



## Insights on Hemophilia

**M. Rangapriya\*, Anisha Merin Varghese, Anna Joseph**

Department of Pharmacy Practice, Swamy Vivekanandha College of Pharmacy, Elayampalayam, Namakkal, Tamilnadu, India.

\*Corresponding author's E-mail: [priyanarayan97@gmail.com](mailto:priyanarayan97@gmail.com)

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### ABSTRACT

Hemophilia is a serious lifelong blood-clotting disorder. Patients with this X-linked genetic disorder can experience frequent bleeding episodes, which may be prolonged and difficult to stop. The frequency of these bleeding events depends on the level of coagulation factor in plasma. Over the years, the hemophilia has evolved from a fatal hereditary bleeding disorder to a disorder with safe and effective treatment available. The prevalence is commonly seen in males than in females. Whereas, females act as carriers; most carriers are asymptomatic. Carriers with clotting factor levels of 40-50% of normal may have an increased bleeding tendency at the case of major trauma. Congenital hemophilia is a rare and complex condition for which dedicated specialized and comprehensive care has produced measurable improvements in clinical outcomes and advances in patient management. This review article focuses on these general aspects of the disease and the pharmacist's role.

**Keywords:** Factor VIII, Factor IX, coagulation, X- linked disorder, genetic testing, treatment.

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### INTRODUCTION

Hemophilia is a congenital X linked bleeding disorder caused by the deficiency or absence of coagulation factors required for hemostasis. This occurs due to the mutation in the gene present in the X sex chromosome responsible for making the clotting factor proteins needed to form a blood clot or to complete the hemostasis. Hemophilia A also called classic hemophilia is due to shortage or lack of coagulation factor 8(FVIII) covering up to 80% of overall hemophilia affected people. Hemophilia B also named as Christmas hemophilia because the first patient with hemophilia B was Stephen Christmas. Hemophilia A is 4 times more common than hemophilia B. This is due to the deficiency of factor 9(FIX). And hemophilia C is the rarest with FXI deficiency. Hemophilia has evolved from a crippling disease with a shortened life expectancy into a disease with a normal life expectancy, significantly less joint arthropathy and acceptable quality of life.<sup>5,6</sup>

The characteristic phenotype is prolonged bleeding that can be spontaneous or trauma related bleeds with the most common bleeding in the joints (hemarthrosis) of knee, elbow and ankle. As bleeding happens, the iron content in blood which is both pro-angiogenic and pro-inflammatory is the key stimulant for the changes in such as hypervascularity and hypertrophy. The changes can

cause cartilage and bone damages causing joint damage resulting in hemophilic arthropathy and disability due to flexion disability without immediate treatment. Intracranial bleeding is a life-threatening bleeding condition as they even cause seizures or paralysis if bleeding prolongs. Others include gastrointestinal and neck/throat.

The severity of bleeding is categorized upon the clotting factor baseline with the normal range 50-150%. According to their residual endogenous FVIII/FIX concentrations, individuals with a factor level in the range of 5- 40% or 5-40 IU/dL have mild hemophilia, 1-5 % ( 1-5IU/dL) and <1 %(< 1 IU/dL) are moderate and severe hemophilia respectively. The manner of bleeding for each hemophilia patient differs as per their clotting factor baseline.

The mainstay treatment is the replacement with clotting factor concentrates (CFC) in blood since it controls the active bleeding by on demand episodic treatment and/or to prevent recurrent bleeds by regular prophylaxis. Therefore, the primary and secondary goal of the treatment is to stop the bleeding process and prevent further bleeding in the future.

### 1. PATHOPHYSIOLOGY

The fundamental function of coagulation system is to sustain the structural integrity of endothelium and preserving the vasculature patency. Vasculature patency is maintained as the inner endothelium layer maintains a non-thrombogenic blood-tissue interface, blood compatible surface<sup>41</sup> physically separating the potent activator, Tissue Factor (TF) preventing inappropriate activation of the clotting cascade and inactivated forms of coagulation factors. Preserving the fluid state of vasculature is a highly complex system balancing the procoagulant, anticoagulant, and fibrinolytic systems and



also a rapid response to an injury by clot formation. This process is characterized by the sequential activation of 3 vitamin K-dependent serine proteases (FVII, FIX, and FX) and their cofactor complexes (tissue factor, FVIII, and FV). Coagulation occurs when an insult occurs in the sub endothelium layer exposing the TF (Tissue Factor) which is the integral membrane protein and major trigger of the coagulation cascade.

