Project on

Literature review on Hemophilia in Children

[In the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy]

Submitted To

The Department of Pharmacy,

Faculty of Allied Health Sciences,

Daffodil International University

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April 2023

APPROVAL

This project paper, **"Literature review on hemophilia in children",** submitted to the Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, has been accepted as satisfactory for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy and approved as to its style and contents.

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DECLARATION

I hereby declare that this project report, **"Literature review on hemophilia in children",** is done by me under the supervision of Md. Sadman Hasib Lecturer, Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University. I am declaring that this Project is my original work. I also declare that neither this project nor any part thereof has been submitted elsewhere for the award of Bachelor or any degree.

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ACKNOWLEDGEMENT

I might want to communicate my profound applause to the All-powerful Allah who has given me the capacity to finish my undertaking work and the chance to concentrate in this subject.

I'm a lot of thankful to my honorable project supervisor of **Md. Sadman Hasib Lecturer**, Department of Pharmacy, Daffodil International University for her brilliant direction and steady oversight just as for giving essential data in regards to the task and furthermore for her help in finishing the project.

I would like to express my humble regards to Dr. Muniruddin Ahmed, Professor and Head, Department of Pharmacy, Daffodil International University.

I also wish to offer my respect to all of the teachers of Pharmacy Department, Daffodil International University and thankful to other members for their excellent cooperation with us.

Finally, I would like to express my gratitude towards my parents and other family members for their kind cooperation and encouragement which helped me in completion of this project.

My Parents

The persons who always encourage me in every sphere of my life.

Abstract

Background: Hemophilia A and B are the most common of the severe bleeding disorders. Due to a lack of blood-clotting proteins, hemophilia is an uncommon disorder in which the blood does not clot normally (clotting factors).

Objectives: The present article focuses on the practical aspects of the management of neonates and children diagnosed with hemophilia.

Method: A framework of research methodologies, as well as methods for gathering and analyzing data, is provided by a methodological review. A search was done using keywords such "Hemophilia A," "factor VIII," "bleeding and clotting disorders," and "dental management" in online search engines, academic bibliographic databases, PubMed, and Medline.

Results: The most important aspect of treating children with hemophilia is managing their treatment regimen, which varies significantly between countries due to differences in the standard of care offered. Controlling sporadic or on-demand bleeding more often leads to the development of a care plan for FVIII or FIX replacement treatment. There is some disagreement regarding the prevalence of caries in adolescents with hemophilia, both in their primary and permanent dentitions. The proportion of individuals with congenital hemorrhagic diatheses in the population is quite low. It can be challenging for dentists to treat these patients because the preponderance of them lack expertise treating oral issues in that population.

Discussion: Hemophilia Carriers desire earlier testing to establish their carrier status and self-report more bleeding than previously approved. There haven't been many studies done on oral health issues in hemophilia patients. Regarding the prevalence of caries in children with hemophilia, both in their permanent and primary incisors and canines, there is some debate

Conclusion: The objective is to review hemophilia with a focus on pediatric care, examinations, and symptoms. Hemophilia treatment for kids can take many different forms.

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Chapter 1
Introduction

1. Hemophilia

The two most prevalent severe congenital coagulation factor diseases are hemophilia A and hemophilia B (both of which lack factor [F] VIII) (factor [F] X deficiency). Hemophilia A is more prevalent than hemophilia B, affecting 1 in 5000 male pregnancies as opposed to 1 in 30,000 male births. Any ethnic group can be affected by hemophilia; there is no preference based on race or location. [1] Simple bruises and extensive mucosal bleeding may be the initial symptoms of hemophilia, but extreme soft tissue bleeding and hem arthroses are the condition's hallmark bleeding manifestations (Pavlovsky, et al, 1947). [2] When assessing a kid who has experienced unexplained bleeding, other bleeding conditions should be taken into account. Factor deficiency may be indicated by bleeding or unusual findings from traditional coagulation studies (FV, FVII, FX, FXI, FXIII, and fibrinogen). [3] Von Will brand element (VWF), which is released at the site of vascular injury by endothelial cells, is necessary for preventing von Will brand disease. Because there are three varieties of psychosis, the symptoms might range from mild mucosal bleeding to hem arthroses (which differ in severity and inheritance). [4] If a bleeding disease seems to be developed, nutritional deficiencies (especially vitamin K insufficiency) or associated illnesses (such liver issues or diffuse intravascular coagulation) should be considered (Biggs, et al, 1952). [5] Mucocutaneous bleeding is a sign of either measurable or qualitative platelet issues. When assessing a potential platelet issue, interactions between medications and systemic diseases that affect platelet function must also be considered (Biggs, R.; Macfarlane, et al, 1958). [6]

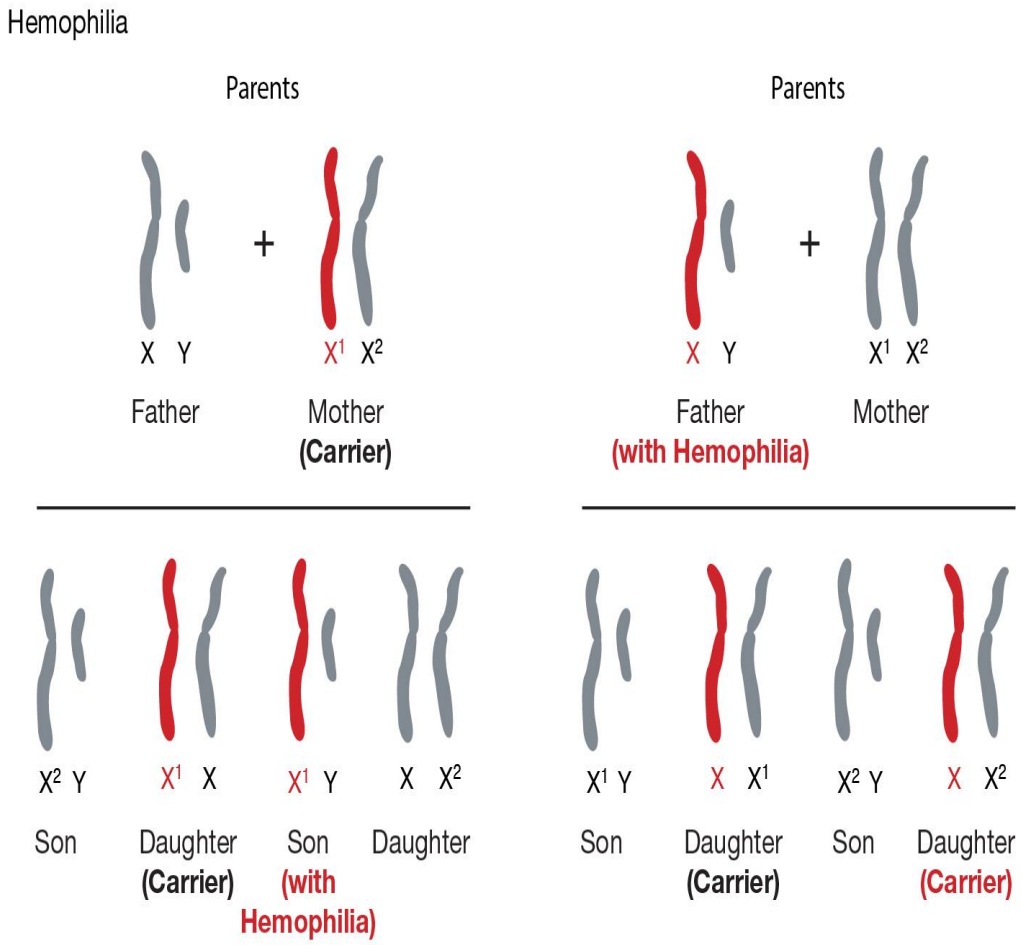

Figure 1: Hemophilia [8]

