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REVIEW ARTICLE

Hemophilia: Global Epidemiology, Molecular Pathophysiology, Clinical Manifestations, and Emerging Therapeutic Strategies: A Comprehensive Narrative Review

Arzoo[1], Abdul Rahman Khan[2], Abha Chaorsiya[3]

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ABSTRACT

The intrinsic coagulation pathway's clotting factor deficiencies are the hallmark of hemophilia, a genetic bleeding disorder (Bolton-Maggs and Pasi, 2003; Mannucci and Tuddenham, 2001). The most common types are hemophilia A, caused by factor VIII deficiency, and hemophilia B, caused by factor IX deficiency (Franchini and Mannucci, 2013; Salen and Babiker, 2023). Individuals with hemophilia frequently experience recurrent bleeding episodes, particularly in muscles and joints, which may lead to long-term complications such as hemophilic arthropathy and disability (Llinás, 2010; Srivastava et al., 2013). Advances in molecular genetics, diagnostic techniques, and therapeutic strategies have significantly improved disease management and patient survival (Peyvandi et al., 2016; Franchini, 2013).

This narrative review provides a comprehensive overview of hemophilia, including its global epidemiology, genetic basis, pathophysiology, clinical manifestations, diagnostic approaches, complications, and current treatment modalities (Stonebraker et al., 2010; Soucie et al., 1998). Special emphasis is placed on emerging therapies such as gene therapy, extended half-life clotting factors, and non-factor replacement treatments (Peyvandi et al., 2016; Franchini, 2013). Despite substantial progress in treatment, disparities in access to care persist across different regions of the world (Srivastava, 2005; Berntorp and Shapiro, 2012). Strengthening healthcare systems, promoting early diagnosis, and improving global access to advanced therapies remain essential for optimizing outcomes in individuals with hemophilia (Srivastava *et al.*, 2013).

AUTHOR'S AFFILIATION:

[1] Student, B.Sc. Nursing 6th Semester, Galgotias School of Nursing, Galgotias University, Greater Noida, Uttar Pradesh, India.

[2] Student, B.Sc. Nursing 6th Semester, Galgotias School of Nursing, Galgotias University, Greater Noida, Uttar Pradesh, India.

[3] Assistant Professor, Galgotias School of Nursing, Galgotias University, Greater Noida, Uttar Pradesh, India.

CORRESPONDING AUTHOR:

Abha Chaorsiya, Assistant Professor, Galgotias School of Nursing, Galgotias University, Greater Noida, Uttar Pradesh, India.

E-mail: Chaurasia.abha85@gmail.com

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• Hemophilia • Bleeding Disorders • Factor Viii Deficiency • Gene Therapy • Hemophilic Arthropathy • Prophylaxis

INTRODUCTION

Hemophilia is a rare inherited bleeding disorder characterized by impaired blood coagulation due to deficiency or dysfunction of specific clotting factors (Bolton-Maggs and Pasi, 2003; Mannucci and Tuddenham, 2001). The condition primarily results from deficiency of clotting factor VIII (hemophilia A) or factor IX (hemophilia B), both essential components of the intrinsic coagulation pathway (Franchini and Mannucci, 2013; Salen and Babiker, 2023). These deficiencies impair thrombin generation and fibrin clot formation, leading to prolonged bleeding after injury and, in severe cases, spontaneous hemorrhage (Goodeve *et al.,* 2010; Peyvandi *et al.,* 2016).

Hemophilia is inherited as an X-linked recessive disorder caused by mutations in genes located on the X chromosome (Mannucci and Tuddenham, 2001; Rogaev *et al.,* 2009). Since males possess only one X chromosome, they are predominantly affected, whereas females are usually carriers with variable clotting factor levels; however, some carriers may exhibit mild bleeding symptoms due to lyonization (Plug *et al.,* 2006; Van den Berg *et al.,* 2007).

Historically, hemophilia gained prominence among European royal families, particularly among descendants of Queen Victoria, leading to its designation as the "royal disease" (Rogaev *et al.,* 2009; Schramm, 2014). Subsequent genetic research confirmed that mutations in the factor VIII gene were responsible for transmission across royal lineages (Mannucci and Tuddenham, 2001).

