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Haemophilia: Problems and achievements (literature review)

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Abstract. Haemophilia is an X-linked disorder characterised by the absence or dysfunction of certain blood clotting factors. Haemophilia A is characterised by a deficiency of factor VIII, while haemophilia B is characterised by a deficiency of factor IX. Factor XI deficiency, known as haemophilia C, is a very rare disorder accompanied by bleeding and characterised by moderate symptoms; although this condition is not widespread, standard treatment is associated with significant difficulties related to socio-economic factors. Sequencing of the genes involved in the development of haemophilia has made it possible to describe and record the main mutations and to establish a correlation with different degrees of disease severity. Haemorrhagic manifestations are related to the level of circulating factor, mainly affecting the musculoskeletal system, and especially the large joints (knees, ankles and elbows). This document provides an overview and consensus on the main genetic aspects of haemophilia A and B, from the nature of inheritance to the concept of female carriers, the pathophysiology and classification of the disease, basic and confirmatory tests for suspected haemophilia, various treatment regimens based on infusion of the deficient blood clotting factor, as well as innovative factor-free treatments

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and recommendations for the management of treatment-related complications, inhibitor development and/or transfusion-transmitted infections. The importance of comprehensive care as a treatment strategy for patients with haemophilia is recognised worldwide. Comprehensive care includes addressing the full range of medical and psychological issues affecting both patients and their families

Keywords: haemophilia; clotting factors VIII and IX; treatment; prevention

Introduction

Haemophilia A and B are the only sex-linked hereditary recessive haemorrhagic disorders, the term literally meaning "love (philia) of blood (haemo)", and it is the most common severe disorder [1]. Both haemophilia A and haemophilia B arise as a result of deficiency or dysfunction of factor VIII and factor IX proteins, respectively, and are characterised by prolonged and excessive bleeding following minor trauma, and sometimes even spontaneously. There is also haemophilia C, which results from deficiency of clotting factor XI, but this is rare. Acquired haemophilia may occasionally occur in association with ageing or childbirth and usually resolves with appropriate treatment [2].

Haemophilia is often referred to as the "royal disease", as frequently described in the pedigree of Queen Victoria [3]. The earliest description in ancient history dates back to the second century AD in the Babylonian Talmud, concerning a woman who lost her first two sons following circumcision. The earliest description in modern history was documented by the American physician Dr John Conrad Otto, who described a hereditary bleeding disorder in several families in which only males born to healthy mothers were affected. He subsequently referred to them as "bleeders". The term "haemophilia" was first described by Johann Lukas Schönlein in his dissertation at the University of Zurich (Switzerland). Dr Friedrich Nasse was the first to publish a genetic description of haemophilia in what became known as Nasse's law, which states that haemophilia is transmitted exclusively from healthy women to their sons [3,4].

The history of haemophilia dates back to the second century AD, while the first "modern" descriptions of the disorder appeared in the nineteenth century. At that time, transfusion medicine and haemophilia became closely linked, and blood transfusion was the only available treatment option. A turning point in the history of haemophilia occurred in the mid-twentieth century, when researchers identified "antihaemophilic globulin", capable of shortening clotting time in patients with haemophilia, paving the way for the introduction of cryoprecipitate and the first clotting factor concentrates for the treatment of haemophilia A, haemophilia B and von Willebrand disease. The emergence in Germany and other countries of pasteurised, and therefore virus-safe, plasma-derived clotting factor concentrates, such as Haemate P® and Beriate® P, significantly improved quality of life and increased life expectancy in patients with haemophilia. These and other advances in treatment made home therapy possible, and many centres began to implement prophylaxis in young patients [2-4]. The aim of this review study was to provide readers with general information to improve understanding of haemophilia A, regarded as a genetic disorder with a significant impact on the quality of life of those affected and among the most costly conditions for healthcare systems.

Materials and Methods

The literature search strategy began with the compilation of a list of key search terms: haemophilia, clotting factors VIII and IX, treatment, prophylaxis, and related keywords for relevant articles in English. Searches were conducted in the PubMed, Web of Science and Scopus databases, as well as by manual review of studies published from January 2015 to December 2024.

