HEMOPHILIA TREATMENT MANAGEMENT: AN UPDATE ON OPTIMAL THERAPIES
PRESENTED BY TAMMY J. BUTLER, PHARM.D.

OBJECTIVES

• Objectives for Pharmacists:
  1. Identify the most common types of hemophilia and degrees of severity.
  2. Outline treatment history for patients with hemophilia and review of product safety for recombinant factor product production.
  3. Discuss certain product attributes that may impact the patient’s treatment adherence.
  4. Review factor replacement therapies and discuss dosing guidelines for hemophilia.
  5. Summarize factor VIII, IX, and other products used for factor replacement and treatment of hemophilia bleeding episodes including the newest long-acting recombinant factor replacement products on the market.
  6. Discuss the clinical impact of inhibitors and evaluate the related costs.

• Objectives for Pharmacy Technicians:
  1. Identify the most common types of hemophilia and degrees of severity.
  2. Outline treatment history for patients with hemophilia and review of product safety for recombinant factor product production.
  3. Discuss certain product attributes that may impact patient treatment adherence.
  4. Discuss factor VIII, IX, and other products used for factor replacement and treatment of hemophilia bleeding episodes including the newest long-acting recombinant factor products on the market.
  5. Define inhibitors and review related costs.

HEMOPHILIA

CLOTTING PROCESS

Male Universal Data Collection (UDC) Participants with Hemophilia

United States
TYPES OF HEMOPHILIA

- Hemophilia A: Factor VIII deficiency
- Hemophilia B: Factor IX deficiency
- Hemophilia C is an autosomal recessive disorder (not covered here)
- Hemophilia A (80-85%) is more common than hemophilia B

DEGREES OF SEVERITY

- Mild: usually no spontaneous bleeding, but can bleed from an injury or dental procedure
- Severe: person can have spontaneous bleeding and bleed from any procedure.

HEMOPHILIA DISEASE OVERVIEW

- Current prevalence in the United States: ~20,000 males across all ethnic and racial groups
  - Hemophilia A (FVIII deficiency): 1 in 5,000 live (male) births
  - Hemophilia B (FIX deficiency): 1 in 30,000 live (male) births

PRINCIPLE OF CARE

- Prevent and treat bleeding
  - Bleeding can occur anywhere in the body.
    - Joints
    - Muscles
    - Intracranial

TREATMENT HISTORY

- 1950s and 1960s: Hemophilia Treatment:
  - Life expectancy of patients with severe hemophilia: 23.2 years
  - Main treatment: fresh frozen plasma (FFP)
- Mid-1960s: Big Advancement in Treatment:
  - Cryoprecipitate: Prepared from fresh frozen plasma by allowing it to thaw in the cold
    - Produced a more concentrated form of FVIII, so less volume is needed
    - Allowed the factor to be stored in frozen form, and enabled outpatient treatment for bleeds.

TREATMENT HISTORY (CONT.)

- Late 1960s, Early 1970s: Freeze-dried, Concentrated FVIII Allowed Patients to Infuse at Home
  - Life expectancy of patients increased to 45 years of age by 1975
  - Methods were developed for separating FVIII and factor IX from pooled plasma, then freeze-drying (lyophilizing) factor concentrates
- Early 1980s: Factor Concentrates Transmitted Potentially Deadly Viruses
  - Life expectancy of patients reached 65 years by 1983, however:
    - Plasma-derived factor products transmitted potentially deadly viruses including hepatitis and HIV
  - The safety of products made from plasma became a significant concern.
TREATMENT HISTORY (CONT.)

- Mid-1980s, Early 1990s: AIDS hit patients with hemophilia hard.
  - By 1985 about 90% of patients with hemophilia were infected with HIV and 95% of those treated with unheated and dry heat-treated factor concentrates were infected with hepatitis C.
  - 1984: Successful cloning of the factor VIII (FVIII) gene led to production of recombinant factor VIII (rFVIII).
  - 1985: First antibody test to detect HIV in blood serum was developed; blood banks began screening donated blood.
  - Heat treatment of FVIII and better screening methods halted HIV transmission to patients with hemophilia through blood products.
  - 1987: Clinical trials of rFVIII in humans began.

