The Prophylaxis and Management of Hemophilia in Adults and Pediatrics

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Target Audience: Pharmacists & Nurses

Program Overview:
This knowledge based, interactive program will assist pharmacists in understanding facets of hemophilia, and the challenges of treating and counseling its victims. It will also enhance their knowledge of available options for those patients under these conditions. The program includes information on pharmacologic treatments, patient counseling, and a question/answer period.

Objectives:
• Summarize the diagnosis of hemophilia and the correct classification of disease severity
• Differentiate the current options for prophylaxis and treatment
• Assess patient adherence and identify appropriate strategies for overcoming barriers to adherence

Learning Objectives
• Summarize the diagnosis of hemophilia and the correct classification of disease severity
• Differentiate the current options for prophylaxis and treatment
• Assess patient adherence and identify appropriate strategies for overcoming barriers to adherence

Speaker: Dr. Lawson is a Clinical Pharmacist Specialist in Hematology and Oncology. She received her Pharm.D from the University of Kentucky in 2002. Her practice area is in Hematology/Oncology, and Hematopoietic Stem Cell Transplantation. Her research interests include graft-versus-host disease, supportive care, and prevention and treatment of regimens-related toxicities.

Speaker Disclosure: Dr. Lawson has no actual or potential conflicts of interest in relation to this program.

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Hemophilias in History

- Sometimes called “The Royal Disease”
- Notable hemophiliacs in history include Abraham Lincoln, Queen Victoria, Mother Theresa

Meet Joshua

- Three years old
- Active child
- Parents noticed he bruised easily as an infant
- Joshua diagnosed with hemophilia after extensive work-up

Hemophilias

- Bleeding disorders resulting from low concentrations of specific coagulation factors
- Recessive X-linked diseases
- Hemophilia A = Factor VIII deficiency
- Hemophilia B = Factor IX deficiency

Epidemiology

- Estimate of worldwide cases: 400,000
  - Approximately 20,000 U.S. cases
- Hemophilia A occurs in approximately 1 of every 5,000 live male births
  - Male-to-female ratio is approximately 32:1
- Hemophilia B occurs in approximately 1 of every 30,000 live male births
- Thirty percent of cases are caused by a spontaneous genetic mutation

The Coagulation Cascade

The Coagulation Cascade involves two pathways: Intrinsic and Extrinsic. The intrinsic pathway begins with Trauma, which leads to the formation of Tissue Factor. Tissue Factor then combines with factor VIII (VIIIa) and factor VII (VIIa) to form factor Xa (Xa). Factor Xa then combines with factor Va (Va) to form thrombin. Thrombin, in turn, converts fibrinogen to fibrin, which forms the fibrin clot.

Extrinsic Pathway:
- Trauma
- Tissue Factor
- Factor VII
- Factor X
- Factor Xa
- Factor Va
- Thrombin
- Fibrinogen
- Fibrin

Intrinsic Pathway:
- Trauma
- Tissue Factor
- Factor XII
- Factor XI
- Factor IX
- Factor VIII
- Factor Va
- Thrombin
- Fibrinogen
- Fibrin

Pathophysiology

- Platelet plug formation without stabilization of fibrin clot due to inadequate thrombin generation
  - Factor VIII and Factor IX are crucial to formation of thrombin within the coagulation cascade
- Bleeding caused by failure of secondary hemostasis

Molecular Basis of Hemophilia

- Factor VIII gene
  - Located on long arm of chromosome X at Xq28
  - Inversion at intron 22 is most common anomaly (~45% of gene abnormalities)
  - Deletions and missense mutations responsible for most severe forms of Hemophilia A
- Factor IX gene
  - Located on long arm of chromosome X at Xq27
  - No predominant mutation is known
  - Majority of mutations are point mutations that are classified as missense mutations

Diagnosis

- Males with family history and/or unusual bleeding
  - Severe hemophilia patients experience first joint bleed within first few years of life
- Factor VIII and Factor IX assays confirm diagnosis
  - Normal factor concentration is 0.5 – 1.5 units/mL
  - One unit/mL = 100% of factor found in 1 mL of plasma
- Factor VIII deficiency should be differentiated from von Willebrand's Disease
- Genetic testing indicated for patient and family members
  - Factor VIII concentrations in female carriers