An additional search for supplementary literature was carried out using Google. Following standardised assessment, only studies that clearly defined haemophilia were included in this review. From the overall list, approximately twenty-five sources reporting on haemophilia were selected for the preparation of this review.

General information

Haemophilia is a hereditary bleeding disorder caused by a quantitative deficiency of clotting factor VIII, known as haemophilia A (HA), which accounts for 80% of cases, or factor IX, known as haemophilia B (HB), which accounts for the remaining 20%. Deficiency of these factors leads to an inability to generate thrombin and enhance the liquid phase of blood clotting, resulting in haemorrhagic diathesis in individuals with haemophilia [5]. The clinical manifestations of HA and HB are similar and depend on the amount of deficient factor in the bloodstream. In severe cases, the main site of bleeding is the joints (haemarthrosis), which without adequate complex therapy can develop into chronic haemophilic arthropathy, which is the main cause of morbidity in this population. The type of inheritance is sex-linked recessive (X chromosome) [5,6]. The disease manifests itself in men, while women are asymptomatic carriers or have minimal haemorrhagic symptoms. The prevalence and genetic changes of haemophilia are similar worldwide and are not influenced by family history or ethnic origin [6].

Genetic defects in factor VIII can be divided into three groups: 1) genetic rearrangements, such as intron 22 inversion, which occurs in 45% of patients with severe haemophilia and is caused by homologous

recombination between the 9.5 kb sequence and two extra-genic homologous regions; in addition, intron 1 inversion may be observed, which occurs in 1-2% of severe cases; 2) insertions or deletions of genetic sequences; and 3) single DNA base substitutions leading to missense mutations, nonsense mutations, or reading frame shift mutations [3].

Coagulopathy in haemophilia patients is a consequence of the inability to enhance, control, and maintain thrombin formation due to factor VIII or IX deficiency. Thrombin formation is considered an event of great biological and physiological significance, as it is an important part of the molecular complex responsible for the liquid phase of haemostasis. When tissue is damaged, factor IXa binds to factor VIIIa on the lipid layer rich in tissue factor (TF), forming an "intrinsic Xase" complex that is capable of generating 90% of thrombin in the event of tissue damage, with an efficiency 10^6 times greater than factor VIII and factor IX alone. This complex is 50 times more effective than the "external Xase" complex (with a high content of factor VIIa) for activating factor X to factor Xa, followed by the activation of factor II (prothrombin) to thrombin, which converts soluble fibrinogen (factor I) to fibrin (insoluble). This simple description of a specific segment of haemostasis explains how the absence of factors VIII and IX clinically manifests itself as classic bleeding in patients with haemophilia [6,7].

Diagnosis and classification

Haemophilia should be suspected in males with prolonged and excessive bleeding unrelated to the severity of injury and/or bleeding that occurs several hours after injury or is recurrent in nature. In primary clotting tests, platelet count, prothrombin time (PT), thrombin time (TT) and fibrinogen will be normal, and activated partial thromboplastin time (APTT) will be prolonged, as described below. Haemorrhagic manifestations in haemophilia A or B are clinically indistinguishable, so it is necessary to identify the deficient factor to ensure specific replacement therapy. The severity of haemophilia is classified according to the activity of circulating plasma levels of factor VIII or factor IX without treatment as severe, moderate or mild (Table 1) [8].

Table 1. Classification of haemophilia and its correlation with haemorrhagic manifestations

Severity	Blood clotting factor levels	Haemorrhagic episodes
Severe	<1 IU/dL (<0.01 IU/mL) or <1%	Spontaneous bleeding into joints or muscles
Moderate	1-5 IU/dL (0.01-0.05 IU/mL) or 1-5%	Occasional spontaneous bleeding; prolonged bleeding following trauma or surgery
Mild	5-40 IU/dL (0.05-0.40 IU/mL) or 5-40%	Severe bleeding after trauma or major surgery. Spontaneous bleeding is rare

Source: created by the authors

The final diagnosis is based on the quantitative determination of blood clotting factors. The World Health Organisation (WHO) has defined the international unit (IU) as the activity of the factor present in 1 ml of plasma, and depending on the nomenclature of each country, it can be equivalently expressed as: 1 IU/dl, 0.01 IU/ml or 1%.