### Extrinsic pathway

On exposure, TF binds to the activated (a) FVII forming TF-FVIIa complex (initiation complex), an extremely potent activator of coagulation, is responsible for initial FXa generation, which provides sufficient thrombin to induce the local aggregation of platelets. This occurs when TF-FVIIa complex activates two downstream substrates in the coagulation cascade: factor IX (FIX) is converted to FIXa, and FX is converted to FXa. FIXa and FXa assemble with its cofactor complexes i.e., FVIIIa, and FVa respectively in order to propagate the clotting cascade. This results in the large quantity release of thrombin, the last serine protease in the clotting cascade processing fibrinogen to fibrin via limited proteolysis. Thrombin is also a potent activator of platelets, further contributing to the formation of a protective hemostatic plug (in normal hemostasis) or a thrombus (in pathologic activation of clotting).

### Intrinsic pathway

On exposure to endothelial collagen, activation of Factor XII (a zymogen, inactivated serine protease) which becomes Factor XIIa (activated serine protease). This process leads to the activation FIXa. FIXa with its cofactor FVIIIa amplifies the FIX activity which is necessary for FX to FXa conversion. FIXa along with FVIIIa, Ca, phospholipids (PL) form Tenase complex, key role in amplifying the clotting cascade for FXa conversion. FXa along with its cofactor FVa forms prothrombinase complex resulting in thrombin and fibrin formation. A defect in either of FVIII or FIX decreases the activation of FXa causing dysfunctional clotting.

Extrinsic pathway requires TF and FVII for coagulation initiation, FXa release to sustain hemostasis. But this initiation complex can be inhibited by TFPI (Tissue factor pathway inhibitor); therefore extrinsic pathway alone cannot sustain the process and must be amplified through the action FIXa and FVIIIa for continued production of FXa.

The TF, transmembrane receptor for Factor VII/VIIa (FVII/VIIa). It is constitutively expressed by cells surrounding outermost layers of the vessel wall<sup>37, 38, 39</sup>. Circulating blood cells, as well as the endothelial cells that line the blood vessels, do not usually express TF. They are also found in keratinocytes in the skin, and epithelial layers such as organ capsules<sup>37,38,39</sup>. TF abundant presence in the outermost layer of the skin can be a possible reason allowing for direct, abundant activation by FX by TF: VIIa. Drake et al., 1989 states that TF plays as a protective "hemostatic envelope" surrounding the vasculature, organ structures, and the organism as a whole. Drake et al., 1989a; Fleck et al., 1990; states, TF is found abundantly in

sites where hemorrhage may occur such as brain, kidney and low in quantity in skeletal muscle and synovial tissues, which is a possible explanation for spontaneous bleeding in hemophilic patients.

### GENETICS

The genes encoding for the FVIII and FIX functionality is located on X chromosome and hence for this reason they called as the sex-linked recessive pattern. The chances of acquiring the mutated gene in the progeny depend upon the parents. The son of a haemophilic father will not acquire the gene but only the female child acquires it, making her a carrier. Whereas the daughter and son of carrier mother have 50-50% chance of acquiring the defected gene as the mother gives away the X chromosome to her children. On other hand, a haemophilic female would have a mother who is a carrier and a father who has haemophilia.

Carrier females have one altered chromosome and a normal functioning chromosome that provides 50% factor levels for haemostasis. It is rare that carrier may have extreme skewed X chromosome inactivation or extreme lyonisation of the normal X chromosome can have very low levels of factors. Women are mostly carriers and as per Dr. David Clarke, the estimated number of carriers is up to 5 times as many as men with hemophilia. The average factor level in carriers is 60% which does not mean they do not suffer from any arthropathy, bleeding or pain. Several studies point to the fact that carriers have reduced range of motion (ROM) indicating of possible joint damage and presumably hemarthrosis.

### DIAGNOSIS

A correct diagnosis should be carried with the help of expertise because most of the bleeding disorders have similar symptoms. Screening test such as platelet count activated partial thromboplastin time, prothrombin time, bleeding time or other platelet function screening test. Avoid taking medication such as aspirin prior to diagnosis. If a patient is particularly stressed that can show elevated levels of FVIII and Von Willebrand factor.

