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Comprehensive approach to hemophilia

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ABSTRACT

Hemophilia A, B are X-linked recessive bleeding disorder that typically results from a deficiency of clotting factor VIII (FVIII) and factor IX (FIX). The severity of the disease is determined according to the FVIII and FIX levels. Hemophilia A and B have similar symptoms and are both characterized by bleeding, particularly in large joints such as ankles, knees, elbows. Recurrent bleeding in joints eventually causes progressive hemophilic arthropathy. Life-threatening hemorrhages may occur rarely. Treatment of hemophilia has improved significantly in recent years with clotting factor concentrates. The average life expectancy was <40 years until the 1960s, but with better accessing clotting factor concentrates and prophylactic replacement of the missing factor, today hemophilia patients can perform social activities like other healthy individuals and live with an almost normal life expectancy. The future of hemophilia seems bright with gene therapy and new non-replacement treatments.

Keywords: Bleeding, factor concentrates, factor VIII, factor IX, hemophilia

DEFINITION AND INHERITANCE OF HEMOPHILIA

Hemophilia is an X-linked recessive bleeding disorder that typically results from a deficiency of clotting factor VIII (hemophilia A) and factor IX (hemophilia B). Coagulation factor XI (FXI) deficiency was previously described as hemophilia C; however, currently only FVIII and FIX deficiencies are defined as hemophilia. The prevalence of hemophilia A and hemophilia B is reported to be almost 1 in 5,000 and 1 in 30,000, respectively, in the male population (1). The severity of the disease depends on the FVIII or FIX levels, determined by the type of mutation in the genes (F8 and F9) encoding the factors: severe (<1 international unit (IU)/dl), moderate (1-5 IU/dl), or mild (6 IU/dl to 40 IU/dl).

Since the disease is X-linked recessive inherited, women are usually carriers and men are affected. About 30-35% of patients with hemophilia A and B have a de novo mutation without a family history (2). The factor 8 (F8) encoding FVIII is located at the distal end of the long arm of the X chromosome (Xq28), consists of 26 exons and encodes the 2,332 amino acids. F8 mutations are numerous, but are largely categorized as deletions, nonsense mutations, intron 22 or intron 1 inversion, and missense mutations. Inversion of intron 22 is the most detected mutation in severe hemophilia A, occurring in approximately 40% of cases. Missense variants of the F8 are observed in about all non-severe cases of hemophilia A.

The factor 9 (F9) encoding FIX is located at the X chromosome (Xq27.1) with 8 exons. Hemophilia B is genetically heterogeneous and missense mutations are the most common in F9. Hemophilia B Leyden (HBL) is a subgroup of hemophilia B characterized by low levels of FIX during the first years of life, which then rises and potentially normalizes in adulthood. HBL accounts for approximately 3% of all hemophilia B cases. HBL is distinct from other forms of hemophilia because, while it is caused by very low levels of clotting FIX early in life, over time, patients begin to produce FIX. This is because mutations causing HBL occur in the promoter region of the gene for clotting FIX. The promoter region is an area in the DNA that controls when a certain gene is turned off or on. In HBL, one activator region is disrupted by mutations, but the promoter region that responds to activation by hormones (estrogen and testosterone) is unaffected (3).

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Hemophilia A and B is known as a male disease. In some cases, it can also be seen in women. Depending on the type of mutation, mild hemophilia may also be present in carrier women. Carrier women appear to have decreased levels of FVIII due to X inactivation. Although rare, a hemophilia woman can be born with a 25% probability from the marriage of a hemophilia male and a carrier woman. In addition, a severe hemophilia clinic can be seen in a woman with Turner syndrome with an X0 chromosome (4).

CLINIC FEATURES OF HEMOPHILIA

The severity of hemophilia is usually correlated with factor deficiency. According to the factor level, it is classified as severe (<1 IU/dl), moderate (1-5 IU/dl), and mild (6-40 IU/dl). Bleeding in patients with hemophilia can occur anywhere. All males in a family who inherit the familial mutation will have approximately the same degree of factor deficiency and similar disease severity, as they share the same genetic defect. Throughout life, age and disease severity affect the site of the bleeding. Common bleeding sites in infants and newborns include the central nervous system, circumcision, and areas of medical intervention. Approximately 3% of infants with severe hemophilia develop subgaleal or intracerebral hemorrhage in the perinatal period (5). Skin bruising, joint bleeding, and other musculoskeletal bleeding become more common as children begin to walk. Common bleeding sites in older children and adults are the joints, muscles, central nervous system, and gastrointestinal tract.

