Hemophilia and Bleeding Disorders: Diagnosis and Clinical Features

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Presentation Outline

1. Epidemiology and genetics
2. Clinical features of hemophilia
3. Inhibitors in congenital hemophilia
4. Acquired hemophilia

Q1: How often do you manage acute bleeding in patients with hemophilia?

a. Quite often, I am associated with a hemophilia treatment center
b. Once a year
c. Every few years
d. Never

What is Hemophilia?

• Congenital bleeding disorder
• Due to deficiency or absence of a coagulation cascade protein
• Hemophilia A = factor VIII deficiency
• Hemophilia B = factor IX deficiency
• Others . . .

Rare Bleeding Disorders

<table>
<thead>
<tr>
<th>Protein</th>
<th>Prevalence</th>
<th>Genetics</th>
<th>Specific Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td>1 : 1,000,000</td>
<td>AR</td>
<td>Yes</td>
</tr>
<tr>
<td>Factor II</td>
<td>1 : 2,000,000</td>
<td>AR</td>
<td>No</td>
</tr>
<tr>
<td>Factor V</td>
<td>1 : 1,000,000</td>
<td>AR</td>
<td>No</td>
</tr>
<tr>
<td>Factor VII</td>
<td>1 : 500,000</td>
<td>AR</td>
<td>Yes</td>
</tr>
<tr>
<td>Factor X</td>
<td>1 : 1,000,000</td>
<td>AR</td>
<td>No</td>
</tr>
<tr>
<td>Factor XII</td>
<td>1 : 1,000,000</td>
<td>AD</td>
<td>Yes *</td>
</tr>
<tr>
<td>Factor XIII</td>
<td>1 : 2,000,000</td>
<td>AR</td>
<td>Yes</td>
</tr>
</tbody>
</table>

AR = autosomal recessive, AD = autosomal dominant
* Not available in U.S.

• Account for 3 - 5% of all inherited coagulation disorders
• Higher prevalence in areas of geographic or social isolation

Hemophilia A

• Factor VIII deficiency
• Classical hemophilia
• 1 in 5,000 to 10,000 male births
• 80% of total cases
• Spontaneous mutations = 30%

Hemophilia B

• Factor IX deficiency
• Christmas disease
• 1 in 30,000 male births
• 20% of total cases
• Spontaneous mutations = 20%

Clinical phenotypes are indistinguishable
Challenges in Managing Acute Bleeding in Patients with Hemophilia

- Hemophilia affects all racial and socioeconomic groups equally
- There are ~20,000 hemophiliacs in the United States
- More than 500,000 hemophiliacs worldwide

Age Distribution of the U.S. Hemophilia Population

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 – 19</td>
<td>8584</td>
<td>48%</td>
</tr>
<tr>
<td>20 – 44</td>
<td>6418</td>
<td>36%</td>
</tr>
<tr>
<td>45 – 64</td>
<td>2274</td>
<td>13%</td>
</tr>
<tr>
<td>65+</td>
<td>524</td>
<td>3%</td>
</tr>
</tbody>
</table>


Genetics of Hemophilia

- Genes for factors VIII and IX are located on the X chromosome
- Females are carriers, males are affected

High rate of spontaneous mutations
- Unaware female carriers
- New mutation in baby boy
- ~30% have no family history of hemophilia

Genetics of Hemophilia

Diagnosis of Hemophilia

- **+ Family History**
  - Identify carriers
  - Pre-conception counseling
  - Cord blood testing of males
  - Defer testing of females until sx or considering pregnancy

- **No Family History**
  - Bleeding with birth trauma, circumcision, immunizations
  - Suspected child abuse
  - Joint bleeds and hematomas start to occur when learning to walk
Diagnosis of Hemophilia

Laboratory testing

- Normal CBC
- Normal platelet function
- Normal PT / INR
- Prolonged aPTT
- Measure factor VIII and IX levels

