Volume 3, Issue 10, 2025

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

CURRENT PERSPECTIVES IN PATHOPHYSIOLOGY, DIAGNOSIS AND THERAPEUTIC STRATEGIES FOR HEMOPHILIA

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DOI: https://doi.org/10.5281/zenodo.18165373

Keywords
Hemophilia, Factor VIII, Factor IX, Hemorrhage, Coagulation

Article History
Received: 11 October 2025
Accepted: 21 November 2025
Published: 31 December 2025

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Abstract

Hemophilia is a genetically uncommon loss of blood disease that described by a shortage of a blood clotting factors. These are uncommon genetically inherited, recessive X-linked condition produced by shortage of coagulating elements correspondingly. Toughness to clinical disorder based on the decline rate of both elements that are resolved by the category of the mutagenic variant among genetic sequence specifying feature. Typical clinically significant aspect, mainly in neglected critical type, is hemorrhage into primary articulations like ankles, knees and elbows that are the output in the formation of arthritic condition. Bleeding in the Brain and Internal organs could harm the body. The intermediate average life span was about 30 years up to the 1960s, however better recognition of disorder and production of effective therapy depending on preventive treatment of the missing component has resulted in a structural change, and contemporary human being with inherited blood clotting problem can expect to a practically normal lifespan and well-being. However, the expected improvement of neutralizing antibodies to delivered factor is yet a crucial barrier in a significant part of sick persons. Gene-therapy for hemophilia A and B has made remarkable progress and could soon become a reality for patients.

INTRODUCTION

These are inherited disease that effect bloods' Clotting due to missing or reduced clotting factor VIII and IX. Women who carry the hemophilia gene are usually only mildly affected, but sometimes, due to uneven activation of one of their X chromosomes, they can experience more severe symptoms, especially heavy menstrual blood loss. Males who have only one X chromosome, are usually affected by gene clotting disorders, while females with XX chromosomes, commonly taken the gene. However, some females can also be affected and may experience blood loss. The span of FVIII intensity values in healthy population are highly variable (Klintman, et al 2013).Instinctive blood loss in affected individuals is usually limited, exceptionally at subcutaneous or internal lining of body cavities as presenting in patients who suffer by muscular disease (Plebani, et.al 2013). Hemorrhage after slightly injury or with operative procedure might result in heavy hemorrhage at the affected area in hemophilia patients. There is a loose connection among the acuteness of the disorder and the forms of blood loss noted in affected individuals. In intense coagulation disorder, articular bleeding, muscle hemorrhage, CNS hemophilia, and urinary hemorrhage are more common regardless of the absence of any visible damage; intermediate hemophilia, intermediate damage or light surgical procedure could cause blood loss, and in less severe disease, blood loss normally happens as a result of significant injury and complex

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ISSN: (e) 3007-1607 (p) 3007-1593

surgery. Typically, hemophilia B is viewed as less harmful as compared to hemophilia A (Jackson,et.al 2018), however, there is differing views on this topic. The dissimilarity in genetic makeup of the two disorders is likely to cause for this variation. In acute hemophilia A, the reversal outcomes or a significant alteration in series. On contrast, hemophilia B, limited anyways exhibit seventeen percent, and protein-altering report (Iorio,et al. 2019).

Types:

Hemophilia A:

This is inborn blood loss case, because of limited "A" factor, presenting with varying clinical features. Besides causing blood loss in various parts of body, hemophilia commonly cause blood loss and harm the joints if treatment is not given. That grouping method, that frequently chosen for rules since start of 21st century , according to the data, plasma level above 40% of the expected value are normally considered as normal, if level fall below this point, blood coagulation activity is not enough (Dumont, et al 2012). Depending on the levels of clotting activity, hemophilia can be categorized into different types: Less-severe: Unprovoked blood loss uncommon sometimes it results as damage. Normally, patients' movement restricted, also therapy given when required. Average: Resulting conditions is apparent, people sometimes noticed big, deep bruises and loss of blood that takes a long time to stop and joint blood loss even with lighter injury. Acute: That type marked easy blood loss, especially with recurrent joint and muscle hemorrhage that happen mostly on their own. Recurrent connection of blood loss and ensuring articular disease permanent disability (Alvarez Román, et al 2017).