Generally, people with severe hemophilia are diagnosed before the age of two, but some people with mild hemophilia may only be diagnosed at the time of injury or when they show symptoms of bleeding associated with surgery. In a data collection study with 13,399 participants; The age at diagnosis for severe, moderate, and mild hemophilia was 1 month, 8 months, and 36 months, respectively (6). Some bleeding sites are mentioned below.

Intra-Articular Bleeding

Hemarthrosis (bleeding into the joint) is the most common site for bleeding in ambulatory patients and represents 80% of bleedings. Bleeding into the joint cavity originates from the synovial vessels. Bleeding episodes often affect various joints, particularly the knees and ankles, which are weight-bearing joints. The ankles are most affected in young children, while the knees and elbows are more commonly affected in adolescents and adults. Hemarthrosis is painful due to stretching of the synovial space and consequent muscle spasm causes increase in intrasynovial pressure. Clinical presentation varies with age; In infants, early signs of bleeding include agitation and reduced use of the affected limb. In older children and adults, it first presents with a characteristic feeling of warmth in a joint, followed by acute pain, swelling and stiffness. The diagnosis of hemarthrosis is clinically based on pain, limitation of movement, and/or physical examination findings. Imaging may be performed in complex situations where the target joint has developed, and it is more difficult to determine whether the findings are new. Target joint is a term used for a joint that has bled three or more times in the past six months. Joint aspiration is usually not performed in patients with hemophilia. With increased joint bleeding frequency, joint damage and inflammation may occur, and the joint may become a target joint with an increased susceptibility to further bleeding.

Hemophilic arthropathy is multifactorial. It is known that repetitive bleeding into synovial joints leads to degenerative articular cartilage damage, as well as severe joint destruction resembling the inflammatory processes (7). In the target joint due to recurrent bleeds, the synovium becomes hypertrophied and protrudes into the joint cavity. The detection of early changes in arthropathy are difficult. Studies show that joint damage in hemophilic arthropathy is induced by direct contact of blood with articular cartilage, interaction with the iron and inflammatory cytokines such as IL-1β and tumor necrosis factor (TNF). These inflammatory cytokines also activate other cytokines, causing progressive joint destruction.

Bleeding into the Muscle

Bleeding into muscles with hematoma formation is common. Often this affects large muscle groups, such as those in the leg (quadriceps), hip (iliopsoas), and arm. Muscle bleeding can be severe, widespread and compromise neurovascular structures. It can cause a compartment syndrome by compressing the vessels and nerve bundles, especially in the lower leg and forearm. In addition, untreated or inadequately treated intramuscular bleeding leads to the formation of a pseudotumor with a hematoma surrounded by a fibrous membrane. Except for iliopsoas, other intramuscular hemorrhages are visible and can be diagnosed and treated at an early stage. However, in the iliopsoas bleeding, a feeling of anesthesia in that leg begins, and then pain and limitation in extension of the hip develop. Usually, ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) are needed for diagnosis. Since it may take a long time until the diagnosis, there may be much bleeding to impair hemodynamics. Therefore, prompt diagnosis and treatment are very important.

Intracranial Bleeding

Intracranial hemorrhage (ICH) is relatively rare compared to other bleeding sites, but it is one of the most dangerous and life-threatening events in patients with

hemophilia. It can occur spontaneously or after trauma in individuals of all ages. The overall incidence of ICH in patients with hemophilia is approximately 3-4% at birth. In a meta-analysis included over 54,000 people with hemophilia in 2021, the pooled ICH incidence was 0.23% per year, compared with a higher incidence of 0.74% per year in children and young adults (8). Risk factors for ICH include trauma (especially in births requiring instrumentation), severe factor deficiency, presence of inhibitors, over 50 years of age, hypertension (9). Prophylaxis was found to be the most effective factor in reducing the risk of ICH.

Nose Beeding, Intraoral and Gastrointestinal Bleeding

Bleeding may occur from multiple oropharyngeal sites such as the nose, oral mucosa, gingiva, and frenulum. This type of bleeding follows minor traumas or dental treatments. Also, bleeding from coughing or vomiting can spread to the neck, which can lead to airway obstruction. With or without various lesions in the gastrointestinal tract such as gastritis, polyps, diverticulum, it may present with blood in the stool or hematemesis.

