Interventions for Hemophilia A & B: Clinical Practice Guidelines & Cost-effectiveness

Prepared for the Washington State Bleeding Disorder Collaborative for Care

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Dr. Ray has no conflicts of interests to disclose
Presentation Overview

- Background
- Prior MED Work
- PICO and Objectives
- Methods
- Overview of Findings
- Findings
  - Guidelines
  - Economic Evaluations
- Summary and Limitations
Background

• Hemophilia is a rare, X-linked, inherited bleeding disorder
  – Insufficient or dysfunctional factor VIII (A) or IX (B)
• Half of patients experience severe disease
  – Characterized by spontaneous bleeding episodes
• Morbidity and mortality arise from bleeding episodes
  – Into brain, joints, head/neck tissues, or deep muscles
• Treatment evolved from whole blood infusions, to isolated factors, now includes recombinant factor products
• Center for Evidence-based Policy (Center) report includes a full list of treatment interventions
Prior MED Work on Hemophilia

- **Home Care Services and Utilization Management for Appropriate Use of Factor Replacement Therapy in Patients with Hemophilia**
  - Participant Request
  - March 2016

- **Use of Ultrasound to Diagnose Hemarthrosis and Monitor Joint Health in Hemophilia**
  - Participant Request
  - March 2016

- **Weight-based Dosing Strategies for Factor Replacement Therapy in Hemophilia A and B**
  - Participant Request
  - March 2016

All reports available at the [MED clearinghouse](#)
PICO and Objectives

• **PICO**
  - **Population**: Adult or pediatric patients with hemophilia A or B
  - **Intervention**: Full list included in Table 2 of the Center report
  - **Comparison**: Usual care, other active interventions
  - **Outcomes**: Direct and indirect economic costs; cost-effectiveness

• **Objectives**
  - Summarize clinical practice guidelines for interventions
  - Summarize evidence on estimated direct and indirect medical costs, non-medical costs, and cost-effectiveness for interventions
## Interventions

### Factor VIII Agents

<table>
<thead>
<tr>
<th>Type</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>Hemofil M, Koate-DVI, Monoclate-P</td>
</tr>
<tr>
<td>Recombinant</td>
<td>Eloctate, Helixate FS, Kogenate FS, Novoeight, Nuwiq, Recombinate, Refacto</td>
</tr>
<tr>
<td>Recombinant Porcine</td>
<td>Obizur</td>
</tr>
<tr>
<td>Recombinant/ Albumin Free Method</td>
<td>Advate</td>
</tr>
<tr>
<td>Recombinant Factor /Platelet Activating Factor</td>
<td>Xyntha</td>
</tr>
<tr>
<td>Human/Won-Willebrand Factor Complex</td>
<td>Alphanate, Humate-P, Wilate</td>
</tr>
</tbody>
</table>

### Factor IX Agents

<table>
<thead>
<tr>
<th>Type</th>
<th>Agents</th>
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</thead>
<tbody>
<tr>
<td>Human</td>
<td>AlphaNine SD, Mononine</td>
</tr>
<tr>
<td>Recombinant</td>
<td>Alprolix, BeneFIX, Ixinity, Rixubis</td>
</tr>
</tbody>
</table>

### Prothrombin Complex Concentrates (PCC)

<table>
<thead>
<tr>
<th>Type</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human/ 3-factor</td>
<td>Bebulin, Bebulin Vapor Heated (VH), Profilnine, Profilnine Solvent/Detergent treated (SD)</td>
</tr>
<tr>
<td>Human/ 4-factor</td>
<td>Kcentra</td>
</tr>
</tbody>
</table>

### Bypass Agents

<table>
<thead>
<tr>
<th>Type</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human Activated PCC</td>
<td>FEIBA</td>
</tr>
<tr>
<td>Recombinant Factor VIIa</td>
<td>NovoSeven RT</td>
</tr>
</tbody>
</table>
Methods

• **Search strategy**
  - Medicaid Evidence-based Decisions Project (MED) core evidence and guidelines sources
  - Ovid MEDLINE® search
    • Systematic reviews, meta-analyses, technology assessments
    • Published after 1/1/2006
    • English

• **Quality assessment**
  - Methodologic quality assessed using standardized MED tools
  - Rated as good, fair, or poor methodologic quality
Overview of Findings

• Guidelines
  – National Blood Authority of Australia (*DRAFT*)
  – Nordic Hemophilia Council (Nordic)
  – United Kingdom Haemophilia Centre Doctors Organization (U.K.)
  – World Federation of Hemophilia (WFH)

• Evidence on Costs
  – No estimates of costs or outcomes comparing specific clotting factors identified
  – One systematic review analyzed estimates of costs for the use of bypass agents in patients with inhibitors
Findings: Guidelines

• **Identified 4 clinical practice guidelines**
  
  – Methodologic quality
    
    • Poor: Nordic, UK, WFH
    
    • Fair: Australia
  
  – Quality downgraded for absence of clearly defined evidence process, method of translating evidence to recommendations, editorial independence
Findings: Guidelines

- Australia, Nordic and UK guidelines all recommend recombinant factors over plasma-derived.
- WFH recommends both viral eradicated plasma-derived and recombinant factors.
- All support prophylaxis beginning by age three and second clinical bleeding episode.
- No single prophylaxis regimen was recommended.
- rFVIIa or aPCC recommended for individuals with inhibitors.
Findings: Cost-effectiveness

• Systematic review on estimates of costs for use of bypass agents in patients with inhibitors
  – Fair methodologic quality
  – Total direct medical costs to treat single episode in home (in 2010 U.S. dollars)
    • aPCC: $11,485-$49,010
    • rFVIIa: $9,078-$49,507
  – Efficacy estimates frequently based on industry funded single arm trials (9 of the 11 included studies)
  – With higher efficacy and lower doses for their product
  – Authors note, head-to-head trials do not demonstrate superior efficacy for either product
Findings: Narrative Reviews

• **Estimates of costs and outcomes for prophylaxis vs. on-demand therapy**
  - Estimates range from cost-saving and clinically beneficial (i.e. “dominant”) to over €1 million per QALY
  - Author recommends adherence to established published guidelines for economic evaluations to allow accurate comparisons

• **Estimates of costs and outcomes for bypass agents**
  - Depending on efficacy estimates rFVIIa or aPCC may be best value
    • rFVIIa better value when efficacy is >90% vs. 60% for aPCC
    • aPCC better value when efficacy equal (85% both)

Findings: Multinational Estimates for Prophylaxis

• Sweden and Netherlands implemented prophylaxis in 1960s with different protocols
  – As of 2013, a citizen with Hemophilia A:
    • In the Netherlands, uses 3 x 1000 IU of FVIII/week
    • In Sweden, uses 3 x 1500 to 2000 IU every other day
  – At a median age of 24 years, more of the Swedish cohort remained free of significant arthropathy (98% vs. 54%, p<0.01)
  – Mean annual costs in US dollars: $179,600 (Dutch) vs. $297,900 (Swedish), difference largely driven by factor costs
  – Notably, Dutch children initiated prophylaxis nearly a year later than the Swedes (1.8 years vs. 0.6 years, p<0.01)

Fischer, K., et al. Blood; 122(7)
Summary and Limitations

• Limited literature on costs related to treatment for hemophilia
  – Available evidence often biased by industry-funded estimates of efficacy and dosing
• All clinical practice guidelines support prophylaxis
• Majority of guidelines support recombinant factors over plasma-derived
• Future treatments, including potential for gene therapy, are likely to increase intervention costs, but may have long-term safety profiles which decrease medical costs and improve quality of life
Questions?