Platelet aggregometry is more preferred than bleeding time because it lacks specificity and sensitivity.

#### Possible diagnosis

##### Hemophilia A and B

PT: normal

PLATELET COUNT: normal

APTT: prolonged

BT: normal

One third of the cases are due to spontaneous mutation with no prior family history.

Factor assay

Factor assays are required in following situation:



1. To determine diagnosis
2. To monitor treatment
3. To test the quality of cryoprecipitate

The type and severity should be known in order to create the best treatment plan.

Normal range of factor levels is between 50% and 150%

Severity	Levels of FVIII & FIX
Mild	Greater than 5% but less than 50%
Moderate	1% to 5%
Severe	Less than 1%

### Prenatal genetic diagnosis

It's imperative to do genetic testing to aid in confirmation of hemophilic child in pregnant hemophilic mother. This step is crucial in the management of treatment and prevention of any post-partum hemorrhage in mother and intracranial hemorrhage in child. The bleeding tendencies in carrier may differ as they have 50% of residual coagulant activity due to the X- inactivation in woman during their embryonic life. FIX is a vitamin K-dependent factor which is reduced at birth whereas FVIII levels are normal at birth. Thus hemophilia A can be diagnosed at early stage and hemophilia B needs to be checked after 6 months of age.

Prenatal diagnosis can be done through amniocentesis after 15 weeks of gestation, cordocentesis after 20 weeks of gestation, chorionic villous sampling at 11-14 weeks of gestation.

The Chorionic villus sampling is the most common route of detection. The sample is taken from the placental tissue through trans cervical or transabdominal route. In Amniocentesis, a needle is inserted into the amniotic sac containing amniocytes (foetal cells). Whereas, cordocentesis also called as percutaneous umbilical cord sampling) collects tissue from the umbilical cord. All these tests are done under direct ultrasound guided needle.

Preimplantation genetic diagnosis is an in-vitro fertilization technique in which a healthy male embryo is selected and implanted to the uterus.

### Inhibitor testing

If there is prolonged APTT then there is a presence of inhibitor which is not fully corrected by mixing patient plasma with PNP. Inhibitor titers are measured in

1. Nijmegen-bethesda units, if the lab test used is Nijmegen-Bethesda assay.
2. Bethesda units, if the lab test used is Bethesda assay.

The Nijmegen modification of FVIII inhibitor assay gives improved specificity and specificity over the original Bethesda assay<sup>77</sup>.

### Complications of Hemophilia

Complication arises in various parts of the body if bleeding occurs spontaneously or trivial bleeding, it can be either severe or life-threatening condition based upon its site. The common bleeding sites are in the diarthrodial- hinged joints such as knee, elbow and ankle with an approximate frequency of 70-80% as per WFH and less common in multi-axial joints: shoulders, wrists, hips.

Profuse and iterative hemarthrosis can lead to hemophilic arthropathy presenting with synovial hypertrophy, cartilage and bone destruction. On bleeding, results in iron deposition which is both pro-angiogenic and pro-inflammatory. The pathobiological changes results in inflammation, hypertrophied, hyper vascularized synovial membrane and fibrous joints. When 3 or more consecutive joint bleeds occurring in a 6-month period is termed as target joints. Target joints progresses to chronic synovitis, if inadequately treated this may lead to decreased range of motion (ROM), pain, joint deformity and contractures causing the significant functional loss within one to two decades of life. A joint bleed is associated with any of the combination of the following termed as aura: pain or an unusual sensation in the joint, palpable swelling, and warmth of the skin over the joint preceding the clinical signs such as increased warmth over the area and discomfort with movement.

Due to hemophilic arthropathy, there is a higher risk for reduced bone mineral density (BMD) attributed to bleeding sequelae from chronic inflammation and decreased weight bearing activity. These findings are more pronounced in those with lower levels of ambulation and intensity of activities<sup>46</sup>. As per several studies on bone disease in hemophilia patients, the rate for reduced BMD and fractures is higher in hemophilia population compared to the general population. Similar study conducted in the Hemophilia Center at Oregon Health & Science University (OHSU), states there is a significant greater relative risk of fracture in hemophilia population than in the control group. Additionally, mild to moderate hemophilia and non-inhibitor patients has decreased incidence of fracture than with severe and with inhibitor patients.