1.1 Basics in Bleeding and Clotting

The endothelium's integrity must be maintained while the lining of the vasculature is preserved for the coagulation system to perform its original goal. Because the coagulation factors move in their immobilized states and because the endothelium is nonthrombogenic, the baseline condition of the coagulation system is nonthrombogenic. [9] The thrombophilic subendothelium is exposed when the endothelium is disrupted, which also starts the hemostatic process. A cell-based paradigm of coagulation (Figure 1) has taken the place of the conventional coagulation pathway, and it emphasizes the important roles that tissue factor (TF), platelets, and thrombin perform in starting, increasing, and spreading blood clotting. For the coagulation process to fulfill its original goal, the endothelium's functioning must be kept while the patency of the vasculature is conserved. [10] The endothelium is nonthrombogenic, the coagulation factors migrate in their immobilized forms, and the basal condition of the coagulation system is nonchromogenic (White, et al, 2001). [11] Disruption of the endothelium also initiates the hemostatic process, exposing the thrombophilic sub endothelium. The traditional coagulation pathway has been replaced with a cell-based coagulation model (Figure 1), which stresses the critical functions that tissue factor (TF), platelets, and thrombin play in initiating, enhancing, and spreading blood clotting. [12] When connecting platelets to the sub endothelium, where the coagulation proteins moor to phospholipid places on the surface of effector cells to produce fibroblast concentrations of thrombin, collagen in low-shear (venous) circuits and VWF in high-shear (arterioles) circuits each other serve a sealant function. In hemostasis, platelets engage intricately with the vessel wall (Ahlberg, et al, 1965). [13] Coagulation frequently starts as a result of the exposure of TF, which is located in the sub endothelium and binds the circulating engaged (a) FVII. The TF-FVIIa complex changes zymogen FX and FIX into FXa and FIXa, correspondingly. FXa converts prothrombin (FII) to thrombin (FIIa). The TF-bearing cell surface produces submicromolar quantities of FIIa, which releases and activates FVIII from its binding proteins. Collagen in low-shear (venous) and VWF in high-shear (arterioles) circuits each other serve an adhesive purpose in connecting platelets to the subendothelium, where the coagulation proteins dock to phospholipid locations on the outer layer of activated platelets to produce

fibrin-generating concentration levels of thrombin. Hemostasis includes the complex interplay of platelets with the vascular system. [14]

The release of TF, which is present in the subendothelium and attaches the circulating energized (a) FVII, usually causes coagulation to begin. Zymogen FX and FIX are converted to FXa and FIXa, correspondingly, by the TF-FVIIa complex. Prothrombin (FII) is transformed to thrombin by FXa (FIIa). [15] The TF-bearing cell surface produces picomolar amounts of FIIa, which liberates FVIII from its transport protein VWF and elevates it to FVIIIa. Additionally, thrombin activates platelets, revealing an opposite charges, phospholipid-rich interface that can bind coagulation proteins, such as FIXa, that were earlier produced on the membrane of TF-bearing cells. [16]

Tenase compound is created by FIXa, coenzyme FVIIIa, calcium, and phospholipids. Tenase complex enlists FX and activates it to FXa. The prothrombinase complex, which is made up of calcium, phospholipids, and FXa, changes a significant amount of prothrombin to thrombin, converting fibrinogen into fibrin monomers. Additionally, FXIII, which crosslinks the fibrin monomers to strengthen the clot, and thrombin-activatable fibrinolysis inhibitor, which stops clot disintegration, are both activated by thrombin and both increase the firmness of the clot. [17]

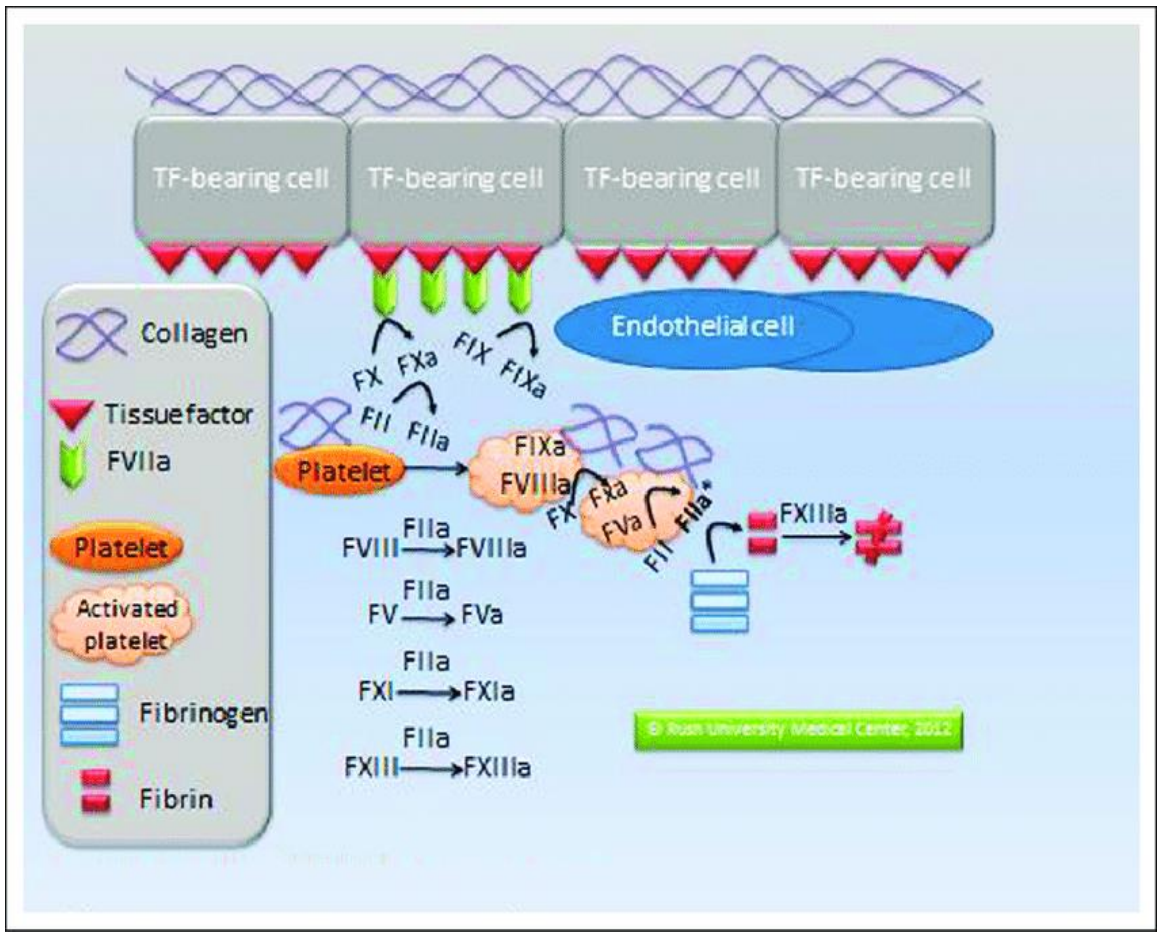

Figure 2: Cell-based model of blood coagulation. F[factor; TF[tissue factor [18]

1.1.1 Genetics

The long reach of the X chromosome is home to the genes that code for FVIII and FIX. The only genetic clotting disorders with a sex-linked recessive pattern are hemophilia A and B. All of a hemophiliac father's female offspring will be bearers, but none of his boys will be afflicted. The daughters of a carrier mother will have a 50% possibility to become a provider, compared to the sons, who have a 50% chance of contracting the illness. [19] Protein production may be reduced quantitatively, qualitatively, or both as a result of the genetic mutations. A malfunctioning protein is produced by 5%–10% of hemophilia A patients and 40%–50% of hemophilia B patients, leading to reduced protein activity without the need for a quantifiable drop. Hemophilia should be recognized in a neonate with hemorrhage and a prolonged PTT even in the lack of a family background due to the high rate of random mutation (about one-third of cases). [20] Females with Turner

syndrome or X chromosomal mosaicism may experience bleeding problems as a result of a decrease in either FVIII or FIX activity.