Hemophilia B:

Hemophilia B is an unusual X-linked hidden inherited condition of the blood clotting mechanism leading to defect DNA sequence in it, encoding clot formation .Clotting IX(FIX), amnio acid peptidase inactive enzyme precursor associated with in the blood clotting pathway and based on Phylloquinone. Inadequacy of the elements acts to extended blood loss that happened automatically or post injury. The occurrence of factor-IX in the worldwide community is commonly calculated male childbirths globally (Srivastava, et.al 2020).However, there is rising appreciation that females can also go through indications of hemorrhagic disorders. While the acute type in females is unusual, one fourth cases of less affecting FIX deficiency, and hemostasis treatments for females.

In an intermediate situation, unexpected blood loss occurrence is unusual, but even slightly wounds provoke continued hemorrhage, and in serious situation, natural bleeding occurs in joints, and deep skin bruises development happened. Especially, clients with acute hemorrhage for 30–40% of all ducted cases of factor-IX, abased on CDC information (Meireles, et.al.2019).

In medical procedure, replacement therapy is utilized, which associated with the venous infusion of commonly accepted hemophilia B, derived anyone through rearrangements, for blood loss preventive treatment and almost two to three weeks of this serious condition(Branchini,et al. 2019) .

3. Inheritance Pattern:

As the hereditary factor present, so these mattered an exclusive hereditary sequence of hereditary elements impacting approximately solely males.Like a male the terminology mono-allelic and has the full expressed characteristics of the disorder. Females hold a pair of traits and genetic unit; so, the abnormality in a single trait balanced standard traits and, two different alleles hold continue with a normal trait commonly (Morfini, et al.2019). Nearly thirty percent examples, each FVIII factor, Fix factor, explained as "isolated" neonate infant firstly blood loss -prone come. Expression for disorder genetic background must clarified with the chance in presence in new mutation hereditary flaw in these. Anyone in the influenced offspring by carrying mother. Quite often, hereditary background stays unidentified because of insufficient data or the small number of cases male childbirth. Mother related play a role in happening like those events, there is non-alteration is identified in female (Bastida. et al2017). Thus, a Normal hereditary history is inadequate to dismiss hemophilia honeypots are indicative of a bleeding susceptibility.

Uncommonly, XX-character manifesting signs so this disease framework of bleeding prone .Those who are determine carrier of bleeding disorder, their

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ISSN: (e) 3007-1607 (p) 3007-1593

concentration similar XY character. Estimated out of 1000 one fourth of the carrier XX character having acute/ intermediate expressed characteristics has recorded for academic reports .That type of complicated hereditary cases, that is described as follows: (1) same-allelic condition in a female (2)Dual-variation Condition,(3) mono-allelic condition (4) Dual-allelic condition(Bastida, et al 2017). and (5) inherited reasons other than bleeding disorder— Women with reduced hemophilia A amount also may have merged clotting V (FV) and last of hemophilia A , an recessive inherited disease marked by slightly reduced concentration of each hemophilia A and Factor V, resulted in mutations in the lectin mannose-binding 1 and multiple coagulated factor deficiency in 2 DNA segment (Boylan et al 2015).

4. Causes and molecular mechanism:

Mutations in genes, which encrypt clotting factors VIII and IX, respectively, are the source of hemophilia. These genes are inherited as X-linked recessive diseases. The production or biological function of the clotting factors is disrupted by these changes, which vary from point mutations to extensive deletions and inversions (Brown et al., 2014). Males usually have the condition since the faulty gene is on the X chromosome, whereas females are normally carriers unless lyonization lowers their clotting factor levels. The intron22 inversion, which disrupts the F8 gene and inhibits the correct production of functional factor VIII protein, is a significant genetic cause of severe hemophilia A (Carter, 2017).

Signs and symptoms:

The residual activity of FVIII or FIX determines the clinical symptoms, with severe deficiencies showing up early in life. Recurrent hemarthrosis is one of the most distinctive signs, particularly in large joints like the knees, elbows, and ankles. If left untreated, recurrent joint bleeding causes inflammation, synovial enlargement, and progressive cartilage loss, which eventually results in chronic arthropathy (Liu et aI.,2015).. Fragile capillary networks are another common cause of mucosal bleeding, such as gum bleeding and epistaxis The most dangerous side effects are profound soft-tissue hemorrhages , gastrointestinal bleeding, and cerebral hemorrhages, all of which are potentially prompt medical attention Although the severity varies greatly, female carriers with skewed X-inactivation may also exhibit clinical signs such heavy menstrual periods, postpartum hemorrhage, and prolonged bleeding following dental treatments(White,2016).