Pseudotumor occurs due to, inadequately treated soft tissue bleeds mostly in muscle and adjacent to bone which is a life-threatening condition to the limb as they may even reach enormous size causing pressure to the adjacent organs and neurovascular structures which may even develop fistula in the skin.

Muscle bleeding can occur in the part of the body muscle especially in the deep compartments in the calf, forearm and iliopsoas muscle. Bleeding may occur due to sudden stretch or blow to the muscle and can be associated with neurovascular compromise, if insult occurs in the deep flexor muscle groups of the limbs. Bleeding in confined muscles, if not prompt treatment not given may lead to compartment syndrome causing significant nerve and



tissue damage resulting from the condition presenting with pain, tingling, or numbness.

Intracranial bleeding is a life-threatening condition, symptoms may include neckache, dizziness, trouble walking, headache, sensitive to light, nausea, vomiting, loss of consciousness. Sudden severe pain in the back can be associated with bleeding around the spinal cord. Immediate treatment should be given to rise the patient's clotting factor level else seizure or paralysis may even occur.

Other complications include throat and neck hemorrhage may lead to airway obstruction and acute gastrointestinal hemorrhage may present as hematemesis, hematochezia, or malena. Both these conditions fall under life-threatening conditions as per WFH.

## INHIBITORS

The major complication and a challenge to hemophilia treatment is the development of alloantibodies or neutralizing antibodies (inhibitors) rendering the replacement therapy with factor 8 or 9 ineffective<sup>62,63</sup>. Congenital hemophiliac with inhibitor (CHWI) patients poses a challenge to treat the bleeds particularly when surgical intervention is necessary and to treat arthropathy. Hemophiliac patients with inhibitors are at increased risk of disease related morbidity, decreased QoL, to develop new target joints and chronic synovitis. Approximately 30% of patients with severe hemophilia A will develop inhibitors, 5% of patients with mild and moderate hemophilia A and 3% of patients with hemophilia B<sup>42-44, 59-61, 65-67,74,75</sup>.

Anti-FVIII antibodies are immunoglobulin (Ig) G antibodies that triggers complement protein systems and binds antigens (in this case, clotting factors) to enhance the effectiveness of phagocytosis. In addition, anti-FVIII antibodies are present in healthy individuals and in patients with hemophilia A without exerting coagulant inhibitory activity<sup>68</sup>. The difference between neutralizing and non-neutralizing antibodies was demonstrated by Hofbauer and colleagues, indicating that anti-FVIII IgG with inhibitory activity has an up to 100-fold higher affinity for FVIII than IgG without inhibitory activity<sup>28</sup>. Few studies have concluded significant amount of IgG antibody presence in plasma before they developed inhibitors<sup>70,72</sup>.

The Anti-fVIII inhibitor titer is measured by the Nijmegen-Bethesda Assay (NBA) i.e. <5 BU/mL are termed as low titer and low responding inhibitors and >5 BU/mL are termed as High-titer inhibitors. The inhibitors can be either transient that resolves within 6 – 10 months while the patient is on standard treatment and persistent inhibitors, defined as an inhibitor that had consistently been present since the initial factor VIII concentrate challenge<sup>46</sup>. Persistent inhibitors' median durations were 8- 19 months as per the Korean study<sup>46</sup>. The percentage of transient inhibitors is known to be inversely proportionate to the level of inhibitors. Caram et al. analyzed data of 46 hemophilia A patients with inhibitors over a 13-year period<sup>47</sup> only 3.4% of patients with inhibitor titers >10 BU/mL became inhibitor negative

for 2 years, whereas 55.6% of patients with inhibitor titers <5 BU/mL became inhibitor negative. In the Korean study, 96.5% of patients with inhibitor titers <5 BU/mL eventually became inhibitor negative. However, for patients with inhibitor titers >10 BU/mL, only 29.9% (17/68) became inhibitor negative. As per the Korean study, it is worthwhile to postpone ITI for 11 months unless a patient's peak inhibitor titer is >10 BU/mL.

The two main therapies to aid in the eradication of inhibitors are immune tolerance induction (ITI) and bypassing agents (BPA) includes Plasma derived activated prothrombin complex concentrate (APCC) and activated recombinant factor VII (rfVIIa)<sup>45</sup>.