Clinical Features of Hemophilia

Severity of bleeding tendency depends on the factor level

<table>
<thead>
<tr>
<th>Factor Level</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild ( &gt; 5% )</td>
<td>Bleed only after severe injury, trauma, or surgery</td>
</tr>
<tr>
<td>Moderate (1-5%)</td>
<td>May have occasional spontaneous bleeding</td>
</tr>
<tr>
<td>Severe ( &lt; 1 % )</td>
<td>Frequent spontaneous bleeding, diagnosis made in early childhood</td>
</tr>
</tbody>
</table>

Clinical Features of Hemophilia: Joint bleed (hemarthrosis)

- Hemarthrosis, primarily involving the ankles, knees, and elbows, is the most common complication of hemophilia
- 45% experience first joint bleed within first year of life
- Median age at first joint bleed: 17 – 26 months
- 90% have at least one joint bleed by 4 years of age
- 90% of those with severe hemophilia have chronic degenerative changes involving at least 1 joint by age 25
- 40% report restricted physical activities due to arthropathy

The Clinical Problem of Joint Bleeding

- Hemophilic arthropathy is characterized by cartilage and bone destruction, bone remodeling, and progressive loss of function
- Prophylactic administration of clotting factor concentrates is essential for preventing hemophilic arthropathy

Clinical Features of Hemophilia: Joint bleed (hemarthrosis)

- 26 yo with severe hemophilia A and FVIII inhibitor
- Recurrent traumatic and spontaneous knee bleeds
- Left side surgically replaced
- Note severe muscular atrophy

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Clinical Features of Hemophilia:

Joint bleed (hemarthrosis)

- 36 year old
- Severe hemophilia A
- Recurrent left knee bleeds
- Severe hemophilic arthropathy

Patient: LF, 22-yo male with severe hemophilia A

March 2008
May 2010
June 2010

Severe hemophilia A, no inhibitor, morbidly obese

Clinical Features of Hemophilia:

Joint bleed (hemarthrosis)

- 36 year old
- Severe hemophilia A
- Recurrent left knee bleeds
- Severe hemophilic arthropathy
- Underwent total knee arthroplasty
- Infected prosthesis had to be removed 3 months later

Clinical Features of Hemophilia:

Joint bleed (hemarthrosis)

- Severe hemophilia A with inhibitor and advanced arthropathy
- Required right total hip arthroplasty

Clinical Features of Hemophilia:

Joint bleed (hemarthrosis)

- 36 year old, severe hemophilia A, followed by hemophilia treatment center since birth. No history of FVIII inhibitor.
- Target joint in childhood, no longer bleeds (or moves).
Challenges in Managing Acute Bleeding in Patients with Hemophilia

Clinical Features of Hemophilia: Soft tissue bleeding

- 56 year old with severe hemophilia A and inhibitor
- Fell on icy sidewalk
- Did not treat aggressively enough
- Required transfusion of 6 units RBCs

Clinical Features of Hemophilia: Deep muscle bleeds

- 20 year old with mild hemophilia A
- No trauma
- Bled after light jogging

44-yo male with severe hemophilia A, right elbow fracture after fall (July 2010)

December 2010 – 4 months s/p arthroplasty, doing well

February 2012 – Resumed truck driving and heavy lifting. Not doing so well.

Acquired hemophilia, non-traumatic elbow bleed
Clinical Features of Hemophilia:

**Deep muscle bleeds**
- 52 year old with severe hemophilia B
- Spontaneous bleed

**Intracranial bleeds**
- 6 year old with severe hemophilia A
- Bumped head on school playground equipment, did not appear to have any significant injury
- Parents noted change in behavior later that evening

Clinical Features of Hemophilia:

**Soft tissue bleeding**
- Severe hemophilia A with inhibitor, neck bleed provoked by coughing

Inhibitors in Congenital Hemophilia
- Some hemophilia patients “see” factor VIII or factor IX as a foreign protein
- Infusion of factor concentrate to prevent or treat bleeding triggers an immune response
- Antibodies (“inhibitors”) directed against factor VIII or factor IX neutralize the procoagulant effect and render standard treatment useless

**Factor VIII**
- Common (~25%)
- Well-studied and characterized
- Eradicated in ~70% with ITT (immune tolerance therapy)

