INDONESIAN JOURNAL OF LIFE SCIENCES
eISSN: 2656-0682

Indonesian Journal of Life Sciences Vol. 07 No. 01 March 2025
https://journal.i3l.ac.id/index.php/IJLS/article/view/187/5
DOI:10.54250/ijls.v7i1.187

REVIEW ARTICLE

Exploring Hemophilia: Understanding the Underlying Mechanisms, Diagnostic Strategies, and Therapeutic Advances

Michelle Danisa[1], Stephanie Grace Maringka[1], Efrando Augusto[1], Aurelia Catherine[1], Melinda Christian[1], Maria Maylyn Evangelina Wong[1], Krystle Hadassa Tjong[1], Gabriella Gita Febriana[1*]

[1]*Department of Biomedicine, Institut Bio Scientia Internasional Indonesia, Jakarta, Indonesia*
**Corresponding author: gabriella.febriana@i3l.ac.id*

A B S T R A C T

Hemophilia is a blood disorder marked by impaired blood clotting due to defective or deficient coagulation factors, resulting in prolonged bleeding upon vascular injury. It is classified into hemophilia A, B, and C, caused by deficiencies in factor VIII, IX, and XI, respectively. Additionally, acquired hemophilia can occur due to autoantibody production against coagulation factors. Hemophilia affects millions globally, with a higher prevalence in Asian countries such as India, Bangladesh, and Indonesia. Despite significant advancements in gene therapy, non-factor replacement therapies, and recombinant factor concentrates, access to diagnosis and treatment remains limited in low-resource settings. This review explores the epidemiology, etiology, pathophysiology, diagnostic strategies, and current and emerging therapeutic approaches for hemophilia, while also highlighting the importance of addressing healthcare disparities and promoting equitable access to care.

K E Y W O R D S

hemophilia; coagulation factors; gene therapy; bleeding disorder; healthcare disparities

H I G H L I G H T S

- Hemophilia A, B, and C are caused by deficiencies in factor VIII, factor IX, and factor XI, respectively, with acquired hemophilia arising from autoantibodies against coagulation factors.
- Gene therapy and non-factor replacement therapies like emicizumab and fitusiran offer promising alternatives to traditional clotting factor replacement.
- Inhibitor development remains a major complication, with immune tolerance induction and bypassing agents as current management strategies.
- Hemophilia prevalence is highest in Asian countries, with significant diagnostic and treatment gaps in low-resource regions like Indonesia.
- Emerging strategies like community-based screening programs, mobile health services, and local plasma-derived factor production are potential solutions to improve healthcare access.

INTRODUCTION

Hemophilia was initially recognized as "the royal disease" since Queen Victoria of England and other European royal families possessed this disease and passed it on to their successors (Lannoy & Hermans, 2010). As disease research advances, hemophilia is now understood as an inherited blood disorder in which blood is unable to clot due to deficient or defective clotting factors, resulting in uncontrollable bleeding. Recent advances in research have improved the understanding of hemophilia genetics and novel treatment approaches such as gene therapy, and innovative non-factor replacement therapies like emicizumab, which provides a significant therapeutic alternative for hemophilia patients (Pasi et al., 2017; Mahlangu et al., 2020). Additionally, advancements in recombinant factor production, extended half-life clotting factors, and targeted molecular therapies have enhanced patient outcomes and reduced treatment burdens (Mahlangu et al., 2020; Konkle et al., 2019).

Hemophilia is classified based on the type of deficient or defective clotting factor: hemophilia A, hemophilia B, and hemophilia C, caused by deficient or defective factor VIII (FVIII), factor IX (FIX), and factor XI (FXI), respectively. The severity of this disease is determined by the degree of clotting factor deficiency and defect (Rodríguez-Merchán & Jiménez-Yuste, 2022). The global prevalence of hemophilia has been widely reported, with hemophilia A affecting approximately 1 in 5,000 male births and hemophilia B affecting 1 in 25,000 male births (Iorio et al., 2019; Stonebraker et al., 2020). A recent study published in the Annals of Internal Medicine suggests that the number of hemophilia patients worldwide is nearly three times larger than previously estimated, highlighting the need for improved diagnosis and reporting (Alblaihed et al., 2022). Regionally, India has the highest prevalence of hemophilia, followed by Bangladesh, Indonesia, and China (World Federation of Hemophilia, 2021). The disparities in hemophilia prevalence and treatment availability across different regions emphasize the need for global efforts to improve access to care.

Hemophilia diagnosis relies on clinical history evaluation, laboratory assays to measure clotting factor activity, and genetic testing for carrier detection and prenatal diagnosis (Srivastava et al., 2020). Management strategies for hemophilia have advanced significantly, including prophylactic clotting factor replacement therapy, bypassing agents for inhibitor cases, and gene therapy as a potential long-term cure (Mahlangu et al., 2020). Despite these advancements, challenges remain in ensuring equitable access to treatments, particularly in low-resource settings, where clotting factor concentrates are scarce (Stonebraker et al., 2020). Novel therapeutic approaches, such as RNA-based therapies and gene editing, are being explored to provide sustainable and cost-effective solutions (Pasi et al., 2020).

All types of hemophilia have similar signs and symptoms since they influence the same downstream pathway. In the case of excessive bleeding, anemia is the most common manifestation of hemophilia because a large amount of blood is lost due to poor clotting. In addition, the patient’s body appears paler and weaker due to reduced oxygen and nutrient levels for the cells. Human homeostasis also attempts to overcome this condition, causing orthostasis due to prolonged vasoconstriction impairment, tachycardia to provide adequate blood supply for cells, and tachypnea to ensure appropriate oxygen supply to the blood (Amoozgar et al., 2017; Sahu et al., 2011). In addition, joint organ systems are commonly damaged by hemophilia, considering that they are covered by a rich network of capillaries and are more prone to bleeding at the synovial membrane (Knobe & Berntorp, 2011). Prolonged bleeding into joints causes hemophilic arthropathy, which results in pain, deformity, and disability. Other symptoms seen in other tissues include muscle pain, stiff neck, hematemesis, and hematuria (Hirayama et al., 2019).

Despite significant progress in hemophilia research, diagnosis, and management, several gaps remain. Many hemophilia cases remain undiagnosed, particularly in developing regions, due to limited awareness and access to diagnostic tools (Iorio et al., 2019). Gene therapy, while promising, faces challenges such as immune responses, durability of treatment effects, and cost barriers (Pasi et al., 2020).

Additionally, the long-term effects of non-factor replacement therapies and their impact on immune responses also require further investigation. While prophylactic therapies have been used to mitigate excessive bleeding episodes in hemophilia patients, breakthrough bleeding and long-term joint damage continue to be major concerns, necessitating more effective preventive strategies (Srivastava et al., 2020). Addressing these gaps requires continued research efforts to improve diagnostic techniques, expand access to effective treatments, and enhance the overall quality of life for individuals with hemophilia.

BLOOD COAGULATION PATHWAY

When a blood vessel is injured, platelets are activated at the site of injury, triggering the beginning of coagulation factors and the production of fibrin blood clumps through the 'Inborn pathway' of coagulation. The coagulation cascade can occur in two different ways: the extrinsic and intrinsic pathways (**Figure 1**). The extrinsic pathway occurs when endothelial damage causes tissue factors (TF) to become exposed, activating factor III and factor VII, forming the TF–VIIa complex. This complex triggers the activation of factor X, linking the extrinsic pathway to the common pathway. Meanwhile, the intrinsic pathway occurs when a damaged blood vessel activates factor XII. Activated factor XII (XIIa) subsequently activates factor XI, which in turn activates factor IX. Factor IXa, together with its essential cofactor factor VIIIa, facilitates the activation of factor X. (Aria et al., 2019; Barbosa & Martins, 2017).