ITI was first reported in late 1970s in Germany<sup>57</sup> requires frequent administration of coagulation factor (CF) at higher doses over several months to years to render immune system tolerant to the antigen i.e. the endogenous coagulation factor (CF) by preventing the production of neutralizing antibodies. This therapy demands frequent infusion of factor, prolonged period of time in subjects with poor venous access. Despite these drawbacks, ITI is the standard treatment with high likelihood of success in 60–80% of cases for patients with congenital hemophilia with inhibitors (CHWI)<sup>58,64,72,73</sup>.

CHWI patients with low level inhibitors can continue receiving factor replacement therapy and to those with high level inhibitors (>5 BU/mL) should be treated with ITI with 100 to 200 IU/kg/d of FVIII<sup>48</sup> and a BPA is added if breakthrough bleeding occurs, such as recurrent joint bleeds, large hematomas, and so through central access. Provided due to the high cost of BPA, the administration of BPA can be initiated when the patient has history of life-threatening bleeding or single joint bleed. The use of BPAs during ITI has been reserved for patients with higher inhibitor titers and persistent bleeding symptoms despite high doses of fVIII replacement. rVIIa is chosen as the first-line BPA for hemophiliac patients due to the anamnesis and allergic reaction with aPCC resulting from small amounts of fVIII and FIX. Also, close monitoring is required as either agents can contribute to the incidence of thromboembolism, although few cases have been reported<sup>49-56</sup>.

## Prophylaxis vs On-demand Treatment

Treatment for hemophilia is a lifelong treatment substituting the missing coagulation factor in the blood. The primary objective is to stop the bleeding and secondary is to prevent further bleedings resulting in complications and secondary damages and preserving the normal musculoskeletal function. Generally, there are two types of treatment involved: in prophylaxis, clotting factor concentrates (CFC) are infused to the patient 1-4 times a week depending upon their severity of bleeding, location and response of patient via central venous access device (CVAD) or peripheral venipuncture. This is done to constantly maintain the CFC in blood. The second method of administration is on-demand treatment where the CFC





is administered to a result of a trauma to improve the hemostasis in order to arrest bleeding. Prophylaxis is considered as superior treatment than on-demand and is recommended first-choice treatment by the World Health Organization, the World Federation of Hemophilia, and many national medical and scientific organizations. It has been found superior to on demand treatment in terms of reducing the risk of arthropathy<sup>1</sup> and considered as gold treatment for children. The half-life of both recombinant and plasma derived F8 concentrates is 10.4 h in adults and 9.4 h in children<sup>16</sup>. Whereas, half-life for FIX is 18–34 h in adults and 11–16 h in children<sup>17</sup>. However, this is not the case, there is a significant difference in half-life of F8 and F9 varying from 6 to 25 h and 25 to 56 h amongst individuals<sup>18,16,13,14</sup>.

The goal of prophylaxis is individualized for QoL, independent functioning, secure employment and enhanced physical activity/ lifestyle in person rather than just focusing on “zero bleeds”. There are various assessment tools for evaluating the joint status and outcome of treatment such as MRI, ultrasound imaging, QoL tools and joint scores. The introduction to prophylaxis was brought by Ahlberg in 1965 and was based on the observation that patients with moderate hemophilia with F8 or F9 levels and above 0.01 IU/ml had much fewer bleeding in joints and less arthropathy<sup>7</sup>. This study shows joint bleeds could be prevented in severe hemophiliac by raising the baseline F8 or F9 in plasma above 0.01 IU/ml and this is done by infusing CFC 3-4 times a week<sup>8-11</sup>. The effectiveness of prophylaxis depends on trough level of clotting factors above 0.01 IU/mL<sup>12</sup>. However, this isn't used much in clinical practice as the main focus is on the dose and frequency of administering the CFC to prevent the anticipating bleeding. The aim of dosing of CFC is to maintain the CF above the minimum threshold level of preventing bleeds and subsequent joint damages. This statement is supported by Collins et al. study showing the efficacy of prophylaxis is based on time above the certain F8 trough levels<sup>15</sup>. Also, below a maximum level in plasma in avoid the over utilization and wastage of replacement factor. Therefore, half-life and frequency of CFC dosing is more important than IVR of CFCs.