Laboratory tests

Haemostasis testing plays a fundamental role in the diagnosis and monitoring of haemophilia. Ensuring the quality of these tests involves internal and external quality control, as well as control of factors that may affect various stages of result processing, such as the pre-analytical phase, where more than 70% of laboratory errors occur (request for tests by a doctor, correct registration of the requested test, preparation, collection and selection of samples). This is important given that clotting tests are extremely sensitive to temperature changes, particularly due to the thermolability of factor VIII.

Below are the relevant aspects of processing laboratory test results for patients with haemophilia, as well as a brief description of the results of screening, confirmatory tests and the detection of inhibitors in haemophilia.

General aspects:

- Venous blood sampling: an atraumatic collection technique is required, with minimal use of a tourniquet, using 19-21G needles (23G in children);
- Test tube for collecting samples with 3.2% sodium citrate anticoagulant: it must be filled to at least 90% of the specified volume (the ratio of the sample to anticoagulant is 9:1);
- The sample must be thoroughly mixed with the anticoagulant by carefully inverting the tip of the tube 4-6 times and ensuring that no clots form;
- Transportation of samples: at room temperature and centrifugation within the first hour after collection. When transporting to the laboratory, it is preferable to immediately freeze the plasma at -20ºC or below and transport it in dry ice;

■ Fasting: not required, although excess lipids may affect the performance of analytical analysers.

Screening tests for suspected haemophilia:

■ Complete blood count: within reference ranges, unless there are other justified changes;

■ Normal prothrombin time and prolonged activated partial thromboplastin time;

■ Plasma correction: in congenital haemophilia, APTT is corrected by mixing the patient's plasma in a 1:1 ratio with normal plasma. If the mixture does not correct the prolonged APTT, this may indicate the presence of an inhibitor or anticoagulant in the plasma.

Confirmatory testing of factor VIII and IX dosages. Factor VIII can be determined by a chromogenic or clotting method. Factor IX dosage is determined by a one-stage clotting test. It is recommended that comprehensive dosing of all factors that can prolong APTT (VIII, IX, XI, and XII) be performed during the initial examination. If there is a family history of haemophilia, factor VIII or IX activity can be determined in the umbilical cord blood of newborn boys [9,10].

Detection of antibodies to factor VIII and factor IX (inhibitors)

Antibodies to factor VIII or factor IX are IgG-type alloantibodies that have neutralising (inhibitory) or non-neutralising activity against blood clotting factors and are a serious complication of replacement therapy with blood clotting factor concentrates, which is why they are more common in patients with severe haemophilia. They should be suspected in patients with an inadequate clinical response to the administration of the deficient factor, especially if a response was previously observed and/or a change in the haemorrhagic phenotype occurred [11].

Confirmation of the presence of an inhibitor and quantitative determination of the titre are performed using the Bethesda method or its modification, Bethesda-Nijmegen, the latter having greater sensitivity and specificity. The method involves mixing equal volumes of the test plasma with normal plasma, incubating at 37ºC for 2 hours, and measuring the residual factor activity in the mixture, using factor VIII- or IX-free plasma as a control. By definition, a Bethesda unit is the amount of inhibitor that neutralises 50% of the factor activity in one millilitre of plasma.

If, after incubation, the residual factor is 100% of the level in the control sample, the inhibitor level is zero. If the residual factor VIII is 50% or 25% of the control, the inhibitor level is 1 or 2 Bethesda units, respectively. If the result is below 25%, the patient's plasma is diluted to varying degrees until the result is visible on the graph, and the result is multiplied by the dilution factor, which is expressed in Bethesda units. For example, if the plasma mixture is diluted 1:5 before incubation and the residual factor is 50%, or one unit, then 1 × 5 = 5 Bethesda units [12].

