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World Hemophilia Day | April 17. From hog.org

Key Inforbits

- What is Hemophilia?
- Type A vs Type B
- Current Guidelines
- New Treatment Developments
- Ongoing Developments
- Role of the Pharmacist in the Community

What is Hemophilia?[1,2]

Hemophilia is the most common severe hereditary hemorrhagic disorder. Hemophilia is marked by prolonged, excessive bleeding, often following minor trauma, but sometimes occurring spontaneously without apparent cause. A definitive diagnosis is established by identifying clotting factor deficiencies through a clotting factor assay.

The earliest mention is in the Babylonian Talmud (approximately 500 CE) that described excessive bleeding after circumcision. Additionally, it was believed that hemophilia had been inherited by many descendants of Queen Victoria of England (1819-1901), earning it the title "the disease of the kings." In modern history, Dr. John Conrad Otto (1774-1844) first detailed the disorder in male children from unaffected mothers, referring to them as "bleeders." The actual term *hemophilia*, meaning love (philia) of blood (hemo), was introduced by German physician, Johann Lukas Schönlein (1793-1864).

John Conrad Otto. From collections.nlm.nih.gov

While the genetic pattern had been observed for centuries, another German physician, Christian Friedrich Nasse (1778-1851), established the pattern as Nasse's Law. The pattern is recessive on the X-chromosome. Essentially, all daughters of affected fathers will be carriers, and female carriers have a 50% chance of passing the gene to each child – resulting in affected sons or carrier daughters. The genetic pattern makes the disorder more common in males, although it is possible for females to be affected.

Unfortunately, hemophilia remains prevalent and continues to impact people today. Estimations suggest there are approximately 400,000 people living with hemophilia worldwide. Its incidence is equally distributed among ethnic groups worldwide and occurs in about 1:10,000 live births.

Type A vs Type B[1,3]

Blood clot formation involves complex pathways: the intrinsic pathway, triggered by internal trauma, and the extrinsic pathway, activated by external trauma. Both pathways converge to form a stable clot.

Hemophilia consists of hemophilia A (HA) and hemophilia B (HB). HA is more common and makes up around 80-85% of the hemophilia population. The incidence for HA is 1:5,000 live male births compared to 1:30,000 live male births for HB. Patients with HA are deficient in clotting factor VIII while patients with HB are deficient in factor IX. Ultimately, the deficiencies result in the same clinical symptoms such as joint bleeding, muscle hematoma, and soft tissue bleeding. A comparison of the two hemophilia types is seen in the image below.

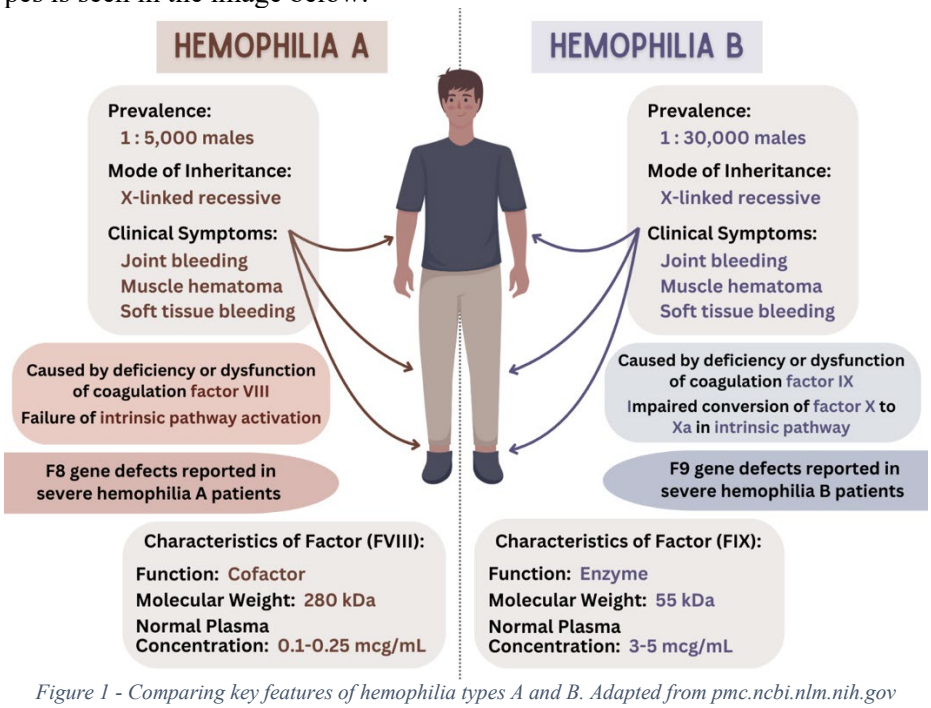

Figure 1 - Comparing key features of hemophilia types A and B. Adapted from pmc.ncbi.nlm.nih.gov

Current Guidelines[2]

The most current hemophilia treatment guidelines were published by the World Federation of Hemophilia in 2022. The guidelines outline 12 principles of care. Those in which pharmacists can have the greatest impact are shown in the table below.

