Improving the Management of Severe Hemophilia

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Fall Managed Care Forum
Las Vegas, NV • November 15, 2013

Disclosures

I have served as an advisory board member, consultant, speaker, and / or received research funding from:

Baxter
Bayer
Biogen Idec
Novo Nordisk
Octapharma
Pfizer
Topic Outline

1. What is hemophilia?
2. Clinical manifestations
3. Treatment of hemophilia
4. How can we make it better?

Magnitude of the Problem

How many people are affected?

- Obesity: 90,500,000
- Diabetes: 25,800,000
- COPD: 15,000,000
- MS: 300,000
- Hemophilia: 20,000

Sources: Centers for Disease Control and Prevention (www.cdc.gov)
National Institute of Neurological Disorders and Stroke (www.ninds.nih.gov)
Magnitude of the Problem

*How much does it cost?*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>Mean annual per patient medical expenditures (1)</td>
<td>$7,900 - 13,700</td>
</tr>
<tr>
<td>COPD</td>
<td>Mean annual per patient COPD-related health care costs (2)</td>
<td>$2,000 - 43,000</td>
</tr>
<tr>
<td>MS</td>
<td>Mean annual per patient specialty drug costs (3)</td>
<td>$28,000 - 42,000</td>
</tr>
<tr>
<td>Hemophilia</td>
<td>Mean annual cost for routine factor prophylaxis (74 kg adult) (4)</td>
<td>$180,000 - 300,000</td>
</tr>
</tbody>
</table>


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
### 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

- 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 US Hemophilia Population

<table>
<thead>
<tr>
<th>Age (y)</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>

Source: Centers for Disease Control and Prevention
Summary Report of UDC Activity (National)
Report Date – May 30, 2011

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
### Diagnosis of Hemophilia

<table>
<thead>
<tr>
<th>+ Family History</th>
<th>No Family History</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Identify carriers</td>
<td>• Bleeding with birth trauma, circumcision, immunizations</td>
</tr>
<tr>
<td>• Pre-conception counseling</td>
<td>• Suspected child abuse</td>
</tr>
<tr>
<td>• Cord blood testing of male newborns</td>
<td>• Joint bleeds and hematomas start to occur when learning to walk</td>
</tr>
<tr>
<td>• Defer testing of females until sx or considering pregnancy</td>
<td></td>
</tr>
</tbody>
</table>

### Clinical Features of Hemophilia

Severity of bleeding tendency depends on the factor level

<table>
<thead>
<tr>
<th>Mild ( &gt; 5% )</th>
<th>Moderate (1-5%)</th>
<th>Severe ( &lt; 1 %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Bleed only after severe injury, trauma, or surgery</td>
<td>- Bleed after injury, surgery</td>
<td>- Frequent spontaneous bleeding</td>
</tr>
<tr>
<td>- May not be diagnosed until adulthood</td>
<td>- May have occasional spontaneous bleeding</td>
<td>- 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 the first year of life
- 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

Lafeber et al., Haemophilia 2008; 14(Suppl. 4):3-9
Valentino et al., Semin Hematol 2008; 45(Suppl. 1):S50-S57
Clinical Features of Hemophilia

Joint bleed (hemarthrosis)

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

TS
Clinical Features of Hemophilia

Joint bleed (hemarthrosis)

- 36 year old
- Severe hemophilia A
- Recurrent left knee bleeds
- Severe hemophilic arthropathy
- Underwent total knee arthroplasty
• 36 year old, severe hemophilia A, followed by HTC since birth. No history of fVIII inhibitor.
• Target joint in childhood, no longer bleeds (or moves).

44 yo male with severe hemophilia A, right elbow fracture after fall (July 2010)
December 2010 – 4 months s/p TEA, doing well

February 2012 – Resumed truck driving and heavy lifting, not doing so well
29 yo with severe hemophilia B, fell and fractured left elbow. Outside hospital did not have sufficient amount of factor concentrate. Transferred to University hospital with ongoing bleeding. Total Hgb drop was 7 gm/dL from baseline.

Clinical Features of Hemophilia

Deep muscle bleeds

- 52 year old with severe hemophilia B
- Spontaneous bleed
Clinical Features of Hemophilia

**Deep muscle bleeds**

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

Clinical Features of Hemophilia

**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

Intracranial bleeds

- 52 year old with severe hemophilia A
- Tripped coming out of restaurant, hit head on curb
- Received factor VIII within 30 minutes

- Presented to ER 2 days later because he had blood on Q-tip
- No neurologic symptoms
- No headache

Clinical Features of Hemophilia

Intracranial bleeds

- 58 year old with severe hemophilia A, on regular factor VIII prophylaxis
- Fell at grocery store, didn’t think he had significant injury, refused transfer to ER
- Found unresponsive at home several hours later
- Died of massive subdural hematoma
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
Inhibitors in Congenital Hemophilia

- Development of inhibitors is currently the most serious complication of factor replacement therapy
- Typically seen in those with severe hemophilia
- May occur in those with mild or moderate hemophilia, usually after intense factor exposure related to trauma or surgery
- No longer associated with increased mortality

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

Inhibitors in Congenital Hemophilia

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

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

- Occur following treatment with both plasma derived and recombinant factor products
- Similar bleeding patterns, diagnosis, and management
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
- Following right TKA he became fully ambulatory (again)

22 yo male with severe hemophilia A and fVIII inhibitor
Rapid progression of arthropathy

- March 2008
- May 2010
- June 2010
**Clinical Features of Hemophilia**

*Joint bleed (hemarthrosis)*

- 28 yo severe hemophilia A with inhibitor and end stage arthropathy, severe pain even when non-weight bearing
- Excellent functional outcome with right total hip arthroplasty