Diagnosis and screening method:

Clinical assessment and laboratory testing are the first steps in the diagnosis process. An intrinsic coagulation pathway problem is suggested by a activated incomplete thromboplastin time (aPTT) with a normal prothrombin time (PT), which prompts additional testing for factor deficits). (Hoffman 2018)In a mixing trial, patient plasma is combined with normal plasma distinguish between an inhibitor and a factor deficiency; chronic prolongation indicates the presence of an inhibitor, whereas correction of aPTT indicates a deficiency . In order to categorize the condition as mild, moderate, or severe, the final diagnosis depends on certain factor assays that evaluate the levels of FVIII or FIX activity. Genetic trial is necessary for families with a known history in order to recognize specific mutations, verify carrier rank, and offer accurate genetic counseling (Tennekoon et al., 2020). Methods like allele-specific PCR, Point change and order in the F8 and F9 genes can be found by sequencing, MLPA, and inversion testing (Collins et al., 2019).

Management and Treatment Options

Factor replacement therapy, which entails intravenous infusion of recombinant or plasma-derived FVIII or FIX focus, is the main treatment for hemophilia. In addition to being used as prophylaxis to stop joint injury in children with severe illness, these treatments successfully manage acute bleeding events (Williams, 2019) Long-term prevention avoids chronic joint degradation and dramatically lowers the incidence of hemarthrosis . Bypassing medications like recombinant active factor VII or activated prothrombin complex concentrates, which uplift clot formation independent of FVIII or FIX, are often needed for patients who develop inhibitors, making management more difficult (Wilson, 2016) Lately, non-factor treatments Due to their long half-

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ISSN: (e) 3007-1607 (p) 3007-1593

life. Long-lasting increases in factor levels have been shown in early clinical inquiry, which may reduce or remove the requirement for frequent factor infusions To enhance quality of life and reduce bleeding chances, supportive care such as physical therapy, joint-protection techniques, and dental precautions is crucial (Ahmed et al., 2018).

Prophylaxis vs on demand Therapy :

In the management of serious hemophilia A, numerous studies have confirmed that prophylactic therapy, involving regular management of coagulate factor concentrates to stop bleeding, is clearly more effective than on-demand episodic therapy initiated only after a bleed occurs. In an essential randomized trial, (Valentino et al.2012) demonstrated that patients treated with prophylaxis experienced significantly lower annualized bleeding rates balance with periods on on-demand treatment, and a significant proportion of subjects on prophylaxis remained bleed-free over the study period, highlighting prophylaxis's superior bleed prevention. Additionally, (Munawar Ali et al.2023) reported that low-dose prophylaxis was related with significantly fewer bleeds, reduced hospitalizations, and absence of inhibitor development compared with an on-demand cohort, even in resource-constrained settings where factor access is limited. Beyond clinical success, broader health economic analyses, such as those discussed by (Bryson 2024), indicate that prophylactic regimens can yield favorable cost-effectiveness outcomes relative to on-demand treatment by improving quality-adjusted life years QALYs and reducing long-term difficulties, supporting the adoption of prophylaxis as the quality of care for serious hemophilia patients (Bryson 2024), (Bryson 2024).

Hemophilia in Children vs Adults:

Recent studies have shown clear age-related differences in the clinical characteristics, treatment patterns, and extended outcomes of hemophilia between children and adults. Advances in pediatric hemophilia care have led to initial diagnosis and broader use of primary prophylaxis, which has reduced bleeding rates and better joint health in children when differentiate with adult patients (Srivastava et al., 2023). In contrast, many adults particularly those diagnosed before routine became standard practice continue to bear from chronic hemophilic, limited mobility, and a greater overall disease load due to joint damage caused by repeated bleeding incidents over time (Iorio et al., 2024).Quality-of-life scales always show superior physical health of the pediatric patients, but more pain, disability, and socioeconomic consequences of hepatitis are seen in adults, which is indicative of the long-term outcomes of early and sustained inhibitory therapy in hemophilia(Srivastava et al., 2023).

Fig. 01: Hemophilia in children

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10. Complications of Hemophilia

Hemophilia is associated with a large range of both chronic and acute issues that have a significant effect on health and quality of life and future physical functions. Inhibitors develop in adults with hemophilia who received on-demand therapy in childhood more often than in young individuals with modern prophylaxis, and it is more difficult to control the disease, which is likely to become more dangerous (Manucci, 2001).The formation of the inhibitors is also more prevalent in children with serious hemophilia A in their early childhood period of treatment, which complicates the management of the disease and predisposes it to become more dangerous (Manucci, 2001). They may cause severe complications such as neurological damage, syndrome, or even death, which underscores the need to treat the disease holistically in a multidisciplinary manner (Franchini et al., 2018).Psychosocial problems, such as anxiety, depression, social isolation, and loss of employment, are additional factors that undermine the overall effect of the disease, and thus the necessity to treat the disease holistically in a multidisciplinary setting (Skinner et al., 2022).