Genitourinary System Bleeding

Hematuria is a common manifestation of severe hemophilia; It is usually benign and does not result in progressive loss of kidney function. Bleeding may originate from the kidneys or bladder. Fibrin clots can form throughout the urinary tract with bleeding. This causes severe colic pain and ureteral obstruction. Intravenous hydration, factor replacement therapy is initiated, and a urinary double J catheter can be inserted if necessary. Antifibrinolytic drugs are not recommended due to increase the fibrin clots in ureter.

Clinical Practice in Heterozygous Women

Female carriers of hemophilia are heterozygous for the associated genetic defect (having one normal allele and an allele with a pathogenic variant in the gene encoding the relevant factor). Therefore, they usually have enough factor activity (factor >50 IU/dl) not to cause bleeding. Since FVIII and FIX levels are normal in heterozygous women, carrier cannot be determined by factor level determination. Only 30% of carrier women have low factor level. Therefore, the causative variant should be performed in likely carrier women. Heterozygous women with low factor levels exhibit similar clinical manifestations to men with mild hemophilia. Causes of severe hemophilia in women include inheritance of pathogenic variants from both parents, X chromosome inactivation (lyonization), loss of the X chromosome containing the normal F8 or F9 allele (as in Turner syndrome) (4). Thus, a woman who is known as heterozygous or likely to be carrier should be monitored closely before any intervention such as surgery that may cause severe bleeding.

Obstetric Problems

Known as a carrier of hemophilia or potential carrier women should get genetic counseling and information about hemophilia. The information includes the risk of having an affected fetus, the timing of diagnosis (at birth and postpartum), the choice to terminate the pregnancy, and potential problems with delivery (such as potential risks from a vaginal delivery if the child has hemophilia). Carriers of hemophilia may have low factor levels as mentioned above. Therefore, if the factor activity level has not been determined before, it should be checked at least once during pregnancy and repeated if it is low (<40%). It should not be forgotten that the FVIII level is found higher than the basal value due to stress and hormones during pregnancy, whereas the FIX level remains more stable. Women with low factor activity levels may be at increased risk of bleeding during procedures, including neuraxial anesthesia, during pregnancy and/or delivery. In addition, even if factor levels are normal during pregnancy, a decrease is observed frequently after delivery, so it should be carefully monitored in terms of postpartum hemorrhage risk. If necessary, postpartum factor levels can be monitored.

Pregnant women should undergo fetal gender assessment using a non-invasive method such as ultrasound, as boys are potentially affected. There are also methods such as detecting Y chromosome sequences from maternal blood for sex determination. There are invasive diagnostic methods (amniocentesis or chorionic villus sampling) for the detection of affected male fetus. In some cases, these invasive methods are recommended if the family will consider terminating the pregnancy when an affected fetus is diagnosed. If prenatal diagnosis is not done, a diagnosis of hemophilia can be made by measuring FVIII or FIX levels in the cord blood of a newborn at birth. While it is reliable for FVIII, FIX level may result in low than expected due to decreased liver maturation and deficiency of vitamin K.

Fetal problems include the absence of a definitive diagnosis at the time of delivery in most cases, and the potential risks of bleeding during or after delivery, particularly intracranial hemorrhage and cephalohematoma (10). Although the best method of delivery (vaginal vs cesarean section) continues to be a matter of debate, most newborns with hemophilia can deliver safely with either method. There is a consensus that instrumental vaginal delivery (use of forceps, vacuum extraction) should be avoided because of the risk of cephalohematoma and ICH. A very large series of births (583,340 births of non-hemophiliacs) in the general population compared various risks with different methods of delivery (11). The risk of subdural or cerebral hemorrhage with spontaneous vaginal delivery, vacuum or forceps delivery was 2.9, 8.0,

or 9.8 per 10,000, respectively. With vacuum plus forceps, the risk was 21.3 per 10,000. The rate of assisted vaginal delivery-associated intracranial bleeding in patients with hemophilia is approximately 4.4% (5).

DIAGNOSIS IN HEMOPHILIA

Diagnostic evaluation in suspected cases of hemophilia begins with a thorough review of the individual's bleeding history and family history. Screening tests are then performed, and the diagnosis is confirmed by specific clotting factor measurements and/or genetic testing.