- 1990s to 2000s: Prophylaxis treatment increased.
  - With the availability of a safe, recombinant supply of FVIII and guidelines to support it, prophylaxis—the regular infusion of clotting factor to prevent bleeding—increased.
  - Preserved normal joint and musculoskeletal function in boys and young men.
  - 2001: Recommended by NHF MASAC.
  - 2007: Documented as effective in reducing joint disease in young boys with severe hemophilia A in a multicenter controlled trial.

TREATMENT GOALS, APPROACH, AND STRATEGIES

- **Goals**
  - Rapid and effective replacement of missing coagulation factor.
  - Increase factor levels.
  - Decrease frequency and severity of bleeding.
  - Prevent the complications of bleeding.

- **Approach**
  - Combination hemophilia treatment center (CHTC), staffed by a multidisciplinary team of experts, tailors care for patients with bleeding disorders.

- **Strategies**
  - Episode or “on demand” factor replacement.
  - Prophylaxis.

FACTOR REPLACEMENT THERAPY

- **Prophylaxis and treatment**
  - Factor VIII products:
    - Plasma derived
    - Recombinant
  - Factor IX:
    - Recombinant
    - Plasma derived

FACTORS VIII AND IX

<table>
<thead>
<tr>
<th></th>
<th>FVIII</th>
<th>FIX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous infusion (either IV push or continuous)</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Dose</td>
<td>20-50 units/kg body weight</td>
<td>20-100 units/kg body weight</td>
</tr>
<tr>
<td>Half-life</td>
<td>4-12 hours</td>
<td>12-24 hours</td>
</tr>
<tr>
<td>Expected change in plasma factor activity with each unit/kg infused</td>
<td>+2%</td>
<td>+6%</td>
</tr>
</tbody>
</table>

| Easy to store | ✔ | ✔ | ✔ | ✔ |
| May contain immunosuppressive proteins | ✔ | ✔ | ✔ | ✔ |
| Increase does up to 1.5 x vs plasma derived | ✔ | ✔ | ✔ | ✔ |

DOSING GUIDELINES – HEMOPHILIA A

- **Prophylaxis**:
  - Factor VIII 15-40 units/kg IV 3 times a week.

- **Acute bleeding**:
  - 1 unit/kg FVIII concentrate raises FVIII by 2%.
  - FVIII dose (units) = (desired level – baseline level) x 0.5 x wt (kg).
  - Most commonly used dosing: 50 to 100 units / Kg for treatment.

- **Doses are adjusted to +/- 10% (even to 5%) and rounded to nearest vial due to costs.**
**DOSING GUIDELINES – HEMOPHILIA B**

- **Prophylaxis**: Factor IX 15-40 units/kg IV 2 times a week.
- **Acute bleeding**
  - Plasma-derived:
    - 1 unit/kg FIX concentrate raises FIX concentration by 1%.
    - FIX dose [units] = desired level - baseline level] x wt [kg].
  - Recombinant (rFIX):
    - rFIX has a lower recovery than plasma derived products, so 1 unit/kg rFIX concentrate raises FIX activity by 0.70 IU dL¹ in kids and 0.80 IU dL¹ in adults.
    - Kids: rFIX dose [units] = (desired level - baseline level] x 1.43 [kids] x wt [kg].
    - Adults: rFIX dose [units] = (desired level - baseline level] x 1.25 adults x wt [kg].