Joshua’s Diagnosis

- Genetic testing reveals a spontaneous mutation
- Genetic counseling plays an important role in family life

Classification of Hemophilia

<table>
<thead>
<tr>
<th>Classification</th>
<th>Factor Concentration (IU/mL)</th>
<th>Percentage of Normal Factor</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>&gt; 0.05 – 0.40</td>
<td>5 - 40%</td>
<td>- No spontaneous bleeding - Bleeding after surgery or dental extractions</td>
</tr>
<tr>
<td>Moderate</td>
<td>0.01 – 0.05</td>
<td>1 - 5%</td>
<td>- Bleeding into muscles or joints following minor injury - Excessive bleeding after surgery or dental extractions</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt; 0.01</td>
<td>&lt; 1%</td>
<td>- Spontaneous joint and muscle bleeding - Bleeding after injuries, accidents, surgery</td>
</tr>
</tbody>
</table>

Clinical Presentation

<table>
<thead>
<tr>
<th></th>
<th>Severe ( &lt; 0.01 units/mL)</th>
<th>Moderate (0.01 – 0.05 units/mL)</th>
<th>Mild ( &gt; 0.05 units/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset</td>
<td>≤ 1 year</td>
<td>1 – 2 years</td>
<td>2 years - adult</td>
</tr>
<tr>
<td>Bleeding post circumcision</td>
<td>Usually</td>
<td>Usually</td>
<td>Rare</td>
</tr>
<tr>
<td>Joint/muscle hemorrhage</td>
<td>Spontaneous</td>
<td>Minor trauma</td>
<td>Minor trauma</td>
</tr>
<tr>
<td>CNS hemorrhage</td>
<td>High risk</td>
<td>Moderate risk</td>
<td>Rare</td>
</tr>
<tr>
<td>Post-surgical hemorrhage</td>
<td>Severe bleeding</td>
<td>Wound bleeding</td>
<td>Wound bleeding (when factor &lt; 0.3 units/mL)</td>
</tr>
<tr>
<td>Hemorrhage with tooth extraction</td>
<td>Usual</td>
<td>Common</td>
<td>Often</td>
</tr>
</tbody>
</table>

Clinical Complications of Hemophilia

- Hemarthrosis (large hinge joints – 70-80%)
  - Joint pain and swelling
  - Decreased range of motion
  - Progressive severe arthropathy leading to disability
- Muscle hemorrhage (10-20%)
  - Pain
  - Nerve or blood vessel compression
- Life-threatening bleeding (< 5%)
  - Spontaneous bleeding or trauma-associated
  - Neurologic symptoms with CNS bleeding
- Development of neutralizing antibodies (inhibitors)
Inhibitor Formation

- Most serious complication of hemophilia treatment
- Genetic mutations result in complete absence of protein product
  – IgG4 antibody development upon exposure to infused products
- Significant increases in cost of treatment due to inhibitors

Risk Factors for Inhibitor Development

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Stratification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemophilia Type</td>
<td>Hemophilia A &gt; Hemophilia B</td>
</tr>
<tr>
<td>Hemophilia Severity</td>
<td>Severe &gt; Moderate &gt; Mild</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>African-Americans are twice as likely to develop inhibitor compared to Caucasians</td>
</tr>
<tr>
<td>Family History</td>
<td>First degree relative with inhibitor increases risk three-fold</td>
</tr>
<tr>
<td>Factor VIII mutation type</td>
<td>Higher risk</td>
</tr>
<tr>
<td></td>
<td>Lower risk</td>
</tr>
<tr>
<td>Intron 22 inversion</td>
<td>Mismatch</td>
</tr>
<tr>
<td>Large deletions</td>
<td>Small deletions</td>
</tr>
<tr>
<td>Nonsense</td>
<td>Splice site</td>
</tr>
</tbody>
</table>

Potential Risk Factors for Inhibitor Development

- Age at first exposure to factor VIII products
- Plasma-derived versus recombinant factor VIII
- Continuous versus bolus infusion of factor VIII products