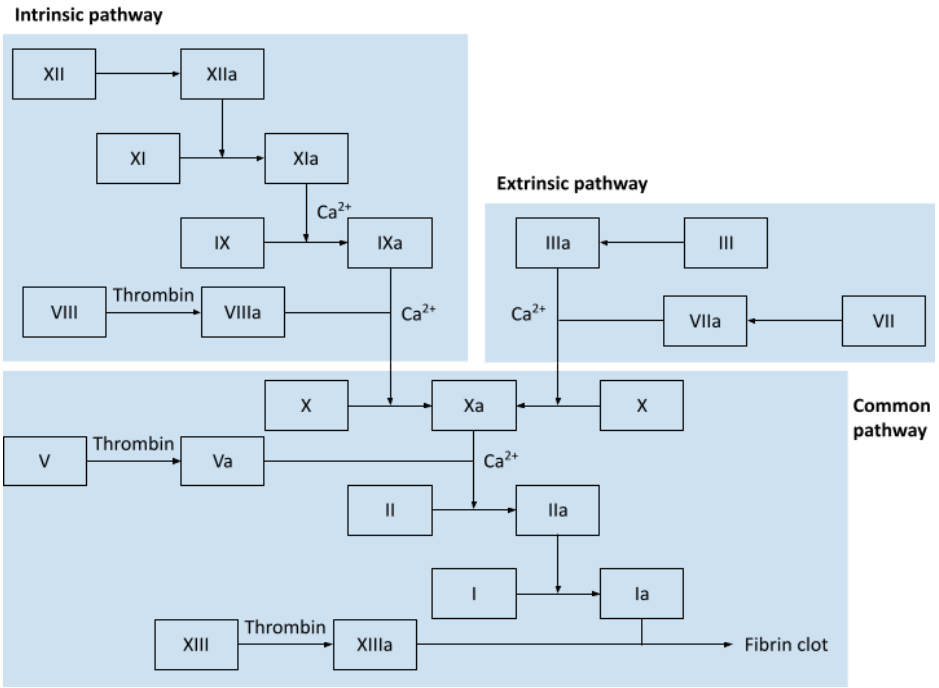

Figure 1. Blood coagulation pathway

Both pathways eventually converge in the common pathway, where the activated factor X binds to its cofactor, factor Va, forming the prothrombinase complex that catalyzes the conversion of factor II (prothrombin) into factor IIa (thrombin), which is a key enzyme in coagulation. Thrombin then cleaves factor I (fibrinogen) to fibrin (factor Ia), which polymerizes to form a soft clot. Finally, factor XIIIa crosslinks with fibrin, strengthening the clot and preventing further bleeding (Aria et al., 2019; Barbosa & Martins, 2017).

Several cofactors and regulators influence the coagulation cascade. Ca^{2+} ions are essential for the activation and binding of coagulation factors to phospholipid surfaces, especially in platelet membranes. Additionally, vitamin K is crucial for the γ-carboxylation of factors II, VII, IX, and X, ensuring their proper function. Deficiencies in these components can lead to impaired clot formation (Barmore et al., 2023).

In hemophilia, mutations or deficiencies in clotting factors—primarily factor VIII (hemophilia A) or factor IX (hemophilia B)—result in impaired thrombin generation and inadequate fibrin formation, leading to prolonged bleeding. The development of inhibitors (alloantibodies against clotting factors) further complicates treatment, making factor replacement therapies less effective (Mehta & Reddivari, 2023).

COMPARISON OF HEMOPHILIA A, B, AND C

Table 1. provides a structured comparison of hemophilia A, B, and C, highlighting key aspects including the deficient clotting factors, genetic causes, inheritance patterns, prevalence, severity, clinical manifestations, and treatment options. It also distinguishes differences in clinical symptoms, noting that hemophilia A and B often cause spontaneous bleeding, whereas hemophilia C primarily leads to bleeding following trauma or surgery. Treatment strategies vary, but they generally involve factor replacement therapy, with gene therapy currently being explored for hemophilia A and B.

Table 1. Comparison of hemophilia A, B, and C in terms of deficient factor, genetic cause, inheritance pattern, prevalence, severity, clinical manifestations, as well as prognosis and management

Feature	Hemophilia A	Hemophilia B	Hemophilia C
Deficient Factor	Factor VIII (FVIII)	Factor IX (FIX)	Factor XI (FXI)
Genetic Cause	Mutation in the F8 gene on X chromosome	Mutation in the F9 gene on X chromosome	Mutation in the F11 gene on chromosome 4
Inheritance Pattern	X-linked recessive	X-linked recessive	Autosomal recessive
Prevalence	Most common (80–85% of cases)	Less common (10–15% of cases)	Rare, mostly found in Ashkenazi Jewish populations
Severity	Can be mild, moderate, or severe	Can be mild, moderate, or severe	Usually mild to moderate
Clinical Manifestations	Spontaneous joint and muscle bleeding, prolonged bleeding after injury or surgery	Similar to Hemophilia A but may have milder symptoms	Post-surgical or trauma-related bleeding, not spontaneous bleeding
Prognosis & Management	FVIII replacement therapy, gene therapy in development	FIX replacement therapy, gene therapy in development	FXI replacement therapy, antifibrinolytics for mild cases

HEMOPHILIA A

Etiology and Pathophysiology

When the blood vessel endothelium is damaged, the hemostatic process initiates the coagulation pathway in order to regain vascular integrity and avoid uncontrolled bleeding. Factor VIII, which deficiency causes hemophilia A, is required for thrombin production and fibrin synthesis. Inadequate thrombin in the

coagulation cascade leads to a fibrin deficit, which leads to poor fibrin stabilization, resulting in the failure of secondary hemostasis (Aria et al., 2019).

The mutations causing hemophilia A can be categorized into three. The first category encompasses classic mutations in FVIII, causing molecular structural changes or even creating a truncated protein that lacks the essential functional domains. These mutations can be in the form of gene rearrangements, deletions or insertions of the genetic sequence, and single DNA base changes that result in amino acid substitution, early peptide chain termination, or mRNA splicing abnormalities (Nogami & Shima, 2019). The second category is caused by mutations of proteins that are intracellularly interacting in the process of FVIII protein folding and trafficking, or mutations of extracellular plasma proteins that play a role in blood coagulation, such as von Willebrand Factor (VWF). VWF plays a role by binding to FVIII, preventing FVIII from protease degradation (Pipe et al., 2016). The third category includes patients who experience the clinical manifestations of hemophilia despite having no mutation in the FVIII gene or in any of the known FVIII interacting partners (Huether et al., 2022).