Genetic diagnosis

Genetic information about people with haemophilia A is a useful tool for predicting the risk of developing inhibitors and facilitates prenatal counselling for carriers. In haemophilia A, initial genetic screening tests are aimed at detecting inversions of introns 22 and 1. If these changes are not found, complete sequencing of the F8 gene is performed. In haemophilia B, eight exons of the F9 gene are sequenced to detect mutations or deletions. Genetic testing of carriers can be complex. Approximately 80% of mothers of sporadic cases may be carriers of the mutation, while in the remaining 20% of cases, the mutation is not detected and may be secondary to mosaicism. Prenatal diagnosis is an integral part of care for carriers of haemophilia and is important for the completion of pregnancy. Tests include non-invasive methods of determining foetal sex, such as analysis of foetal DNA in the mother's blood (possible in the first trimester of pregnancy) or ultrasound examination starting at 15 weeks of pregnancy, but these methods do not provide definitive results.

Centres with diagnostic resources should perform genetic profiling of haemophilia patients, starting with screening for inversions 1 and 22 in the case of haemophilia A. If the result is negative, complete sequencing of the F8 gene should be performed. For haemophilia B, the F9 gene should be sequenced in the patient and in carriers and/or samples should be sent for research protocols [13].

Multidisciplinary management

Appropriate attention to the diverse needs of haemophilia patients and their families is ensured through the intervention of a multidisciplinary team consisting of healthcare professionals, psychologists, dieticians, orthopaedists, rehabilitation specialists, dentists, occupational therapists, social workers and geneticists, coordinated by a haematologist and in accordance with national treatment guidelines. All team members should have experience and skills in treating blood clotting disorders and be prepared to provide timely assistance to patients. A haemophilia treatment centre infrastructure is required to provide emergency care at any time, with access to specialised laboratory tests (determination of clotting factors and inhibitors) and the necessary medications and clotting factor concentrates [14].

A multidisciplinary team will inform the patient and their family members about the early symptoms of bleeding in order to provide timely assistance, and will also teach them methods of preservation, preparation and administration techniques for blood clotting factors, as well as care for venous access in patients with haemophilia, as these are vital access lines, thereby establishing effective communication between the patient, family and members of the comprehensive care team,

which will facilitate compliance with the treatment regimen based on the following recommendations:

1. Use a 23 or 25G butterfly needle;
2. Venous dissection should not be performed except in emergency situations;
3. After venipuncture, pressure should be applied for 3-5 minutes. The use of permanent venous access devices should be avoided whenever possible, although they may be necessary in certain cases.

Pharmacotherapy. Treatment on demand

The primary pharmacological treatment for haemophilia is the use of deficient blood clotting factor concentrate (BCFC), both recombinant and plasma-derived [5,7]. Therapeutic options can be either on-demand or prophylactic, as described below.

BCFC is used when there are clinical signs of acute bleeding, with the dose to increase factor activity calculated based on the severity of the bleeding. On-demand treatment has been shown to reduce mortality and the progression of arthropathy, but does not prevent it. In life-threatening bleeding, the initial dose of BCFC should be administered immediately, even before the initial diagnostic evaluation is complete, to achieve 80% to 100% activity, whereas in mild to moderate bleeding, the goal is to maintain factor activity in the range of 35% to 50%. Maintenance doses for haemophilia A are usually administered every 12 hours, and for haemophilia B every 24 hours. The doses and duration of treatment with BCFC depend on the location, severity of bleeding and response to treatment. Any acute bleeding in patients with haemophilia should be treated as soon as possible, preferably within the first two hours after its onset. If there is any doubt about the symptoms in a patient with haemophilia, the use of BCFC intravenous bolus is calculated based on the ideal weight of the patient with haemophilia as follows:

- Factor VIII: patient's weight in kg × (desired percentage) × (0.5);
- Factor IX: patient's weight in kg × (desired percentage).