**EXAMPLE OF HEMOPHILIA TREATMENT CENTER ORDER**

**PROPHYLAXIS**

- **Prophylactic use** of clotting factor concentrates forms the basis of modern treatment of severe hemophilia A and B.
- **Use of prophylaxis in patients with hemophilia without inhibitors**, even in the setting of preexisting joint disease, has become more routine.
- **In children**, the early start of prophylaxis as primary or secondary prophylaxis has become the "gold standard" of care.
- **In adults**, prophylaxis is reasonably continued when started as primary or secondary prophylaxis in childhood to maintain healthy joint function.

**PREVENTION OF JOINT DISEASE IN HEMOPHILIA: HISTORICAL BASIS FOR PROPHYLAXIS**

- **Review of Study**:
  - Data from 21 international hemophilia treatment centers.
  - 6-year longitudinal study of patients aged <25 years with severe hemophilia A.
- **On-demand vs prophylaxis**
  - Prophylaxis group demonstrated the following:
    - Fewer joint bleeds.
    - Fewer total bleeding episodes.
    - Better initial and final orthopedic and radiological scores.
    - Three times higher annual use of clotting factor concentrate.

**ESTABLISHING THE CASE FOR PROPHYLAXIS IN CHILDREN**

- **Review of Study**:
  - In the Joint Outcome Study, 65 boys aged <30 months were randomly assigned to one of the following groups:
    - Prophylaxis (n=32) with rFVIII.
    - Enhanced episodic therapy (n=33).
  - At 6 years of age, normal index-joint structure on MRI was found in:
    - 93% of those in the prophylaxis group.
    - 55% of those in the episodic-therapy group (P=0.006).
  - The relative risk of MRI-detected joint damage with episodic therapy as compared with prophylaxis was 4.1 (95% CI 1.5-24.4).
  - The mean annual numbers of joint and total hemorrhages were higher at study exit in the episodic-therapy group than in the prophylaxis group (P=0.001 for both comparisons).


**Childhood Prophylaxis in Severe Hemophilia A** is associated with fewer bleeding episodes and increased factor utilization.

**Long-Acting Factor Products**

- Extended half-life (EHL)/longer-acting factor products
  - FVIII and FIX agents have been recently approved with several more expected in the next few years.

**Recent Approvals**

<table>
<thead>
<tr>
<th>FVIII Agent</th>
<th>Description</th>
<th>Status</th>
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<tbody>
<tr>
<td>NOVONATE</td>
<td>Factor VIII</td>
<td>Approved October 2013</td>
</tr>
<tr>
<td>ELOCTATE™ (rFVIIIc)</td>
<td>Factor VIII, long-acting</td>
<td>Approved June 2014</td>
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<tr>
<td>MVMXQ</td>
<td>Factor VIII</td>
<td>Approved September 2015</td>
</tr>
<tr>
<td>ADVENATE</td>
<td>Factor VIII, long-acting</td>
<td>Approved November 2015</td>
</tr>
<tr>
<td>RONIVIGEN</td>
<td>Factor VIII</td>
<td>Approved March 2016</td>
</tr>
<tr>
<td>NB-GP</td>
<td>Factor VIII, long-acting</td>
<td>Phase 3</td>
</tr>
<tr>
<td>APF29-0027</td>
<td>Factor VIII, long-acting</td>
<td>Phase 3</td>
</tr>
<tr>
<td>FIX Agents</td>
<td>Description</td>
<td>Status</td>
</tr>
<tr>
<td>RESILICA</td>
<td>FIX</td>
<td>Approved June 2013</td>
</tr>
<tr>
<td>ALPROLIX™ (rFIXFc)</td>
<td>Factor IX, long-acting</td>
<td>Approved March 2014</td>
</tr>
<tr>
<td>IXity</td>
<td>Factor IX</td>
<td>Approved June 2015</td>
</tr>
<tr>
<td>OCIROYN</td>
<td>Factor IX, long-acting</td>
<td>Approved March 2016</td>
</tr>
<tr>
<td>ZG55238539</td>
<td>Factor IX, long-acting</td>
<td>Phase 3</td>
</tr>
<tr>
<td>NB-90 (NS-GP)</td>
<td>Factor IX, long-acting</td>
<td>Phase 3</td>
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**Recent Approvals** (Cont.)

