenic DI
Clinical Pharmacology: Levels of Factor VIII:C Following Administration of STIMATE® (desmopressin acetate) Nasal Spray, 1.5 mg/mL

Treatment of Hemophilia

Spontaneous bleeds:

- 1-2 doses of FVIII or FIX (≈ 30 U/kg/dose) for joint or muscle bleeds, when treatment is initiated early

- Significant muscle bleeds or established hemarthroses may require more prolonged treatment (5-10 days)
Treatment of Hemophilia

Considerations for surgery:

- Minimal plasma levels and duration depend on site of surgery
- Risk of delayed bleeding extends to 3-5 days postoperatively
- On-site factor assay capability essential
- Factor given by bolus or continuous infusion
Treatment of Hemophilia: “Prophylaxis”

- Maintain trough FVIII/FIX >1-2% (0.01-0.02 U/ml)
- Begin at early age (1-2 years)
  → FVIII: 25-40 u/kg t.i.w.
  → FIX: 25-40 u/kg b.i.w.
- High expense, need for reliable i.v. access
- Prevents progressive arthropathy
Factor Dosing: Comparison of FVIII Half-Life for Patients on 5\textsuperscript{th} and 95\textsuperscript{th} Percentiles

Collins PW et al. \textit{Haemophilia} 2011;17(1):2
By age 6, 93% of those in the prophylaxis group and 55% of those in the (intensive) on-demand group were considered to have a normal index-joint structure on MRI (p = 0.006)

Relative risk of joint damage with episodic therapy compared to prophylaxis = 6.1 [95% CI, 1.5-24.4]
Hemophilia Carriers

“If she circumcised her first son and he died, and a second son and he died, she must not circumcise a third one”

“In the case of circumcision there are families in which the blood flows freely and there are families in which the blood is held tight”

Babylonian Talmud, 200 A.D.
FVIII Levels in Women: Hemophilia Carriers vs. Normals
Table 4. Risk of bleeding after medical interventions

<table>
<thead>
<tr>
<th></th>
<th>Carriers, event/total (%)</th>
<th>Noncarriers, event/total (%)</th>
<th>RR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tooth extraction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged bleeding;</td>
<td>61/228 (27)</td>
<td>26/219 (12)</td>
<td>2.3 (1.5-3.4)</td>
</tr>
<tr>
<td>more than 3 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment after</td>
<td>24/228 (11)</td>
<td>1/219 (0.5)</td>
<td>23.1 (3.1-169)</td>
</tr>
<tr>
<td>intervention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tonsillectomy or</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>adenotony</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged bleeding;</td>
<td>29/123 (24)</td>
<td>16/122 (13)</td>
<td>1.8 (1.0-3.1)</td>
</tr>
<tr>
<td>more than 3 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment after</td>
<td>10/123 (8)</td>
<td>1/122 (0.8)</td>
<td>9.9 (1.3-76.3)</td>
</tr>
<tr>
<td>intervention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Operations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged bleeding;</td>
<td>46/163 (28)</td>
<td>16/146 (11)</td>
<td>2.6 (1.5-4.3)</td>
</tr>
<tr>
<td>more than 3 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment; ever</td>
<td>16/174 (9)</td>
<td>6/149 (4)</td>
<td>2.3 (0.9-5.7)</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>29/174 (17)</td>
<td>18/149 (12)</td>
<td>1.4 (0.8-2.4)</td>
</tr>
</tbody>
</table>

Participants who had been treated prior to the clinical intervention with clotting factor preparations, tranexamic acid, or desmopressin were excluded from the analysis.

Hemophilia Carriers: Diagnosis

1. **Family history:**
   - Obligate carrier (father has hemophilia)
   - Presumed carrier (mother of hemophilic child)

2. **Low FVIII:c/vWF:Ag ratio:**
   - Substantial error rate
   - FVIII level very variable: normal in some carriers

3. **DNA diagnosis (the gold standard):**
   - A. Screen for Intron 22 inversion (if severe hemophilia A)
   - B. If negative (or other diagnosis); direct gene sequencing
Intron 22 Inversion In The Factor VIII Gene: The Most Prevalent Genotype in Severe Hemophilia A

Hemophilia Carriers and Pregnancy

- Check FVIII/FIX level prior to delivery in 3rd trimester
  - Epidural OK if FVIII/FIX >40%
  - Avoid DDAVP while pregnant:
    - OK post-delivery
  - Higher risk of 1˚ and 2˚ PPH:
    - maintain FVIII/FIX >50% for 5-7 days
Hemophilia Carriers and Pregnancy

- Determine fetal sex by ultrasound; if male child:
  - Vaginal delivery OK
  - Avoid scalp sampling
  - Avoid vacuum extraction
  - Avoid prolonged delivery
  - Arrange for cord blood sampling at delivery (cord blood FVIII = adult levels; cord blood FIX < adult levels)
  - Avoid i.m. vitamin K until result of cord sampling known
Hemophilia: Complications