The Swedish has been practicing continuous prophylaxis since 1960s at a very early age to prevent the factor levels below 1% of normal baseline of factor level; this strategy has preserved the joint function and leads a normal life<sup>19</sup>. The secondary and tertiary prophylaxis has shown decreased annual bleeding rate (ABR), rate of joint deterioration, and number of days lost from school or work compared to episodic treatment<sup>20-22</sup>. There are studies contrary to the former, suggesting 1% is not sufficient to prevent the bleeds but a higher trough levels to maintain the healthiest joints possible due to near zero ABR<sup>23</sup>. The epidemiologic evaluation on a Dutch cohort at diagnosis demonstrates levels > 10-12% has zero joint bleeds compared to 5 joint bleeds with 1% F8 level<sup>14</sup>. In the plenary address by Mark Skinner at the 2012 International Congress of the WFH, states hemophilia community should

aim for a baseline replacement factor activity level of 15%, and the absence of joint bleeds, for all<sup>21</sup>. A single bleed can result in inflammation and deleterious effects to the cartilage to cause permanent damage which is common in both adults and children<sup>25,26</sup>. A CDC-sponsored clinical trial shows less evidence of arthropathy in children treated prophylactically by 6 years of life. Another study in children of 1-7 years treated prophylactically showed signs of joint damage in 29 % and 74% to those in episodic treatment. The investigators noted that prophylaxis was more effective when started early (3yrs or younger)<sup>2,3</sup>. Similarly, the group recommends starting the prophylaxis between 2 and 4 years as their veins are well developed<sup>4</sup>. The early initiation in children (1-2 yrs.) is challenging due to the venous access requiring the need for CVAD<sup>32-35</sup>. To provide increased coverage for high impact sports or physical activities, increasing the trough level of prophylaxis by increasing the dose help to prevent breakthrough bleeding and ensuing joint disease that is thought to occur in more vulnerable patient<sup>18</sup>.

Expenses of prophylaxis compared to on-demand are higher due to the higher consumption of factor of about 2-3 times higher than on-demand treatment option. Administering higher doses of factor does not harm the patient but over utilization can increase the overall healthcare expense by 12-25%. Higher doses of prophylaxis can bring financial instability to patients and families concerned. Studies from Thailand, China and India provide evidence that low dose prophylaxis can also provide an equal chance of QoL and functional participation in society. Four pediatric pilot studies, 3 from Thailand and China, and a small randomized study from India, with a small study population and a follow up of <1yr states low dose prophylaxis of 8-10 IU/kg twice a week demonstrates reductions in ABRs, AJBRs, fewer days absenteeism from school, and improved QoL despite only 37 % of children in the Indian study had measured trough levels  $\geq 1$  %<sup>27-30</sup>. Similarly, a study conducted in China using 5-10 IU/kg shows 77% ABR and significant improvement in functional independence scores (FISH)<sup>31</sup> highlighting the significance of low dose prophylaxis.

To monitor the efficacy of prophylaxis, 2 global coagulation assays such as thromboelastography and the thrombin generation test. In thromboelastography uses whole blood to determine the characteristics of clot formation i.e. with higher maximum thrombin/fibrin generation are seen in patients with a milder bleeding phenotype than in those patients who had a more severe bleeding tendency<sup>36</sup>.

### Pain Management

Spontaneous bleeding into joints and muscles is the symptomatic hallmark of congenital hemophilia A and B<sup>78-80</sup>. Joint bleeds which account for 70-80% of all bleeding episodes in patients with severe hemophilia<sup>80</sup>, are extremely painful; repeated joint bleeds predispose to a vicious cycle of bleeding, synovitis, and more bleeding<sup>78,81</sup>. The joint pain associated with hemarthrosis causes flexion deformities, which become fixed over time<sup>81</sup>.



Repeated hemarthrosis trigger progressive damage to the joint cartilage, which, in turn, results in hemophilic arthropathy<sup>81</sup>. This joint damage impacts on bone health, which results in chronic pain and reduces the quality of life. Pain in one or more joints is a daily reality for as many as two-thirds of patients with severe hemophilia<sup>82</sup>.

### Acute pain in hemophilia

In hemophilia, bleeding episodes in joints and muscles cause acute pain. Therefore, pain can initially serve as an early warning sign of active joint (or other) bleeds<sup>83,84</sup>. Outward signs of a joint bleed include pain combined with an unusual sensation in the joint, swelling, warmth, and decreased range of motion<sup>85</sup>. In infant's decreased range of motion may be the only indication that a joint bleed has occurred. While clotting factor concentrates should be administered as quickly as possible to stop bleeding, additional drugs are often needed for pain management in case of joint and muscle bleeding.