The half-life of the available factor, its purity, the presence of other components such as von Willebrand factor, or the use of recombinant factor should be taken into account. Recombinant factor IX (RFIX) has less effect than plasma-derived products, so each unit of factor IX administered per kilogram of body weight will increase factor IX activity by approximately 0.8 IU/dL in adults and 0.7 IU/dL in children under 15 years of age. The reason for the lower efficacy of rFIX is not fully understood.

If the type of haemophilia is unknown, it is recommended to administer activated prothrombin complex concentrate (aPCC) at a dose of 50 to 100 IU per kg of body weight, not exceeding a daily dose of 200 IU/kg/day. The effectiveness of treatment in cases of acute haemarthrosis is determined according to the criteria presented in Table 2, which allows for a standardised assessment of the response to treatment, facilitates comparison of the results of different studies, and enables therapeutic decisions to be made [15-17].

Table 2. Criteria for assessing the effectiveness of treatment for acute haemarthrosis

Level of response	Response to treatment
Excellent	Complete resolution of pain within 8 hours and/or disappearance of signs of bleeding after the first infusion of clotting factor concentrate, with no need for further dosing to relieve symptoms and signs in the same joint within 72 hours
Good	Marked reduction in pain or signs of bleeding observed 8 hours after the initial administration of clotting factor, but additional doses were required over the following 72 hours to achieve complete resolution of symptoms
Moderate	Partial reduction in pain or signs of bleeding 8 hours after the initial administration of clotting factor concentrate, requiring further doses during the subsequent 72 hours, but without complete resolution of symptoms
Poor	No improvement or only minimal improvement in bleeding, or worsening of bleeding within 8 hours after the initial administration of clotting factor concentrate

Source: created by the authors

New treatment methods

Replacement therapy using BCFC has been effectively controlling and/or preventing bleeding in patients with haemophilia for decades; however, its effectiveness is limited by the availability and safety of drugs, the relatively short period of haemostasis and the development of complications such as the appearance of neutralising antibodies (inhibitors) against factor VIII or factor IX. The search for treatment options remains the ultimate goal. In order to normalise the lives of patients with haemophilia, new therapeutic agents are being developed to improve treatment: 1) BCFC with an increased half-life; 2) gene therapy; 3) specific antibodies that mimic the function of factor VIII; and 4) molecules that modify the action of natural anticoagulants [18].

Factor VIII with an extended half-life

The effectiveness of factor VIII preparations with an extended half-life is limited: the average increase in half-life is 1.5 times, which allows the preparation to be used prophylactically in adults twice a week, but the half-life varies significantly between patients and is shorter in children. Thus, the dosage should be selected individually depending on the bleeding phenotype and the half-life of the standard drug and the drug with an extended half-life [18].

The first technology used to extend the half-life of FVIII was fusion with the constant region of immunoglobulin G (Fc). Efmoroctocog alfa is an analogue of factor VIII linked to the Fc domain of human immunoglobulin G1, which lacks the B domain. The second method of prolonging the half-life of factor VIII is the covalent binding of polyethylene glycol (PEG) to factor VIII (pegylation). There are three drugs approved by the US Food and Drug Administration (FDA) that use this technology:

1. Octocog alfa;
2. Turoctocog alfa pegol;
3. Damoctocog alfa pegol.

The third mechanism for reducing factor VIII clearance involves the addition of negative charges via polysialic acid, which inhibits receptor-mediated clearance [18].

Factor IX with an extended half-life

The traditional regimen for the prevention of severe haemophilia B involves intravenous administration of factor IX twice a week. Structural modifications of factor IX preparations using half-life, as with factor VIII, include pegylation and fusion with an Fc fragment or albumin. The first recombinant factor IX with a half-life to appear on the market was fused with the Fc protein (rFIX-Fc) eftrenonag alfa, with a half-life of 86.5 ± 32.2 hours. In patients receiving 50 IU/kg weekly, a minimum factor IX level of 1-3 IU/dL was achieved with a rapid decline in the first 24-72 hours after infusion, followed by a longer half-life [19]. The second FDA-approved factor is recombinant factor IX linked to albumin (rFIX-FP) albutrepenonacog alfa, which has an advantage over rFIX-Fc in terms of pharmacokinetics, consisting of a gradual decline after infusion, with a half-life of 104 hours. The increased half-life of this drug is due to its high molecular weight (above the renal threshold) and pH-dependent interaction with the neonatal Fc receptor (FcRn), which prevents its intracellular degradation [20].