Hemophilia remains one of the most common inherited bleeding disorders worldwide. Approximately 80–85% of cases are hemophilia A and 15–20% are hemophilia B (Stonebraker et al., 2010; Soucie *et al.,* 1998). The estimated incidence is about 1 in 5,000 male births for hemophilia A and 1 in 25,000 for hemophilia B (Peyvandi *et al.,* 2016; CDC, 2021). Global data indicate that more than 250,000 individuals are affected, although underdiagnosis remains a concern in many regions (Stonebraker *et al.,* 2010; Srivastava, 2005).

The clinical severity of hemophilia depends on circulating clotting factor levels. Severe hemophilia (<1% activity) is characterized by spontaneous bleeding, particularly into joints and muscles, whereas moderate and mild forms typically present with bleeding following trauma or surgery (White *et al.,* 2001; Srivastava *et al.,* 2013). Hemarthrosis, especially involving knees, ankles, and elbows, is a major complication and may lead to chronic hemophilic arthropathy, pain, and disability (Llinás, 2010; Berntorp and Shapiro, 2012). Other manifestations include muscle hematomas, mucosal bleeding, gastrointestinal hemorrhage, and, rarely, life-threatening intracranial bleeding (Hegde *et al.,* 2016; Darby *et al.,* 2007).

Management of hemophilia has evolved significantly over time. Early therapies relied on whole blood and plasma transfusions, which were associated with limited efficacy and a high risk of infection (Mannucci, 2001; Franchini, 2013). The introduction of factor replacement therapy marked a major breakthrough, allowing targeted correction of clotting deficiencies (Srivastava *et al.,* 2013; Franchini, 2013). Subsequently, recombinant clotting factor concentrates improved treatment safety by eliminating the risk of transfusion-transmitted infections (Peyvandi *et al.,* 2016).

Recent advances have further transformed hemophilia care, including extended half-life factor products, monoclonal antibody therapies, and gene therapy approaches (Peyvandi *et al.,* 2016; Kruse-Jarres *et al.,* 2017). These innovations aim to reduce treatment burden, prevent bleeding episodes, and potentially provide long-term or curative outcomes.

Despite these advances, significant global disparities in hemophilia care persist. Limited access to diagnostic tools, clotting factor concentrates, and specialized care in low-resource settings leads to poorer outcomes (Srivastava, 2005; Berntorp and Shapiro, 2012). Addressing these challenges requires improved healthcare infrastructure, early

diagnosis, and equitable access to modern therapies worldwide.

Thus, this narrative review aims to provide a comprehensive overview of hemophilia, including its epidemiology, molecular pathogenesis, clinical features, diagnostic approaches, and emerging therapies. Understanding these aspects is essential for improving patient care and guiding future research in inherited bleeding disorders (Peyvandi et al., 2016).

Epidemiology

Although hemophilia is considered a rare disorder, it remains one of the most common inherited bleeding diseases worldwide (Stonebraker et al., 2010; Soucie *et al.,* 1998). The condition affects all ethnic groups and geographic regions, although variations in prevalence exist due to differences in healthcare infrastructure, diagnostic capabilities, and national reporting systems (Srivastava, 2005; Stonebraker *et al.,* 2010). Approximately 80–85% of cases are hemophilia A, while 15–20% are hemophilia B (Peyvandi *et al.,* 2016; Franchini and Mannucci, 2013).

Hemophilia A is estimated to occur in about 1 in 5,000 male births, whereas hemophilia B affects approximately 1 in 25,000 male births (Peyvandi *et al.,* 2016; CDC, 2021). Epidemiological data indicate that hemophilia A is four to five times more common than hemophilia B (Stonebraker *et al.,* 2010). However, the true prevalence is likely underestimated due to underdiagnosis, particularly in low-and middle-income countries with limited diagnostic resources (Srivastava, 2005; Berntorp and Shapiro, 2012).