### Chronic pain in hemophilia

Chronic pain is more complicated than acute pain and is associated with neurobiological, psychological, and social changes that can maintain the pain<sup>84</sup>.

A physiotherapist with experience of hemophilia is a vital member of the comprehensive care team and should evaluate the patient's musculoskeletal status at least once or twice a year. Physiotherapy is far less expensive than replacement therapy and may be more easily performed by patients and caregivers in the home setting<sup>86</sup>.

### Strategies for Managing Pain in Hemophilic Patients

#### Rapid bleed control to minimize acute pain

Unrelieved pain can interfere with healing and turn acute pain into chronic pain. Accordingly, the world federation of hemophilia recommends that acute bleeds are treated at home as soon as possible and preferably within 2h of onset<sup>80</sup>. Hemophilia patients, it is particularly important for inhibitor patients, who have limited treatment options and who experience more joint pain and poorer outcomes than non-inhibitor patients<sup>87</sup>. It is therefore essential that treatment be optimized to minimize pain and resolve bleeding quickly when an inhibitor is present. Early initiation of treatment with the bypassing agent recombinant activated factor VIII (rFVIII) in inhibitor patients has been shown to reduce rebleeding<sup>88</sup>, produce better outcomes, significantly reduce the need for analgesics and provide faster bleed resolution and faster pain relief versus late treatment.

Replacement therapy (or bypassing agent therapy for inhibitor patients) is often sufficient to relieve acute pain associated with a bleed.

#### Analgesic use for acute and chronic pain

COX-2 inhibitors are useful for acute and chronic pain management. It was also thought that a short course of steroids is sometimes necessary for major hemarthrosis

and that the use of anti-inflammatory drugs as soon as possible after a bleed might be useful; however, using this strategy to manage chronic pain may mask pain from acute bleeds.

Paracetamol/acetaminophen

*If not effective*



COX-2 inhibitor (E.g.: nimesulide, celecoxib, meloxicam, and others)

Or

Paracetamol/acetaminophen plus codeine (3-5 times /day)

Or

Paracetamol/acetaminophen plus tramadol (3-4 times /day)

### Beyond medication

These include rest, ice, compression, and elevation; complementary therapies such as acupuncture, hypnosis; physiotherapy. Lifestyle changes may also be beneficial.

### Post-operative pain

Intramuscular injection of analgesia should be avoided. Post-operative pain should be managed in coordination with the anesthesiologist. Initially, intravenous morphine or other narcotic analgesics can be given, followed by oral opioid such as tramadol, codeine, hydrocodone and others. When pain is decreased, paracetamol/acetaminophen may be used.

Pain is a critical aspect of hemophilia and that can become a burden of the disease. That can greatly influence the quality of life. Replacement or bypassing therapy is generally the first response to pain, although it is not necessarily the only solution. There are numerous pharmacological and other options, both invasive and noninvasive, for pain management.

### PHARMACIST ROLE

Providing education about the disorder and its treatment is essential for a successful patient care.

### Education and counseling

Pharmacists should make sure that the caregivers or patients know the signs and symptoms of bleeding and how to respond. Education should include recognizing when to call a physician or go to an emergency department, in case of heavy bleeding or oozing of blood; signs and symptoms of bleeding in brain; or limited motion; pain or swelling of any joint<sup>93</sup>. Pharmacists working in specialized pharmacies that supply factor products for home treatments can provide vital services in the education and monitoring of patients and their factor use.

1. Remind them to follow the treatment plan exactly as prescribed.
2. Recommend that patients have regular checkup and vaccinations.
3. Emphasize the importance of regular dental care, advising them that the dentist can provide medication that reduces the bleeding after dental work.
4. Suggest that they call their HTC when planning life events such as travel, upcoming surgical procedures, or routine diagnostic procedures such as colonoscopy because factor may be needed prior to these events.
5. Advise seeking genetic counseling for themselves and their family members to identify carrier.