11. Advances in Therapy

The last several years have been marked by the significant advances in the treatment of hemophilia due to the tremendous knowledge of the disease mechanisms and the requirements of the patients. As (Pipe et al.2021) states, prophylactic treatment to achieve near-normal bleeding elimination rather than bleeding depletion, especially in children, irreversible damage to the joints and the enhancement of lifelong functional outcomes, have been enhanced. Based on the real-world study evidence, it is indicated that EHL factors can offer protection to the bleed in children and adults, especially in the patients who switch on-demand to prophylaxis treatment (Collins et al.,2022). The introduction of non-factor therapies has also transformed the care of hemophilia. This has been shown to offer support in bleeding events in both patients with and without inhibitors, and it leads to a significant reduction in the treatment burden (Shima et al., 2022)

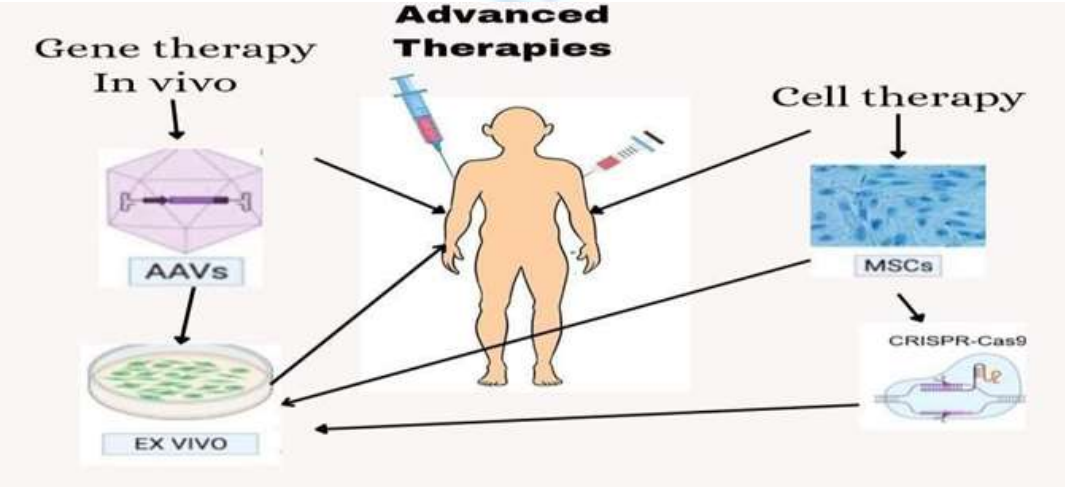

Fig. 02: Advanced therapies of hemophilia

12. Lifestyle management and preventive care:

The prevention of bleeding incidences and the enhancement of health among people living with hemophilia is based on effective prevention and lifestyle management. Prophylaxis therapy- periodical intake of clotting factor concentrates or more recent drugs like omalizumab have been demonstrated to decrease the frequency of bleeds, keep up with joint soundness, and expand functional autonomy. The interventions ensure healthier long-term joint and daily activity levels since they prevent spontaneous bleeds and reduce the emergency care requirement. (Borhany et al., 2024).

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Physiotherapy and custom-made physical activity are also essential to be incorporated. Muscle-strengthening and joint-stabilizing exercise programs can decrease musculoskeletal complications and the risks of unnecessary injuries can be minimized through education on how to engage in activities safely. Outpatient multidisciplinary programs which adhere to total care models have proved to reduce instances of avoidable bleeds and curtailment of medical expenditure, it is important to stress that preventative interventions should be based on medical and lifestyle assistance (AJMC Contributor, 2024).

13. Physiology Impact on Patients and Families

The persistent bleeding on the joints (hemarthroses) causes' chronic pain, diminished physical activity, and consequently, arthropathy, which in turn makes psychosocial well-being more complex. The impact of this chronicity is not only on patients, but also on family members- increasing the level of anxiety related to everyday operations, long-term planning, and emergency preparedness (Rasul et al., 2023).

Psychological outcomes are also important. Research has found out that despite prophylactic management, most of the patients still live in constant fear of breakthrough bleed, which causes work restrictions and they are not able to engage in recreational activities and have their quality of life restricted. Such difficulties frequently turn into emotional pressure on individuals who explain the need to provide support daily and worry about the long-term term of their health and security (Grossi, 2024).