Bethesda Assay

- One Bethesda unit (BU) = amount of inhibitor needed to inactivate 50% of factor VIII or factor IX in plasma mixture
- **Low responders** (< 10 BU/mL) have minimal rise in antibody titers upon exposure to factor
- **High responders** (> 10 BU/mL) have an increase in antibody titers upon exposure to factor
POLL QUESTION # 1

Management of Inhibitors

- Treatment approach depends on many factors
  - Inhibitor titer quantification
  - Site and magnitude of bleeding
  - Past response to inhibitor treatment
- Low inhibitor titers may respond to aggressive factor replacement to overcome effect
- High inhibitor titers may require a factor bypassing agent
  - Prothrombin complex concentrates
  - Activated prothrombin complex concentrates
  - Recombinant factor VIIa

Joint Disease

- Hemarthroses will affect about 90% of patients with severe hemophilia A
  - Target joints: knee (45%), elbow (30%), ankle (15%), shoulder (3%), wrist (2%)
- Short-term effects: warmth, tingling, pain, spasm
- Long-term effects: Joint damage progresses throughout lifetime to potentially permanent disability

Pathogenesis of Arthopathy

- Recurrent Joint Bleeding
- Inflammation
- Synovial hypertrophy
- Hemosiderin deposition in phagocyes
- Fibrosis of subsynovial tissues
- Proteolytic enzymes
- Bone and cartilage destruction

References:
Infectious Risks

- Viral complications of plasma-derived concentrates
  - Enveloped viruses
    - Hepatitis B and Hepatitis C
    - Human immunodeficiency virus (HIV)
  - Non-enveloped viruses
    - Hepatitis A
    - Parvovirus B19
- Viral attenuation steps minimize viral transmission risk


Question...

- Prophylaxis with regular infusions of factor concentrate in patients with severe hemophilia has been proven to decrease index joint damage.
  a. True
  b. False

Management of Hemophilia

- Prophylaxis versus on-demand treatment
- Selection of factor concentrate product
  - Management of inhibitors
- Adjunctive treatments
- Patient education and adherence

Definitions of Prophylaxis

- Primary Prophylaxis
  - Regular continuous treatment started before 2 years of age after first joint bleed
  - Regular continuous treatment started before 2 years of age without prior joint bleed
- Secondary Prophylaxis
  - Regular continuous treatment started after ≥ 2 joint bleeds or at an age > 2 years
  - Intermittent regular treatment due to frequent bleeds

Prophylaxis vs. On Demand Treatment

<table>
<thead>
<tr>
<th></th>
<th>Prophylaxis</th>
<th>On-Demand Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Goal</strong></td>
<td>• Eliminate spontaneous hemarthroses in severe hemophilia</td>
<td>• Prevention of life-threatening bleeding</td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td>• Prevents long-term complications</td>
<td>• Less resource utilization (short-term)</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>• Labor-intensive</td>
<td>• Progressive arthropathy and associated complications</td>
</tr>
<tr>
<td></td>
<td>• Central-line complications</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Adherence issues</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Resource utilization</td>
<td></td>
</tr>
<tr>
<td><strong>Unknowns</strong></td>
<td>• Initiation and duration?</td>
<td>• Long-term economic benefit?</td>
</tr>
<tr>
<td></td>
<td>• Improved quality of life?</td>
<td>• Less inhibitor formation?</td>
</tr>
<tr>
<td></td>
<td>• Long-term economic benefit?</td>
<td></td>
</tr>
</tbody>
</table>

Prophylaxis: Malmö Protocol

Severe Hemophilia A and B (n=60)
Prophylaxis initiated at age ≤ 2 years or at time of first bleed
Factor VIII or IX trough level maintained at > 1% for lifetime

Factor VIII 25-40 IU/kg three times weekly
Factor IX 25-40 IU/kg twice weekly

Breakthrough joint bleeding treated with ≥ 1 infusion of Factor VIII or IX
(dose of 25-40 IU/kg until resolution of bleeding)