- **Long-term disability 2° to bleeding**
  - neurologic (intra-cranial bleed)
  - psycho-social
  - arthropathy (repetitive hemarthrosis)
  - compartment syndrome or pseudo-tumor (unresolved muscle bleed)

- **Infectious 2° to blood product exposure**
  - Hepatitis A
  - Hepatitis B, C: prior to 1983
  - HIV: prior to 1983
  - Parvovirus

- **Inhibitors**
Factor VIII Inhibitors

- Polyclonal, high affinity IgG molecules that neutralize FVIII

- Occur in ~ 25% of patients with severe hemophilia A (especially with large deletions, nonsense mutations, and intron 22 inversion)

- Median number of exposure days = 9-15; median age = 0.8-3.3 years

- Gene therapy will not eliminate

- Cause significant morbidity and mortality
Age at Inhibitor Appearance in Severe Hemophilia A


<table>
<thead>
<tr>
<th>Age (years)</th>
<th>n</th>
<th>Incidence*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>155</td>
<td>64.29</td>
<td>9.45-14.49</td>
</tr>
<tr>
<td>5-9</td>
<td>26</td>
<td>9.36</td>
<td>1.15-2.70</td>
</tr>
<tr>
<td>10-49</td>
<td>106</td>
<td>5.31</td>
<td>-- (referent)</td>
</tr>
<tr>
<td>50-59</td>
<td>11</td>
<td>5.25</td>
<td>0.53-1.84</td>
</tr>
<tr>
<td>≥ 60</td>
<td>17</td>
<td>10.49</td>
<td>1.18-3.29</td>
</tr>
<tr>
<td>Total</td>
<td>315</td>
<td>10.92</td>
<td></td>
</tr>
</tbody>
</table>

[*per 1,000 patient years at risk]

Indications for Inhibitor Screen: Patient with Known Hemophilia

- Poor clinical response to adequate therapy and/or sub-optimal recovery/half-life of FVIII or FIX *in vivo*
- Prior to major surgery
- Annual evaluation
- Anaphylactic reaction to FIX
Inhibitor Screening - Principle

- Equal mix of patient and inhibitor plasma
- Assay mixture (FVIII activity)
- Incubate at 37°C for 2 hours
- Assay mixture (residual FVIII activity)

(Note: FVIII antibodies are time-dependent, FIX antibodies are not)
The Bethesda (Inhibitor) Assay

- “Gold standard” for quantifying FVIII/IX antibodies
- 1 B.U. = inhibitor concentration that results in 50%↓ FVIII activity (after incubating 2h @ 37°C)
Treatment of Bleeding in High-Responder Patients

High responder patients with low inhibitor titer

- Mild hemorrhagic episodes
  - rFVIIa or APCC

High responder patients with high inhibitor titer

- Severe hemorrhagic episodes
  - FVIII concentrates 1st choice
  - rFVIIa or APCC

- rFVIIa or FEIBA

Bypassing Agents

- **FEIBA™**
  - Plasma-derived mixture of partially activated clotting factors, including II, VII(a), IX(a), X(a)
  - Dosed at 50-75 units/kg IV q 8-12 hrs
  - Should not be combined with Amicar (thrombosis risk)

- **NovoSeven™**
  - Recombinant VIIa
  - Standard dosing = 90-120 mcg/kg IV q2-3 hrs x 2-3 doses
  - High dose = 270 mcg/kg x 1 (or more)
FEIBA

**Efficacy:**
50-80%

**Drawbacks:**
1. No laboratory method to monitor effectiveness
2. Unpredictable hemostatic effect
3. Thrombotic complications
   → MI, DIC, DVT/PE all reported
   → usually seen with frequent, repeated doses
FVIIa in Hemophilia: Promotion of TF-Independent Activation of FX on Platelets

Recombinant Factor VIIa

**Advantages:**
1. 70 to 90% efficacy
2. Viral safety

**Drawbacks:**
1. Short half-life (2.5 hours in adults, less in children)
2. High cost
3. Incomplete information on dose-response
4. No accepted monitoring strategy
5. Thrombotic complications rare but may occur
Efficacy Ratings in the FENOC Study
(Crossover Comparison of FVIIa x2 doses vs FEIBA x1 dose)

*Prior to the second dose of NovoSeven.

* * *
Immune Tolerance Induction (ITI)

- Daily exposure to high dose factor over weeks to months to achieve immunological tolerization
- Most centers now initiate as soon as inhibitor detected in childhood – expense, compliance, i.v. access issues
- Overall, ITI is successful in ~70% of patients with hemophilia A
- Historical peak inhibitor titer < 200 B.U. and the presence of low inhibitor titer at the time of enrollment are best predictors of success
- Lower success rates in hemophilia B (~30%)
Factor IX Inhibitors

- Rare: only 2-3% of severe hemophilia B (especially with large gene deletions)
- Associated reactions to FIX products, including anaphylaxis and nephrotic syndrome
- Treatment options include high dose FIX, or by-passing therapies (FEIBA, rFVIIa); rFVIIa preferred if history of allergic reactions to FIX
Thank you for your attention!