1.2 Hemophilia in early child

Hemophilia A and B both have a sexual aspect. The genes required for factor VIII and factor IX expression are found on the X chromosome. The hemophilia trait in women is inherited, despite the fact that a healthy X chromosome is also accessible and accountable for roughly 50% of the level of coagulation factor VIII or factor IX. If a hemophiliac guy with one faulty X chromosome and a healthy woman with two normal X chromosomes have offspring, all of their daughters will be hemophilia transmitters, but all of their males will be healthy (Chambost, et al, 2002). [21] On the other hand, if a woman who is a hemophilia provider has children together through a healthy man, a male child is at 50% risk of being impacted and a female child is at 50% risk of developing broadcaster of hemophilia. A new mutation on the factor VIII or IX gene on the X chromosome will be found in about one-third of the so-called sporadic cases when there is no known family history of hemophilia (Conway, et al, 1994). [22] Globally, 13 to 18 males out of every 100,000 are affected with hemophilia, with hemophilia A and B having a roughly 4:1 ratio. Hemophilia is the most common serious bleeding disorder that is successfully treated (Ljung, 1990). [23]

1.3 Pathophysiology

Three processes work in concert to hasten the healing process after a blood artery is damaged. Blood vessel first tightens to lessen the quantity of blood loss. Circulating platelets at the injury site cause a blockage. The blood then experiences coagulation. A string of clotting factor proteins, identified by Roman numbers, must be engaged for coagulation to take place (Giannelli, et al, 1996). [24] This approach will ensure that the vessel wall may heal by anchoring the platelet plug by creating a fibrin matrix across its surface (Waugh and Grant, et al, 2002). [25] Factors VIII and IX make up just two of the 13 proteins that play a role in the cascade process of coagulation.

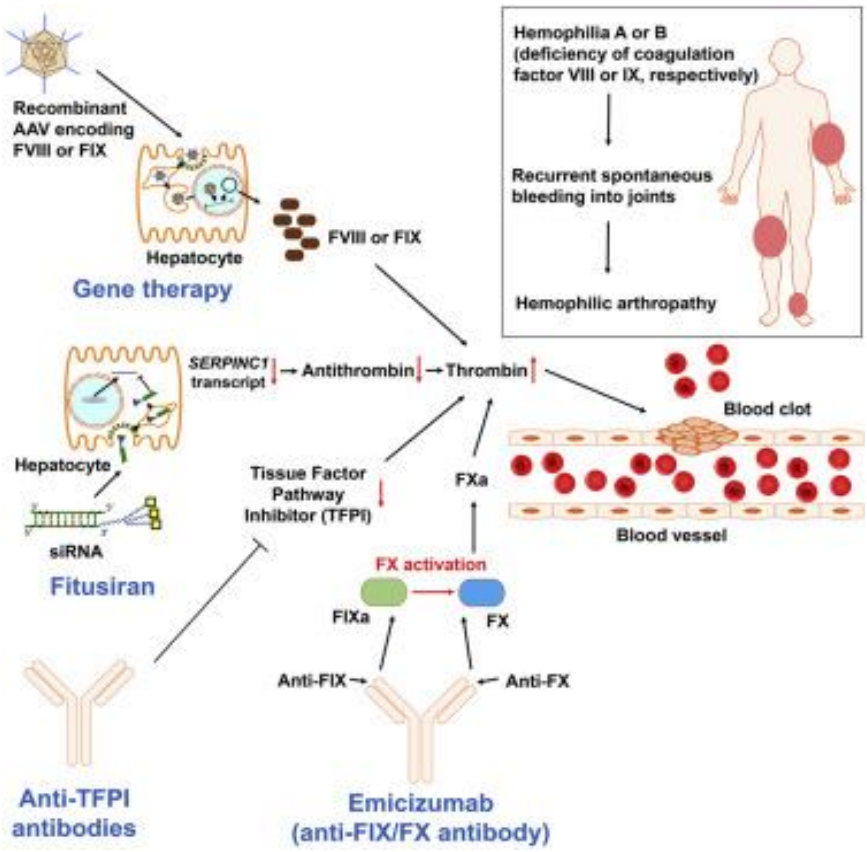

Figure 3: Pathophysiology haemophilia [26]

1.4 Epidemiology

Worldwide, hemophilia is common and affects people of all ethnic and socioeconomic backgrounds. 5. There are about 15–20 cases of HA and HB for every 100,000 male babies produced globally. About 80% of hemophilia cases are classified as "Classical hemophilia," which affects 1 in 10,000 male pregnancies. 8. In about 1 in 25,000 male births, HB, also referred as "Christmas sickness," develops. [27] The World Federation of Hemophilia (WFH) reported in its Results of the Annual Global Survey 2009 that there are 153,253 hemophiliacs worldwide, of which 115,209 have hemophilia A and 24,038 have hemophilia B9. The reported number of hemophiliacs with HIV and HCV infections was 5,665 and 24,340. The number of HA and HB cases with experimentally confirmed antagonists was 5013 and 363, respectively. These numbers, though, are underestimates of the true numbers. Because according to WFH estimates, there would have been 399,000

hemophilia cases globally with a frequency of HA and HB of 135 per million male children (the world's population is 6 billion). Therefore, the majority of patients have undiagnosed conditions, and it is accurate that a majority of them reside in developing nations. [28]

1.5 Haemophilia and joint disease

Joint disease, which occurs as a consequence of repeated bleeding into joints, is a debilitating and frequent consequence of extreme (and, to a lesser degree, moderate) hemophilia. Joint problems and decreased motion range (ROM) of joints are more likely to occur in people with severe hemophilia. [29] Age and a higher body mass index are additional risk factors for ROM restrictions. Increased likelihood of ROM limitation is also linked with serious disease, high intensity of bleeds, the existence of antagonists, and recent orthopaedic procedures. Patients with severe haemophilia had a higher risk of developing an intended joint (a joint where reoccurring bleeding has happened four or even more times in the previous six months) than those with reasonable or mild haemophilia (33.1% versus 18.8% and 5%, respectively), according to data from the Universal Data Collection (UDC; US national public health surveillance project). [30] The joints that are most frequently impacted in patients who are not receiving prophylaxis are the knees (45%), elbows (30%), ankles (15%), shoulders (3%), and wrists (2%). This pattern seems to have altered today, at least in patients receiving prophylaxis, and the ankle joint now accounts for the majority of bleeding sites. [31] Haemarthrosis typically develops for the first time in people with serious hemophilia by the time they are 2 years old. By the age of 20, these people will have haemophilic arthropathy if their condition is not properly treated. As the pressure in the synovial cavity and bone marrow increases, an acute bleed into a joint causes excruciating pain and may end in avascular osteonecrosis (especially in the femoral head after a bleed into the hip joint). [32] In response to harming the synovium, repeated bleeding causes persistent synovitis and damages the bone and cartilage. Patients with severe illness will experience clinical signs like discomfort, swelling, and decreased range of motion by early adolescence, which will have a negative impact on their health.

1.6 Hemophilic arthropathy

The rare X-linked bleeding illnesses hemophilia A and hemophilia B are brought on by a full or partial lack of coagulation factors VIII (FVIII) or IX (FIX). Joint bleeding (hemarthrosis) is the most common clinical demonstration in children and adults with severe hemophilia (i.e., plasma FVIII or FIX levels 1 U/dl), but latest information indicates that it may also (although less commonly) occur in patients with moderate (plasma factor levels of 1–5 UI/dl) or gentle illness (plasma factor levels of >5 UI/dl). [33] In order to overcome the shortage of plasma-derived coagulation factors, recombinant coagulation factors were developed and marketed in the 1990s. More recently, the use of methods like coagulation factor fusion with the crystallizable segment of immunoglobulin G1 or albumin or the addition of polyethylene glycol3 has increased plasma factor half-life and decreased the number of intravenous injections needed. [34] The administration of prophylaxis regimens that are successful in preventing clinically overt bleeding episodes has increased as a result of the greater accessibility and convenience of such substitute and nonreplacement therapies, especially when they are tailored to the style of living and pharmacokinetic characteristics of each patient. [35] There is proof that a single hemarthrosis incident can trigger the inflammatory reaction that results in synovial swelling and permanent angiogenesis, predisposing to repeated hemorrhage. At any and all ages, prophylaxis reduces the likelihood of bleeding, but joint motion can only be maintained if it begins well before age of three. It is best to begin prophylactic therapy as soon as feasible and to keep doing so for the rest of your life because it prevents joint disease better than intermittent infusions. [36] Notwithstanding, despite getting prophylaxis, MRI data show that 20% of commercially asymptomatic patients can still be determined to have joint damage. It has been proposed that this is because subclinical bleeds are quietly leaking into clinically asymptomatic joints.