The gene responsible for producing FVIII is located in the distal end of the X chromosome (Tantawy, 2010). The FVIII gene contains a high level of guanine and cytosine, making it more vulnerable to DNA methylation and cytosine deamination mutations (Payne et al., 2013). Additionally, two hotspot inversions, especially in intron 1 and intron 22, have been revealed to contribute to 40-50% of individuals with severe hemophilia A (Zimmermann et al., 2011). These hotspot inversions are induced by intrachromosomal homologous recombination between identical inverted repeats, which are the two lengthy repeats inside the FVIII locus: Int22h-1 in intron 22 and Int1h-1 in intron 1 (Jamil et al., 2019). Another factor that causes hemophilia A is the overexpression of non-coding RNAs or microRNAs, especially the miR-374b-5p and miR-30c-5b, which bind with the FVIII gene mRNA and inhibit its translation process (Jankowska et al., 2020; Zimta et al., 2021).

HEMOPHILIA B

Etiology and Pathophysiology

Hemophilia B is caused by mutations in the gene coding for factor IX (FIX), causing FIX to be deficient or defective. The coding sequence for FIX is located on the X chromosome location X127.1, with a size of 33 kbp and containing seven introns and eight exons. The mutations in FIX causing hemophilia B include point mutations (64%), small insertions or deletions (18%), splice mutations (9%), and large insertions or deletions (6%), with most of these mutations occurring in the FIX promoter region (Liu et al., 2024). Specifically, point mutations in the catalytic domain can lead to amino acid substitutions that disrupt the active site conformation, impairing substrate binding and enzymatic activity. Mutations in the Gla domain may interfere with the γ-carboxylation process, reducing calcium ion affinity and preventing proper membrane binding, which is critical for coagulation cascade progression (Vatandoost & Sani, 2017). Additionally, splice mutations can lead to aberrant mRNA splicing, resulting in truncated or misfolded proteins that are rapidly degraded or lack functional activity (Shen et al., 2022). Large insertions or deletions may disrupt the overall tertiary structure of FIX, rendering it unable to undergo necessary interactions with factor VIIIa or phospholipid surfaces. As a result, dysfunctional or defective FIX fails to activate factor X efficiently, leading to impaired thrombin generation and inadequate fibrin clot formation. (Ishii, 2018; Shen et al., 2022).

Hemophilia B Leyden

Hemophilia B Leyden (HBL) is a genetic disorder characterized by a deficiency of factor IX (FIX) in early life. It is caused by mutations in transcription factor binding sites on the X chromosome, except for the androgen-responsive sites, resulting in reduced FIX production. This phenotype is severe at birth, but as the

level of androgen rises during adolescence, the transcription level of FIX increases due to the binding of androgen to its promoter, compensating for the faulty transcription factors binding sites. This also leads to the activation of FIX gene expression to a certain extent, thus by midlife, the patients would have a normal level of FIX and may no longer need bleeding treatments (Rallapalli et al., 2013).

HEMOPHILIA C

Etiology and Pathophysiology

Hemophilia C is an autosomal recessive disorder of factor XI (FXI) deficiency, caused by a mutation occurring in the gene coding for FXI, which is located at the distal end of chromosome 4 in humans (Alghamdi et al., 2019). Hemophilia C is most predominant in the Ashkenazi Jews, affecting 1 in 450 people. Meanwhile, the severe form of hemophilia C, causing less than 20% of FXI activity, is rare in the general population (around 1 case per million). FXI is a plasma glycoprotein with the size of 160 kDa that works in the blood coagulation pathway by binding to macromolecules necessary for blood coagulation. FXI deficiency leads to the interference of the blood coagulation pathway, with the most common sites for hemorrhage including the oral cavity, nasopharynx, and urinary tract.

There have been more than 250 FIX gene mutations identified in hemophilia C patients (Saba & Roberts, 2014). The two most common mutations causing this condition are Glu117Stop and Phe283Leu. Glu117Stop mutation, also called “type II” mutation, is observed to cause premature termination of FXI expression in its A2 domain, preventing the synthesis of FIX by the cells. Meanwhile, Phe283Leu mutation, or “type III” mutation, causes dimer formation interference, resulting in the retention of the FXI monomeric protein. Other mutations in the FXI gene causing hemophilia C, including Ser225Phe and Cys398Tyr, are also commonly observed to interfere with FXI protein synthesis and/or protein dimerization (Jayakrishnan et al., 2019).

ACQUIRED HEMOPHILIA

Acquired hemophilia is a condition in which the body produces alloantibodies that bind to coagulation factors, inhibiting their role in the blood coagulation pathway. These alloantibodies, also known as inhibitors, are high-affinity immunoglobulin G (IgG) (Franchini & Mannucci, 2011). Acquired hemophilia primarily affects individuals with preexisting hemophilia or other coagulation disorders who undergo repeated exposure to clotting factors, such as factor VIII (FVIII) and factor IX (FIX). The development of inhibitors represents one of the most severe and clinically significant complications of hemophilia treatment. This condition is more common in hemophilia A patients compared to hemophilia B patients (Goodeve, 2015). The International Society of Hemostasis and Thrombosis (ISTH) classified inhibitors into high- or low-responder subtypes, with high-responder inhibitors reaching a maximum activity level of more than 5 Bethesda Units (BU)/mL at their peak. Additional risk factors of coagulation factor inhibitors include hemophilia severity, family history of inhibitor development, and race, in which the production of inhibitors is more likely to happen in black children. In addition, the production of inhibitors, both in hemophilia A and B, is commonly associated with disruptive mutations, such as large gene deletions, frameshift mutation, and stop codon formation (Franchini & Mannucci, 2011; Key, 2004).

DIAGNOSIS

Since hemophilia is a genetically linked disease, genetic testing plays a crucial role in confirming a diagnosis and identifying carriers. Genetic testing involves analyzing the F8 (factor VIII) and F9 (factor IX) genes to detect mutations responsible for hemophilia A and B, respectively. This method is particularly

useful for identifying carriers in families with a history of hemophilia and for prenatal or preimplantation genetic diagnosis (PGD). Confirmation of prenatal diagnosis is often done through polymerase chain reaction (PCR) and denaturing high-performance liquid chromatography (DHPLC), especially to identify a rare large fragment insertion mutation (Yang et al., 2024). Techniques such as next-generation sequencing (NGS) and multiplex ligation-dependent probe amplification (MLPA) allow for the detection of point mutations, insertions, deletions, and large gene rearrangements that may not be identified through traditional methods (Cheng et al., 2024). Additionally, linkage analysis using DNA markers near the hemophilia genes can be applied in cases where direct mutation detection is challenging. Genetic testing not only confirms hemophilia diagnosis but also provides valuable insights into disease severity, as specific mutations correlate with factor activity levels and potential inhibitor development (Pezeshkpoor et al., 2022).

In addition to genetic testing, diagnosis of hemophilia also relies on laboratory testing, which is usually performed immediately after birth if the newborn is suspected of having the disease. This involves measuring factor VIII and IX activity in blood samples collected from the umbilical cord or a vein. The level of factor activity determines the severity of hemophilia, which is categorized into three groups: severe (<1% factor activity), moderate (1–5%), and mild (6–40% for hemophilia A; 6–50% for hemophilia B) (Castaman & Matino, 2019). Severe hemophilia is typically diagnosed before the age of one, while moderate cases are usually detected before the age of six. Mild hemophilia, on the other hand, is often diagnosed later in life when unexplained bleeding episodes occur (Castaman & Matino, 2019).