**Factor IX**
- Rare (< 5%)
- Risk factors poorly defined
- ITT often fails
- Allergic reactions, nephrotic syndrome

However . . .
- **Bleeding more difficult to control**
- **Devastating joint disease and disability**
- **Major clinical and economic challenges**

Inhibitors in Congenital Hemophilia
- Development of inhibitors is currently the most severe complication of factor replacement therapy
- Typically seen in those with severe hemophilia
- Hemophilia A – inhibitors develop in ~25%
- Hemophilia B – inhibitors develop in < 5%
- No longer associated with increased mortality

However . . .
- **Bleeding more difficult to control**
- **Devastating joint disease and disability**
- **Major clinical and economic challenges**

**Factor VIII**
- Common (~25%)
- Well-studied and characterized
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- Rare (< 5%)
- Risk factors poorly defined
- ITT often fails
- Allergic reactions, nephrotic syndrome

May develop following treatment with both plasma derived and recombinant factor products
- Similar bleeding patterns, diagnosis, and management
Factors Influencing Inhibitor Development in Hemophilia A

**Patient Variables**
- Disease severity
- FVIII gene defect
- Ethnicity
- FH of inhibitors
- HLA type
- Individual immune response traits

**Treatment Variables**
- Number and pattern of FVIII exposures
- Type of FVIII product
- Concurrent immune system challenges
- Frequency of monitoring

Inhibitor Titer = 5 BU/mL

**Clinical Recognition of Inhibitors**
- Usually develop in small children, after only a small number of factor exposures
- Change in bleeding pattern
- Poor response to treatment with factor
- Allergic reactions often herald the development of factor IX inhibitors
- May develop later in life in those with mild or moderate hemophilia
  - Often after intense factor exposure following surgery or trauma

**Measurement of Factor VIII Inhibitors: Bethesda Assay**

**Treatment of Inhibitors**
- "Bypassing Agents"
  - Prothrombin complex concentrates
  - Recombinant factor VIIa
- Bypassing agents have unpredictable efficacy (50 – 90%)
  - More bleeding, more joint damage
  - Surgery is risky
- Immune Tolerance Therapy
  - Expensive: ~ $1 million per patient
  - Only ~ 70% effective
- Overall costs
  - Routine treatment: $200,000 – 250,000 per year
  - Major bleed, surgery: $500,000 – 1,000,000 ++

**Acquired Hemophilia**
- Inhibitors can develop in those who are not genetically deficient in factor VIII
- Rare autoimmune condition
- Occurs in 0.2 – 1 per million per year
- Must have a high index of suspicion to make a timely diagnosis
- Delayed diagnosis and lack of appreciation of risk to patient are common mistakes

**Why You Should Care About Acquired Hemophilia**
- Morbidity: > 80% have serious bleeding
- Mortality: as high as 20%

(Translation: 1 in 5 patients may bleed to death)
Acquired Hemophilia: Clinical Features

- Median age at presentation: 60 - 67 yrs; range: 2 - 89 yrs
- Males and females both affected
- Bleeding pattern
  - Hemarthroses rare
  - Mucocutaneous bleeding common (epistaxis, ecchymosis, gastrointestinal bleeding, hematuria)
  - Severe intramuscular bleeding
  - Intracranial hemorrhage
  - Postsurgical or postpartum bleeding


Acquired Hemophilia: Associated Conditions

- 50 – 60% of AH cases are idiopathic
- 40 – 50% of AH cases are associated with other underlying conditions . . .
  - Pregnancy
  - Autoimmune disorders
  - Malignancy
  - Drugs
  - Infections


Treatment of Acquired Hemophilia

1. **Stop Bleeding**
   - Factor VIII
   - Prothrombin complex concentrates
   - Recombinant factor VIIa

2. **Eradicate inhibitor**
   - Plasma exchange
   - Immunosuppression (steroids)
   - Cyclophosphamide
   - Rituximab

Acquired Hemophilia: Diagnostic Barriers, Management Pitfalls

1. **Delay in establishing correct diagnosis**
   - Dismissal of prolonged aPTT
   - Not included in differential diagnosis
   - Requires specialized coagulation lab testing

