Congenital Hemophilia

Disease background

October 2024

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Overview of hemophilia

Hemophilia is an inherited bleeding disorder, caused by a deficiency in the production of clotting proteins (clotting factors)[1,2]

Hemophilia A	Hemophilia B

• FVIII deficiency[1]
• Classic hemophilia[2]
• Most common form
  • Affects approximately 80% of hemophilia population[1,3]
	• FIX deficiency[1]
	• Also known as Christmas disease[2]
	• Less common form
	  • Affects approximately 20% of hemophilia population[1,3]

Severity of disease can be predicted by the level of residual FVIII or FIX activity[1,2]

WFH estimates that there are ~271,359 cases of hemophilia globally[3]

WFH and CDC estimates that there are 18,580–33,000 people with hemophilia in the US[3,4]

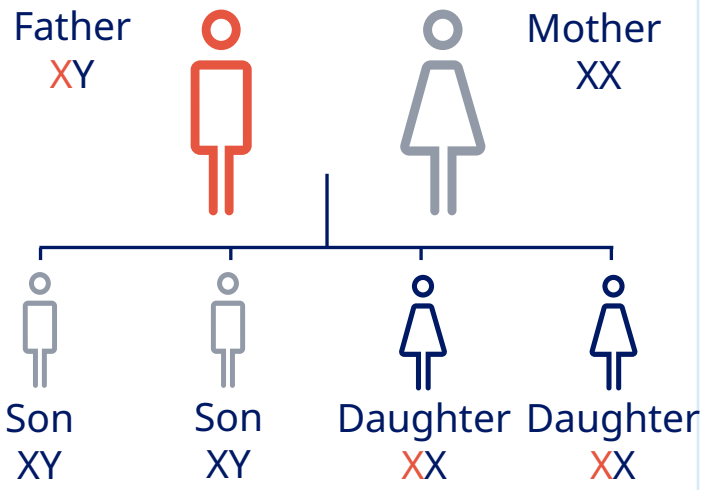
CDC, Centers for Disease Control and Prevention; FIX, factor IX; FVIII, factor VIII; US, United States; WFH, World Federation of Hemophilia.

1. Srivastava A et al. Haemophilia 2020;26(Suppl 6):1–158; 2. Escobar MA, Key NS. Hemophilia A and Hemophilia B. In: Kaushansky K et al. eds. Williams Hematology. New York, NY: McGraw Hill; 2016; 3. WFH. Report on the Annual Global Survey 2022. October 2023. Available at: https://www1.wfh.org/publications/files/pdf-2399.pdf. Accessed June 2024; 4. Soucie JM et al. Haemophilia 2020;26:487–93.

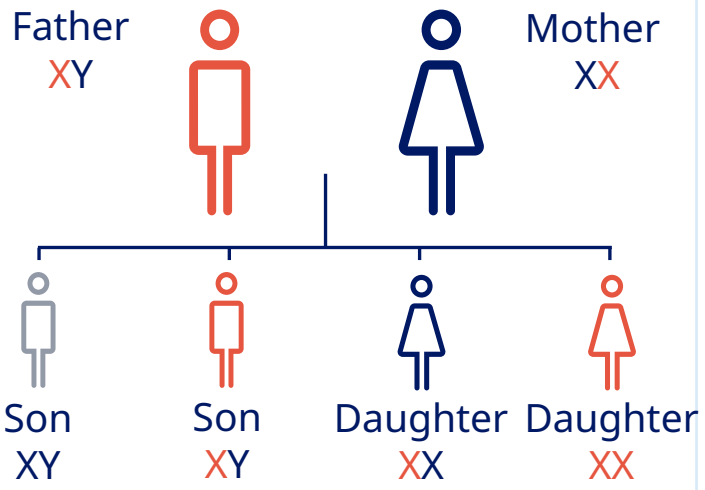
Inheritance pattern of hemophilia

Hemophilia A and B are both X-linked recessive traits with the gene mutation appearing on the X chromosome:[1]