Laboratory testing for hemophilia involves several coagulation assays to assess blood clotting function. A complete blood count (CBC) helps evaluate overall blood health, while prothrombin time (PT) assesses the extrinsic and common coagulation pathways (Chuansumrit et al., 2023). Partial thromboplastin time (PTT) and activated partial thromboplastin time (APTT) evaluate the intrinsic and common pathways, which are prolonged in hemophilia A and B due to factor VIII or IX deficiencies. APTT is the preferred screening test as it is more sensitive to factor deficiencies compared to PTT (Yolanda et al., 2022). Additionally, von Willebrand factor antigen (VWF:Ag) testing is performed to differentiate hemophilia from von Willebrand disease, which shares similar bleeding symptoms (Botero, 2024).

For a more precise diagnosis, functional factor assays are used to measure factor VIII (for hemophilia A) and factor IX (for hemophilia B) activity. The one-stage clotting assay, a widely used method, measures clot formation in response to a clotting activator. In contrast, the chromogenic assay, a two-stage test, is considered more reliable in certain cases (Josset et al., 2024). This assay involves mixing the patient's plasma with reagents containing activated factor X and a chromogenic substrate. If factor VIII or IX is present, it facilitates factor X activation, leading to a measurable color change. The chromogenic assay is particularly useful for reducing false positives seen with low-titer results in the one-stage assay (Krishna et al., 2024). Moreover, it is the preferred method for monitoring patients receiving emicizumab, a bispecific antibody therapy for hemophilia A, as emicizumab interferes with one-stage APTT-based assays, making them unreliable for measuring factor VIII activity. In such cases, either the chromogenic assay or a modified one-stage factor VIII assay should be used instead (Peyvandi et al., 2020).

By integrating genetic testing with laboratory assessments, a comprehensive approach to hemophilia diagnosis can be achieved, ensuring early detection, personalized treatment strategies, and informed genetic counseling for affected families.

TREATMENTS

Initially, direct blood transfusion was the main treatment for hemophilia (Peyvandi et al., 2020). However, since the invention of plasma and cryoprecipitates, including human plasma-derived clotting factor concentrates and recombinant factors, hemophilia treatment has advanced remarkably quickly in

recent decades (Jeanpierre et al., 2020; Rodríguez-Merchán et al., 2021). These developments have made it possible to create highly effective treatments aiming to replace the inadequate clotting factor. Nowadays, the golden standard treatment for hemophilia is the replacement of the missing factors, which utilizes plasma-derived factor concentrates as well as recombinant factor concentrates (Matuk-Villazon et al., 2021).

The factor replacement therapy protocol consists of intravenous administration of the deficient clotting factor, either on-demand upon the occurrence of bleeding episodes or prophylactically two or three times a week to prevent bleeds (Trakymiene & Carlsson, 2014). The on-demand treatment for hemophilia A consists of the injection of octocog alfa, a recombinant factor VIII that integrates into the coagulation cascade by acting as a cofactor for factor IXa, ultimately enhancing the conversion of factor X to factor Xa, which is essential for fibrin clot formation and hemostasis. In contrast, treatment for hemophilia B involves the injection of nonacog alfa, a recombinant factor IX that directly participates in the coagulation pathway by activating factor X, leading to thrombin generation and stable clot formation to control bleeding (Aria et al., 2019). In addition, PEGylation, Fc fusion, albumin fusion, as well as polysialic acid may increase the half-life of these drugs (Knobe & Berntorp, 2012). Although they are generally highly effective, these replacement treatments may occasionally fail due to the presence of inhibitors present in up to 30% of hemophilia cases (Eckhardt et al., 2013). Inhibitor eradication called immune tolerance induction (ITI), can be done to overcome this problem by administering corticosteroid alone or in combination with other drugs such as cyclophosphamide and rituximab (Kruse-Jarres et al., 2017).

Other treatments for hemophilia include non-factor replacement therapies, such as bevacizumab, which works by enhancing the body's natural coagulation process or inhibiting anticoagulant pathways (Nogami & Shima, 2019). Bevacizumab is a monoclonal antibody that induces the binding of factor X and factor IXa, replacing the role of FVIII in FVIII deficiency (Kitazawa et al., 2012). As the monoclonal antibody has no structural homology toward FVIII, it is expected to not induce any inhibitors or be affected by it (Weyand & Pipe, 2019). Another drug, called fitusiran, is a small interfering RNA (siRNA)-based therapy that targets antithrombin (AT), reducing its levels and thereby increasing thrombin generation and FXa activity, which enhances hemostasis in hemophilia patients, regardless of factor deficiency (Gualtierotti et al., 2022). A different therapy method involves interfering with activated protein C (aPC). The thrombin-thrombomodulin complex activates PC to create aPC, which in conjunction with its cofactor protein S, inactivates FVIIIa and FVa, preventing the production of new thrombin and as a result, the prothrombinase and tenase complex activities are rendered inactive (Polderdijk et al., 2017). Furthermore, aminocaproic acid can also be used to improve hemophilia patients' condition through the inhibition of fibrinolysis (Alblaihed et al., 2022). Desmopressin, which is a vasopressin analog, is also used to treat mild hemophilia by inducing von Willebrand factor, leading to the increase of circulating FVIII (Zwagemaker et al., 2022).

In recent years, gene therapy has emerged as a promising treatment approach for hemophilia, targeting deficiencies at the genetic level. Ongoing clinical trials and recently approved therapies aim to provide long-term solutions by delivering functional copies of the clotting factor genes to patients. Several investigational gene therapy candidates for hemophilia B are currently in late-stage clinical trials. One notable approach involves adeno-associated virus (AAV) vector-mediated gene transfer, which introduces a functional FIX gene into liver cells to enable sustained production of the clotting factor. Trials such as those for etranacogene dezaparvovec (previously AMT-061) have shown promise, with sustained FIX activity levels reducing the need for regular clotting factor infusions. Another candidate, fidanacogene elaparvovec (SPK-9001), has demonstrated significant improvements in reducing annual bleeding rates in clinical trial participants. These therapies offer the potential for long-term or even curative treatment by addressing the genetic root cause of hemophilia B (Soroka et al., 2023). Beyond hemophilia B, gene therapy has also been explored for hemophilia A, with valoctocogene roxaparvovec (BMN 270) being one of the leading

candidates under investigation. This therapy aims to restore FVIII production through AAV-mediated gene transfer. These developments highlight the growing potential of gene therapy as a transformative approach to treat hemophilia.

CURRENT STANDINGS

The Indonesian Hemophilia Society Association (HMHI) reported that as of 2020, only 2,706 hemophilia cases were diagnosed in Indonesia, which accounts for merely 10% of the estimated 28,000 cases nationwide. This significant discrepancy is likely due to low awareness among the general population, insufficient early diagnosis, and limited access to healthcare facilities equipped for hemophilia testing. Many cases may remain undiagnosed because individuals with mild or moderate hemophilia do not experience spontaneous bleeding and may not seek medical attention until a major bleeding episode occurs. Additionally, misdiagnosis or underdiagnosis may arise due to the lack of routine screening programs, particularly in rural areas where healthcare access is limited. Public education on hemophilia remains inadequate, which further contributes to low awareness. A study by Mantik et al. (2020) found that only a small proportion of teachers in Indonesia had knowledge about hemophilia. However, details such as the sample size, specific regions covered, and data collection methods of this study are necessary to assess the robustness of this finding. Furthermore, healthcare professionals, including clinicians, nurses, and laboratory personnel, often lack sufficient training and resources for hemophilia diagnosis and management, particularly in primary and secondary healthcare centers. Many tertiary hospitals, which are better equipped, are concentrated in urban areas, leaving many provincial and rural regions underserved.

