Hemophilia

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Disclosures

- Baxter Bioscience
  - Speaker/Clinical Investigator
- Bayer Healthcare
  - Clinical Investigator
- Grifols
  - Clinical Investigator
- Quintiles
  - Clinical Investigator
- Novartis
  - Speaker/Consultant
Objectives

• History
• Diagnosis
• Types of Bleeding and Treatment
• Inhibitors
• Prophylaxis
• Advances
Hemophilia described in Talmud

Hemophilia

First Blood Transfusion

First Plasma Transfusion

Home Infusion

First Treatment Center

Cryoprecipitate

HIV

rFIX

rFVIII

Gene Therapy

0 AD

1000

1800

1846

1930s

1950s

1959

1965

1982

1987

1992

2000
For it was taught: If she circumcised her first child and he died [as a result of bleeding from the operation] and a second one died [similarly], she must not circumcise her third child.

R. Judah, the Patriarch, redactor of the Mishnah.
Pedigree of Hemophilia in the Royal Families of Europe

Selected members of the pedigree
- I-1 = King George III
- III-1 and III-2 = Prince Albert and Queen Victoria
- IV-5 and IV-6 = Alice of Hesse and Ludwig IV of Hesse
- V-13 and V-14 = Alix and Nicholas II (Tsar of Russia)
- VI-16 = Alexei
- VIII-1 = Prince Charles
Hemophilia in the Royal Families of Europe
Definition

• Congenital bleeding disorder
  – X-linked, 1:5000 born males

• Deficiency of Factor VIII or IX
  – 80-85% VIII deficiency
  – Severe hemophilia most common
    • 15% moderate
    • 25% mild
Laboratory Diagnosis

- Screening laboratory
  - CBC and platelet count: normal
  - PT: normal
  - Fibrinogen: normal
  - aPTT: prolonged
- FVIII/ FIX activity: low
Coagulation Cascade
<table>
<thead>
<tr>
<th>Type</th>
<th>FVIII/IX</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>&lt;1%</td>
<td>Spontaneous bleeds</td>
</tr>
<tr>
<td>Moderate</td>
<td>1-5%</td>
<td>Minor trauma/surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Occasional joint bleeds</td>
</tr>
<tr>
<td>Mild</td>
<td>6-40%</td>
<td>Major trauma/surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rare joint bleeds</td>
</tr>
</tbody>
</table>
Genetics

- Genetic mutation known in 90%-95%
- Mild-moderate hemophilia
  - Missense (85%)
- Severe hemophilia
  - Inversions (42%)
  - Frame shift (17%)
  - Missense (15%)
  - Nonsense (14%)
  - Large deletions (8%)

http://europium.csc.mrc.ac.uk/
http://www.kcl.ac.uk/ip/petergreen/intro.html
Father is affected with hemophilia

Mother is the carrier
Prenatal Diagnosis

- Detection of inversion 22 (11/15 wks)
- RFLP: CVS/Amnio (11/15 wks)
  - 99% accurate if affected male/carrier
- Fetal cord blood for FVIII/IX levels (18 wks)
- Carrier testing: FVIII/vWF antigen < 0.8; DNA mutation analysis
Women Can Have Hemophilia

- Lyonization of the normal X chromosome
- Turner syndrome (XO)
- Father with hemophilia/mom is a carrier
- vWD type 2N (Normandy)
Diagnosis at Birth

• Positive family history prior to delivery
  – Always send FVIII/IX level - not just aPTT
  – Send cord blood

• Negative family history in 20-30% patients
  – High index of suspicion
  – Know patterns of bleeding
Patterns of Bleeding

• Neonatal: circumcision, umbilical cord, cephalhematoma

• Infant: tongue/teeth/frenulum, soft tissue (forehead, bruising, immunization)

• Older children: hemarthrosis, muscle, soft tissue
Bleeding in Hemophilia

• Hallmark: musculoskeletal bleeding
• Triggers: surgery, trauma
• Other:
  – CNS
  – GI tract
  – GU
  – Oral/nasal
  – Soft tissue
Bleeding in Hemophilia
Hemarthrosis

<table>
<thead>
<tr>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pain alleviated by factor replacement</td>
<td>• Pain not alleviated by factor replacement</td>
</tr>
<tr>
<td>• Marked swelling</td>
<td>• Minimal swelling</td>
</tr>
<tr>
<td>• Redness and warmth</td>
<td>• Minimal redness and warmth</td>
</tr>
<tr>
<td>• Temporary loss of mobility</td>
<td>• Persistent limitation in range of motion</td>
</tr>
</tbody>
</table>
Hemarthrosis
Life-Threatening Bleeding
Treatment Overview

- Factor replacement
- DDAVP
- Antifibrinolytics
- Fibrin sealant

- 1u/kg ↑ FVIII level 2%
  - $t_{1/2}$ life: 8-12 hrs
- 1u/kg ↑ FIX level 1%
  - $t_{1/2}$ life: 18-24 hrs
- Dosing may be ↑ in pediatric patients
  - rFIX dosing = 1.4x pFIX
Recombinant Factor Concentrates