Malmö Protocol: Results

<table>
<thead>
<tr>
<th>Age at evaluation (years)</th>
<th>3-6</th>
<th>7-12</th>
<th>13-17</th>
<th>18-23</th>
<th>24-32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>6</td>
<td>9</td>
<td>20</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Mean age of initiation (years)</td>
<td>1.1</td>
<td>1.2</td>
<td>2.6</td>
<td>4.9</td>
<td>7</td>
</tr>
<tr>
<td>Number of annual joint bleeds</td>
<td>0.1</td>
<td>0.1</td>
<td>3</td>
<td>5.6</td>
<td>5.0</td>
</tr>
<tr>
<td>WHF orthopedic joint score</td>
<td>0</td>
<td>0</td>
<td>1.2</td>
<td>2.9</td>
<td>6.6</td>
</tr>
<tr>
<td>Pettersson score</td>
<td>0</td>
<td>0</td>
<td>4.8</td>
<td>14.2</td>
<td>20.8</td>
</tr>
</tbody>
</table>

Intermediate Dose Prophylaxis

- Dutch protocol: prophylaxis initiated after occurrence of ≥ 1 joint bleeds
  - Factor VIII 15-25 IU/kg given 2-3 times weekly
  - Factor IX 30-50 IU/kg given 1-2 times weekly
- No target trough levels of factor VIII or IX
- Dose adjusted based on intensity of breakthrough bleeding
- Prophylaxis continued throughout adulthood
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Prophylaxis: Intermediate vs. High Dose

Data for patients born 1980-1989

<table>
<thead>
<tr>
<th></th>
<th>Intermediate Dose</th>
<th>High Dose</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of initiation (y)</td>
<td>4.6 (3.1-6.2)</td>
<td>1.2 (0.8-1.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Number of joint bleeds per year</td>
<td>3.7 (1.7-5.0)</td>
<td>0.2 (0.0-0.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>% without joint bleeds</td>
<td>10%</td>
<td>50%</td>
<td>0.001</td>
</tr>
<tr>
<td>Pettersson score = 0</td>
<td>54%</td>
<td>100%</td>
<td>0.797</td>
</tr>
<tr>
<td>Annual clotting factor (IU/kg/year)</td>
<td>2126 (1743-2755)</td>
<td>4616 (4105-5571)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

No differences in quality of life were noted between the groups


Prophylaxis vs. Episodic Treatment: Joint Outcome Study

Males with Hemophilia A
- Ages 6-30 months
- Factor VIII activity ≥ 1% at home
- > 2 hemarthroses in each male joint
- Normal joint function
- Normal platelets
- Undetectable Factor VIII inhibitors

Prophylaxis: 25 IU/kg QOD
- Treatment: 40 IU/kg x 1, then 20 IU/kg at 24h and 72h

Primary Outcome: Preservation of index joint function at 6 years old
Secondary Outcomes: Joint bleeds, other bleeding events, number of infusions, total units of Factor VIII infusions

Joint Outcome Study: Results

<table>
<thead>
<tr>
<th></th>
<th>Prophylaxis (n=32)</th>
<th>Episodic Therapy (n=33)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint Damage (% MRI)</td>
<td>7</td>
<td>45</td>
<td>0.002</td>
</tr>
<tr>
<td>Joint Damage (% X-ray)</td>
<td>4</td>
<td>19</td>
<td>0.1</td>
</tr>
<tr>
<td>Mean # of Factor VIII infusions</td>
<td>653 ± 246</td>
<td>187 ± 100</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean # of Factor VIII units infused</td>
<td>352,793 ± 150,454</td>
<td>113,237 ± 65,494</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Median Joint Hemorrhages (no/participant/year)</td>
<td>0.2</td>
<td>4.35</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Median Total Hemorrhages (no/participant/year)</td>
<td>1.15</td>
<td>17.13</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>No. life-threatening bleeding episodes</td>
<td>0</td>
<td>3</td>
<td>0.24</td>
</tr>
</tbody>
</table>


Recommendations for Prophylaxis

- Optimal therapy for patients with severe hemophilia A or B
  - Maintain trough factor levels > 1%
- Factor VIII: 25-50 IU/kg every other day or 3 times per week
- Factor IX: 40-100 IU/kg 2-3 times per week
- Optimal time for discontinuing prophylaxis remains unknown