Laboratory tests are similar for most people with clotting factor deficiency. Initial tests include hemostasis screening tests, including prothrombin time (PT), activated partial thromboplastin time (aPTT), and platelet count (**Figure 1**). If elongation is detected in the aPTT test, the mixing test is performed to distinguish the presence of a factor deficiency or inhibitor. The mixing test is performed by mixing patient plasma and normal plasma in equal proportions. Improvements in aPTT of less than 50% because of mixing suggest the presence of inhibitor, while improvement of more than 50% indicates factor deficiency. Especially coagulation factors (FVIII, FIX, FXI, FXII) that work in the intrinsic pathway are studied. In patients with factor VIII deficiency, it is important to exclude von Willebrand disease (VWD) with the von Willebrand factor (VWF) antigen test (VWF:Ag). Patients with mild hemophilia may have a normal aPTT because aPTT may result in normal with factor levels greater than 15%, especially in hemophilia B (12). Whatever the scenario leading to the suspicion of hemophilia, the definitive diagnosis is made by measurement of residual FVIII and FIX coagulation activity (FVIII:C and FIX:C). These measurements can be performed by using one-stage or chromogenic coagulation methods. The one-stage method is the most widely used due to its long-term use and less costly than the chromogenic assay (13).

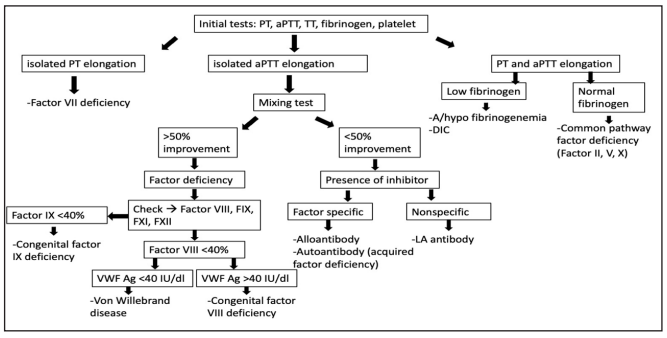

Figure 1. Laboratory differential diagnosis of hemophilia.

PT; prothrombin time, aPTT; activated partial thromboplastin time, TT; thrombin time, VWF; von Willebrand factor, LA; lupus anticoagulant, DIC; disseminate intravascular coagulopathy

Genetic testing (also called molecular testing) is appropriate for most patients. This information helps to estimate the risk of inhibitor formation in the patient and facilitates carrier identification in female family members. It should be done routinely for severe to moderate hemophilia but is less frequently needed for mild hemophilia. For hemophilia B, full gene sequencing is usually done for F9, whereas inversions of intron 22 (40% frequency) and intron 1 (1%) is initially studied for severe hemophilia A (14). Since hemophilia A families with mild to moderate disease are more likely (approximately 90%) to have a point mutation, whole gene sequencing is recommended in families with mild to moderate disease if genetic testing is indicated (15). About 30% of individuals with hemophilia do not have a family history.

Differential Diagnosis

The differential diagnosis of hemophilia includes other inherited bleeding disorders and other causes of aPTT isolated prolongation. Generally, these diseases can be easily distinguished by measuring the appropriate factor level. Like hemophilia, VWD is an inherited bleeding disorder that may be associated with a normal or long aPTT; Some patients with VWD will also have decreased FVIII levels. Most types of VWD show mucosal bleeding patterns clinically different from hemophilia, while some types of VWD (type 2N and type 3) have bleeding patterns similar to hemophilia.

Like hemophilia A and B, factor XI deficiency is characterized by a long aPTT. Unlike hemophilia A and B, patients with factor XI deficiency tend to exhibit provoked bleeding rather than spontaneous bleeding. Factor XI deficiency is more common in Ashkenazi Jews (Jews from Eastern Europe).

Someone may have combined FVIII and FV deficiency due to a defect in a gene that affects cellular transport (endoplasmic reticulum and Golgi apparatus) rather than a defect in the coagulation factor gene. These patients have a longer PT as well as aPTT. It shows autosomal recessive inheritance.

Acquired factor inhibitors are autoantibodies that disrupt the normal activity of clotting factors. Inhibitors of factors, particularly factor VIII, have been reported; they may develop during pregnancy in patients with an underlying systemic disorder such as rheumatoid arthritis, systemic lupus erythematosus, malignancy, or drug reaction. Like hemophilia, acquired inhibitors may present with bleeding and prolonged aPTT.