- Genetically engineered – not derived from pooled human plasma
  - 1\textsuperscript{st}, 2\textsuperscript{nd}, 3\textsuperscript{rd} generation
Treatment Principles of Factor Replacement

• When in doubt: Treat!
• Early factor replacement
• Ice and splinting help, but do not substitute factor
• Prophylaxis vs. demand; bolus vs. continuous


http://www.wfh.org/2/docs/Publications/Diagnosis_and_Treatment/Guidelines_Mng_Hemophilia.pdf
Joint Bleeding

• The standard approach: 50-80% correction x 1
• Follow-up treatments QD until improved, QOD until normal
• Target joint bleeding protocol:
  – Day 1 of joint bleed: 80% correction
  – Day 2: 40% correction
  – Day 4: 40% correction
Low-Risk Hemorrhage

- Laceration/Fracture: 50-80% correction day 1; continue QD or QOD dosing until sutures removed or cast off (delayed healing)
- Dental extractions: 50-80% correction day 1 and antifibrinolytics
- Oral hemorrhage (e.g. frenulum tear):
  - May require 80% correction day 1 and 50% correction 3 and 5
- Muscle bleed: 40-50% correction days 1 and 2
- Hematuria:
  - Hydration and bed rest
  - 50-80% correction day 1
  - Consider prednisone
  - Antifibrinolytics contraindicated
High-Risk Hemorrhage

- 80-100% correction
- Maintain factor levels > 80% for two weeks
- Consider continuous infusion FVIII or IX
- Prophylaxis (40-50% correction q.o.d.) until bleeding resolved
- Surgery: Initial 100% correction
  - > 50% levels: week 1
  - > 30% levels: week 2

- **Head trauma:**
  - Neurological exam is necessary, not sufficient to rule out ICH
  - Consider head CT (w/o contrast) based on force of injury
  - Treat ICH for 14-21 days; lifelong prophylaxis
DDAVP

• Useful in hemophilia A only
• vWF release from EC, increased platelet adhesion, increased TF expression
• Dose: IV 0.3 μgm/kg in 30 cc NS; 15-30 min
  IN < 50 kg: 150 μgm (1 spray)
  > 50 kg: 300 μgm (2 sprays)
• Duration: Q 24 h for 2-3 days
• Side Effects:
  – Hyponatremia, tachyphylaxis, thrombosis, headache, blood pressure changes
Antifibrinolytic Therapy

- **Aminocaproic acid**
  - **Dose:** 100 mg/kg q6h po (max: 6 gm/dose)
  - **Duration:** 3-7 days

- **Tranexamic acid**
  - **Dose:** 25 mg/kg po (max: 1.5 gm/dose) q8h
  - **Duration:** 3-7 days
  - **Mouthwash:** dilute 10% IV solution with NS
Perinatal Management of Infants at Risk

- Gender determination prior to delivery
- Vaginal delivery vs C-section
- No vacuum extraction or forceps
- Cord blood for PTT and factor VIII/IX level
- Avoid venipuncture
- No arterial sticks
- Head ultrasound if baby irritable
- Vitamin K po or SC, hepatitis vaccine SC
- Apply pressure 10 minutes after heelstick
- Hold circumcision
What is an Inhibitor?

- Antibody to FVIII molecule
  - IgG4 subclass
- Measured in Bethesda units (BU)
- 1 BU = amount of antibody that inactivates 50% of normal FVIII/IX in 2 hrs. at 37°C
  - Normal < 0.6 BU
- Low-responding inhibitor (0.6-5 BU)
  - Transient or persistent
- High-responding > 5 BU
- Clinical hallmark is failure to respond to replacement therapy
Inhibitor Development

• Usually occurs in young patients
  – Median 20 months\(^1\)
  – 2% incidence for previously treated adults\(^2\)

• 25-30% incidence in severe HA
  – Mild/moderate (2.5-3% incidence)

• 1-3% incidence in severe HB

• Develops early after exposure: 50 ED (median 10 ED)

\(^1\) Lusher, 1993; Bray, 1994; \(^2\) McMillan, 1988
Inhibitor Risk Assessment

- Type of FVIII/IX mutation
  - Molecular abnormalities highly associated with inhibitor development
    - large deletions (65-85% risk)
    - nonsense mutation
    - inversion of intron 22 (21% risk)
  - Absence of protein may be associated with inhibitor development
- Severity of hemophilia
- Level of circulating FVIII:Ag
- Age
- Race
  - Higher risk with African heritage
- History of FVIII therapy
  - Type of product(s) used
  - No. of exposure days
  - Cumulative exposure
  - Pattern of exposure