2. **Failure to recognize seriousness of diagnosis**
   - Immunosuppressive therapy should begin as soon as the diagnosis is established
   - Optimal treatment requires expertise rarely found outside of a hemophilia treatment center

Clinical Challenges in Managing Congenital Hemophilia with Inhibitors and Acquired Hemophilia

- Rare patients, higher risk of bleeding, increased morbidity
- Unpredictable and incomplete efficacy of bypassing agents
- No routine lab monitoring available
- Extremely expensive
- Optimal management of acute bleeding and surgery requires HTC expertise
Clinical Considerations in Managing Acute Bleeding in Patients with Hemophilia

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Pharmacy Clinical Coordinator, Hematology
University of Virginia Health System
Charlottesville, Virginia

Timeline of Hemophilia Treatment

• Before 1940s: supportive care, transfusions of whole blood or fresh plasma
  – Average life expectancy 27 years
  – Disabled by age 20
• 1960: transfusion medicine improved
  – Average life expectancy 40 years
  – Still severely disabled and unemployed
• 1964: expanding treatment options with cryoprecipitate
• 1968: development and availability of plasma-derived factors products
  – Average life expectancy 60 years
  – Hemophiliacs able to travel, work, and attend school with regularity

Timeline of Hemophilia Treatment

• 1982: First reported case of AIDS in patients with hemophilia
• 1985: Virally inactivated factor concentrates introduced
• 1992: Recombinant factor VIII
• 1997: Recombinant factor IX

Treatment of Hemophilia

• Hemophilia A or B
  – Severity of factor deficiency
  – Past clinical course
• Develop an ongoing relationship with regional hemophilia treatment center
  – Assist in day-to-day management and provide information on available therapeutic products

Q2: Prophylactic administration of clotting factor concentrate is recommended as standard of care by the World Federation of Hemophilia.

   a. True
   b. False


Strategies for Bleeding Management

• Goal is rapid and effective replacement of missing coagulation factor
  – Episodic or “on demand”
    • Conventional treatment approach
  – Prophylactic
    • Primary
      – Given at early age to prevent expected complication
    • Secondary
      – Begun after complication has occurred to prevent recurrence
  – Bolus vs. continuous infusion
    • Surgical procedures
Q3: The choice of factor VIII product for hemostasis is usually based upon the safety, purity, cost and risk of inhibitory antibodies.

a. True  
b. False  

Factor VIII Products

<table>
<thead>
<tr>
<th>Plasma Derived</th>
<th>Immunoaffinity Purified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alphanate®</td>
<td>Hemofil M®</td>
</tr>
<tr>
<td>Koate®-DVI</td>
<td>Monoclate-P®</td>
</tr>
<tr>
<td>Humate-P®</td>
<td>Monarc-M®</td>
</tr>
</tbody>
</table>

Recombinant

<table>
<thead>
<tr>
<th>First Generation</th>
<th>Second Generation</th>
<th>Third Generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recombinate®</td>
<td>Kogenate® FS</td>
<td>Advate®</td>
</tr>
<tr>
<td>Kogenate®</td>
<td>Helixate® FS</td>
<td>Xyntha®</td>
</tr>
<tr>
<td>Helixate®</td>
<td>Refacto®</td>
<td></td>
</tr>
</tbody>
</table>

Comparison of Recombinant Factor VIII Products (rFVIII)

- First generation
  - Required bovine or human serum for stabilization
- Second generation
  - Required plasma during manufacturing process, but plasma is removed in final product
- Third generation
  - Serum free during manufacturing process and final product
  - Smaller infusion volumes
  - Safety advantage is theoretical only

Factor VIII Products: Choice of Product

- Safety and purity
  - No documented cases of viral transmission with any plasma-derived or recombinant factor concentrate in more than 25 years
  - All rFVIII products are hemostatically equivalent
  - There is no difference in immunogenicity between different generations of rFVIII products

