Improving Patient Outcomes in the Management of Hemophilia

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Disclosures

I have received grant / research funding, honoraria, and/or serve on advisory boards for:

- Baxalta
- Bayer
- Biogen
- Novo Nordisk
- Pfizer
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

Clinical phenotypes are indistinguishable
• Hemophilia affects all racial and socioeconomic groups equally
• There are ~20,000 hemophiliacs in the United States
• ~500,000 hemophiliacs worldwide

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
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>
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Joint bleed (hemarthrosis)
The Clinical Problem of Joint Bleeding

- 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

Lafabber 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
• 36 year old, severe hemophilia A, followed by HTC since birth
• Target joint in childhood, no longer bleeds (or moves)
Clinical Features of Hemophilia

Deep muscle bleeds

- 52 year old with severe hemophilia B
- Spontaneous bleed

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

- 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
**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
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)

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

Clinical Features of Hemophilia
Soft tissue bleeding
Inhibitors in Congenital Hemophilia

*Unique Challenges*

- Factor replacement therapy not possible; treatment options currently limited to bypassing agents
- Bypassing agents only have 75 – 90% efficacy in stopping acute bleeds
- High degree of variability in response between patients and bleeding episodes
- No established routine method of lab monitoring
- Risks of thrombosis with bypassing agents
- Extreme cost
- Very small number of patients

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Treatment of Hemophilia

1. Historical perspectives
2. On-demand vs. prophylaxis
3. New treatment options
Treatment of Hemophilia

What happens if you don't treat bleeds?

- Severe hemophilia, no access to factor concentrate
- 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
Factor Replacement Therapy

- Plasma derived and recombinant factor VIII and factor IX concentrates are available
- 1st, 2nd, 3rd and 4th generation recombinant factor concentrates
- No documented case of viral transmission in more than 25 years
- Goal is for every child to learn self-infusion

On-Demand
- Treatment of bleeds when they occur
- Good at stopping bleeds after they start, but does not prevent bleeds

Prophylaxis
- Regular administration of factor to prevent bleeds form occurring
- Goal is elimination of all bleeds
- Pioneered in Sweden (1958); standard of care since 1990s
Factor Replacement Therapy

**On-Demand Treatment**

**Benefits**
- Fewer infusions
- Less annual factor consumption (?)
- Lower factor costs (?)
- More convenient for some patients

**Problems**
- Bleeds are not prevented
- Joint damage is ongoing
- End stage arthropathy is unavoidable
- Bleeds may become more difficult to control over time
- Long term functional disability

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Factor Replacement Therapy

**Prophylactic Treatment**

**Benefits**
- Proven to decrease bleeds and prevent joint damage
- Improves functional status and QoL
- May delay progression of arthropathy
- Protection from traumatic and unexpected bleeds

**Problems**
- Requires frequent intravenous infusions
- Venous access
- Maintaining adherence long-term
- Cost
**Factor VIII Prophylaxis**

- Typical dose: 20 - 40 U/kg
- Frequency: every 48 - 72h
- Often M / W / F, with larger dose on Friday

**Factor IX Prophylaxis**

- Typical dose: 40 - 60 U/kg
- Frequency: twice weekly
- Often M / Th or Tu / Fri

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**New Treatment Strategies for Hemophilia**

**Extended Half-Life Factor Products**

- Fc fusion
- Albumin fusion
- PEGylation

**Factor VIII Mimetic**

**Rebalancing the Coagulation System**
New Treatments for Hemophilia

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Advantages</th>
<th>Current Status</th>
</tr>
</thead>
</table>
| Extended half life (EHL) factor products | • Less frequent infusions  
• Increased adherence | • Alprolix (March 2014)  
• Eloctate (June 2014)  
• Adynovate (Nov 2015)  
• Idelvion (March 2016)  
• N9-GP, N8-GP, BAY 94-9027 (phase 3 trials completed) |
| Factor VIII mimetic               | • SQ administration  
• Less frequent infusions  
• Increased adherence  
• Unaffected by inhibitors | • ACE910 / emicizumab (phase 3 trials underway) |
| Rebalancing the coagulation system | • SQ administration  
• Less frequent infusions  
• Increased adherence  
• Unaffected by inhibitors | • ALN-AT3 (siRNA)  
• Concizumab (anti-TFPI) (pre-clinical and early phase trials completed) |
| Gene therapy                      | Cure (?)                                        | Still a work in progress…                                                     |