Table 1 - Principles of hemophilia care in which pharmacists can have the greatest impact.

Principle 4: Education and training in hemophilia care	Because hemophilia is a rare disorder, recruiting and training specialists is essential to improving care and reducing complications, regardless of a country's resources. Pharmacists can support education and training efforts by staying current on treatment advances and educating patients, caregivers, and healthcare providers on safe and effective medication use in hemophilia.
Principle 5: Clinical and epidemiological research	Research grounded in evidence is essential for advancing hemophilia care, but progress is often limited by the small patient population. Pharmacists can contribute to hemophilia research by participating in data collection, identifying medication-related trends, and supporting real-world evidence generation to improve patient outcomes.
Principle 7: Multidisciplinary care for hemophilia	Providing the best care for individuals with hemophilia - particularly severe cases - requires a multidisciplinary team to deliver both treatment and comprehensive support. As integral members of the care team,

	pharmacists collaborate with other specialists to ensure appropriate medication management, monitor for adverse effects, and optimize treatment plans.
Principle 11: Management of specific conditions and comorbidities	People with hemophilia and their families may face specific complications at different life stages, and treatment should be incorporated into national hemophilia programs. Pharmacists help manage comorbidities in patients with hemophilia by reviewing medication regimens for interactions, promoting adherence, and providing preventive care guidance tailored to each life stage.

New Treatment Developments

Coagulation factor replacement had been the standard of care for hemophilia patients throughout much of the disease's history. However, different treatments with unique mechanisms are now available, such as monoclonal antibodies and gene therapies. Monoclonal antibodies target areas within coagulation pathways to help the blood clot more effectively. Additionally, gene therapies deliver a functional gene, often via a modified virus, to replace the defective gene in hemophilia patients. Lastly, a small interfering ribonucleic acid (siRNA) agent was recently approved that decreases the activity of antithrombin (AT). Additional information about these treatments is provided in the table below.

Table 2 - New treatment developments for hemophilia.

Drug Name	Indication	Dosage/Administration
Gene Therapy[4,5,6]		
Etranacogene dezaparvovec (Hemgenix)	Treatment of adults with hemophilia B	One-time dose: 2 x 10^{13} genome copies per kg (which is 2 mL per kg) of body weight as an intravenous infusion.
Fidanacogene elaparvovec (Beqvez)	Treatment of adults with moderate to severe hemophilia B	One-time dose: 5 x 10^{11} vector genomes per kg of body weight as an intravenous infusion. Dose based on adjusted body weight for those with a BMI >30 kg/m^2.
Valoctocogene roxaparvovec (Roctavian)	Treatment of adults with severe hemophilia A	One-time dose: 6 x 10^{13} vector genomes per kg (which is 3 mL per kg) of body weight as an intravenous infusion.
Monoclonal Antibody[7,8]		
Emicizumab (Hemlibra)	Routine prophylaxis: • Hemophilia A • Age newborn and older • With or without inhibitors	Initial: 3 mg/kg SUBQ weekly x 4 weeks Maintenance: ▪ 1.5 mg/kg SUBQ weekly or 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks
Concizumab (Alhemo)	Routine prophylaxis: • Hemophilia A and B • Age ≥ 12 years • With inhibitors	Loading dose: ▪ Day 1: 1 mg/kg SUBQ once, then ▪ Day 2: 0.2 mg/kg SUBQ once daily for 4-8 weeks Maintenance dosing by plasma concentration: ▪ < 200 ng/mL: increase to 0.25 mg/kg SUBQ daily ▪ 200-4000 ng/mL: continue 0.2 mg/kg daily ▪ ≥ 4000 ng/mL: decrease to 0.15 mg/kg daily
Marstacimab (Hympavzi)	Routine prophylaxis: • Hemophilia A and B • Age ≥ 12 years • Without inhibitors	▪ Loading dose: 300 mg SUBQ (2 x 150 mg syringe) ▪ Maintenance: (1 week after LD) 150 mg once weekly *Consider increase to 300 mg weekly if patient is ≥50 kg and bleeding events poorly controlled
Antithrombin-directed siRNA agent[9]		
Fitusiran (Qfitlia)	Routine prophylaxis: • Hemophilia A and B • Age ≥ 12 years • With or without inhibitors	Starting dose: 50 mg SUBQ once every 2 months. *Maintain AT activity between 15-35% by adjusting the dose and/or frequency of administration