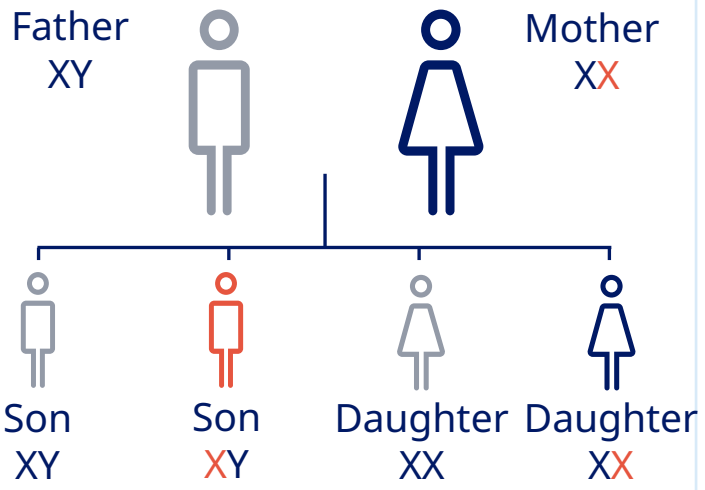
Inheritance from a male with hemophilia



Inheritance from a male with hemophilia and a female carrier



Inheritance from a female carrier



Healthy non-carrier Hemophilia Carrier

1. Powell JS et al. In: Greer JP et al. eds. Wintrobe's Clinical Hematology. 13th edn. Philadelphia, PA: Lippincott Williams & Wilkins; 2014:1143–87.

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Diagnosis and clinical classification

Screening for hemophilia is based on:

- Family history[1]
  - Known carrier mother (30% of cases are spontaneous)
- Laboratory features[1,2] (prolonged aPTT; normal PT; low levels of FVIII or FIX)
- Preoperative screening[1]

Severe hemophilia A: 44.4%[3] B: 25.2%[3]	Moderate hemophilia A: 16.4%[3] B: 35.4%[3]	Mild hemophilia A: 37.4%[3] B: 37.7%[3]
<1% factor level[2]	1–5% factor level[2]	>5% to <40% factor level[2]
Spontaneous bleeding into joints or muscles[2]	Occasional spontaneous bleeding; prolonged bleeding with minor trauma or surgery[2]	Rare spontaneous bleeding; severe bleeding with major trauma or surgery[2]
Usually have joint problems[4]	May have joint problems[4]	Rarely have joint problems[4]

aPTT, activated partial thromboplastin time; FIX, factor IX; FVIII, factor VIII; PT, prothrombin time.

1. Escobar MA, Key NS. Hemophilia A and Hemophilia B. In: Kaushansky K et al. eds. Williams Hematology. New York, NY: McGraw Hill; 2016; 2. Srivastava A et al. Haemophilia 2020;26(Suppl 6):1–158; 3. Centers for Disease and Control and Prevention. Factor VIII and Factor IX. Community counts. Available at: https://www.cdc.gov/hemophilia-community-counts/php/htc-population-profile/2023-sept-factor-viii-and-factor-ix.html. Accessed July 2024; 4. World Federation of Hemophilia. Protocols for treatment of hemophilia and von Willebrand Disease (3rd Edition) 2008. Available at: https://www1.wfh.org/publication/files/pdf-1137.pdf. Accessed August 2024.

Clinical presentation

- Prolonged bleeding[1,2]
- Severe bleeding[1]
  - Large joints: ankle, elbow, knee
  - Soft tissues: muscle, mucocutaneous
- Life-threatening bleeding[1]
  - Intracranial hemorrhage (usually traumatic in origin)
  - Retroperitoneal bleeding
  - Episodic bleeding in the gastrointestinal tract
- Postoperative bleeding[1]

Repeated bleeding leads to arthropathy, even in young adults[3,4]

1. Escobar MA, Key NS. Hemophilia A and Hemophilia B. In: Kaushansky K et al. eds. Williams Hematology. New York, NY: McGraw Hill; 2016; 2. Srivastava A et al. Haemophilia 2020;26(Suppl 6):1–158; 3. Luck JV Jr et al. J Am Acad Orthop Surg 2004;12:234–45; 4. Weyand AC, Pipe SW. Blood 2019;133:389–98.

Clinical management: current therapies

Treatment priorities include prevention of bleeding and joint damage and prompt management of bleeding episodes[1]

Replacement therapy[2,3]

Hemophilia A

- Standard half-life
- Extended half-life
- Ultra-long half-life[3]

Hemophilia B

- Standard half-life
- Extended half-life

Challenges remain:

- Frequent IV administration[2]
- Lack of adherence[4]
- Development of alloantibodies[2]

Non-factor therapies[1,2,5–9]

Hemophilia A with and without inhibitors

- FVIIIa mimetics[1,7]

Hemophilia A and B without inhibitors

- Anti-TFPI mAb[8]

For FVIIIa mimetics:

- Subcutaneous dosing weekly, biweekly, or monthly[2,5]
- Not intended to treat acute bleeding episodes[1]
- No development of FVIII inhibitors observed[2,6]
- Not seen to be inhibited by existing FVIII inhibitors[7,9]

Adjunctive therapies[1]

Hemophilia A

- DDAVP
- Antifibrinolytics

Hemophilia B

- Antifibrinolytics

Guidelines suggest a comprehensive care model involving a multidisciplinary approach is adopted, which prioritizes psychosocial wellbeing and quality of life as well as the treatment of acute bleeding[1]

DDAVP, desmopressin acetate; FVIIIa, activated factor FVIII; FVIII, factor VIII; IV, intravenous; mAb, monoclonal antibody; TFPI, tissue factor pathway inhibitor.