Factor VIII Products: Dosing

- Administration of 1 international unit per kg increases plasma factor VIII level by 2%
  - Number of units depends upon
    - Body weight
    - Volume of distribution
    - Desired factor level
  - Half life approximately 8 to 12 hours
  - Check factor VIII level near end of 12-hour period
## Factor VIII Products: Control and Prevention of Bleeding

<table>
<thead>
<tr>
<th>Type of Bleeding Episode</th>
<th>Factor VIII Level Required (% of normal)</th>
<th>Dosage and Frequency</th>
<th>Factor VIII Level Required</th>
<th>Dosage and Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor</td>
<td>20 - 40</td>
<td>10 - 20 units/kg; repeat dose every 12 - 24 hours or add antifibrinolytic</td>
<td>Early hemarthrosis</td>
<td>Minor muscle or oral bleed</td>
</tr>
<tr>
<td>Minor</td>
<td>50 - 80</td>
<td>25 - 40 units/kg every 12 - 24 hours until bleeding resolved</td>
<td>Moderate</td>
<td>Bleeding into muscles or oral cavity, definite hemarthrosis, known trauma</td>
</tr>
<tr>
<td>Major</td>
<td>80 - 100</td>
<td>Initial dose: 40 - 50 units/kg; repeat dose 20 - 50 units/kg every 8 - 12 hours until bleeding resolved</td>
<td>Major</td>
<td>GI, intracranial, intra-abdominal, intraarachnoid, CNS, or retroperitoneal bleeding</td>
</tr>
</tbody>
</table>

Adiate (antihemophilic factor [recombinant], plasma/albumin-free method) PI; 2012 Jul. Helixate FS (antihemophilic factor [recombinant], formulated with sucrose) PI; 2011 Apr.

### Monitoring Parameters

<table>
<thead>
<tr>
<th>Concept</th>
<th>Factor VIII</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure and heart rate</td>
<td>✓</td>
</tr>
<tr>
<td>Partial thromboplastin time (PTT)</td>
<td>✓</td>
</tr>
<tr>
<td>Factor levels</td>
<td>✓</td>
</tr>
<tr>
<td>Development of factor inhibitors</td>
<td>✓</td>
</tr>
<tr>
<td>Signs of bleeding (hemoglobin, hematocrit)</td>
<td>✓</td>
</tr>
</tbody>
</table>

### Adjuvant Therapy: Desmopressin Acetate
- Increase circulating level of factor VIII by 2 to 10 fold (mild to moderate hemophiliac)
- Dose 0.3 mcg/kg IV over 30 min or 150-300 mcg intranasal
  - Repeated at 12-24 hour interval
- Limited use
- Adverse effects
  - Flushing, headache, tachycardia, nausea, abdominal cramping


### Adjuvant Therapy: Antifibrinolytics
- Used for mild bleeding episodes
- Stabilizes clot and discourages re-bleeding
- Aminocaproic acid
  - Adult dose: 5 g orally or IV during the first hour then 1g/hr for 8 hours or until bleeding is controlled
  - Pediatric dose: 50 – 100 mg/kg orally or IV every 6 hours
- Tranexamic acid
  - Adult and pediatric dose: 10 mg/kg IV every 8 hours for 2 to 8 days


### Adjuvant Therapy: Fresh Frozen Plasma (FFP)
- Same factor VIII and IX concentrations as normal plasma
  - 1 unit of FFP contains 200-250 units of factors VIII, IX and XI
- Each unit increases patient’s factor VIII level by only 5-10%
  - Large volumes needed to get factor levels above 50%
- Limited use
- Complications
  - Allergic reactions, transmission of viral infections

vWF = von Willebrand factor

### Adjuvant Therapy: Cryoprecipitate
- Prepared from FFP: contains high levels of factor VIII, XIII, vWF, and fibrinogen
- One unit of cryo contains 80-150 units of factor VIII
  - 30-fold more concentrated compared with FFP
- Limited use
- Complications
  - Allergic reactions, transmission of viral infections

vWF = von Willebrand factor
Challenges in Managing Acute Bleeding in Patients with Hemophilia

Factor IX Products

**Plasma Derived**
- AlphaNine® SD
- Mononine®

**Recombinant**
- BeneFix®

**Prothrombin Complex Concentrates (PCCs)**
- Profilnine® SD
- Bebulin® VH

**Activated Prothrombin Complex Concentrates**
- Factor VIII inhibitor bypassing activity (FEIBA® NF)

Also see prescribing information (PI) in reference list.