Guidelines for Factor Replacement

• Minimal doses of clotting factor replacement to restore adequate hemostasis have not been established
• Factors that influence choice of product include:
  – Safety
  – Cost
  – Availability

Evolution of Treatment Options

Plasma-derived Factor VIII and IX concentrates


Eradication of HIV and Hepatitis C transmission
Recombinant Factor VIII available
Recombinant Factor IX available

Second and third generation recombinant Factor VIII products are now available

Plasma-derived Factor Products

• Allowed for exclusive administration of factor VIII or factor IX concentrates for the first time
• Risk for viral transmission and development of viral attenuation techniques
  – Factor VIII: Hemofil M, Monarc-M, Monoclate-P
  – Factor IX: AlphaNine SD, Mononine
• Recombinant technologies allow for reduction or elimination of human/animal proteins in final product

Recombinant Factor VIII Products

<table>
<thead>
<tr>
<th></th>
<th>Fermentation</th>
<th>Purification</th>
<th>Stabilization</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Generation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1993)</td>
<td>Human albumin</td>
<td>Immunoadsorptivity, Ion exchange</td>
<td>Human albumin</td>
</tr>
<tr>
<td></td>
<td>Bovine albumin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bovine insulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second Generation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2000)</td>
<td>Human albumin</td>
<td>Immunoadsorptivity, Ion exchange</td>
<td>Sucrose</td>
</tr>
<tr>
<td></td>
<td>Recombinant human insulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Third Generation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2003)</td>
<td>No human or animal proteins</td>
<td>Immunoadsorptivity, Ion exchange, Solvent detergent</td>
<td>Trehalose</td>
</tr>
</tbody>
</table>

Recombinant Factor Concentrates

**Factor VIII**

<table>
<thead>
<tr>
<th>Product</th>
<th>Manufacturer</th>
<th>Viral Inactivation</th>
<th>Stabilizer</th>
<th>Other Content</th>
<th>Generation</th>
<th>Activity (Factor IU/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xyntha</td>
<td>Wyeth</td>
<td>IC, SD, nanofiltration</td>
<td>Sucrose</td>
<td>None</td>
<td>Third, B domain deleted</td>
<td>5,500 - 9,900</td>
</tr>
<tr>
<td>Advate</td>
<td>Baxter</td>
<td>IC, SD</td>
<td>Trehalose</td>
<td>None</td>
<td>Third</td>
<td>4,000 - 10,000</td>
</tr>
<tr>
<td>Helixate FS</td>
<td>Bayer</td>
<td>IC, SD</td>
<td>Sucrose, Human plasma</td>
<td>None</td>
<td>Second</td>
<td>4,000</td>
</tr>
<tr>
<td>Kogenate FS</td>
<td>Bayer</td>
<td>IC, SD</td>
<td>Sucrose, Human plasma</td>
<td>None</td>
<td>Second</td>
<td>4,000</td>
</tr>
<tr>
<td>Refacto</td>
<td>Wyeth</td>
<td>IC</td>
<td>Sucrose, Human albumin</td>
<td>None</td>
<td>Second, B domain deleted</td>
<td>9,110 - 13,700</td>
</tr>
<tr>
<td>Recombinate</td>
<td>Baxter</td>
<td>IC</td>
<td>Human albumin, Bovine albumin</td>
<td>None</td>
<td>First</td>
<td>1.65 - 19</td>
</tr>
</tbody>
</table>

**Factor IX**

<table>
<thead>
<tr>
<th>Product</th>
<th>Manufacturer</th>
<th>Viral Inactivation</th>
<th>Stabilizer</th>
<th>Other Content</th>
<th>Generation</th>
<th>Activity (Factor IU/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefix</td>
<td>Wyeth</td>
<td>Affinity chromatography, nanofiltration</td>
<td>Sucrose</td>
<td>None</td>
<td>Third</td>
<td>200 - 360</td>
</tr>
</tbody>
</table>

Recombinant Product Selection

- All recombinant products demonstrate comparable efficacy
- Inhibitor formation is similar across products
- Potential advantage with third generation products
  - Theoretical decreased viral transmission risk
  - No documented cases of viral transmission with first or second generation products