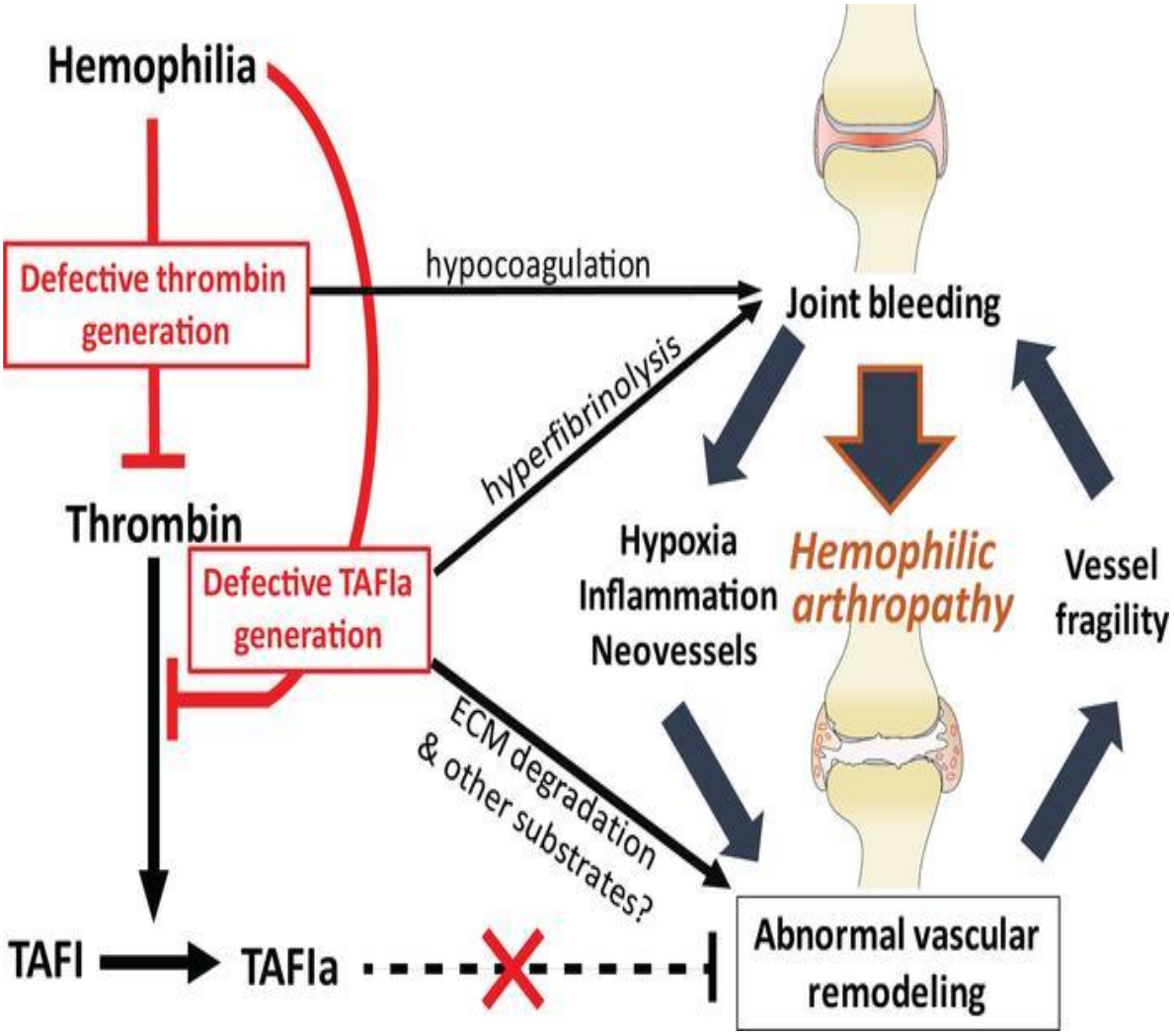

Figure 4: Hemophilic arthropathy [37]

Chapter 2
Purpose of the study

2.1 Purpose of the study

- The goals of this project are to get a thorough understanding of the medical problem being researched.
- To learn more about the variables that contribute to the development of hemophilia in children.
- To have a better grasp of the many diagnostic procedures used to diagnose this disease.
- To gain a thorough understanding of the disease, including its cause, signs and symptoms, consequences, and medical and nursing treatment choices.
- The purpose of this research was to understand more about hemophilia in children in the world.
- Describe the epidemiology of hemophilia in children.
- Review the presentation of a patient infected with hemophilia.
- Identify common complications of hemophilia in children.
- Summarize the role of the interprofessional healthcare team in hemophilia disease prevention and mitigation measures.

Chapter 3
Methodology

3.1 Methodology

A framework of research methodologies, as well as methods for gathering and analyzing data, is provided by a methodological review. This chapter discusses the techniques used in the investigation. A search was done using keywords such "Hemophilia A," "factor VIII," "bleeding and clotting disorders," and "dental management" in online search engines, academic bibliographic databases, PubMed, and Medline. It gives an account of the learning environment. There are many variables to take into account, including the study sample, the study population, the research tools, the methodology, and the data analysis. This is an overview of earlier research on hemophilia in young children. studies on the causes, diagnoses, and therapies of hemophilia. A piece of the information was collected by directly reading previous research articles, while the other part came from scouring the internet for pertinent data. All of the information gathered from prior study publications was numerically coded and imported.

Chapter 4
Literature Review

4.1 Effects of Hemophilia on Articulations of Children and Adults.

Patients with hemophilia tend to experience bleeding episodes mostly in the joints. Nearly 80% of these hem arthroses affect the knees, elbows, and ankles. If the bleeding continues, the synovium begins to swell, which sets off a vicious cycle of chronic synovitis that eventually results in joint degeneration. Synovitis causes the epiphyseal growth plates to swell in an immature articulation, which can lead to serious structural deficits. Leg length disparity, angular abnormalities, and bone hypertrophy are all effects of this stimulation to the epiphyseal plate. The joints cartilage is severely harmed by hemophilia in adult articulate. Joint function progressively declines as it gets worse. The most significant radiography development to motion range is the loss of joint space. The synovium gradually changes from friable hyperemic tissue to fibrotic scar tissue as it grows more and more injured. The normal progression of hemophilic arthroplasty is this procedure. Adult hemophiliacs often experience a situation where their joints, although radiographically seeming to be badly damaged, have seemed to function quite well for years. [38]

4.2 Effects of Hemophilia on Children's

Patients with hemophilia tend to experience bleeding episodes mostly in the joints. Nearly 80% of these hem arthroses affect the knees, elbows, and ankles. If the bleeding continues, the synovium begins to swell, which sets off a vicious cycle of chronic synovitis that eventually results in joint degeneration. Synovitis causes the epiphyseal growth plates to swell in an immature articulation, which can lead to serious structural deficits. Leg length disparity, angular abnormalities, and bone hypertrophy are all effects of this stimulation to the growth plates. The joint cartilage is severely harmed by hemophilia in adult articulation. Joint function progressively declines as it gets worse. The most significant radiography finding related to range of motion is the loss of joint space. [39]