Factor IX Products: Dosing
- Administration of 1 international unit per kg increases plasma factor IX level by 1%
  - Number of units depends upon:
    - Body weight
    - Volume of distribution
    - Desired factor level
  - Half life approximately 18 to 24 hours
  - Check factor IX level near the end of 24-hour period

Factor IX Products: Control and Prevention of Bleeding

<table>
<thead>
<tr>
<th>Type of Bleeding Episode</th>
<th>Factor IX Level Required (% of normal)</th>
<th>Dosage and Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor</td>
<td>15 – 30</td>
<td>Initial dose: 15 – 30 units/kg</td>
</tr>
<tr>
<td>Uncomplicated hemarthrosis</td>
<td></td>
<td>Maintenance dose: 20 units/kg every 12 - 24 hours</td>
</tr>
<tr>
<td>Superficial muscle or soft tissue bleed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>25 – 50</td>
<td>Initial dose: 30 – 60 units/kg</td>
</tr>
<tr>
<td>Bleeding into muscles or oral cavity, definite hemarthrosis, and known trauma</td>
<td></td>
<td>Maintenance dose: 30 units/kg every 12 - 24 hours</td>
</tr>
<tr>
<td>Major</td>
<td>50 – 100</td>
<td>Initial dose: 60 – 100 units/kg</td>
</tr>
<tr>
<td>GI, retroperitoneal, CNS, or retroperitoneal bleeding</td>
<td></td>
<td>Maintenance dose: 60 units/kg every 12 - 24 hours</td>
</tr>
</tbody>
</table>

BeneFix (coagulation factor IX [recombinant]) PI; 2011 Nov.

Factor VIII and Factor IX Products: Monitoring Parameters

<table>
<thead>
<tr>
<th>Concept</th>
<th>Factor VIII</th>
<th>Factor IX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure and heart rate</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Partial thromboplastin time (PTT)</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Factor levels</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Development of factor inhibitors</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Signs of bleeding (hemoglobin, hematocrit)</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Signs of hypersensitivity reactions</td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>

Comparison of Factor VIII and IX Products

<table>
<thead>
<tr>
<th>Concept</th>
<th>Factor VIII</th>
<th>Factor IX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Easy to store and prepare</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Straightforward dosing</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>May contain immunomodulatory proteins</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Contains vWF</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Biologically identical to human factor</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>No risk of pathogen transmission</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>More expensive*</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Increase dose up to 1.5x vs. plasma derived</td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>

*Compared with plasma-derived products.

Inhibitors in Hemophilia

- Antibody against factor VIII or factor IX
  - Most serious treatment-related complication in hemophilia
- Higher incidence in hemophilia A than hemophilia B
- Appear following median of 8 to 12 exposure days

Inhibitors in Hemophilia

- **Risk factors**
  - Type of mutation in the factor VIII or factor IX gene
  - Human leukocyte antigen types and polymorphisms in gene
    that codes for cytokines
  - rFVIII products pose increased risk?
- **Low inhibitor titer is <5 BU/mL**
  - May have historically had higher titers
  - Higher (4-5 times) doses of exogenous factor may be required
- **High inhibitor titer is ≥ 5 BU/mL**
  - Control of acute bleeding episodes
  - Reduction of inhibitor titer


Management of Acute Bleeding in Patients with High Inhibitor Titer

- **Goal:** to “bypass” the need for factor VIII or IX in coagulation cascade
  - Led to exploring the efficacy and safety of PCCs
- **Two bypass products**
  - Factor VIII inhibitor bypassing agent (FEIBA)
    - Activated PCC
  - Recombinant factor VIIa (rFVIIa)

FEIBA® NF

- **Consists of**
  - Factors II, IX, X (mainly non-activated)
  - Factor VII (activated form)
- Provides both factor II and Xa at site of the bleed
- **Dose**
  - 50 – 100 units/kg every 6 to 12 hours (not to exceed daily dose 200 units/kg)
- **Risk of DIC or thromboembolism**
- **Cannot monitor clinical efficacy**
  - Thrombin generation time (TGT)?