Factor Pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th>% increase for each unit/kg administered</th>
<th>Volume of Distribution</th>
<th>Half-life</th>
<th>Dosing Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor VIII</td>
<td>2%</td>
<td>Intravascular (50 ml/kg)</td>
<td>8-15 hours</td>
<td>Every 12 hours</td>
</tr>
<tr>
<td>Factor IX</td>
<td>1%</td>
<td>Intravascular + extravascular (100 ml/kg)</td>
<td>24 hours</td>
<td>Every 24 hours</td>
</tr>
</tbody>
</table>

- Patient weight and inhibitor titers also influence dosing

Bolus vs. Continuous Infusion

- Continuous infusion factor VIII replacement may be utilized in prolonged treatment
  - Infusion rates of 2-4 units/kg/hour to maintain trough levels of 60-100%
    - Concern for thrombophlebitis, bacterial contamination, and inhibitor formation
  - Avoids high peaks while maintaining adequate trough levels
    - Decrease factor utilization by 20-50% = cost-effective
    - Daily factor monitoring for dosage adjustment
Factor Dosing for Bleeding Episodes

<table>
<thead>
<tr>
<th>Site</th>
<th>Factor Level</th>
<th>Dose Hemophilia A</th>
<th>Dose Hemophilia B</th>
<th>Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joints, Muscles</td>
<td>30%–70%</td>
<td>15–25 U/kg</td>
<td>10–70 U/kg</td>
<td>1–3 days</td>
</tr>
<tr>
<td>Life Threatening</td>
<td>80%–100%</td>
<td>40–50 U/kg</td>
<td>80–100 U/kg</td>
<td>10–14 days</td>
</tr>
<tr>
<td>Soft Tissue</td>
<td>30%–50%</td>
<td>15–25 U/kg</td>
<td>10–50 U/kg</td>
<td>3–5 days</td>
</tr>
<tr>
<td>Surgery</td>
<td>80%–100%</td>
<td>40–50 U/kg</td>
<td>80–100 U/kg</td>
<td>10–14 days</td>
</tr>
<tr>
<td>Oral</td>
<td>20%–50%</td>
<td>10–25 U/kg</td>
<td>20–50 U/kg</td>
<td>3–5 days</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>30%–100%</td>
<td>15–50 U/kg</td>
<td>30–100 U/kg</td>
<td>2–3 days</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>30%–50%</td>
<td>15–25 U/kg</td>
<td>10–50 U/kg</td>
<td>3–2 days</td>
</tr>
</tbody>
</table>

Adjunctive Therapies

- Desmopressin acetate
- Antifibrinolytic therapy
  - Aminocaproic acid
  - Tranexamic acid
- Routine immunizations
  - Hepatitis A vaccine
  - Hepatitis B vaccine

Patient Adherence

- Over one-third of physicians reference non-adherence as a barrier in implementing prophylaxis
- Adherence is highest in patients less than 12 years of age
  - Survey revealed 59% of patients in this age group report an adherence rate of ≥ 90%
  - Adherence rate of 6% in 19-28 year-old age group

Adherence Barriers for Patients

- Time and inconvenience of infusions
- Cost and availability of clotting factors
- Age
- Bleeding pattern
- Perception of need by patient
- Lack of direct medical supervision
- Concerns with venous access
Adherence Barriers for Parents

- Inability to understand benefits of prophylaxis
- Denial of severity of disease
- Poor venous access
- Lack of family commitment
- Interference with lifestyle
- Teenage rebellion
- Lack of time


POLL QUESTION # 2

Please choose your answer and click SUBMIT!

Optimizing Patient Adherence

- Education for patients and caregivers
  - Stress benefits of prophylaxis
  - Data supports family involvement improves adherence
- Identify and target patients at risk for sub-optimal adherence
  - Teenagers and young adults
  - Patients with infrequent bleeds
  - Patients lacking psychosocial support


A Promising Future for Joshua...

- Comparable lifespan to unaffected males
- May enjoy excellent quality of life
- Avoid contact sports
- Avoid aspirin and NSAIDS
For More Information

• World Federation of Hemophilia
  www.wfh.org

• National Hemophilia Foundation
  www.hemophilia.org

• Centers for Disease Control and Prevention
  www.cdc.gov