Antiphospholipid antibody syndrome (APS) results from autoantibody that prolongs aPTT in vitro but clinically creates a risk of thrombosis rather than bleeding. Thromboembolism and/or recurrent pregnancy loss may occur in patients with APS. The expected improvement in aPTT is not seen in the mixture test (16).

INFECTION IN HEMOPHILIA

Existing coagulation factor products from human plasma undergo a variety of procedures to reduce the risk of transmission of infectious organisms, including extensive pre-donation screening, viral reduction and inactivation processes, and other methods to eradicate human immunodeficiency (HIV). Patients treated with plasma-derived factor concentrates, which began to be produced in the late 1970s, were at increased risk for infection with HIV, HCV, and other hepatitis viruses (A, B, D [delta]). Prior to factor concentrates, patients had been treated with blood products such as whole blood and fresh frozen plasma (FFP) were at higher risk for hepatitis viruses. The risk of viral transmission has been greatly reduced by the use of viral inactivation procedures and recombinant factor products produced in cell culture. Co-infection with HCV and HIV is clinically important as it can cause refractory liver disease and poses a high risk for hepatocellular carcinoma. Other potentially infections are Parvovirus B19 and prion.

INHIBITOR IN HEMOPHILIA

Inhibitors are allo-antibodies in immunoglobulin G (IgG) structure that develop against exogenous coagulation factors (FVIII or FIX) in Hemophilia A and B and neutralize the activity of the factors. Peptides from exogenous FVIII (eFVIII) are presented on the surface of antigen-presenting cells via class II MHC proteins, stimulating a population of T helper (TH) cells. This causes the antibody-producing B cells to mature and produce allo-antibodies. The anti-eFVIII allo-antibodies formed recognize the infused eFVIII as a foreign antigen and inhibit eFVIII function; therefore, these antibodies are called inhibitors.

The risk of developing inhibitors in hemophilia with severe FVIII and FIX deficiency is approximately 30% and 5%, respectively. The risk of developing inhibitors varies with the level of deficiency, race/ethnicity, some genetic (complete deletions, nonsense mutations, etc.) and environmental factors, but not all contributing effects have been fully explained. Inhibitor determination is made with the Bethesda test, and the inhibitor titer that neutralizes 50% of 100% factor activity is called one Bethesda unit (BU/ml). A positive inhibitor is defined as ≥ 0.6 BU/mL for FVIII and ≥ 0.3 BU/mL for FIX. Detection of inhibitor titer of <5 BU/mL is called low titer inhibitor, and ≥5 BU/mL is called high titer inhibitor. High titer inhibitors tend to be persistent. When an inhibitor is suspected, a mixture test should be done first, and if it is positive, inhibitor measurements should be made with the Nijmegen-Bethesda test (NBT) to determine the exact inhibitor titer. NBT reduces false positive measurements in the range of 0.6-2 BU/mL as measured by the Bethesda test (17).

Although inhibitors can occur at any time during a patient's life, they occur most frequently within the first 50 exposure days. For this reason, while screening is recommended for inhibitors more frequently in the first applications, is recommended once a year after the first 100 exposure days. The SIPPET study pointed out that the inhibitor development was increased with the recombinant clotting factor concentrates compared to products derived from plasma in the first 50 exposure days (18). For this reason, plasma derived FVIII concentrates are recommended for the first 50 exposure days in many European countries as in Turkey. There is no such recommendation for FIX concentrates, since the inhibitory risk is low in hemophilia B.

THERAPY IN HEMOPHILIA

Although there are many treatment options in hemophilia, treatment is determined according to different geographical and economic conditions around the world. Effective and multidisciplinary approach to the hemophilia is major to prevent bleeding and ensure healthy life. Prophylactic or on-demand treatments are considered mainstay of the treatment in hemophilia. Patients with hemophilia should be treated in comprehensive care unites with a multidisciplinary team of specialists such as hematology, physical therapist, orthopedist, radiology, physiotherapists, nurses, and psychologists specialized in the hemophilia.