<table>
<thead>
<tr>
<th>Inhibitor Agent</th>
<th>Description</th>
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<tbody>
<tr>
<td>OBIZUR</td>
<td>Factor VIII (porcine)</td>
<td>Approved October 2014</td>
</tr>
<tr>
<td>BAY 86-6150</td>
<td>Factor VIII</td>
<td>Phase 3</td>
</tr>
<tr>
<td>LR769</td>
<td>Factor VIII</td>
<td>Phase 2/3</td>
</tr>
<tr>
<td>ACE910</td>
<td>Factor VIII-mimetic bispecific antibody</td>
<td>Phase 2/3; Breakthrough Therapy Designation</td>
</tr>
<tr>
<td>ALN-AT3</td>
<td>siRNA knockdown of antithrombin</td>
<td>Phase 2/3</td>
</tr>
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</table>
**INHIBITORS**

- **Inhibitors** (antibodies to the infused replacement factor) may develop in ~15%-20% of patients.1
- **Prevalence is higher in hemophilia A (~30%) vs hemophilia B (2%-5%).**
- Inhibitors neutralize the pro-coagulant effect of the infused factor as well as naturally produced factor protein.1
- **Typically develop early in life** (median age 1.7-3.3 years).1
- Greatest risk for inhibitor development occurs within the first 50 exposures to infused product.1,2


**INHIBITORS**

- **Antibodies** that a person develops to “fight off” the foreign proteins neutralizing the effects of replacement procoagulant factors.
- **20-30% risk in hemophilia A and ~5% in hemophilia B.**
- **Treatment: bypass factor product**
  - If low levels of inhibitor (<5 BU/mL), can give higher doses of Factors more frequently
  - If high levels (>5 BU/mL), give bypassing Factor product.
  - Anti-inhibitor coagulant complex (Plasma): FEIBA
  - Coagulation Factor VIII Recombinant: NovoSeven RT

**WHAT ARE INHIBITORS?**

- **Polyclonal allo-antibodies of the IgG molecules**, predominantly of the IgG4 subclass that is directed to clotting factor
  - Highly heterogeneous among patients
  - Display changes in epitope specificity over time
  - Synthesis requires activated CD4+ cells
  - Neutralize the pro-coagulant activity of clotting factor and render infusion of clotting factor concentrate ineffective
  - Difficult to treat

**HOW DO INHIBITORS DEVELOP?**

- Clotting factor is a soluble glycoprotein; administration to an individual with normal immunocompetence will result in immune response
  - **Genotype of deficient clotting factor protein** has major influence for the development of inhibitors


**WHO WILL DEVELOP AN INHIBITOR?**

- **HLA and the risk of developing inhibitor:**
  - Ethnicity
  - African-Americans and Hispanics have a 2x greater risk
  - Family history of antibodies to factor
  - Inherited predisposition
  - Siblings with hemophilia>> Extended relatives with hemophilia
  - **FVIII genotype and the risk of developing an inhibitor:**
    - large deletion (~68%)
    - nonsense mutations (~60%)
    - intron-22 inversion (~21%)
    - small deletions/insertions (~20%)
    - missense mutations (~13%)
    - Severe hemophilia


**INHIBITORS NEGATE THE CLINICAL EFFECT OF ALREADY COSTLY FACTOR REPLACEMENT THERAPY**

- Individuals who develop an inhibitor are twice as likely to be hospitalized for a bleeding complication as those without an inhibitor
- **Patients with inhibitors** are vulnerable to potentially severe bleeding episodes, especially when the inhibitor goes undetected
  - This drives further health care expenditures realized through emergency department utilization and potential inpatient facility charges

MANAGEMENT OF BLEEDING AND ERADICATION OF INHIBITORS LIKEWISE RESULTS IN FURTHER COSTS

- Inhibitors have the highest reported cost burden among the potential complications of all chronic diseases
- In terms of product utilization, inhibitors result in astronomical medical expenditures
- The cost and amount of clotting factor concentrate required to stop bleeding
- Immune tolerance induction (ITI) used to neutralize inhibitors carries a substantial cost, with a duration of 18 months to 3 years, in addition to polypharmacy interventions incorporating bypassing agents and recombinant factor products.