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**Clinical Features of Hemophilia**

*Soft tissue bleeding*

- Inhibitor patient, presented to ER with left elbow bleed
- Failed attempts to place IV in right arm
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

Severe hemophilia A with inhibitor, neck bleed provoked by coughing
Treatment of Hemophilia

1. Historical perspectives
2. Factor replacement options
3. On-demand vs. prophylaxis
4. Treatment of inhibitor patients
5. New therapeutics
Clinical Features of Hemophilia

Joint bleed (hemarthrosis)

- Severe hemophilia, no access to factor concentrates
- Recurrent bleeds may lead to pseudotumors

Historical Overview

- 1900 – 1940s: Hemophilic life expectancy 25 – 30 years, usually disabled by age 20
- 1960: Life expectancy increased to 40 years due to transfusions of whole blood and plasma, but most hemophiliacs still severely disabled and unemployed
- 1968: First commercially available factor VIII concentrate
- 1980: Life expectancy reaches 60 years
- 1982: First reported cases of AIDS in hemophilia patients. More than 50% ultimately infected with HIV and more than 75% infected with viral hepatitis
- 1985: Virally inactivated factor concentrates introduced
- 1992: Recombinant factor VIII
- 1997: Recombinant factor IX
**Historical Perspective**  
*Diabetes vs. Hemophilia*

- **First human treated with insulin (1922)**
- **First human pancreas transplant (1966)**
- **Commercially available insulin pump (1978)**
- **Commercially available factor concentrate (1968)**
- **Viral inactivation of factor concentrates (1985)**
- **Recombinant factor concentrates (1992, 1997)**

**Factor Replacement Therapy**

- Plasma derived and recombinant factor VIII and factor IX concentrates are available
- 1st, 2nd, and 3rd generation recombinant factor concentrates
- No documented case of viral transmission in more than 25 years
- Goal is for every child to learn self-infusion
**Factor Replacement Therapy**

**On-Demand**
- Stops bleeds after they occur
- Progressive joint damage still develops
- Appropriate only for those with mild bleeding phenotypes

**Prophylaxis**
- Prevents bleeds from occurring
- Protects joints from progressive arthropathy
- Allows for more “normal” physical activities

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**Prophylactic Factor Therapy**

**Children**
- Pioneered in Sweden in the 1960s
- Standard of care since introduction of recombinant factor concentrates in the 1990s
- Initiated after first joint bleed or before age 3
- Decreases bleeding frequency AND prevents joint damage

**Adults**
- Much less data than in children, but increasingly used
- Decreases bleeding frequency and improves QOL, but . . .
- Does it prevent progression of arthropathy?
- What do we do with kids who enter adulthood on regular prophylaxis and with preserved joints?

Treatment of Inhibitor Patients

*Three things you need to know...*

1. This is very complicated
2. This can be extremely expensive
3. This absolutely requires HTC expertise

*Why?*

- These patients are rare
- Treatment options have significant limitations

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**Immune Tolerance Therapy**

- Costs approximately $1 million per patient
- Only 70% effective, *BUT...*
- The effects of a long-term inhibitor can be devastating

**Bypassing Agents**

- 2 options: aPCC and rfVIIa
- Efficacy is incomplete (75 – 90%) and unpredictable
- No standard laboratory monitoring exists
- Thrombosis is a real risk
## New Therapeutics

### Long Acting Factor

- Both VIII and IX products coming
- First approval expected in early 2014
- Several products expected in the next 3 years

<table>
<thead>
<tr>
<th>We Know</th>
<th>We Hope</th>
<th>We Wonder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longer half-life</td>
<td>More effective prophylaxis</td>
<td>How much it will cost</td>
</tr>
<tr>
<td>Less frequent dosing</td>
<td>Better adherence</td>
<td>Will it work as we hope</td>
</tr>
</tbody>
</table>

### Gene Therapy

- Area of active investigation for 20 years
- Clinical trials are ongoing
- It works in animal models
- Scale up to humans has been challenging
- Still expected to be a clinical reality, but not anytime soon
How Can We Improve the Management of Severe Hemophilia?

1. The Easy Stuff
- Effective factor replacement therapy ✓
- Safe factor products ✓
- Access to factor ✓

2. Every patient followed by an HTC
- Approximately 30% of hemophilia patients in the US receive care outside of an HTC
- HTCs offer multidisciplinary team approach to care of these complex patients
- 40% reduction in mortality among those who receive HTC care vs. those who do not
- We need to educate patients, community providers, and managed care organizations about the benefits of HTC-based care, and eliminate barriers

How Can We Improve the Management of Severe Hemophilia?

3. Increased collaboration and support
   • Academia / industry / managed care
   • Clinical trials to answer key questions and fill in knowledge gaps
     ➢ Prophylaxis in adults
     ➢ Managing co-morbidities of aging
   • Development of new therapeutics
     ➢ Optimal clinical use of long acting agents
     ➢ Improved treatments for inhibitor patients
   • National database (ATHN)

4. Address cost issues
   • Factor accounts for 45 – 93% of the total health care cost of hemophilia, depending on severity and treatment regimen
   • 340B pricing is generally 20 – 40% lower than non-340B pricing
   • Eliminate barriers to accessing HTC / 340B programs
   • Collaboration between providers, industry, and managed care is needed

Johnson KA, Zhou ZY. Hematology, Am Soc Hematol Educ Prog 2011; 437-42
Take Home Points

• Hemophilia is a rare condition, with a large economic burden on our healthcare system

• We have made great progress in the management of hemophilia, but many important unanswered questions remain

• HTC-based care is key to the optimal management of this complex condition

• We need more collaboration across the boundaries of academia, industry, and managed care

Questions and Discussion