FEIBA NF (anti-inhibitor coagulant complex, nanofiltered and vapor heated) PI; 2011 Feb.

Recombinant Factor VIIa (rFVIIa)

- **Complexed with tissue factor can activate coagulation factor X and factor IX**
- Minimizes risk of systemic coagulation seen with FEIBA
- **Dose**
  - 90 mcg/kg every 2 hours until hemostasis is achieved

NovoSeven RT (coagulation factor VIIa [recombinant] room temperature stable) PI.; 2012 Jan.

Review of Literature

- **FEIBA vs. rFVIIa¹**
  - Both had an efficacy rate of 80 to 90%
  - Neither product was superior to the other
- **FEIBA plus rFVIIa²**
  - Hemostatic efficacy appears to be satisfactory
  - Higher incidence of thrombotic complications
  - Reserved for life-threatening bleed


Formulary Considerations

- **Product considerations**
  - Dosage and storage
  - Safety and purity
- **Availability**
- **Physician’s experience**
- **Cost**
Conclusion

• Patients with hemophilia require life-long integrated care

• Use of either plasma or recombinant factor product for the treatment or prevention of bleeding in patients with hemophilia

• A serious complication of hemophilia is the development of an inhibitor
Patient Scenarios: Innovative Strategies for Managing Patients with Hemophilia in the Hospital Setting

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Could this occur on your watch?
• A 26 yo male with factor IX deficiency presents to the ED with trauma, including a fractured leg after crashing his motorcycle
• A 50 yo male with factor VIII deficiency is scheduled for surgery

Changes in the Hemophilia Population Needs
• Established management considerations
  – Younger population
  – Hemarthrosis
• New challenges – population getting older
• Diseases of older populations
  – Atrial fibrillation
  – Coronary artery disease
  – Cancer

The Hemophilia Management Team
• Multidisciplinary
  – Medicine (primary physician, hematologist, surgeon, …)
  – Nursing (bedside, hematology program, …)
  – Pharmacy
  – Genetics
  – Coagulation laboratory
  – Social work
  – Physical therapy
• Coordinated
• Easy to notify
• Communication

Skill: Assess the Situation
• Active bleeding vs. planned procedure
  – Confirm type of hemophilia
    • Insights from patient’s hemophilia treatment center or hematologist
    • Inhibitors present
  – Laboratory assay
  – What additional or related therapies may be necessary
• Urgency of situation

Surgical Considerations
• Is the center familiar with hemophilia
  – Multidisciplinary team present
  – Experience
    • Surgical procedure
    • Hemophilia as a special population
  – Site: risk of a complication
• Discuss with the patient and family
• Type of anesthesia
  – General preferred over epidural or spinal block
• Preoperative - Intraoperative - Postoperative Plan


# Challenges in Managing Acute Bleeding in Patients with Hemophilia

## Avoiding Complications

- Frequent bleeding a concern
  - Consider minimally invasive procedure
- Advanced age
  - More conservative procedures
- Risk assessment
  - Scar tissue from multiple procedures
  - Other non-invasive options
  - Patient’s physical and clinical presentation
- Simplify agents used
  - Singular therapies vs. multiple agents
- Clinical support nearby or easy to contact
  - Consider when scheduling

## Pharmacology Considerations

- Hemostatic agents
  - Recombinant vs. pooled sources
  - rFVIIa, PCC, FEIBA
  - Is supply adequate?
  - Reimbursement evaluated and handled accordingly
- Antifibrinolytic agents
  - Tranexamic acid
  - Aminocaproic acid
- Topical therapies
- Immunomodulators

## Preoperative Management Considerations

- Consider ability to perform the procedure before accepting the case
- Develop plan in advance of surgery
  - Adequate hemoglobin
- Arrange availability of the agents
- Determine what should be withheld
- Prophylactic hemostatic agent pre-op
  - Pre-surgical factor concentration (level)
  - Type of surgery
  - Type of hemophilia