MANAGING INHIBITORS

- Use of bypassing agents
  - Activated prothrombin complex concentrates (aPCC)
  - Factor VIII/Bypassing Activity
  - Recombinant FVIIIa
  - Limitations include their unpredictable efficacy
  - Increasingly used prophylactically to prevent joint bleeding
  - In 78% of children and 28% of adults with inhibitors
  - Immune Tolerance Induction (ITI)
  - Regular infusions of factor VIII or IX administered for a period of weeks to years in an effort to increase the tolerance of the immune system
  - Limitations include variable efficacy (70%-85% for FVIII and ~30% for FIX)
  - Time-consuming and expensive

DOSING ITI

- High-titer inhibitors (≥ 5 BU)
  - High-dose regimen
  - 100-200 IU kg⁻¹ day⁻¹
  - Either with high- or low-dose regimen
  - 50 IU kg⁻¹, 3x/week

- Low-titer inhibitors (< 5 BU)

COSTS

- Products with higher purity yield less costlier.
- Purity refers to the % of desired ingredient (e.g. FVIII) relative to the other ingredients present.

COSTS PROPHYLAXIS AND INHIBITORS’ CONTRIBUTION TO ANNUALIZED FACTOR COSTS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>MedSpan AMP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tranexamic Acid</td>
<td>100mg/mL - 10mL vial</td>
<td>4.25</td>
</tr>
<tr>
<td></td>
<td>110mg/mL - 10mL amp</td>
<td>7.0420</td>
</tr>
<tr>
<td></td>
<td>60mg/mL, tablet</td>
<td>3.2143</td>
</tr>
<tr>
<td></td>
<td>500mg tab</td>
<td>3.3333</td>
</tr>
<tr>
<td>Aminocaproic Acid</td>
<td>1000mg</td>
<td>7.3250</td>
</tr>
<tr>
<td></td>
<td>230mg/mL vial</td>
<td>0.3120</td>
</tr>
<tr>
<td></td>
<td>25% syrup</td>
<td>4.0176</td>
</tr>
<tr>
<td></td>
<td>25% syrup (oral)</td>
<td>1.6804</td>
</tr>
<tr>
<td>Novaseven®</td>
<td>2.5900</td>
<td></td>
</tr>
<tr>
<td>FEIBA</td>
<td>2.4500</td>
<td></td>
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</tbody>
</table>
PROPHYLAXIS DECREASES OVERALL HEALTHCARE UTILIZATION

HEMOPHILIA MANAGEMENT CHALLENGES

- Management Challenges:
  - Prophylaxis: Identification of optimal trough level
  - Cost-benefit of targeting higher trough levels
  - Use of prophylaxis beyond pediatric patients
  - Perisurgical considerations
  - Impact of prophylaxis on CVD risk
  - Formation of inhibitory antibodies
  - Genetic predisposition
  - Factor exposure during heightened immune response
  - Infections, immunizations, surgery
  - More frequent (or continuous) factor infusions in mild or moderate cases
  - Eradication of the inhibitor in severe cases

CONCLUSION

Optimal Care is Realized by Balancing Benefits, Risks, and Costs

REFERENCES

- UpToDate: hemophilia. https://www.uptodate.com/contents/treatment-of-hemophilia
- Wfh.org
- Srivista et al. Hemophilia 2013;19(1);e1-47