4.3 Hemophilia Treatment in Children

The most prevalent severe bleeding disorder, hemophilia, can cause chronic illness and lasting impairments if it is not treated appropriately starting in early childhood. But among the most common monogenic illnesses, it has the most effective and secure therapy. In the

case of extraordinary bleeding or in the presence of a favorable family history, hemophilia should be taken into account during the newborn period. Later, abnormal bruising/bleeding or unusual bleeding after invasive surgeries, including tonsillectomy or circumcision, might raise suspicions of hemophilia, especially in men. The gold standard of care for hemophilia A and B is prophylactic treatment that is initiated early with clotting-factor concentrates since it has been demonstrated to prevent hemophilic arthropathy. [40]

4.4 Hemophilia (Pediatrics in Review)

The two most prevalent significant congenital coagulation factor deficiencies are hemophilia A (factor [F] VIII deficiency) and hemophilia B (factor [F] X deficiency). Hemophilia A is more prevalent than hemophilia B, occurring in 1:5000 male births compared to 1:30,000 male births. All ethnic groups can have hemophilia; there is no regional or racial preference. The hallmark bleeding symptoms of hemophilia are severe soft tissue bleeding and hemarthroses, while simple bruising and profuse mucosal bleeding may be the initial indicators. When assessing a child who has experienced unexpected bleeding, other bleeding problems should be taken into account. The symptoms of factor deficits (FV, FVII, FX, FXI, FXIII, and fibrinogen) can include bleeding or abnormal laboratory test findings for coagulation. [41]

4.5 A Hemophilic Child's Spontaneous Hematomyelia

There have been sporadic reports of hemorrhagic problems in the spinal column and spinal cord in hemophilia patients. As neurologic dysfunction develops and occurs in relation to the interval between the onset of symptoms and the factor replacement, treatment is based on rapid replacement therapy. In this case report, a 7-year-old hemophilic kid who had flaccid paraparesis from thoracic hematomyelia is described. After receiving cryoprecipitate infusions for medical care, the patient gradually improved. The therapy options for spinal hematomyelia in individuals with hemophilia are highlighted, and this case emphasizes the importance of timely diagnosis based on clinical symptoms and radiologic characteristics. [42]

Chapter 5
Results & Discussion

5.1 Results

The most important aspect of treating children with hemophilia is their medication regimen, which varies widely between countries because to differences in the type of healthcare that is often offered. The management of sporadic or on-demand bleeding is often where the pattern of care for FVIII or FIX replacement therapy evolves. [43] Today, coagulation factor abnormalities are the most prevalent inherited bleeding condition, but they are far less common than acquired coagulation problems, occurring in only around 10,000 to 50,000 male births annually. [44] 95–97% of all coagulation deficits are caused by Von Willebrand disease, hemophilia A, and hemophilia B. Based on how active the factor is in the blood, hemophilias A and B are divided into three categories: mild, medium, and chronic. Like with the overall population, hemophiliac patients most commonly experience dental caries and gingivitis/periodontitis. [45] There hasn't been many research published on oral health problems in hemophilia patients. Regarding the prevalence of caries in children with hemophilia, both in their initial and permanent dentitions, there is some debate. [46] The population's share of people with congenital hemorrhagic diatheses is quite minimal. Due to the fact that the majority of dentists lack experience treating oral problems in those kind of people, treating these patients can be difficult for them. The primary choice must be peripheral vein access. It may be necessary to consider a central venous line because doing so in early newborns can be difficult or even impossible (Astermark J, et al, 2006). [47] Anti-inflammatory drugs including celecoxib and rofecoxib may be helpful in some circumstances to reduce joint pain and synovial inflammation (Bom JG, et al, 2003). [48] In order to prevent immune system challenge and inhibitor formation, it is generally advised not to provide a vaccine on the same day that a factor concentration infusion. Contrarily, it has been proposed that vaccinations could act as a "danger sign" for the development of inhibitors (Gouw SC, et al, 2007). [49] Inhibitor production is still the predominant adverse effect of hemophilia medication, and it occurs in 30-35 percent of symptomatic relief children with severe hemophilia A and in 2–5 percentage of people with acute hemophilia b who take the usually prescribed medicine (Aledort L, et al, 1998). [50]

5.1.1 Treatment of hemophilia: the past

Hemophiliacs could only be treated with whole blood or new plasma in the 1950s and the early 1960s. Regretfully, these blood products do not contain sufficient FIX or FVIII proteins to completely halt severe bleeding. hence most frequent causes of death for individuals with severe hemophilia were hemorrhages following surgery, trauma, or in critical organs (especially the brain). [51] These deaths typically occurred in childhood or in early adulthood. An important development in the treatment of hemophilia occurred in 1964 when Judith Pool discovered that the fraction cryoprecipitate from plasma held considerable quantities of FVIII. For the first time, major surgery was possible because comparatively modest amounts of FVIII could be used to manage severe bleeding. [52] The real beginning of modern hemophilia administration, though, came in the 1970s, when the availability of lyophilized plasma concentrates of coagulation factors enhanced and home replacement therapy became widely used. These developments allowed hemorrhages to be controlled early on and the musculoskeletal destruction classic of untreated or inadequately treated patients to be reduced. [53] In order to avoid the preponderance of bleeding events and lessen the effects of arthropathy, primary prophylaxis was effectively developed in Sweden and then adopted in other nations. The strain of delivering emergency treatment was lessened for specialized hemophilia centers, allowing them to create programs of holistic care with the help of professionals like orthopedic surgeons, physiotherapists, dentists, and social workers. [54] The musculoskeletal defects that had arisen as a result of untreated or improperly treated bleeding episodes into joints and muscles were reduced or corrected with the aid of elective surgery, especially orthopedic procedures. Desmopressin, a synthetic drug that raises plasma levels of FVIII and von Willebrand factor, was discovered in 1977. [55] It offered patients with mild hemophilia A (and type 1 von Willebrand illness) a new, affordable, and secure treatment option, allowing them to avoid or significantly reduce the use of plasma derived goods, the associated high costs, as well as the potential dangers of blood borne illnesses. Early in the 1980s, when 60–70% of those with severe hemophilia contracted the human immunodeficiency virus (HIV), which had affected coagulation factor preparations, this positive view of the condition underwent a significant shift. [56] The hepatitis C virus (HCV), which was then known as the non-A, non-B hepatitis virus, was spread by factor concentrates created from plasma gathered from

thousands of donors and affected nearly all treatment hemophiliacs [57]. A means of receiving safe treatment had become critical for the hemophilia population as a result of the devastating effects of the AIDS and hepatitis epidemics. The adoption of new techniques to detect viruses in blood donations (such as NAT testing) and the development and application of viral inactivation techniques for the production of plasma-derived factor focuses both significantly increased the security of plasma-derived products, as evidenced by the fact that blood-borne transmission of HIV or hepatitis viruses has not happened in the last 25 years. [58] The cloning of the FVIII and FIX genes in 1982 and 1984, moreover, marked the most significant advancement in this field. This enabled the industrial production of recombinant FVIII (and later FIX), which culminated in the 1989 publishing of the first document on the clinical effectiveness of this product in two patients with hemophilia A [59]. Even though the wellbeing of plasma-derived factors has significantly increased over the past 25 years, hemophilia caregivers in western countries have been forced to treat initial therapy hemophilic infants primarily with recombinant products out of concern that new or unknown pathogens could be transmitted by blood or its derivatives. [60] Parallel to this, with protection as a top priority, the production of recombinant factors has changed over the past few years to further minimize the likelihood of pathogen transmission through the development of protein purification methods, the introduction of viral growth inhibition steps, and the prevention of human or animal proteins at any stage of their production process. The availability of high-quality factor focuses for replacement therapy was crucial for lowering the risk of hemorrhage-related death as well as for the widespread adoption of prophylactic treatment training regimes to stop bleeding and the subsequent joint damage, permitting patients to live relatively normal lives. [61] This, along with advancements in the administration of blood-borne viral infections though the monitoring of patients with chronic hepatitis (especially with respect to hepatocellular carcinoma and liver failure), the accessibility of newer treatment options like antiviral treatment against HIV (Highly Active Anti-Retroviral Therapy [HAART]) and HCV (merged medication with -interferon and ribavirin), significantly enhanced life expectancy and decreased mortality rates. [62] After the first "golden era" of hemophilia therapy in the 1970s, the last 15 years mark a "new golden era" in this regard, with patients' life

expectancies gradually approaching those of males in the general public, at least in high- and middle-income nations.