## Perioperative Management Considerations

- Maintaining hemostasis
  - Hemostatic agents
  - Antifibrinolytic agents
  - Catheter insertion
  - Antibiotic prophylaxis

## Intraoperative Management Considerations

- Monitor hemostasis
  - Thromboelastograms
  - Consider ability to perform the procedure before accepting
- Control bleeding (expected vs. non-expected)
  - Avoid diluting clotting factors
  - Mechanical
  - Topical
  - Systemic therapy
  - Cooling patient
- Consider thromboembolism vs. bleeding risks
- Determine what should be withheld
- Prophylactic hemostatic agent pre-op

## Postoperative Management Considerations

- Minimizing bleeding
  - Wound care (healing slower)
  - Timing of concentrated clotting factors
    - Drains
  - Suture removal
  - Physical therapy
- Monitoring and maintaining hemostasis
  - Avoid excessive blood draws
  - Monitor for inhibitor development
  - Hemostatic agents
  - Antifibrinolytic agents
- Transfusing to maintain Hgb/Hct
Challenges in Managing Acute Bleeding in Patients with Hemophilia

Postoperative Management Considerations (cont)

- Unexpected bleeding
- Supportive and preventive therapy
- VTE prophylaxis
  - Compression stockings
  - Pharmacologic: caution in patients with inhibitors

Managing Acute Bleeding

- Increasing blood loss → ↑ morbidity and mortality
- Patients at risk for catastrophic bleeds
  - Trauma (major or to a vital location)
  - Gastrointestinal bleeding
  - Vascular injury (aneurysms, graft failure, postoperative)
  - Cerebral vascular bleed
  - Congenital or acquired coagulopathy

Q4: For a given concentrated clotting factor (hemostatic agent), the dose is the same no matter what type of hemophilia is present.

a. True
b. False

Hemostatic Agent Considerations

- Dosing: Prophylaxis vs. active bleeding
  - Baseline factor levels
  - Presence of inhibitors
  - Type of hemophilia (rFVIIA dose < in factor VII deficiency vs. Hemophilia A or B with inhibitors)
- Administration
  - Bolus
  - Continuous Infusion
  - Inhibitors
    - < 5 BU/mL → High dose factor replacement
    - ≥ 5 BU/mL → Agent bypassing the inhibitor (rFVIIa or FEIBA)
- Single or combined therapies

Q5: What laboratory measure may be useful to determine if internal bleeding is occurring?

a. Bleeding time
b. Factor level <60%
c. Hemoglobin
d. Prothrombin time

Monitoring Hemostatic Agent

- Titrating infusion
  - Time assessment with revised dose
    - Change rate or dosing interval just prior to physician assessment
- Factor levels
  - Establish targets
  - Inhibitors developing?
Assessing Hemostasis with Hemostatic Agent in Use

- Assessing hemostasis
  - Onsite expert
  - Risk for undesirable clotting
- Severity of bleeding
  - Assessing wound (site, packing removed, etc.)
  - Hgb for internal bleeding
  - Improving or limited/no progress
- Thrombosis risks

Adjunctive Therapies

- Antifibrinolytic agents
- Desmopressin
- Steroids
- Cytotoxic immunosuppressants
  - IVIG
  - Cyclophosphamide
  - Rituximab
- Topical agents
- Plasma exchange
- Single or combined therapies

Systems Support

- Keep key personnel current
- 24/7 process
- Identify necessary hemostatic agents and labs
- Guidelines on using available therapies
  - Easy for clinicians to locate and follow
  - Adapted for patients with hemophilia
- Rapid ability to implement management
- Periodic review and quality improvement

Key Pharmacy Considerations

- Is the right agent being sent out?
- Is the dose correct?
- Who and how is the dose being determined?
- Is it safe?
- Is it working?
- Do we have enough clotting factor concentrates available?
- Is a change in therapy being considered?
- Is the dose going to be adjusted?
- How can we minimize cost and wastage?
- Was the correct pre-authorization or billing done?
APPENDIX: COAGULATION CASCADE