According to global survey data from the World Federation of Hemophilia, more than 250,000 individuals have been identified with hemophilia worldwide, including approximately 208,000 cases of hemophilia A and over 40,000 cases of hemophilia B (Stonebraker *et al.,* 2010). Nevertheless, experts suggest that a substantial proportion of affected individuals remain undiagnosed, especially in developing countries (Srivastava, 2005). In high-income countries with well-established healthcare systems, most individuals with hemophilia are diagnosed and receive appropriate treatment, whereas in many low-income regions, only a small fraction of patients are identified and managed (Berntorp and Shapiro, 2012; Srivastava, 2005).

Large population-based studies have demonstrated significant regional variation in hemophilia prevalence. Higher detection rates are reported in North America and Europe due to comprehensive healthcare systems and national registries, while underreporting remains common in regions with limited access to hematology services and laboratory diagnostics (Stonebraker *et al.,* 2010; Srivastava, 2005).

An important aspect of hemophilia epidemiology is the presence of female carriers. Although the disease predominantly affects males, female carriers may exhibit reduced clotting factor levels and mild to moderate bleeding symptoms (Plug *et al.,* 2006; Van den Berg *et al.,* 2007). Studies suggest that approximately 10–30% of carriers may experience clinically significant bleeding, highlighting the importance of genetic counseling and screening (Plug *et al.,* 2006).

Over recent decades, advances in treatment have significantly improved survival among individuals with hemophilia. Historically, life expectancy was reduced due to complications such as uncontrolled bleeding and transfusion-transmitted infections (Mannucci, 2001; Darby *et al.,* 2007). However, modern therapeutic approaches, including safer clotting factor products and comprehensive care, have markedly enhanced patient outcomes (Darby *et al.,* 2007; Peyvandi *et al.,* 2016).

Furthermore, advancements in surveillance systems and international registries have improved understanding of hemophilia epidemiology. Global databases maintained by organizations such as the World Federation of Hemophilia provide valuable insights into disease distribution, treatment patterns, and long-term outcomes, which are essential for guiding healthcare policies and improving access to care worldwide (Stonebraker *et al.,* 2010; Srivastava *et al.,* 2013).

Pathophysiology

Hemophilia is caused by genetic mutations that impair the synthesis or function of clotting factors involved in the intrinsic pathway of the coagulation cascade (Mannucci and Tuddenham, 2001; Goodeve *et al.,* 2010). The two major forms of the disease are hemophilia A and hemophilia B, resulting

from deficiencies of factor VIII and factor IX, respectively (Franchini and Mannucci, 2013; Salen and Babiker, 2023). These clotting factors are essential for the activation of factor X and subsequent thrombin generation, which is necessary for the formation of stable fibrin clots (Peyvandi *et al.,* 2016; Goodeve *et al.,* 2010).

The genes encoding factor VIII and factor IX are located on the X chromosome, explaining the characteristic X-linked recessive inheritance pattern of hemophilia (Mannucci and Tuddenham, 2001; Rogaev *et al.,* 2009). Various types of mutations—including point mutations, insertions, deletions, and inversions—can disrupt normal protein synthesis (Goodeve *et al.,* 2010; Franchini and Mannucci, 2013). Among these, the intron 22 inversion of the factor VIII gene is one of the most common mutations associated with severe hemophilia A (Goodeve *et al.,* 2010).

In individuals with hemophilia, reduced or absent clotting factor activity disrupts the intrinsic coagulation pathway. Normally, coagulation involves a cascade of enzymatic reactions in both intrinsic and extrinsic pathways, ultimately leading to thrombin generation and fibrin clot formation (Peyvandi *et al.,* 2016). Thrombin plays a central role in converting fibrinogen into fibrin, thereby stabilizing the clot and preventing further bleeding (Mannucci, 2001).

A major complication in hemophilia is the development of inhibitors—neutralizing antibodies directed against infused clotting factor concentrates used in treatment (Kruse-Jarres *et al.,* 2017; Franchini, 2013). Approximately 20–30% of patients with severe hemophilia A develop inhibitors, significantly complicating management and requiring alternative therapeutic strategies (Kruse-Jarres *et al.,* 2017).

Recent studies have also highlighted the role of vascular abnormalities and chronic inflammation in the pathogenesis of hemophilic arthropathy. Recurrent joint bleeding leads to synovial hypertrophy, cartilage destruction, and progressive joint damage (Llinás, 2010; Berntorp and Shapiro, 2012).