Treatment strategies without replacement therapy

The main advantages of this treatment method are minimising the risk of inhibitor development, subcutaneous administration, and increasing the intervals between weekly and/or monthly applications. These therapies aim to enhance thrombin formation through various mechanisms of action or to increase endogenous production of the deficient factor through gene therapy, as described below. Therapeutic methods that enhance thrombin formation:

1. Biospecific antibody mimicking the function of factor VIII.

Emicizumab, approved by the FDA, is a bispecific humanised monoclonal antibody that mimics the biological function of factor VIIIa, creating a procoagulant effect through its antigen-binding fragment (Fab), which binds factor IXa and the coagulation substrate FX on the phospholipid layer, generating thrombin with a dose-dependent effect and, consequently, shortening the APTT [20,21]. It is administered subcutaneously and has a half-life of approximately 4-5 weeks. The approved dose for treating patients with factor inhibitors is 3 mg/kg weekly for the first 4 weeks, followed by 1.5 mg/kg weekly or 3 mg/kg every two weeks or 6 mg/kg monthly. It has no structural homology with factor VIII, except for the binding sites, so the development of inhibitors against this molecule is not expected, and it is not neutralised by factor VIII inhibitors.

Studies evaluated the frequency of bleeding in haemophilia patients taking highly effective inhibitors and noted an 87% reduction in the annual frequency of bleeding with weekly emicizumab. Based on these studies, emicizumab was initially approved in 2017 as a prophylactic agent to prevent or reduce the frequency of bleeding episodes in patients with haemophilia taking factor VIII inhibitors. As emicizumab increases the enzymatic activity of factor IXa present in prothrombin complex concentrates by approximately 20,000-fold, its concomitant use, when necessary, is recommended at low doses. No thrombotic events associated with the use of recombinant factor VIIa or emicizumab as monotherapy have been reported [22]. Subsequently, clinical studies have shown a 96-97% reduction in the annual bleeding rate compared to placebo, as well as a median value of 0. In light of these indications, it has been suggested that emicizumab be considered for use in patients without inhibitors, with difficult venous access, who are not candidates for central venous catheter placement, who require high doses of factor VIII (with a clinical course similar to patients with inhibitors) or at high risk of developing inhibitors.

2. Substances that alter the function of natural anticoagulants, such as tissue factor pathway inhibitor, antithrombin, and activated protein C.

Tissue factor pathway inhibitor: in haemophilia, blood clotting and thrombin formation are impaired due to a deficiency of factor VIII or IX. Tissue factor pathway inhibitor (TFPI) is a serine protease that plays an important role in the initial formation of thrombin by inhibiting the tissue factor complex with factor VIIa (TF-FVIIa) and prothrombinase [21,22].

Antithrombin inhibitor: Fitusiran is an interfering ribonucleic acid (RNAi) that binds to messenger RNA

(mRNA) and interrupts its production, leading to a subsequent decrease in antithrombin (AT) synthesis in the liver. AT is the main natural anticoagulant that inactivates thrombin and FXa. A decrease in AT levels in patients receiving various subcutaneous doses of fitusiran was accompanied by an increase in thrombin formation and a decrease in mean annual bleeding.

Gene therapy

Gene therapy involves the introduction of a specific gene sequence into a target cell. The use of a virus as a vector for genetic material is referred to as transduction, which may be performed in two ways: direct *in vivo* injection of the therapeutic gene using a vector, most commonly adeno-associated virus (AAV), and/or transplantation of cells into which the gene has been introduced *ex vivo* using lentiviral (LV) vectors [23,24].