Drug Name	Indication	Dosage/Administration
Factor Products[7,8]		
Antihemophilic factor (Altuviiio)	Adults and children with hemophilia A (without inhibitors) • Treatment for acute bleeding episodes • Surgical prophylaxis • Routine prophylaxis	Routine prophylaxis: 50 units/kg once weekly Bleeding/Surgery: If no factor VIII levels available: 50 units/kg; Can repeat 30-50 units/kg doses every 2-3 days PRN ▪ If factor VIII levels present: 1 unit/kg raises circulating factor VIII by ~2.6 units/dL; calculate dose using desired factor VIII level based on bleed/surgery type.
GlycoPEGylated Recombinant Factor IX (Rebinyn)	Hemophilia B (without inhibitors) • Treatment for acute bleeding episodes • Surgical prophylaxis • Routine prophylaxis	▪ Routine prophylaxis: 40 units/kg IV once weekly ▪ Bleeding/Surgery: If factor IX levels are present, 1 unit/kg will raise circulating factor IX by 1.9 units/dL; calculate dose using desired factor IX level based on bleed/surgery type.

Ongoing Developments – What's Next?

Research has emerged from a phase 1 trial for a novel treatment approach with hematopoietic stem-cell transplant (HSCT).[10] Similar to other gene therapies for hemophilia, a lentiviral vector introduces a new *F8* transgene into a patient's harvested stem cells. Following myeloablative conditioning, the HSCT is performed to reintroduce cells, now with a functioning gene. This approach had promising results for patients and eliminated spontaneous bleeding events over a 14-month period. There is also a possibility for lifelong therapeutic levels of coagulation factors following HSCT. However, additional clinical trials are necessary to fully assess safety and efficacy with this treatment method.

Additional adeno-associated virus gene therapies are being developed for the treatment of hemophilia A and B. The phase 3 AFFINE study for giroctocogene fitelparvovec is showing positive results with a decrease in annual bleeding rate.[11] This medication, if approved, would provide an additional option for patients with moderately severe to severe hemophilia A. Similarly, verbrinacogene setparvovec is currently undergoing trials for treatment of moderately-severe to severe hemophilia B. In a phase 1-2 trial, the drug demonstrated efficacy for sustained factor IX levels.[12]

Role of the Pharmacist in the Community[13]

Community pharmacists play a vital role in supporting individuals with hemophilia through education, medication management, and advocacy. As accessible healthcare professionals, they are uniquely positioned to identify needs, reinforce treatment plans, and promote safe practices. The following recommendations highlight key ways pharmacists can enhance care for patients with hemophilia.

Community Pharmacist with Patient. From cochrane.org

- Recommend a medical alert bracelet that would let medical personnel know which type of clotting factor that's best in case of an emergency.
- Encourage patients to exercise.
    - Some activities like swimming, bicycle riding and walking can build muscles while protecting joints.
    - Patients will want to avoid contact sports like football, hockey, or wrestling.
- Counsel patients not to take certain pain medications that could make bleeding worse like aspirin and ibuprofen. A safer over-the-counter alternative is acetaminophen.
- When reviewing patient medications, ensure patients are avoiding medications that may increase the patient's risk of bleeding.
- Emphasize to patients and caregivers the importance of keeping all providers informed on all current medications, dietary and herbal supplements, and medical conditions (including

hemophilia) to ensure that pertinent information that may impact the patient's bleeding risk or health status is not overlooked.

- Encourage patients to practice good dental hygiene that prevents tooth and gum disease.
- Recommend patients with hemophilia receive all appropriate vaccinations. When administering vaccinations to people with hemophilia, use the smallest gauge needle and apply pressure or ice for 3-5 minutes after injection.
- Counsel parents of children with hemophilia to protect the child from injuries that could cause bleeding. Help prevent injuries from falls and other accidents by using kneepads, elbow pads, helmets, and safety belts. Parents may also want to remove furniture with sharp corners from the home.

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- FREDERICK BUECHNER (1926 to 2022, American writer and theologian)

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