The management of hemophilia-related complications, particularly joint bleeding (hemarthrosis), remains suboptimal in Indonesia. Repeated joint bleeding in moderate and severe hemophilia patients often leads to joint damage, disability, and reduced quality of life. However, many hospitals lack the necessary clotting factors for treatment, leading to delayed or inadequate care. The Indonesian Ministry of Health (2021) has acknowledged that bleeding in organs other than joints, as well as perioperative bleeding, cannot be effectively managed in all healthcare facilities. The challenge is further exacerbated by limited human resources, including a shortage of hematologists, specialized nurses, and laboratory technicians trained in coagulation disorders. Currently, not all provincial-level referral hospitals have dedicated hemophilia treatment centers, leaving many patients reliant on self-management or traveling long distances for care.

Despite these challenges, efforts are being made to improve hemophilia therapy in Indonesia. The Indonesian Ministry of Health recommends prophylactic therapy to reduce bleeding episodes, though widespread implementation remains a challenge due to cost and resource limitations. A promising approach under evaluation is Minipool Cryoprecipitate (MC) therapy, first developed in Egypt in 2010. Unlike standard cryoprecipitate therapy, this method provides coagulation factors while reducing the risk of developing inhibitors (El-Ekiaby et al., 2018). Additionally, virally inactivated plasma-derived factor therapy is preferred, as it minimizes the risk of transfusion-transmitted infections and allergic reactions.

Looking forward, gene therapy offers a potential long-term solution by correcting the underlying genetic mutation responsible for hemophilia. Techniques under investigation include gene transfer using recombinant adeno-associated viral (AAV) vectors (Hartmann & Croteau, 2016), as well as gene editing with zinc finger nucleases (Davidoff & Nathwani, 2016) and CRISPR-Cas9 technology (Nathwani, 2019). Another experimental therapy involves the injection of mesenchymal stem cells into the liver, which could stimulate the sustained production of coagulation factors and prevent spontaneous bleeding episodes (Sokal et al., 2015). While hemophilia treatment in Indonesia is still developing, expanding public awareness, improving healthcare infrastructure, and increasing access to specialized medical professionals and clotting factor therapies will be crucial in improving hemophilia diagnosis and treatment.

FUTURE CONSIDERATION

As the number of undiagnosed hemophilia cases remains high, increasing awareness among Indonesians, especially in rural areas, is crucial. This can be achieved through targeted educational campaigns, increased accessibility to diagnostic tools, and collaboration with non-governmental organizations (NGOs) and government agencies. The Indonesian Ministry of Health has initiated public health campaigns to improve awareness of rare diseases, including hemophilia, although efforts remain limited. The Indonesian Hemophilia Society (HMHI) has also played a role in educating the public and advocating for better access to care (Hagembe et al., 2023). Expanding partnerships between the government, HMHI, and international organizations such as the World Federation of Hemophilia (WFH) could further strengthen awareness programs, facilitate early diagnosis, and ensure equal treatment accessibility. Implementing mobile health services, telemedicine consultations, and community-based screening programs in rural regions could also help bridge the gap in early detection and management. Gene therapy presents a promising avenue for hemophilia treatment, offering the potential for a one-time, long-term cure. Advances in gene-editing technologies such as CRISPR-Cas9 and base editing may further enhance the precision and efficacy of gene therapy by correcting specific mutations responsible for hemophilia (Mishra et al., 2024). Additionally, emerging research on non-viral gene delivery methods, such as lipid nanoparticles and polymer-based vectors, could offer safer and more accessible alternatives to traditional viral vector-based gene therapies (Jony et al., 2025). However, challenges such as high costs, limited access to clinical trials, and ethical concerns regarding genetic modifications remain significant barriers to widespread implementation. Currently, gene therapy trials for hemophilia are primarily conducted in high-income countries, with limited accessibility for patients in Indonesia (Loo et al., 2024). Collaboration with international research institutions and pharmaceutical companies could facilitate the inclusion of Indonesian patients in clinical trials, accelerating access to innovative therapies.

Beyond treatment, genetic advancements hold potential for improving hemophilia diagnosis and disease management. Next-generation sequencing (NGS) and other genomic screening techniques could enable earlier and more accurate detection of hemophilia mutations, allowing for prenatal and preimplantation genetic diagnosis (PGD) to help families make informed reproductive decisions. Additionally, personalized medicine approaches leveraging genetic data could enable tailored treatment regimens, optimizing factor replacement therapy and minimizing adverse effects. Artificial intelligence (AI)-driven diagnostic tools may also enhance early detection by analyzing genetic markers and predicting disease severity, ultimately improving patient outcomes (Inaba et al., 2017; Waggiallah et al., 2025).

In order to improve treatment affordability, the Indonesian government has taken steps to enhance local plasma-derived factor production through initiatives such as state-owned enterprises investing in blood plasma fractionation technology. However, current production remains insufficient to meet national demand. Encouraging partnerships with private pharmaceutical companies and international manufacturers could help scale up production and reduce costs. Expanding research efforts within Indonesia, including exploring cost-effective methods for factor replacement therapy and alternative treatments, could further contribute to making hemophilia care more sustainable. Additionally, implementing price regulations, subsidies, and insurance coverage for hemophilia medication could improve accessibility.

CONCLUSION

Hemophilia is generally a genetically inherited blood disorder that causes reduced blood clotting ability due to defective or deficient coagulation factors. There are three types of hemophilia: hemophilia A, hemophilia B, and hemophilia C, which are associated with defective or deficient factor VIII (FVIII), factor IX

(FIX), and factor XI (FXI), respectively. Both hemophilia A and B are X-linked recessive disorders, making them more common in males, whereas hemophilia C follows an autosomal recessive inheritance pattern and affects both males and females equally. Another type of hemophilia is acquired hemophilia, resulting from the production of coagulation factors-neutralizing alloantibodies. The diagnosis methods of hemophilia include familial history evaluation, blood laboratory testing, as well as DNA mutation markers observation. These tests are more accessible in larger hospitals, though availability may be limited in rural areas of Indonesia. Currently, the gold standard of hemophilia treatment is through the replacement of the missing factor by plasma-derived factor concentrates injection. However, it may lead to the production of inhibitors, which neutralize the injected factors, remaining as a major challenge in hemophilia treatment. Other treatments for hemophilia include non-factor replacement therapy using monoclonal antibodies, drugs, and gene therapy. In order to improve hemophilia treatment, current approaches in development include gene therapy advancements, non-factor replacement therapies, and novel strategies to overcome inhibitor development. These emerging treatments aim to provide long-term solutions, reduce treatment burdens, and improve accessibility, particularly in low-resource settings, ultimately enhancing the quality of life for individuals with hemophilia.

REFERENCES

Alblaihed, L., Dubbs, S. B., Koyfman, A., & Long, B. (2022). High risk and low prevalence diseases: Hemophilia emergencies. *The American Journal of Emergency Medicine*, *56*, 21–27. https://doi.org/10.1016/j.ajem.2022.02.045

Alghamdi, M. A., Almubarak, A. O., Alsedrani, N., Alshehri, W. M., & Alturki, A. Y. (2019). Pretruncal nonaneurysmal subarachnoid hemorrhage with underlying hemophilia C. *World Neurosurgery*, *127*, 109–112. https://doi.org/10.1016/j.wneu.2019.03.278

Amoozgar, H., Fath, M., Jooya, P., & Karimi, M. (2017). Evaluation of heart function in patients with hemophilia. *Clinical and Applied Thrombosis/Hemostasis*, *23*(4), 374–378. https://doi.org/10.1177/1076029615614394

Aria, M., Erten, A., & Yalcin, O. (2019). Technology advancements in blood coagulation measurements for point-of-care diagnostic testing. *Frontiers in Bioengineering and Biotechnology*, *7*, 395. https://doi.org/10.3389/fbioe.2019.00395

Barbosa, M., & Martins, C. M. L. (2017). *Peptides and Proteins as Biomaterials for Tissue Regeneration and Repair (Woodhead Publishing Series in Biomaterials)* (1st ed.). Woodhead Publishing.