Gene therapy for haemophilia employs AAV to achieve direct transduction of the clotting factor gene into hepatocytes. In certain clinical trials, sustained expression levels of factor VIII and factor IX sufficient to maintain therapeutic effect have been achieved. However, this approach has limitations, as approximately 40% of the population possess antibodies to the capsid of at least one AAV serotype, thereby limiting transduction, and cellular immune responses may develop, characterised by transaminitis and/or reduced transgene expression. Current research in haemophilia gene therapy focuses on intravenous administration of the AAV vector directly to the liver, with immune responses managed using high-dose corticosteroids. Recent studies in patients with haemophilia B suggest the potential for a functional cure of the disease [24].

Replacement therapy with factor VIII concentrates remains the standard of care for patients with haemophilia A. In 2023, the medicinal product "Eitoplazm" was registered in the Russian Federation as the first modern plasma-derived factor VIII concentrate developed in the country. In a multicentre prospective open-label clinical trial, in which 18 of patients (14.2%) participated, Eitoplazm proved effective for the prophylaxis and treatment of bleeding, as well as during surgical interventions, including major procedures. The product demonstrated a favourable safety profile; its use was not associated with the development of inhibitory antibodies, allergic reactions, thrombotic, or thromboembolic complications [25].

Prevention plan

Available data confirm the effectiveness of early prophylaxis (up to 36 months) in terms of improving quality of life and reducing the risk of joint damage. The ESPRIT (Evaluation Study on Prophylaxis: a Randomised Italian Trial) study used recombinant factor VIII at a dose of 25 IU/kg^3 per week, and it was shown that in patients who started prophylaxis at the age of ≤ 3 years, the frequency of all bleeding and haemarthrosis was lower, at 0.35 and 0.12 cases per patient per month, respectively, compared to patients who started prophylaxis after 3 years (0.62 and 0.25). The impact on joint health was significant, as it was documented that none of the patients who started early prophylaxis had radiographic signs of arthropathy on the Pettersson scale, compared to 46% of patients who started prophylaxis after 3 years of age. Even in patients receiving factor VIII on demand, earlier initiation of replacement therapy in children younger and older than 3 years was associated with a lower degree of arthropathy (57% vs. 85%). The challenge is to identify patients who may benefit from low-dose BCFC prophylaxis without compromising joint health and quality of life. Prophylactic treatment regimens fall into two categories: regimens with fixed doses of BCFC (high, medium, low, or alternating doses) and regimens tailored to the patient's needs [26].

Conclusions

As discussed, haemophilia is a hereditary blood clotting disorder caused by a quantitative deficiency of clotting factor VIII, which accounts for 80% of haemophilia A cases, or factor IX, which accounts for the remaining 20%. A deficiency of these factors leads to an inability to generate thrombin and enhance the liquid phase of blood clotting, resulting in haemorrhagic diathesis. Clinical manifestations depend on the amount of the deficient factor in the bloodstream. In severe cases, the main site of bleeding is the joints, which without adequate comprehensive therapy can develop into chronic haemophilic arthropathy, which is the main cause of morbidity in this population. The type of inheritance is sex-linked recessive. The prevalence and genetic changes of haemophilia are similar throughout the world, regardless of family history or ethnicity.

In patients without a family history of haemophilia, with a clinical haemorrhagic profile and prolonged APTT, plasma correction should be performed and the activity of the deficient blood clotting factor should be confirmed by chromogenic or clotting analysis for factor VIII and clotting analysis for factor IX. In cases of a family history of haemophilia, a targeted search for the specific blood clotting factor should be performed in the umbilical cord blood or peripheral blood of the newborn.

The main method of treatment is intravenous administration of the deficient factor. This can be on demand (during bleeding episodes) or prophylactically (regular administration of the factor) with the main goal of preventing spontaneous haemarthrosis, but with a significant risk of developing inhibitors in severe haemophilia. Thus, although haemophilia is a rare blood clotting disorder, it requires doctors to be knowledgeable about its clinical manifestations, as well as diagnostic and therapeutic approaches. New drugs, such as recombinant factor VIII and emicizumab, are widely

used and may become first-line drugs. This literature review aims to provide an objective and straightforward update and review of this disease, with the aim of describing the most important aspects.

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Conflict of Interest

The authors declare that there are no conflicts of interest.

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