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

Pelland-Marcotte MC, et al. *Hematol Oncol Clin North Am*. 2019;33(3):409-423; Peters R, et al. *Nat Rev Drug Discov*. 2018;17(7):493-508.

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

Mannucci PM, et al. *Blood*. 2009;114(26):5256-5263.

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.

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Hemophilia: FDA-Approved Replacement Factors

Product	Brand Name	Half-life (h)	Cell Line	FDA Approval Year
Factor VIII (FVIII)				
rFVIIIFc	Eloctate/Elocta	19	HEK	June 2014
BAX 855	Adynovate/Adynovi	14–16	CHO	Dec 2016
BAY 94-9027	Jivi	19	CHO	Aug 2018
FVIII non-factor replacement product	Hemlibra	N/A	MoAb mimicking cofactor activity of FVIII	Nov 2017
Factor IX (FIX)				
rFIXFc	Alprolix	82	HEK	Mar 2014
rFIXFP	Idelvion	102	CHO	Mar 2016
N9-GP	Rebinyn/Refixia	93	CHO	May 2017

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

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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