5.1.2 Treatment of hemophilia: the present

In this favorable environment, the formation of blocking alloantibodies against FVIII or FIX has emerged as the most difficult therapeutic complication. These inhibitors, which only appear in 3-5% of patients with hemophilia B and only in 25–30% of severe hemophilia A patient, make substitution therapies useless, restrict patient access to a safe and efficacious standard of care, and put patients at higher risk for morbidity and mortality [63]. Recombinant functionalized factor VII (rFVIIa, NovoSeven) and stimulated prothrombin complex preparations (APCC), which are bypassing agents, have significantly enhanced the administration of acute bleeding in inhibition patients, enabling at-home care and significantly enhancing their quality of life. Since the last century, there has been much discussion about which product is better. Although an uncertain uncontrolled study suggested that the efficacy and safety of FEIBA and rFVIIa were largely comparable, a recent systematic review discovered that rFVIIa has better overall efficacy and bleeding control rates than APCC (81-91% and 64-80%, respectively). [64] Another latest review article reported that the cumulative rate of control of bleeding at 12, 24 and 36 hours for a standard rFVIIa schedule was 66%, 88%, and 95% but was slightly lower for a standard APCC treatment (39%, 62%, and 76%). This review article used a Bayesian meta-regression model to evaluate the result of more than 2000 joint bleeds. In contrary, a Cochrane evaluation on the clinical efficacy of rFVIIa concentrate in the treatment of acute bleeding episodes in patients with hemophilia and antagonists published in 2010 found that rFVIIa and APCC have a comparable hemostatic impact without raising the incidence of thromboembolism. [65] Therefore, the question of which product is better is still up for debate, but it is widely acknowledged that both are quite effective in reducing bleeding episodes in patients who take antagonists. Despite significant effort in the production of inhibitors, the mechanism underlying this problem is still only partly understood. There are external modifiable risk factors as well as patient-related, non-modifiable risk factors. [66] rFVIIa and APCC, on the other hand, have a comparable hemostatic effect without raising the dangers of thromboembolism, according to a Cochrane review that was published in 2010 on the clinical effectiveness of rFVIIa concentrate in comparison to plasma-derived

for the management of sudden bleeding episodes in people with hemophilia and antagonists. [67] Because of this, it is still debatable which product is better, but it is widely acknowledged that both are very effective at reducing bleeding episodes in patients who take antagonists. The mechanism of this difficulty remains only partly understood despite extensive study in the area of inhibition creation. Risk factors have been found that are both environmental and patient-related, non-modifiable. [68] A research study and meta-analysis included there many as 2094 PUPs (1167 on plasma-derived and 927 on recombinant FVIII concentrates) enrolled in 24 prospective and retrospective studies in an effort to surmount the conflicting and inconclusive literature data. In this investigation, antagonists were generated in 14.3% of patients treated with plasma-derived FVIII and 27.4% of patients treated with recombinant FVIII; the incidence of high-titre inhibition was higher in the recombinant FVIII-treated patient population (17.4% versus 9.3%). [69] Moreover, when a number of potential variables were taken into account in the study, the greater immunogenicity of recombinant FVIII vanished. Regrettably, there is presently no randomized controlled clinical study that can provide conclusive proof of whether or not there is a variation in immunogenicity among plasma-derived and recombinant FVIII. This is the rationale behind the new launch of the Inventory of Inhibition in Plasma-Product Exposure Toddlers (SIPPET). SIPPET is an observational, controlled, open-label clinical study that is led by the experimenter and compares inhibition incidence in PUPs or patients who have received only minimal treatment after being subjected to plasma-derived VWF/FVIII concentrates or recombinant FVIII. [70] At least one-third of the anticipated cases have as of this writing been registered in SIPPET since the study's commencement. These goals may also be achieved by other sizable prospective cohort studies of PUPs with serious hemophilia, such as the European PedNet Registry and the French cohort (FranceCoag Network). The relative effectiveness of plasma-derived or recombinant FVIII in promoting antigen-specific immune resistance development remains a contentious topic (ITI). The only treatment for inhibition that has been demonstrated effective is ITI, but it is prohibitively expensive in many nations and poses significant difficulties for patients and the community in considerations of venous access. [71] A number of clinical research studies have looked into the role of FVIII origin in ITI, and some clinical experience in Europe and the USA recommend that plasma-derived FVIII products rich in VWF may

increase the likelihood of effective ITI. This is because several in vitro studies demonstrated a reduction in inhibitor activity against FVIII complexed with VWF (VWF/FVIII) especially in comparison to that against recombinant FVIII. [72] The method of administering replacement therapy has become a vital problem with the wider adoption of main prophylaxis programs and the application of ITI protocols that require intensive and frequent infusions of factor concentrates. Even though peripheral venipuncture is the preferred method, very small children with inadequate venous access frequently require central venous access devices (CVADs). Completely implantable catheters (ports) are preferable to external CVADs even though there is less of a chance for problems, particularly infections and thrombosis. [73] With positive outcomes documented in two experiments done in Italy and the United States, transient arteriovenous fistulae are also a prospective option for children one year of age and older, especially for those who have suffered recurrent CVAD failing. While basic prophylaxis continues to be the gold standard for maintaining joint function in infants with severe hemophilia, there is controversy over the impacts of secondary prophylaxis versus on-demand treatment on joint condition in older children, teens, and adults. [74] The outcomes of two randomized trials, the SPINART (Trial to Assess the Impact of Secondary Prophylaxis with Recombinant FVIII Medication in Intense Hemophilia A Adult Subject matters Especially in comparison to That of Episodic Therapies) and the POTTER (Prophylaxis vs. On-demand Medication Through Economic Report) experiments, are awaited by the scientific community in this setting, taking into account also that all published data are produced from small retrospective studies. People with hemophilia are getting previously unheard-of medical and surgical conditions like cancers and cardiovascular diseases as they get older. [75] Caretakers of people with hemophilia face challenges in managing these diseases because they constitute novel causes of morbidity and mortality. Their best care requires close collaboration between medical professionals from various disciplines, including hematology, oncology, cardiology, nephrology, surgery, and internal medicine. Regretfully, there aren't many data on the health care needs of elderly hemophiliac patients, so therapy suggestions are largely based on expert panels' personal experiences, which has a low level of evidence. [76] To best handle comorbidities in elderly hemophiliacs, particularly cardiovascular diseases and cancer, well-designed clinical trials are still

needed. The hunt for a permanent treatment for hemophilia, which would entail correcting the fundamental DNA defect via gene transfer, has been the ultimate objective of researchers over the past ten years. Starting in the third millennium, a few phase 1/2 studies of somatic cell gene treatment carried out in patients with FVIII or FIX deficiency looked to maintain the high hopes following the excellent outcomes seen in animal models of hemophilia. [77] In the bulk of them, it was possible to achieve detectable levels of FVIII or FIX in plasma by transferring the healthy gene either in vivo or ex vivo. Although these early encouraging findings inspired a lot of optimism, subsequent research fell short of the initial hopes and overly enthusiastic optimism.