1. Srivastava A et al. Haemophilia 2020;26(Suppl 6):1–158; 2. Weyand AC, Pipe SW. Blood 2019;133:389–98; 3. Hermans C, Pierce GF. J Thromb Haemost 2024;22:1844–6; Thornburg CD et al. Patient Prefer Adherence 2017;11:1677–86; 5. Nogami K, Shima M. Blood 2019;133:399–406; 6. Mahlangu J et al. N Engl J Med 2018;379:811–22; 7. Ellsworth P, Ma A. Hematology Am Soc Hematol Educ Program 2021;2021:219–25; 8. Business Wire. U.S. FDA Approves Pfizer's HYMPAVZI™ (marstacimab-hncq) for the Treatment of Adults and Adolescents with Hemophilia A or B Without Inhibitors. Accessed October 11, 2024; 9. Young G et al. Blood 2019;134:2127–38.

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Novel therapies

Anti-TFPI[1–3]	mAbs against TFPI recently approved for hemophilia A and B without inhibitors[4]. MOA: Restores thrombin generation by blocking the inhibitory effect of TFPI on the initiation of coagulation
Bispecific antibodies with FVIIIa mimetic properties[1–3]	Recombinant technology approved for hemophilia A MOA: Bridges FIXa and FX to restore the function of missing activated FVIII
siRNA knockdown of antithrombin[2,5]	RNAi therapeutic targeting antithrombin to rebalance the coagulation system and promote hemostasis[2,5]. Under investigation for use in the US (phase 3). MOA: Inhibits antithrombin, an anticoagulant that inactivates FXa and thrombin[5]
Gene therapy[1,6,7]	AAV gene therapy treatments recently approved for hemophilia A and B MOA: Replacement of a defective FVIII or FIX gene sequence with the corrected version
Anti-APC protease inhibitors[8,9]	SerpinPC: serine protease inhibitor (SERPIN) engineered to inhibit APC. Under investigation for use in the US (phase 1/2) MOA: Promotes clotting by prolonging the lifespan of the prothrombinase complex

AAV, adeno-associated virus; APC, activated protein C; FIX, factor IX; FIXa, activated factor IX; FVIII, factor VIII; FVIIIa, activated factor VIII; FX, factor X; FXa, activated factor X; mAb, monoclonal antibody; MOA, mechanism of action; RNAi, ribonucleic acid interference; siRNA, small interfering ribonucleic acid; TFPI, tissue factor pathway inhibitor.

1. Gogia P et al. Expert Rev Hematol 2023;16:417–33; 2. Ellsworth P, Ma A. Hematology Am Soc Hematol Educ Program 2021;2021:219–25; 3. Olasupo OO et al. Cochrane Database Syst Rev 2024;2:CD014544; 4. Business Wire. U.S. FDA Approves Pfizer's HYMPAVZI™ (marstacimab-hncq) for the Treatment of Adults and Adolescents with Hemophilia A or B Without Inhibitors. Accessed October 11, 2024; 5. Young G et al. Res Pract Thromb Haemost 2023;7;:100179; 6. Ay C et al. Haemophilia 2024;30:5–15; 7. Kaczmarek R et al. Haemophilia 2024:30(Suppl 3):12–20; 8. Baglin T et al. Blood 2023;142(Suppl 1):2619; 9. Polderdijk SGI et al. Blood 2017;129:105–13.

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Summary

Hemophilia is a rare inherited condition[1] that can be challenging to manage[2]

Five decades of advances have brought the widespread availability of effective hemophilia treatments[3,4]

Several unmet needs remain:

- Bleeding events still occur[5]
- Progression of joint disease[2,6]
- Poor adherence to prophylaxis[7]
- Inhibitor development[8]

Further technological advances may offer more effective and less burdensome hemophilia treatments, addressing the remaining unmet needs and enabling patients to achieve a hemophilia-free mindset[9,10]

1. Srivastava A et al. Haemophilia 2020;26(Suppl 6):1–158; 2. Weyand AC, Pipe SW. Blood 2019;133:389–98; 3. Mannucci P. Haematologica 2020;105:545–53; 4. Gogia P et al. Expert Rev Hematol 2023;16:417–33; 5. Levy-Mendelovich S et al. J Clin Med 2021;10:4303; 6. Soucie J et al. Blood Adv 2018;2:2136–44; 7. Mancuso ME et al. Lancet 2021;397:630–40; 8. Blatný J et al. Thromb Res 2021;198:196–203; 9. Hermans C, Pierce GF. Haemophilia 2023;29:951–53; 10. Skinner MW et al. Haemophilia 2020;26:17–24.