Factor Replacement Therapy

The main aim of hemophilia treatment is to increase plasma coagulation factor levels with exogenous factor replacement to stop or prevent bleeding. Whenever possible, only the missing factors should be replaced. Because products such as FFP and prothrombin complex concentrates may have thrombotic potential with high factor levels. Plasma-derived and recombinant products are available for patients with hemophilia. They have no superiority over each other in terms of their effects. What is only known is that recombinant FVIII products increase the inhibitory risk, especially in the first 50 exposure days (19). When FVIII is given 1 IU/kg, the plasma FVIII level increases by 2%, with a half-life of 8-12 hours. Plasma-derived FIX, when given 1 IU/kg, increases the plasma FIX level by 1%, and its half-life is 18-24 hours. Since the dose calculations of recombinant products of FIX may differ, the information of the product used should be checked. Factors should be administered as a slow intravenous bolus for at least 5 minutes (not to exceed 3 mL/minute in adults and 100 IU/minute in children).

There are two main approaches to replacement, prophylaxis or on-demand therapy.

Prophylaxis in Hemophilia

It is the continuous and regular use of clotting factor concentrates that aim to prevent heavy bleeding, especially joint bleeding, and damage, as well as increase the quality of life of patients and provide hemostasis. Prophylactic treatment targets a trough level of >1 IU/dl of the missing factor. However, higher factor VIII levels can be targeted depending on lifestyle and activity of a person in hemophilia.

Time-based prophylaxis classification is determined by the time of prophylaxis initiation (**Table 1**). Primary prophylaxis is the treatment that is started before the second joint bleeding and before the age of three, before physical examination and/or imaging methods reveal signs of joint damage. Secondary prophylaxis is the treatment that is started after two or more joint bleedings, but before "joint damage" occurs by physical examination and radiological imaging methods. Tertiary prophylaxis is the treatment applied after the onset of joint damage in the affected joints by physical examination and radiological imaging methods. It is the type of prophylaxis that is usually started in adult with hemophilia.

Table 1. Definitions of prophylaxis by onset time

Prophylaxis model	Description
Primary prophylaxis	The continuous and regular* treatment that is started before the second joint bleeding and before the age of three, is before the signs of joint damage are revealed by physical examination and/or imaging methods.
Secondary prophylaxis	The continuous and regular* treatment that is started after two or more joint bleedings but is before signs of joint damage are revealed by physical examination and/or imaging methods.
Tertiary prophylaxis	The continuous and regular* treatment is applied after the onset of signs of joint damage by physical examination and/or imaging methods. The initial prophylaxis in adulthood is usually of this type.
Intermittent prophylaxis	The short-term treatment that is applied <45 weeks in a one-year period to prevent bleeding.

*Application of the treatment is >45 weeks in a one-year period

On-demand Therapy

Although prophylaxis reduces the frequency of breakthrough bleeding, it may not prevent them completely, so additional factor doses are needed for bleedings. Treatment should be adjusted to achieve individual best results based on the location, extent, and severity of the bleeding. Immediate treatment is essential for all bleeding episodes. The targeted factor level and duration according to the bleeding site and severity are summarized in **Table 2**.

Inhibitor Therapy

Inhibitor therapy varies depending on the titer usually measured by NBT; however, non-specific coagulation inhibitors (lupus anticoagulants) may cause false positives in the in vitro test. As mentioned above, a titer of <5 BU/mL is called a low titer inhibitor, and a titer of ≥5 BU/mL is called a high titer inhibitor. In the presence of a low-titer inhibitor, it can be treated with high-dose factor concentrate to achieve hemostasis. However, in patients with an inhibitor titer of >5 BU/ml, bypassing agents (BPAs) are preferred to achieve hemostasis. However, such a strategy is not suitable for patients with inhibitor titers >5 BU/ml; instead, bypassing agents (BPAs) are used to achieve hemostasis. BPAs which are commonly used in the treatment or prophylaxis, are recombinant factor VIIa (rFVIIa) and activated prothrombin complex concentrates (aPCCs).

Table 2. WFH recommended dosage and duration of replacement therapy according to bleeding site and type of hemophilia[c]

