Hereditary and Acquired Bleeding Disorders: Hemophilia
Hemophilia: Epidemiology and Pathophysiology

- Hemophilia is a rare inherited X-linked bleeding disorder characterized by lack of one of the proteins involved in blood clotting.
- Ability to form a stable fibrin clot depends on a complex network of proteins and cells that comprise the clotting cascade.
- FVIII and FIX are the only coagulation cascade proteins that are encoded by genes on the X chromosome.
- Hemophilia is named according to the factor deficiency.
  - Hemophilia A
    - 1 in 5,000 male births
    - Lack functional copies of factor VIII (FVIII)
  - Hemophilia B
    - 1 in 25,000 male births
    - Lack functional Factor IX
- Spontaneous deep bruising, muscular hematomas, or bleeds into joints are related to level of factor deficiency.
- Classified based on severity of deficiency
  - Severe: < 1% of normal factor activity levels; highest risk of spontaneous bleeding
  - Moderate: 1%–5% of normal factor levels; occasionally spontaneous, risk with minor trauma or surgery
  - Mild: 5%–50% of normal factor levels; risk with major trauma or surgery, rarely spontaneous

Hemophilia: Collaborative Management

• Most patients with hemophilia are managed by comprehensive hemophilia centers (CHCs)
  • Birth through adulthood
  • Advanced practitioners (APs) may work as members of these interdisciplinary programs and assume a primary role in monitoring and management of hemophilia across the life span

• APs in hematology and oncology
  • For patients with access to regular factor replacement, life expectancy is now approaching that of the general male population
  • Patients with other forms of cancer or benign hematology disorders may be seen in a general practice
  • Co-management/collaboration with the CHC is recommended, particularly for APs in surgical oncology subspecialties

Hemophilia: General Principles of Treatment

- Recombinant and plasma-derived factors are available.
- **Hemophilia A**
  - Cryoprecipitate contains factor VIII (FVIII) but is not used commonly due to risk of blood-borne pathogens and high volume required.
  - FVIII dosing is calculated based on the desired FVIII level, the baseline level, and the patient’s weight in kilograms.
  - The desired factor VIII (FVIII) level and frequency of dosing will vary based on the bleed severity/location, product being used, and other patient factors.
- **Hemophilia B**
  - Recombinant factor IX (FIX) or plasma-derived product replacements are available.
  - Factor VIII dosing is calculated based on the desired FVIII level, the baseline level, and the patient’s weight in kilograms.
  - Antifibrinolytic agents may be added to improve clot integrity and reduce early degradation.
## Hemophilia: FDA-Approved Replacement Factors

<table>
<thead>
<tr>
<th>Product</th>
<th>Brand Name</th>
<th>Half-life (h)</th>
<th>Cell Line</th>
<th>FDA Approval Year</th>
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<td><strong>Factor VIII (FVIII)</strong></td>
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<tr>
<td>rFVIIIFc</td>
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<td>19</td>
<td>HEK</td>
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<td>BAX 855</td>
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<td>14–16</td>
<td>CHO</td>
<td>Dec 2016</td>
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<td>FVIII non-factor replacement product</td>
<td>Hemlibra</td>
<td>N/A</td>
<td>MoAb mimicking cofactor activity of FVIII</td>
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<td><strong>Factor IX (FIX)</strong></td>
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<td>Rebinyn/Refixia</td>
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</table>

CHO = Chinese hamster ovary; Fc = fragment crystallizable [region]; FP = fusion protein; HEK = human embryonic kidney; MoAb = monoclonal antibody; N9-GP = nonacog beta pegol; r = recombinant

Hemophilia: Clinical Resources

• General Information from the Centers for Disease Control and Prevention (CDC):
  https://www.cdc.gov/ncbddd/hemophilia/facts.html

• Hemophilia Treatment Center (HTC) Directory, from the CDC:
  https://dbdgateway.cdc.gov/HTCDirSearch.aspx