Barmore, W., Burns, B., & Bajwa, T. (2023). Biochemistry, Clotting Factors. Nih.gov; StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK507850/

Botero, J. P. (2024). von Willebrand disease and heavy menstrual bleeding: when and how to test. *Hematology, 2024*(1), 376–381. https://doi.org/10.1182/hematology.2024000563

Castaman, G., & Matino, D. (2019). Hemophilia A and B: Molecular and clinical similarities and differences. *Haematologica*, *104*(9), 1702–1709. https://doi.org/10.3324/haematol.2019.221093

Cheng, Z., Zhang, Z., Zhou, L., & Zhai, Z. (2024). Analysis of genetic test results of 47 hemophiliacs in Anhui and nearby areas in China. *Blood, 144*(Supplement 1), 5490. https://doi.org/10.1182/blood-2024-205317

Chuansumrit, A., Natesirinilkul, R., Sirachainan, N., Kadegasem, P., Surapolchai, P., Tangbubpha, N., Kempka, K., & Khlangtan, T. (2023). Multicenter study of diagnostic tool for patients with hemophilia: From

bedside to comprehensive investigations. *The Application of Clinical Genetics, 16*, 215–223. https://doi.org/10.2147/tacg.s434470

Davidoff, A. M., & Nathwani, A. C. (2016). Genetic targeting of the albumin locus to treat hemophilia. *New England Journal of Medicine*, *374*(13), 1288–1290. https://doi.org/10.1056/NEJMcibr1600347

De Brasi, C., El-Maarri, O., Perry, D. J., Oldenburg, J., Pezeshkpoor, B., & Goodeve, A. (2014). Genetic testing in bleeding disorders. *Haemophilia*, *20*, 54–58. https://doi.org/10.1111/hae.12409

Eckhardt, C. L., Van Velzen, A. S., Peters, M., Astermark, J., Brons, P. P., Castaman, G., … Fijnvandraat, K. (2013). Factor VIII gene (F8) mutation and risk of inhibitor development in nonsevere hemophilia A. *Blood*, *122*(11), 1954–1962. https://doi.org/10.1182/blood-2013-02-483263

El Ekiaby, M., Burnouf, T., Goubran, H., Radosevich, M., & El Ekiaby, A. (2018). Role of the mini-pool cryoprecipitate technology for cost-saving and guarantee of local Factor VIII, Von Willebrand Factor and Fibrinogen product supply: Egypt experience. *Annals of Blood*, *3*, 22–22. https://doi.org/10.21037/aob.2018.02.07

Franchini, M., & Mannucci, P. M. (2011). Inhibitors of propagation of coagulation (factors VIII, IX and XI): A review of current therapeutic practice: Inhibitors of factors VIII, IX and XI. *British Journal of Clinical Pharmacology*, *72*(4), 553–562. https://doi.org/10.1111/j.1365-2125.2010.03899.x

Goodeve, A. C. (2015). Hemophilia B: Molecular pathogenesis and mutation analysis. *Journal of Thrombosis and Haemostasis*, *13*(7), 1184–1195. https://doi.org/10.1111/jth.12958

Gualtierotti, R., Pasca, S., Ciavarella, A., Arcudi, S., Giachi, A., Garagiola, I., … Peyvandi, F. (2022). Updates on novel non-replacement drugs for hemophilia. *Pharmaceuticals*, *15*(10), 1183. https://doi.org/10.3390/ph15101183

Hagembe, J., Baumann, A., Santaella, M. E., Sannié, T., Lambert, C., Cruickshank, A., Gaitan-Fitch, C., Suwantaroj, E., Garrido, C., & Mekhuzla, S. (2023). Bridging the gap: Survey highlights challenges and solutions in outreach and identification of people with inherited bleeding disorders. *Haemophilia, 29*(6), 1456–1466. https://doi.org/10.1111/hae.14862

Hartmann, J., & Croteau, S. E. (2016). 2017 Clinical trials update: Innovations in hemophilia therapy. *American Journal of Hematology*, *91*(12), 1252–1260. https://doi.org/10.1002/ajh.24543

Hirayama, A. B., Silva, A. K. C. D., Rocha, J. S., & Roberti, M. D. R. F. (2019). Prevalence of symptoms in hemophilia carriers in comparison with the general population: A systematic review. *Hematology, Transfusion and Cell Therapy*, *41*(4), 349–355. https://doi.org/10.1016/j.htct.2019.02.006

Huether, S. E., McCance, K. L., Parkinson, C. F., Brashers, V. L., & Rote, N. S. (2022). *Study Guide for Understanding Pathophysiology* (5th ed.). Elsevier Saunders.

Artificial intelligence (AI)-driven diagnostic tools may also enhance early detection by analyzing genetic markers and predicting disease severity, ultimately improving patient outcomes

Indonesian Ministry of Health. (2021). *Keputusan Menteri Kesehatan tentang Pedoman Nasional Pelayanan Kedokteran Tata Laksana Hemofilia [HK.01.07/MENKES/243/2021]*. Kementerian Kesehatan Indonesia.

Iorio, A., Stonebraker, J. S., Chambost, H., Makris, M., Coffin, D., Herr, C., … for the Data and Demographics Committee of the World Federation of Hemophilia. (2019). Establishing the prevalence and prevalence at birth of hemophilia in males: A meta-analytic approach using national registries. *Annals of Internal Medicine*, *171*(8), 540. https://doi.org/10.7326/M19-1208

Ishii, E. (2018). *Hematological Disorders in Children: Pathogenesis and Treatment.* Springer.

Jamil, M. A., Sharma, A., Nuesgen, N., Pezeshkpoor, B., Heimbach, A., Pavlova, A., … El-Maarri, O. (2019). F8 Inversions at Xq28 Causing Hemophilia A Are Associated With Specific Methylation Changes: Implication for Molecular Epigenetic Diagnosis. *Frontiers in Genetics*, *10*, 508. https://doi.org/10.3389/fgene.2019.00508

Jankowska, K. I., McGill, J., Pezeshkpoor, B., Oldenburg, J., Sauna, Z. E., & Atreya, C. D. (2020). Further Evidence That MicroRNAs Can Play a Role in Hemophilia A Disease Manifestation: F8 Gene Downregulation by miR-19b-3p and miR-186-5p. *Frontiers in Cell and Developmental Biology*, *8*, 669. https://doi.org/10.3389/fcell.2020.00669

Jayakrishnan, T., Shah, D., & Mewawalla, P. (2019). Hemophilia C: A Case Report With Updates on Diagnosis and Management of a Rare Bleeding Disorder. *Journal of Hematology*, *8*(3), 144–147. https://doi.org/10.14740/jh522