Factor VIII Inhibitory Epitopes

Inhibitor Treatment Options

• High Dose FVIII or IX:
  2 x BU x % correction desired

• Bypassing products
  – Activated prothrombin complex concentrates
    (APCC)= FEIBA® (50-75 u/kg)
  – Recombinant factor VIIa = NovoSeven RT®
    (90–120 mcg/kg)

• Immune tolerance (65-70% success rate)
Inhibitor Treatment Strategies

Define inhibitor type and titer

Low-responding titer < 5 BU

High-responding titer > 5 BU

Define bleeding episode

Life-threatening

Not Life-threatening

Life-threatening

Consider:
- rFVIIa
- aPCC
- High-dose FVIII
- Porcine FVIII

MS bleeding:
- rFVIIa: 90 µg/kg q2h x 2-3 doses or 270 µg/kg x 1
- Target Joint Prophylaxis: aPCC 75 U/kg 3x/wk or rFVIIa 270 µg/kg 2x/wk

Consider:
- rFVIIa
- aPCC
- Immunoadsorption
- Porcine FVIII
Immune Tolerance Induction (ITI)

- Administration of HD FVIII or IX for months to years, usually daily, until inhibitor disappearance

**Hemophilia A:**
- 75% success rate
- Interval to immune tolerance: 1.5-19.5 mo
- No benefit of immune-mod (IVIG, CPM, steroids)
- Dutch: 50 U/kg 3x/wk; German: 200 U/kg/day; US: 100 U/kg/day vs. 50 U/kg/TIW

**Hemophilia B:**
- Allergic Rxs
- FIX antigen/antibody complexes in kidney
- Nephrotic syndrome
- 6 to 9 months into ITI
- 45% success rate

✓ International ITI Study
Factors of Importance in ITI

- Historical peak (BU)
- Age at inhibitor development
- Pre-induction titer (BU < 10)
- Time interval (Dx to ITI)
- Peak BU while on ITI
- Interruptions in treatment
- Dose and frequency?
Determining Inhibitor Disappearance

- Bethesda assay < 0.6 BU x 2 (4 wks apart)
- FVIII recovery (50 U/kg) monthly until >66%
- Half-life (t\(^{1/2}\)) every 3 mo until > 6 hrs
  - 3 day washout period
- Changing to prophylactic dose: normal BU, recovery, and t\(^{1/2}\)
Prophylaxis

- IV factor replacement given at least 46 wks/year in anticipation of, and to prevent, bleeding
- By 2003, recommended for patients with severe hemophilia by WHO, WFH, and NHF
- Most US centers initiate prophylaxis after first joint bleed
- PAC vs. peripheral venipuncture
- 25-40 u/kg FVIII 3x/wk; 25-40 u/kg FIX 2x/wk
- Maintain factor level > 1% at all times
Types of Prophylaxis

Primary
• Regular and long term use of factor replacement from early childhood to prevent joint bleeding and damage

Secondary
• Periodic use of factor replacement for either a short or long time period to diminish bleeding and lessen progression of joint disease

Tailored
• Individualizing therapy to patient’s needs
Factor VIII Recovery

1 unit/kg raises plasma level by 2%

Half-life = 8 hours
Prophylaxis: Long-Term Goals

- Avoid target joint (4 bleeds/joint in 6 mo or 20 per lifetime)
- Prevent chronic arthropathy
- Improvement in individual/family QOL
- Reduction in long-term societal costs through prevention of disability, improved outcome, maximization of human potential

Fischer et al. *Haemophilia*. 2003;9(suppl 1):75-82
Gene Therapy

- Involves the transfer of genes that express a particular gene product into human cells
- Goal is aimed at the secretion of a functional factor VIII or IX protein
- Retroviral, lentiviral, adenoviral, and adeno-associated viral vectors (AAV)
- Phase I clinical trials have shown no stable production of the coagulation protein
- Only one active clinical trial in severe HB, evaluating the safety of AAV vector in delivering human factor IX gene into the liver using immunomodulation
Novel Bioengineering Technologies

- **Goals:**
  - Improve rFVIII and rFIX synthesis, secretion, and/or functional activity
  - Prolong plasma t^{1/2} of rFVIII

- **Polyethylene Glycol Conjugation ( pegylation):**
  - Modification of proteins by conjugation with polyethylene glycol polymers
  - Increases size of conjugated protein above the renal threshold for filtration resulting in an extended t^{1/2}
  - Antigenic shielding
  - Animal studies have shown increased t^{1/2} of pegylated FVIII
Novel Bioengineering Technologies

- **PEGylated liposomes**
  - Encapsulate drugs within lipid bilayer
  - Structural modifications to reduce clearance and extend $t^{1/2}$
  - Animal studies using PEGLip-FVIII have shown increased $t^{1/2}$ and hemostasis
  - Phase I trial with PEGLip formulation of Kogenate® has shown similar PK as native Kogenate®

- **Polysialic acids (PSA)**
  - Polymers of N-acetylmuraminic acid
  - Hydrophilic properties of PSA allow formation of a “watery cloud” that protects the molecule from degradation
  - Biodegradable polymers