Advances in the understanding of molecular mechanisms underlying hemophilia have facilitated the development of innovative therapeutic approaches, including recombinant clotting factor products, extended half-life therapies, and gene therapy (Peyvandi *et al.,* 2016; Franchini, 2013). These strategies aim to restore hemostatic balance, reduce bleeding frequency, and improve the overall quality of life of individuals with hemophilia.

Clinical Manifestations

Individuals with hemophilia frequently experience recurrent episodes of spontaneous bleeding, particularly into muscles and joints (Srivastava *et al.,* 2013; Peyvandi *et al.,* 2016). One of the most characteristic clinical features is hemarthrosis, commonly involving the knees, ankles, and elbows (Llinás, 2010; Berntorp and Shapiro, 2012). Repeated joint bleeding leads to progressive joint damage known as hemophilic arthropathy, resulting in chronic pain, stiffness, and functional impairment (Llinás, 2010).

Other common clinical manifestations include:

- Easy bruising (CDC, 2021; National Heart, Lung, and Blood Institute, 2021)
- Prolonged bleeding following injury, surgery, or dental procedures (Srivastava *et al.,* 2013)
- Muscle hematomas, which may lead to compartment syndrome in severe cases (Peyvandi *et al.,* 2016)
- Epistaxis (nosebleeds), often recurrent and difficult to control (CDC, 2021)
- Gastrointestinal bleeding (Darby *et al.,* 2007)
- Intracranial hemorrhage, a rare but life-threatening complication (Hegde *et al.,* 2016; Darby *et al.,* 2007)

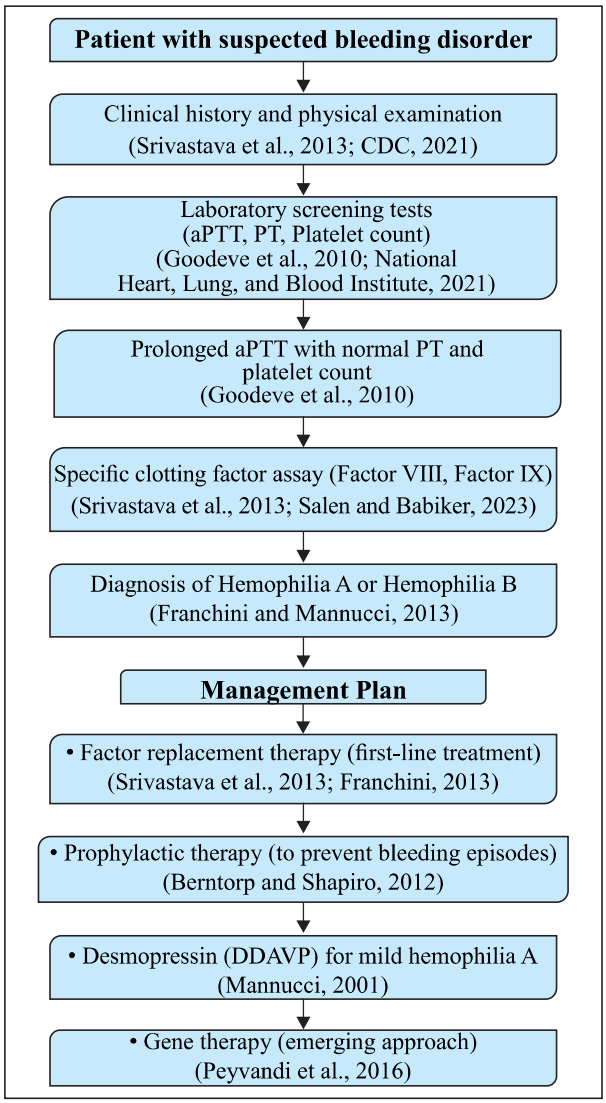
Diagnosis

The diagnosis of hemophilia is based on a combination of clinical assessment and laboratory investigations (Srivastava *et al.,* 2013; CDC, 2021). Screening tests typically reveal a prolonged activated partial thromboplastin time (aPTT), while prothrombin time and platelet count usually remain within normal limits (Goodeve *et al.,* 2010; National Heart, Lung, and Blood Institute, 2021). A definitive diagnosis is established by measuring specific clotting factor levels, particularly factor VIII and factor IX activity, which help distinguish hemophilia A from hemophilia B (Srivastava *et al.,* 2013; Salen and Babiker, 2023). Genetic testing may also be performed to identify the exact mutation responsible for hemophilia, which is useful for confirming the diagnosis, carrier detection, prenatal counseling, and family screening (Mannucci and Tuddenham,