Bleeding site	Hemophilia A		Hemophilia B	
	Target factor level[b] (IU/dl)	Duration of the treatment	Target factor level[b] (IU/dl)	Duration of the treatment
Joint bleeding	40-60	1-2 days, 1-3 doses[a], every 8-12 hours	40-60	1-2 days, 1-3 doses[a], every 18-24 hours
Intramuscular bleeding (Except iliopsoas)	40-60	2-3 days, longer if response is not sufficient	40-60	2-3 days, longer if response is not sufficient
Iliopsoas bleeding *Initial **Following	*80-100 **40-60	*1-2 days **7-10 days, longer if response is not sufficient	*60-80 **30-60	*1-2 days **7-10 days, longer if response is not sufficient
Intracranial bleeding *Initial **Following	*80-100 **50	*1-7 days **8-21 days, longer if response is not sufficient	*60-80 **30-60	*1-7 days **8-21 days, longer if response is not sufficient
Neck/throat *Initial **Following	*80-100 **50	*1-7 days **8-14 days, longer if response is not sufficient	*60-80 **30-60	*1-7 days **8-14 days, longer if response is not sufficient
Gastrointestinal tract *Initial **Following	*80-100 **50	*1-7 days **8-14 days, longer if response is not sufficient	*60-80 **30-60	*1-7 days **8-14 days, longer if response is not sufficient
Urinary system	40-60	3-5 days, longer if response is not sufficient	40-60	3-5 days, longer if response is not sufficient
Deep laceration	40-60	3-7 days, longer if response is not sufficient	40-60	3-7 days, longer if response is not sufficient
Surgery (major) *pre-surgery **post-surgery	*80-100 **60-80 **40-60	1-3 days 4-14 days (longer if needed)	*60-80 **40-60 **30-50	1-3 days 4-14 days (longer if needed)

WFH; World Federation of Hemophilia, [a]Discontinue if bleeding symptoms have resolved after the first dose, [b]for hemophilia A, dose of factor=(target level-current level)xkgx0.5 for hemophilia B, dose of factor=(target level-current level)xkgx1, [c]WFH recommended dosage and duration of replacement therapy in acute bleeding (27), *Initial doses are given as calculated above, followed by half of dose (every 8-12 hours for hemophilia A, 18-24 hours for hemophilia B).

In low responders, inhibitors may resolve spontaneously over time. Both low-responders and high-responders can be treated with immune tolerance induction (ITI). ITI is given in frequent doses of FVIII or FIX over time to increase tolerance. This practice can be intensive, long-term, and costly (20).

Non-replacement and Bypassing Therapy

A new agent, emicizumab is a biphenotypic antibody and mimics the role of FVIII as in the tenase complex (21). So, emicizumab cannot be used in patients with hemophilia B. Prophylactic use of emicizumab has been shown to be effective in patients with inhibitory hemophilia A. Clinical studies have shown a significant reduction in annual bleeding rate (ABR) as compared to bleeding or prophylactic BPA regimens. Emicizumab is not preferred in acute bleeding; FVIII should be given in patients without inhibitors and BPA should be given in patients with inhibitors. Instead of aPCC, rFVIIa is preferred as BPA for the treatment of acute bleeding in a patient receiving emicizumab prophylaxis treatment. aPCC is a mixture of plasma-derived activated coagulation factors acting by the presence of prothrombin and FXa and therefore the risk of thrombotic events is very high. No thrombotic events have been reported in the use of rFVIIa during emicizumab prophylaxis (22).

The Future of Hemophilia Treatment and Gene Therapy

There have been significant advances in the treatment of hemophilia in recent years. Despite this, there are important issues that continue to be lacking in treatment; establishing new treatment centers that every patient can easily reach and access to safe therapeutic agents. In addition, long-term and effective treatments are being developed. The important point to be considered in the treatment of hemophilia is that the pharmacokinetics, bleeding phenotype and lifestyle of each patient, so the treatment should be individualized. In personalized therapy, the pharmacokinetics and efficacy of the infused factor concentrate, the individual's bleeding phenotype, access to treatment, compliance, and societal perspectives should be considered. In the future, it is hoped that personalized therapy may replace weight-based, fixed-dose prophylaxis regimens, but difficulties in accessing drugs in different countries, cost and compliance limit the widespread use of this therapy. Newly developed treatments are entering the market and are promising for the near future. Several agents are currently under investigation, including fitusiran (23), Super FVa, factor Xa, APC inhibitors, and TFPI inhibitors (24).

Gene therapy trials using adeno-associated virus (AAV)-based vectors have now been reported in hemophilia A and B. In the interim evaluations of the studies, the almost complete elimination of bleeding episodes and the decreased need for factors seem promising. In non-insertional gene therapy products, the levels of the nascent factor may decrease over time; stable expression of coagulation factor transgenes should be provided to avoid the need for treatment. A recent hemophilia A gene therapy trial demonstrated sustained F8 expression for >2 years (25). It was observed to show sustained F9 expression over 8 years in a hemophilia B gene therapy trial (26). However, further studies and observations are required to achieve persistent factor 8 or factor 9 expression.

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