Jeanpierre, E., Pouplard, C., Lasne, D., Le Cam Duchez, V., Eschwege, V., Flaujac, C., … Voyer, A. (2020). Factor VIII and IX assays for post-infusion monitoring in hemophilia patients: Guidelines from the French BIMHO group (GFHT). *European Journal of Haematology*, *105*(2), 103–115. https://doi.org/10.1111/ejh.13423

Jony, M. J., Joshi, A., Dash, A., & Shukla, S. (2025). Non-Viral Delivery Systems to Transport Nucleic Acids for Inherited Retinal Disorders. *Pharmaceuticals, 18*(1), 87–87. https://doi.org/10.3390/ph18010087

Josset, L., Hamdi Rezigue, & Yesim Dargaud. (2024). Thrombin generation assay to support hematologists in the era of new hemophilia therapies. *International Journal of Laboratory Hematology.* https://doi.org/10.1111/ijlh.14406

Key, N. S. (2004). Inhibitors in congenital coagulation disorders: Review. *British Journal of Haematology*, *127*(4), 379–391. https://doi.org/10.1111/j.1365-2141.2004.05168.x

Kitazawa, T., Igawa, T., Sampei, Z., Muto, A., Kojima, T., Soeda, T., … Hattori, K. (2012). A bispecific antibody to factors IXa and X restores factor VIII hemostatic activity in a hemophilia A model. *Nature Medicine*, *18*(10), 1570–1574. https://doi.org/10.1038/nm.2942

Knobe, K., & Berntorp, E. (2011). Haemophilia and joint disease: Pathophysiology, evaluation, and management. *Journal of Comorbidity*, *1*(1), 51–59. https://doi.org/10.15256/joc.2011.1.2

Knobe, K., & Berntorp, E. (2012). New treatments in hemophilia: Insights for the clinician. *Therapeutic Advances in Hematology*, *3*(3), 165–175. https://doi.org/10.1177/2040620712440007

Konkle, B. A., Skinner, M., & Iorio, A. (2019). Hemophilia trials in the twenty-first century: Defining patient important outcomes. *Research and Practice in Thrombosis and Haemostasis, 3*(2), 184–192. https://doi.org/10.1002/rth2.12195

Krishna, G., Diljith, H., & Majeed, A. (2024). Chromogenic assay : A critical diagnostic tool for accurate diagnosis of severe hemophilia A. *Indian Journal of Child Health, 11*(5), 46–48. https://doi.org/10.32677/ijch.v11i5.468

Kruse-Jarres, R., Kempton, C. L., Baudo, F., Collins, P. W., Knoebl, P., Leissinger, C. A., … Kessler, C. M. (2017). Acquired hemophilia A: Updated review of evidence and treatment guidance. *American Journal of Hematology*, *92*(7), 695–705. https://doi.org/10.1002/ajh.24777

Lannoy, N., & Hermans, C. (2010). The 'royal disease'- haemophilia A or B? A haematological mystery is finally solved: The royal disease. *Haemophilia*, *16*(6), 843–847. https://doi.org/10.1111/j.1365-2516.2010.02327.x

Liu, D., Guo, R., Chen, M., Shi, B., Weng, J., & Fu, Z. (2024). Study on the mutation of FIX gene in 31 patients with type B hemophilia. *Clinical and Applied Thrombosis/Hemostasis, 30.* https://doi.org/10.1177/10760296241275454

Loo, T. Y., Saripuddin, Z., Cheng, B. Y., Kyle, A., & Levent, A. (2024). Unwavering priorities: Global physician alignment on gene therapy for hemophilia. *Blood, 144*(Supplement 1), 7711. https://doi.org/10.1182/blood-2024-211444

Lu, Q., Yang, L., Chandrashekhara Manithody, Wang, X., & Rezaie, A. R. (2015). Expression and characterization of Gly-317 variants of factor IX causing variable bleeding in hemophilia B patients. *Biochemistry, 54*(24), 3814–3821. https://doi.org/10.1021/acs.biochem.5b00270

Mahlangu, J. N. (2020). Requirements to participate in haemophilia clinical trials. *Haemophilia, 26*(S3), 22–25. https://doi.org/10.1111/hae.13886

Mannucci, P. M. (2020). Hemophilia therapy: The future has begun. *Haematologica*, *105*(3), 545–553. https://doi.org/10.3324/haematol.2019.232132

Mantik, M. F. J., Gunawan, S., & Wowiling, S. (2020). Knowledge about hemophilia among teachers of patients with hemophilia in Indonesia. *Pediatric Hematology Oncology Journal*, *5*(3), 126–129. https://doi.org/10.1016/j.phoj.2020.06.003

Matuk-Villazon, O., Roberts, J. C., & Corrales-Medina, F. F. (2021). Hemophilia: The past, the present, and the future. *Pediatrics In Review*, *42*(12), 672–683. https://doi.org/10.1542/pir.2020-004143

Meeks, S. L., & Batsuli, G. (2016). Hemophilia and inhibitors: Current treatment options and potential new therapeutic approaches. *Hematology*, *2016*(1), 657–662. https://doi.org/10.1182/asheducation-2016.1.657

Mehta, P., & Reddivari, A. K. R. (2022, September 30). Hemophilia. PubMed; StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK551607/

Mishra, D. K., Rath, A., Mayur Parihar, Vinarkar, S. S., & Kundu, A. (2024). Current diagnosis of bleeding disorders in lower income countries. *International Journal of Laboratory Hematology.* https://doi.org/10.1111/ijlh.14377

Nathwani, A. C. (2019). Gene therapy for hemophilia. *Hematology*, *2019*(1), 1–8. https://doi.org/10.1182/hematology.2019000007

Nogami, K., & Shima, M. (2019). New therapies using nonfactor products for patients with hemophilia and inhibitors. *Blood*, *133*(5), 399–406. https://doi.org/10.1182/blood-2018-07-820712

Pasi, K. J., Rangarajan, S., Georgiev, P., Mant, T., Creagh, M. D., Lissitchkov, T., Bevan, D., Austin, S., Hay, C. R., Hegemann, I., Kazmi, R., Chowdary, P., Gercheva-Kyuchukova, L., Mamonov, V., Timofeeva, M., Soh, C. H., Garg, P., Vaishnaw, A., Akinc, A., Sørensen, B., … Ragni, M. V. (2017). Targeting of antithrombin in Hemophilia A or B with RNAi therapy. *The New England Journal of Medicine, 377*(9), 819–828. https://doi.org/10.1056/NEJMoa1616569

Payne, A. B., Miller, C. H., Kelly, F. M., Soucie, J. M., & Hooper, W. C. (2013). The CDC Hemophilia A Mutation Project (CHAMP) Mutation list: A new online resource. *Human Mutation*, *34*(2), E2382–E2392. https://doi.org/10.1002/humu.22247

Peyvandi, F., Kenet, G., Pekrul, I., Pruthi, R. K., Ramge, P., & Spannagl, M. (2020). Laboratory testing in hemophilia: Impact of factor and non-factor replacement therapy on coagulation assays. *Journal of Thrombosis and Haemostasis*, *18*(6), 1242–1255. https://doi.org/10.1111/jth.14784

Pezeshkpoor, B., Oldenburg, J., & Pavlova, A. (2022). Insights into the Molecular genetic of hemophilia A and hemophilia B: The relevance of genetic testing in routine clinical practice. *Hamostaseologie*, *42*(06), 390–399. https://doi.org/10.1055/a-1945-9429