2001; Goodeve *et al.,* 2010)

Clinical assessment and laboratory testing are used in the diagnosis process Prothrombin time and platelet count are normal, but screening tests usually show extended activated partial thromboplastin time (aPTT). Clotting factor levels are measured to confirm a definitive diagnosis. To pinpoint the precise mutations causing hemophilia, genetic testing may also be carried out.

Diagnostic and Management Algorithm for Hemophilia



Management and Treatment

Replacement of deficient clotting factors using factor concentrates remains the cornerstone of hemophilia management (Srivastava *et al.,* 2013; Franchini, 2013). Prophylactic therapy, which involves regular administration of clotting factor concentrates, has become the standard of care in many countries as it significantly reduces the frequency of bleeding episodes and prevents long-term joint damage (Berntorp and Shapiro, 2012; Srivastava *et al.,* 2013).

The development of recombinant clotting factor products has markedly improved treatment safety by eliminating the risk of transmission of blood-borne infections associated with plasma-derived products (Peyvandi *et al.,* 2016; Mannucci, 2001).

Recent therapeutic advancements include gene therapy and non-factor replacement therapies, which aim to reduce treatment burden, improve hemostatic control, and provide long-term or potentially curative outcomes (Peyvandi *et al.,* 2016; Kruse-Jarres *et al.,* 2017)

DISCUSSION

Over the past few decades, the management of hemophilia has undergone significant transformation (Mannucci, 2001; Peyvandi *et al.,* 2016). Early therapeutic approaches primarily relied on cryoprecipitate and plasma transfusions, which were associated with limited efficacy and a substantial risk of transmitting viral infections such as hepatitis and HIV (Mannucci, 2001; Franchini, 2013). A major milestone in hemophilia care was the development of recombinant clotting factor concentrates, which significantly improved treatment safety by eliminating the risk of blood-borne infections (Peyvandi *et al.,* 2016).

Prophylactic therapy has been shown to dramatically reduce bleeding frequency and prevent joint damage (Srivastava *et al.,* 2013; Berntorp and Shapiro, 2012). Studies indicate that regular prophylactic administration of clotting factor concentrates can reduce annual bleeding rates by up to 70–80% compared to on-demand treatment (Srivastava *et al.,* 2013). Furthermore, early initiation of prophylaxis in children has been associated with improved long-term joint outcomes and better functional status (Berntorp and Shapiro, 2012)

Recent studies have highlighted the potential of gene therapy as a transformative approach in the management of hemophilia (Peyvandi *et al.,* 2016). Gene therapy aims to achieve sustained endogenous production of clotting factors, thereby increasing factor levels over time and reducing or even eliminating the

need for frequent factor infusions (Peyvandi *et al.,* 2016; Franchini, 2013).

Despite these advances, significant disparities in access to treatment remain a major global challenge (Srivastava, 2005; Berntorp and Shapiro, 2012). Studies conducted in low and middle-income countries indicate that many individuals with hemophilia receive inadequate care due to high treatment costs, limited availability of clotting factor concentrates, and insufficient healthcare infrastructure (Srivastava, 2005). Addressing these inequalities requires strengthening healthcare systems, improving access to diagnostic and therapeutic services, and fostering international collaboration to ensure equitable care for all patients with hemophilia (Srivastava *et al.,* 2013; Berntorp and Shapiro, 2012)

CONCLUSION

Hemophilia is a complicated hereditary bleeding illness that has important social and therapeutic ramifications. Medical science breakthroughs have significantly enhanced patient outcomes and illness management. To guarantee fair access to diagnosis and treatment, however, further research and international healthcare initiatives are required. Future medical advancements, especially gene therapy and tailored medication, have the potential to turn hemophilia from a chronic illness into one that may be cured.

Declarations

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