5.1.3 Management of bleeding

Early prevention and therapy of acute joint bleeds before the onset of degenerative disease is necessary for the best care of hemophilic joint disease. Substitute clotting factor concentrates can be used to address joint hemorrhages early on. [78] To stop bleeding and stop it from happening again, the number of clotting factor must be high enough and sustained for a long enough period of time. Intra-articular bleeding is still a significant clinical expression of the illness, especially in people with severe haemophilia or antagonists, despite the success of factor replacement treatment. Early factor concentrate prophylaxis in children, especially in those with serious hemophilia, can not only stop joint bleeding but also enhance joint outcomes. [79] The World Health Organization and the World Federation of Hemophilia suggest prophylaxis as the first line of treatment for severe hemophilia. Primary prevention and therapy of acute joint bleeds before the beginning of degenerative disease is necessary for the best care of hemophilic joint disease. Substitute clotting factor concentrates can be used to address joint hemorrhages early on. To stop bleeding and stop it from happening again, the number of clotting factor must be high enough and sustained for a long enough period of time. [80] Intra-articular bleeding is still a significant clinical expression of the illness, especially in people with severe haemophilia or antagonists, regardless of the efficacy of factor replacement treatment. Early factor concentrate prophylaxis in children, especially in those with serious hemophilia, can not only stop joint bleeding but also enhance joint outcomes. The World Health Organization and the World Federation of Hemophilia suggest prophylaxis as the first line of treatment for severe hemophilia. [81] The timing of stopping tertiary

prophylaxis is still unclear and inadequately understood. Retrospective studies of prophylaxis in people with severe hemophilia have revealed some patients may be able to end prophylaxis in adulthood and transition to on-demand treatment, such as those with no or few joint bleeds. [82] Outcomes from Denmark and the Netherlands demonstrated that, over the course of a 4-year follow-up period, one-third of young adult patients with severe hemophilia who had been going to receive prophylaxis as children stopped doing so while still maintaining a low regularity of joint bleeds and a comparable arthropathy to those who had proceeded prophylaxis. Short treatment sessions (6–8 weeks) of secondary prophylaxis with vigorous physical therapy are advised for patients with active chronic synovitis and commonly reoccurring haemarthroses. When prophylaxis is not practicable or necessary, on-demand treatment should be administered as soon as a bleeding episode starts.[83]

5.1.4 Adjunctive management

For the relief of pain brought on by bleeding into the joint, analgesics might be needed. Analgesics, such as those that carry aspirin or other non-steroidal anti-inflammatory medications, can, moreover, make bleeding worse. Acetaminophen/paracetamol and milder opioid painkillers are safer substitutes. [84]

Anti-inflammatory treatment

After the acute haemarthrosis period has passed, the synovitis that frequently occurs must be taken into account. Even though non-steroidal anti-inflammatory medications have traditionally been contraindicated in the community with bleeding disorders, each person should be evaluated to determine whether this medicine or the more recent cyclo-oxygenase 2 antagonists are suitable for them. Chronic synovitis has been treated with intra-articular glucocorticoid injections. [85] Systemic corticosteroids have a limited role because of their side effects, but they may be used in certain situations where there is a serious inflammatory response that is resistant to other therapies. Hermans et al. lately looked at the proof for medical anti-inflammatory therapy in this patient group and found that it was very low. [86]

5.1.5 Diagnosis

A number of characteristics need to be considered when diagnosing hemophilia in a patient without a historical family history. It is crucial to meticulously record the patient's bleeding

complaints before making any therapeutic options. You should also find out if any maternal blood relatives may be dealing with excessive or chronic bleeding (Dietrich S, et al, 1996). Blood samples for a clotting test should have the platelet count, prothrombin time, reactivated partial thromboplastin time, and thrombin time assessed. A definitive diagnosis can be made after factor VIII and factor IX assays are done if the clotting screen reveals hemophilia (Higgins, et al, 1997). [87] After a diagnosis, the patient or caregiver needs to be given information and support. People who have never experienced the sickness before will require knowledge about it, how to treat it, and how to access hospital care quickly. It's possible that those with a family history of hemophilia are unaware of new developments or existing treatments (nitrix, et al, 2005). [88] Localizing symptoms like seizures, papilledema, and vision disturbance typically point to a significant bleed. A comprehensive physical examination, a noncontrast CT scan of the head, or an MRI scan should be performed on any patient with moderate or severe hemophilia who reports a background of head trauma or a prolonged, unexplained headache. All investigations should be preceded by factor replacement treatment to bring deficient factor levels to 100 IU/dl. If the\spatient is asymptomatic and the imaging studies show\sno indication of ICH, the patient can be released under\sthe care of a responsible adult with clear instructions\sto watch for any modification in the state of consciousness, headache, photophobia, or vomiting in the following\s24–48 h. [89] For identifying a posterior fossa bleed, an MRI scan is more beneficial than a CT scan. Until an ICH is ruled out, factor replenishment to keep a trough level of 50 IU/dl should continue. Going to follow a head injury, a hemophiliac patient with an inhibitor to factor VIII or factor IX should be treated similarly to a patient with serious factor insufficiency. [90] The original replacement treatment chosen, however, is determined by the inhibition titer and whether the blockade is a low or high responding type. It is better to use activated prothrombin complex concentrate (FEIBA) or recombinant activated factor VII (rFVIIa). In a retrospective analysis of the US experience managing ICH in hemophiliac patients, Nakar et al. discovered that rFVIIa was clinically efficient. [91]

5.1.6 Causes of Hemophilia

Hemophilia is caused by a change or modification in one of the genes that codes for the clotting factor proteins necessary to form a blood clot. The clotting protein may no longer

function at all as a consequence of this alteration or modification (Jones P, et al, 2002). These genes are found on the X chromosome. Males have one X and one Y chromosome (XY), while females have two X chromosomes (XX). [92] The X and Y chromosomes are given to males by their mothers and fathers, respectively. Each primary purpose of providing one X chromosome to a female (Jayandharan G, et al, 2003). [93] The Y chromosome lacks many genes that are present on the X chromosome. As a result, while the bulk of X chromosome genes are duplicated in two copies in females, they are only present in one copy in males. Consequently, a man who receives an X chromosome with a change in the factor VIII or factor IX gene may experience hemophilia-like symptoms. Women can have hemophilia, but it is far less prevalent. In these cases, the X chromosomes are now either both impacted or only one is diseased while the other is missing or dormant (humnil, et al, 2005). [94] Similar to male hemophiliacs, these women could occasionally undergo bleeding episodes. A female who carries hemophilia has one impacted X chromosome. It is possible for a female hemophilia transmitter to infrequently display hemophilia symptoms. She can also transmit the X chromosome with the altered clotting factor gene to her progeny. Learn more about the hereditary history of hemophilia. Even though hemophilia runs in families, some families have never had a member of their family suffer from the condition. [95] By happenstance, the family may sometimes contain both afflicted boys and transmitter females. However, about one-third of the time, a clotting factor gene mutation impacts the newborn who has hemophilia as the first member of the family to be affected (Jones, et al, 1998). The two most prevalent significant congenital coagulation factor deficiencies are hemophilia A (factor [F] VIII deficiency) and hemophilia B (factor [F] X deficiency). Hemophilia A is more prevalent than hemophilia B, occurring in 1:5000 male births compared to 1:30,000 male births. All ethnic groups can have hemophilia; there is no regional or racial preference. [96] The hallmark bleeding symptoms of hemophilia are severe soft tissue bleeding and hemarthroses, while simple bruising and profuse mucosal bleeding may be the initial indicators. When assessing a child who has experienced unexpected bleeding, other bleeding problems should be taken into account. The symptoms of factor deficits (FV, FVII, FX, FXI, FXIII, and fibrinogen) can include bleeding or abnormal laboratory test findings for coagulation. [97]

5.1.7 Prophylactic therapy

External coagulation factors are routinely infused into a hemophiliac patient as part of prophylactic treatment to stop uncontrolled bleeding. In adolescents with severe hemophilia, prophylactic infusion of factor concentrates of FVIII and FIX is considered the gold standard of care. In order to maintain normal musculoskeletal function, prophylaxis should be the main focus. It stops bleeding and joint damage. [98] Numerous studies have demonstrated that postponed prophylaxis can also minimize the number of bleeds in addition to the patient's physical and psychological limitations. Long-term prophylaxis has also been shown to be effective in decreasing bleeds in avoiding hemophilic arthropathy. Besides keeping the trough level of factors basically >1% of normal, prophylaxis aims to reduce severe hemophilia to a milder form. [99] In patients with high levels of antagonists, prophylaxis with FVIII and FIX bypassing FVII is also helpful. WFH and WHO have suggested prophylaxis according to the table since 1994. Basic prophylaxis: Regular, ongoing care that is begun before the second clinically obvious large joint bleed and before age 3 years, as established by physical examination and/or imaging studies in the exclusion of osteochondral joint disease. Secondary prophylaxis is a routine, ongoing course of therapy initiated following two or more bleeds into sizable joints but prior to the onset of joint disease as determined by physical evaluation and imaging tests. [100]