14. Prognosis and Long-Term Outcomes in Hemophilia

Modern management of hemophilia has had a drastic effect on prognosis in the long term. Primary prophylaxis is closely connected with a better prognosis of the joints and fewer complications in the long term, which allows a significant proportion of patients to continue physical activity with limited joint involvement in the future. Early prophylaxis is also beneficial in enhancing lifespan by averting accumulation of joint damage and related morbidity. New therapeutic agents including gene therapy can change the course of the disease. Gene therapies also seek to achieve long-term expression of deficient clotting factors, which will greatly decrease or remove the lifelong factor replacement. The longitudinal studies and predictive models will imply maintained levels of factors years after treatment, which may result in a reduction of bleeding incidents and better life quality than traditional prophylaxis (Konkle,et.al 2022.

15. Global prevalences and public health significance

Global prevalences

Unusual bleeding diseases are caused by genetic abnormalities in the trait carriers necessary for blood clotting. Hemophilia A and B are caused by deficiencies in factor IX (FIX) and element VIII (FVIII). Each of the two disorders affects 1 in 3333 live births. Identification and therapy vary widely across the globe, usually reflecting national economic systems. This implies that the majority of instances in affluent nations are not even recognized, and many patients die at a young age due to a lack of access to therapy. Nowadays, less developed nations with poor healthcare systems frequently lack the fundamental information and abilities needed for diagnosis and treatment (WFH Survey on Hemophilia 1999).

In wealthier nations, promoting the most recent medical advancements requires a thorough awareness of the realities of one's own nation as well as the capacity to contrast its exposures overseas primarily Korea with South Korea's style of living, industries, and anticipated incomes. Through the release of annual global surveys over the past 200 years, WFH has acquired primary demographic data and information regarding hemophiliac care resources globally to aid in the dissemination of knowledge on these issues. The most recent AGS is in fact its 20th edition, which was released in 2019. The first of the aforementioned reports was created in 1999, with WFH gathering global data starting a year earlier (Montreal: WFH; 2019.)

One monitoring initiative to detect and describe individuals with hemophilia (PWH) or other unusual bleeding disorders worldwide is called WFH AGS. Better healthcare planning will result from increased knowledge, but it will also highlight specific areas that require significant improvement. Every year, this

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ISSN: (e) 3007-1607 (p) 3007-1593

monitoring program gathers standardized data from NMOs associated with the WFH. The distribution and planning of PWH on a global scale have been greatly praised by the AGS. AGS data are self-reported and are regarded as trustworthy for national healthcare program planning because of their internal consistency within states (Evatt. 2001).

Public health significance

Public health now prioritizes non-communicable diseases over infectious diseases. Public health policies, practical implementation strategies, and a long-term vision are necessary for sustainable assistance for individuals with genetic abnormalities and uncommon diseases, which are thought to be the most vulnerable groups. Hemophilia was diagnosed in 273,043 people in 2023. Prevalence estimates of this ailment have been inferred from national patient registries in six high-income nations (Montréal 2024).

According to the data extrapolation estimate, an additional 563,000 individuals with undiagnosed illnesses such as hemophilia are expected to be added globally. Assuming that there are 8 billion people on the planet in 2023, a total of 836 thousand diagnosed and undiagnosed patients will result in roughly 284 thousand persons who are thought to have severe cases. Starting numbers show how severe hemophilia is (acute <1%, medium 1–5%, minor >5–<40%), and they closely match the number of bleeding episodes that occur each year. If prophylaxis is not made the norm of care for all patients, severe hemophilia does lead to reduced life expectancy, higher rates of musculoskeletal issues, and worse quality of life and well-being (Coffin, et al.2019)

16. Conclusion

Factor of clotting factor IX (FIX) and factor VII (FVIII) deficiencies cause hemophilia A and B, two uncommon, inborn, recessive X-linked disorders. Clinical manifestations include bleeding (without trauma or trauma-induced) into major joints, such as ankles, knees, and elbows, which may result in the start of arthropathy, especially in severe forms of the disease regardless of therapy. Internal organ and cerebral bleeding can be fatal. Before a paradigm shift occurred in the 1960s and effective therapy based on replacement prophylaxis—whose efficacy is based on replacing the missing factor—was developed, the life expectancy of affected individuals was approximately thirty years. Today, the quality of life and life expectancy of individuals with hemophilia are almost normal (Berntorp,et.al 2012) However, for a considerable portion of patients, the potential for the generation of inhibitory antibodies that counteract infused factor remains a major obstacle to be overcome. Finally, gene therapy for the two types of hemophilia has advanced significantly and could become a reality in the near future.

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