EHL Factor Products

- Extend half-life by modifying rVIII / IX protein
- Fc fusion, Albumin fusion, PEGylation
- Longer half-life = less frequent infusions = improved adherence = better protection
- Current status…
  - Alprolix (March 2014)
  - Eloctate (June 2014)
  - Adynovate (Nov 2015)
  - Idelvion (March 2016)
  - N9-GP, N8-GP, BAY 94-9027 (Phase 3 trials completed)
Is an EHL factor product the right choice for THIS patient?

**Variables that affect decision making**

- Age
- Adherence
- Activity type and pattern
- Joint status
- Venous access
- Bleeding phenotype
  - Peak / trough
  - Half-life

**Consider two patients with severe hemophilia A, both on prophylaxis...**

**Patient 1**
- Sedentary
- Deconditioned
- Not socially engaged

**Patient 2**
- Active, exercises regularly
- Physically fit
- Attends school / work

**Think beyond the ABR**
EHL Factor Products

*Experience thus far…*

- Effective for prophylaxis and acute bleeds
- No safety concerns*
- High degree of patient satisfaction
- Adherence generally improved
- Ongoing challenges: management of acute bleeds, role in inpatient settings, cost

* Limited PUP data, relatively short follow-up

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EHL Factor Products

*Experience thus far…*

Unlike standard half-life factor products, *EHL products*…

- Do not all look the same
- Have clinically meaningful PK differences
- Have more complex and varied dosing schedules
### EHL Factor VIII Comparison

<table>
<thead>
<tr>
<th>Product</th>
<th>Mean Half-Life (hours)</th>
<th>Prophylactic Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eloctate</td>
<td>19.7</td>
<td>50 U/kg every 4 days, then adjust… dose: 25 – 65 U/kg interval: 3 – 5 days</td>
</tr>
<tr>
<td>Adynovate</td>
<td>14.7</td>
<td>40 – 50 U/kg 2x/week</td>
</tr>
<tr>
<td>N8-GP</td>
<td>18.4</td>
<td>???</td>
</tr>
<tr>
<td>BAY 94-9027</td>
<td>18.5</td>
<td>??? (maybe every 7 days)</td>
</tr>
</tbody>
</table>

### EHL Factor IX Comparison

<table>
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<tr>
<th>Product</th>
<th>Mean Half-Life (hours)</th>
<th>Prophylactic Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprolix</td>
<td>86</td>
<td>50 U/kg every 7 days, OR 100 U/kg every 10 days; then adjust based on individual response</td>
</tr>
<tr>
<td>Idelvion</td>
<td>104</td>
<td>25-40 U/kg every 7 days; If well controlled, may try 50-75 U/kg every 14 days</td>
</tr>
<tr>
<td>N9-GP</td>
<td>96</td>
<td>???</td>
</tr>
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Take Home Points

1. Those with hemophilia now have reliable access to safe factor replacement therapy

2. Aside from development of inhibitors, hemophilic arthropathy is currently the most significant complication of hemophilia

3. Strict adherence to long-term prophylaxis is the only way to prevent hemophilic arthropathy and its devastating consequences

4. New treatments are beginning to address many of the barriers to effective prophylaxis

5. However, optimal use of these new treatments for personalized prophylaxis has made clinical decision making much more complex

6. The resources and expertise necessary for optimal management of hemophilia in the current era do not exist outside of HTCs

7. Expect continued and substantial evolution in the management of hemophilia over the next several years
Questions and Discussion