5.1.8 Gene therapy

Gene therapy seeks to restore, change, or enhance cellular functions by inserting a functional gene into a target cell. Due to their monogenic illness, hemophiliacs were considered a perfect target. for gene therapy, as only a modest increase in factor quantities to more than 2% of normal would enable prophylaxis without frequent focus infusions and guarantee a significant change in lifestyle for people with severe hemophilia. [101] The immediate repair of the molecular abnormality in the mutated gene would be the final goal of gene therapy for hemophilia A and B. Although such direct gene editing has been established, 50, 51 this strategy is still far off in the future for hemophilias A and B. In order to treat hemophilia, regular factor VIII or IX genes are added. In animal models, gene

therapy can give the possibility of a true hemophilia cure with current technology, but this is not currently possible in humans. More than 25 hemophilia sufferers have now received phase I gene-therapy treatments. [102] However, no research has conclusively demonstrated that factors VIII and IX can be reliably acquired at medicinal concentrations5. Still a top candidate for gene therapy is hemophilia. Moreover, with today's safe and efficient therapy, hemophilia is no longer a condition that poses a danger to life. When considering gene-based methods to therapy, it is important to strike a balance between the potential advantages and potential risks. [103]

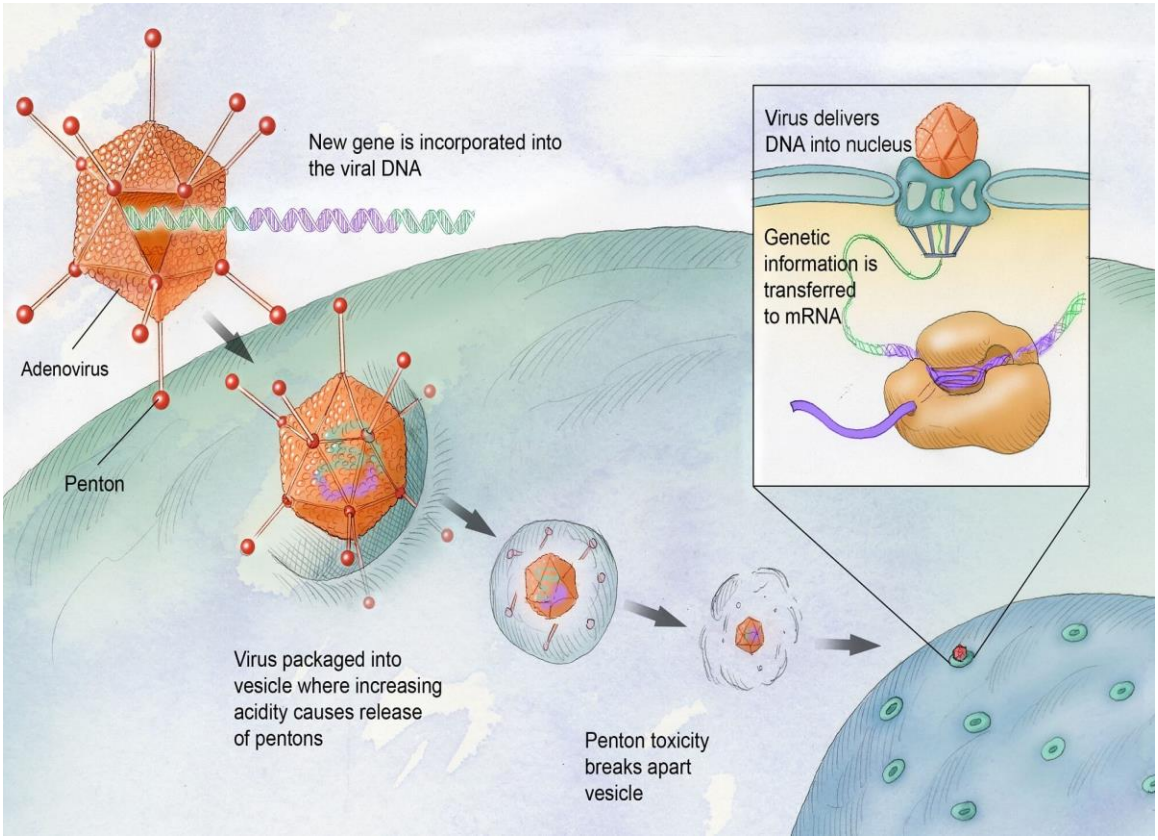

Figure 5: The Current State of Gene Therapy for Hemophilia [104]

5.2 Discussion

Some patients face financial difficulties because to the cost of clotting factor drugs, health insurance limitations, and out-of-pocket costs. There may occasionally be difficulties with venous access or home infusion. Last but not least, it could be challenging to adhere to

treatment regimens due to several psychosocial barriers. [105] According to our poll, 51% (36/51) of doctors and 78% (36/46) of carriers think that hemophilia p0.001; 72% (33/36) of hemophilia A carrier with normal FVIII activity have an ongoing trend to bleed; A high frequency of bleeding symptoms is reported by carriers (Bildmark, et al,2006). [106] In contrast, 65% (29/45) of Hemophilia C physicians advocate carrier testing after age 14 and 72% (50/69) of medical providers urge carrier testing before age 14. An owner like having testing done before this age (p = 0.001). Hemophilia Carriers desire earlier testing to establish their carrier status and self-report more bleeding than previously approved. There haven't been many studies done on oral health issues in hemophilia patients. Regarding the prevalence of caries in children with hemophilia, both in their permanent and primary incisors and canines, there is some debate. The population's share of people with congenital hemorrhagic diatheses is quite minimal. Microsatellite linkage analysis PGD for the F8 intron 22 inverted was supported by the delivery of healthy twins to one of the couples (Dwyer G, et al, 2009). [107] The predicament of the other family brought to light the difficulties surrounding de novo mutations and potential germline mosaicism.

Chapter 5
Conclusion

6.1 Conclusion

Hemophilia has changed over the last three decades from being an underappreciated and frequently fatal hereditary hemorrhagic disease to a well-defined collection of molecular entities. Hemophilia currently has the most effective and secure therapy of all the common monogenic disorders (cystic fibrosis, thalassemia, and muscular dystrophy). After the dramatic events of extensive blood-borne virus transmission in the 1970s and 1980s, there has been a significant push for improving the effectiveness and stability of replacement treatment as well as for developing gene therapy as a means of curing the illness. the consciousness method provides tools to help personality when hemophiliac kids shift to self-care. We believe that providers can more successfully address the challenges that hemophiliac children and adolescents with self-care motivation face by being conscious of and using these options. Reviewing hemophilia with an emphasis on children's care, inquiries, and manifestations is the goal. Care for children with hemophilia can take many different forms. The hematologist, a specialist in hemostasis and thrombosis with communication in pediatric patients, the surgeon with engagement in CVADs in children, the psychologist and social worker, the pharmacist, the orthopedic, physiatrist, and physiotherapist, and the nurse team must all regularly assist the patient and his family. It is essential to create a connection between both the family and the hemophiliac child in order to promote trust, trustworthiness, and good communication seen between family and their caregivers. It is possible to influence how the illness manifests in adulthood by laying this framework in childhood. Two things are necessary to keep healthcare and development at this high standard. First, international cooperation is required for clinical study on hemophilia. In fact, only a small number of the aforementioned important unanswered issues can be addressed by research conducted in a single, albeit sizable, hemophilia center. Achieving an adequate sample size is crucial when studying a rare condition like hemophilia, and cooperative multicenter trials are the only way to accomplish this. Second, it's critical to keep a high level of interest and knowledge in the field of hemophilia, particularly among younger generations of doctors who seem drawn to the more alluring thrombotic side of hemostasis.

Chapter 7
Reference

7.1 Reference

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