Pipe, S. W., Montgomery, R. R., Pratt, K. P., Lenting, P. J., & Lillicrap, D. (2016). Life in the shadow of a dominant partner: The FVIII-VWF association and its clinical implications for hemophilia A. *Blood*, *128*(16), 2007–2016. https://doi.org/10.1182/blood-2016-04-713289

Polderdijk, S. G. I., Adams, T. E., Ivanciu, L., Camire, R. M., Baglin, T. P., & Huntington, J. A. (2017). Design and characterization of an APC-specific serpin for the treatment of hemophilia. *Blood*, *129*(1), 105–113. https://doi.org/10.1182/blood-2016-05-718635

Rallapalli, P. M., Kemball-Cook, G., Tuddenham, E. G., Gomez, K., & Perkins, S. J. (2013). An interactive mutation database for human coagulation factor IX provides novel insights into the phenotypes and genetics of hemophilia B. *Journal of Thrombosis and Haemostasis*, *11*(7), 1329–1340. https://doi.org/10.1111/jth.12276

Rodríguez-Merchán, E. C., De Pablo-Moreno, J. A., & Liras, A. (2021). Gene therapy in hemophilia: Recent advances. *International Journal of Molecular Sciences*, *22*(14), 7647. https://doi.org/10.3390/ijms22147647

Rodríguez-Merchán, E. C., & Jiménez-Yuste, V. (2022). Pathophysiology of hemophilia. In E. C. Rodríguez-Merchán (Ed.), *Advances in Hemophilia Treatment* (pp. 1–9). Cham: Springer International Publishing. https://doi.org/10.1007/978-3-030-93990-8_1

Saba, H. I., & Roberts, H. R. (2014). *Hemostasis and Thrombosis: Practical Guidelines in Clinical Management* (1st ed.). Wiley-Blackwell.

Sahu, S., Lata, I., Singh, S., & Kumar, M. (2011). Revisiting hemophilia management in acute medicine. *Journal of Emergencies, Trauma, and Shock*, *4*(2), 292. https://doi.org/10.4103/0974-2700.82225

Shen, G., Gao, M., Cao, Q., & Li, W. (2022). The molecular basis of FIX deficiency in hemophilia B. *International Journal of Molecular Sciences*, *23*(5), 2762. https://doi.org/10.3390/ijms23052762

Sokal, E. M., Lombard, C., & Mazza, G. (2015). Mesenchymal stem cell treatment for hemophilia: A review of current knowledge. *Journal of Thrombosis and Haemostasis*, *13*, S161–S166. https://doi.org/10.1111/jth.12933

Soroka, A. B., Feoktistova, S. G., Mityaeva, O. N., & Volchkov, P. Y. (2023). Gene therapy approaches for the treatment of hemophilia B. *International Journal of Molecular Sciences, 24*(13), 10766. https://doi.org/10.3390/ijms241310766

Srivastava, A., Santagostino, E., Dougall, A., Kitchen, S., Sutherland, M., Pipe, S. W., Carcao, M., Mahlangu, J., Ragni, M. V., Windyga, J., Llinás, A., Goddard, N. J., Mohan, R., Poonnoose, P. M., Feldman, B. M., Lewis, S. Z., van den Berg, H. M., Pierce, G. F., & WFH Guidelines for the Management of Hemophilia panelists and co-authors (2020). WFH guidelines for the management of hemophilia, 3rd edition. *Haemophilia: The Official Journal Of The World Federation Of Hemophilia, 26*, 1–158. https://doi.org/10.1111/hae.14046

Stonebraker, J. S., Bolton-Maggs, P. H. B., Brooker, M., Evatt, B., Iorio, A., Makris, M., O'Mahony, B., Skinner, M. W., Coffin, D., Pierce, G. F., & Tootoonchian, E. (2020). The world federation of hemophilia annual global survey 1999-2018. *Haemophilia: The Official Journal of The World Federation Of Hemophilia, 26*(4), 591–600. https://doi.org/10.1111/hae.14012

Tantawy, A. A. G. (2010). Molecular genetics of hemophilia A: Clinical perspectives. *Egyptian Journal of Medical Human Genetics*, *11*(2), 105–114. https://doi.org/10.1016/j.ejmhg.2010.10.005

Tokugawa, T. (2020). *Diagnosis and treatment of hemophilia*. *61*(9), 1338–1348. https://doi.org/10.11406/rinketsu.61.1338

Trakymiene, S. S., & Carlsson, K. S. (2014). On-demand treatment in persons with severe haemophilia. *European Journal of Haematology*, *93*, 39–47. https://doi.org/10.1111/ejh.12373

U.S. Food and Drug Administration. (2023). FDA approves first gene therapy for adults with severe hemophilia A. U.S. Food and Drug Administration. https://www.fda.gov/news-events/press-announcements/fda-approves-first-gene-therapy-adults-severe-hemophilia

Vatandoost, J., & Zarei Sani, O. (2017). Effect of propeptide amino acid substitution in γ-carboxylation, activity and expression of recombinant human coagulation factor IX. Biotechnology Progress, 34(2), 515–520. https://doi.org/10.1002/btpr.2582

Waggiallah, H. A., Al-Garni, A., Ghazwani, A. A. M., Shaya, A. S. B., Al Shmrany, H., & Almosaad, Y. M. (2025). *The Future Insights of AI Applications In Hematology Diseases Diagnosis and Prognosis.*

Weyand, A. C., & Pipe, S. W. (2019). New therapies for hemophilia. *Blood*, *133*(5), 389–398. https://doi.org/10.1182/blood-2018-08-872291

World Federation of Hemophilia. (2022). *World Federation of Hemophilia Report on the Annual Global Survey 2021*. https://www1.wfh.org/publications/files/pdf-2324.pdf

Yang, Y. Y., Wang, Y., & Gao, J. (2024). Genetic diagnosis and prenatal diagnosis of a rare FVIII family with haemophilia A. *Journal of Cellular and Molecular Medicine*, *28*(23). https://doi.org/10.1111/jcmm.70275

Yolanda, R., Prihatni, D., Rita, C., & Turbawaty, D. K. (2022). Correlation between slope 2 in clot waveform analysis of activated partial thromboplastin time with factor viii activity in hemophilia A. *Indonesian Journal of Clinical Pathology And Medical Laboratory, 28*(3), 274–277. https://doi.org/10.24293/ijcpml.v28i3.1869

Zimmermann, M. A., Oldenburg, J., Müller, C. R., & Rost, S. (2011). Unusual genomic rearrangements in introns 1 and 22 of the F8 gene. *Hamostaseologie*, *31 Suppl 1*, S69-73.

Zimta, A.-A., Hotea, I., Brinza, M., Blag, C., Iluta, S., Constantinescu, C., … Tomuleasa, C. (2021). The possible non-mutational causes of FVIII deficiency: Non-coding RNAs and acquired hemophilia A. *Frontiers in Medicine*, *8*, 654197. https://doi.org/10.3389/fmed.2021.654197

Zwagemaker, A., Kloosterman, F. R., Coppens, M., Gouw, S. C., Boyce, S., Bagot, C. N., … Fijnvandraat, K. (2022). Desmopressin for bleeding in non-severe hemophilia A: Suboptimal use in a real-world setting. *Research and Practice in Thrombosis and Haemostasis*, *6*(6), e12777. https://doi.org/10.1002/rth2.12777