Young children need extra protection from events that can cause injury or bleeding;

1. Protect toddler with kneepads, elbow pads, and helmets.
2. Use safety belts and straps in highchairs, car seats, and strollers.
3. Remove furniture with sharp corners or pad the edges.
4. Check play equipment and outdoor play areas for possible hazards [93].

As children mature, they should be fully educated about their disorder. For patients who are embarking on an on-demand approach, the pharmacist can address common challenges that parents and caregivers have about home treatment. Research has yielded the following areas of concern among parents of children with hemophilia [95].

1. Lack of confidence in their ability to carry out the treatment correctly.
2. Fear of doing something wrong or causing their children pain.
3. Dealing with their child's resistance to treatment.
4. Anxiety about contamination of blood products.
5. Concern about long term adverse effects of prophylaxis.
6. Difficulty balancing the desire for their child to have a normal, active lifestyle and the desire to protect them from risk of injury.

Pharmacists can provide reassurance and refer parents to their HTC for further education and training. Pharmacists can suggest accessing support groups such as telephone support networks or internet-based discussion forums, or put parents in touch with local families who have mastered home treatment <sup>95</sup>.

### Dosing

One unit of factor per kilogram of body weight increases the clotting factor level in the blood by approximately 2% in hemophilia A and 1% in hemophilia B. A reasonable dosage calculation guide for factor VIII is: <sup>97</sup>

$$\text{FVIII dose (U)} = \text{body weight (kg)} \times 0.5 \text{ U/kg}$$

Clotting factor prescriptions are written as ranges. For example, a person may be described a prophylactic dose of 2,000 units  $\pm$  10% three times per week [98]. A patient with a major bleed may be prescribed 25-50 units intravenously every 12 hours for 2-5 days <sup>97</sup>. Variables that contribute to the complexity of clotting factor dosing include the degree of severity, the patients weight, and the manufacturing of clotting factors <sup>98</sup>.

### Exercise

Exercise may be encouraged for all hemophilia patients to improve their physical, psychosocial, and medical status. Many patients with hemophilia, especially those using long-term prophylaxis or those with mild to moderate disease, are as active as their healthy peers. These individuals benefit from increasing their muscle strength, joint health, balance, and flexibility, which may ultimately lead to improved quality of life <sup>100</sup>. Patients with severe hemophilia should avoid contact sports and other activities that are likely to cause bleeding injuries such as football, hockey, and wrestling <sup>93</sup>.

### Medications

Patients with severe hemophilia and those with inhibitors or acquired hemophilia should receive vaccinations subcutaneously, not intramuscularly, to avoid muscle bleeds.

Use of aspirin or other drugs that can cause bleeding should be avoided. Many nonprescription medications, such as cold remedies contain aspirin therefore contact a physician or HTC or pharmacist or consult the pharmaceutical company's printed in instruction before taking any new medication.

Chronic pain is prevalent in elderly patients with hemophilia. Widely used analgesics such as acetaminophen and NSAIDs have adverse effects that may become more clinically significant with aging; these may include gastric toxicity, acetaminophen associated liver dysfunction, hypertension, and renal insufficiency. Patients and their physicians should adopt a stepwise approach for use of analgesics, becoming more aggressive as previously used products fail to relieve pain. The initial medication of choice is acetaminophen (500mg-1000mg up to a maximum of 4000mg daily). Subsequent steps with physician may include cyclooxygenase 2 inhibitors, acetaminophen plus codeine or tramadol, or morphine <sup>94</sup>.

### Adherence

Barriers to adherence include lack of understanding of the disease and the time-consuming nature of infusions. Overcoming adherence issues can minimize disability in patients with severe hemophilia. Individualized support from health care professionals and pharmacists can help improve adherence <sup>99</sup>. Persistence is also required to ensure that a therapeutic level of the coagulant factor concentrate is maintained <sup>96</sup>.



## CONCLUSION

Hemophilia treatment is a lifelong process including a wide array of healthcare professionals with comprehensive care. Early diagnosis of hemophilia is important for early management and to decrease disease progression in patients. Pain is another critical aspect in hemophilia as they are a part of their reality. Through effective management, a behavioral, sociological and psychosocial change is brought forth to hemophiliacs as they are equally important as clinical treatment. In hemophilia treatment center (HTC) provides collaborations with haematologists with pain specialists, orthopedists, physical therapists, nurses, social workers, pharmacists, psychologists, dentists, and registered dieticians.

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