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Treatment Modalities for Hemophilia Type A

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ABSTRACT

Hemophilia Type A is a genetic disorder caused by inheriting an X chromosome from the parents. It causes an individual to produce an ineffective factor VIII, diminishing the blood's clotting ability. Patients with Hemophilia Type A experience uncontrollable bleeding episodes, unexplained bruising, joint pain, or, in more extreme cases, bleeding in the brain. When patients present with a family history of Hemophilia, physicians will order testing to determine if the disorder is a possible etiology of abnormal bleeding episodes. Testing is essential because symptomology alone is not enough to diagnose Hemophilia A. Other bleeding disorders, such as different types of Hemophilia or Von Willebrand, present similarly in patients. Even with no reported family history, Hemophilia A should be considered as a potential diagnosis for spontaneous bleeding episodes because specific individuals acquire the disorder. Physicians need to rule out all potential causes of symptoms, regardless of their commonality, to ensure the patient receives proper and timely treatment. Therefore, Doctors should order a PTT, a PT, and a clotting factor test to determine the patient's clotting ability and, if abnormal, identify a clotting factor deficiency. After determining a patient has Hemophilia Type A, a treatment plan may consist of replacing clotting factors through medications and injections, as well as managing symptoms at home. Again, without proper testing and diagnosis, prolonged absence of treatment can lead to the patient developing potentially life-threatening problems or complications that could significantly decrease their quality of life. While the current treatments are effective at preventing clotting episodes in some, more research is needed to determine a more effective solution to increase the patient's quality of life.

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Abbreviations

PTT: Partial Thromboplastin Time Test
PT: Prothrombin Time Test
FFP: Fresh Frozen Plasma
CBC: Complete Blood Count
EDTA: Ethylenediaminetetraacetic acid
RBC: Red Blood Cell
VWF: Von Willebrand Factor
DDAVP: Desmopressin

Introduction

Over the centuries, civilizations have sought to explain bleeding disorders. One of the first accounts was in the 2nd Century A.D., where a law was written in the Talmud, a Jewish doctrine that prohibits circumcision if a relative had died from the procedure [1]. More notable examples include the European royal families of Germany, Russia, and Spain because the descendants of Queen Victoria, thought to be a carrier of Hemophilia, presented with the illness or had children with the disorder [2]. However, it was not until the 17th Century that physicians recognized the genetic component of the disorder. In 1803, John Conrad Otto first published this idea [2]. The term "Haemophilia" was coined in 1828 by a German professor, Dr. Johann Lukas Schonlein and his student Friedrich Hopoff [2]. Despite numerous observations throughout history, treatments were not available until the 20th Century. In the 1940s, blood transfusions were used and found to increase the life expectancy of those impacted [2]. In 1948, Betty Jane and Bob Henry established the first Hemophilia Treatment Center because of their success in increasing access to treatment for Hemophiliacs; treatment centers were subsequently established all over the US [2,3]. During the 1950s, patients were required to be hospitalized for treatment of bleeding episodes with FFP, which was the primary method of treatment at the time [3]. In the 1960s, Judith Pool revolutionized treatment by isolating clotting factors, referred to as Cryoprecipitates from FFP, allowing for outpatient treatment and elective surgeries for some patients [3]. These advancements in knowledge of clotting disorders led to an increased life expectancy for patients and paved the way for the current understanding and treatment of Hemophilia.

Hemophilia is a blood-clotting disorder caused by a deficiency in clotting factors, rendering the patient unable to stop bleeding naturally [4]. There are four types of Hemophilia: Type A, B, C, and acquired [5]. Usually, the disorder is inherited. However, roughly 30 percent of cases are developed without a family history [6]. While symptoms of each type are almost identical, the classifications of Hemophilia are based on a deficiency of a specific clotting factor. Therefore, a physician would need to order genetic and clotting factor testing to determine the classification and proper treatment. The most common classifications of Hemophilia are type A and B, however, they have different deficiencies in clotting factors. Hemophilia type A is caused by a deficiency in clotting factor VIII, and approximately 12 in 100,000 people in the U.S. are diagnosed with Hemophilia type A [5,6].

In most cases, the clotting factor deficiency is attributed to a mutation on the X chromosome that produces nonfunctional Factor VIII. However, a physician should consider Hemophilia type A as a possibility for all patients who have excessive bleeding because the condition can leave the patient in extreme pain, reducing their quality of life, and it may cause life threatening conditions if left untreated [6]. This paper aims to analyze the advancement in treatment, understanding, and diagnosis of Hemophilia type A and how these advancements were key to increasing long-term patient outcomes.

Discussion

In 1944, Pavolsky discovered the distinction between types of Hemophilia by transfusing Hemophilia patients with each other's blood, and he found this method was successful because the patients had different clotting deficiencies [7]. The experiment set the foundation for subsequent treatments for many years to come. In the 1950s through the 60s, patients were treated by blood transfusions donated from other humans, but most of the therapies did not provide enough clotting factors to completely resolve bleeding episodes. As a result of a lack of knowledge, most people with severe Hemophilia died due to complications associated with the condition. It was not until 1964 that scientist Judith Poole was able to isolate factor 8 for the treatment of Hemophilia Type A, thereby, providing enough clotting factor to combat that deficiency [7]. In the 1970s, widespread use of human plasma was incorporated into the treatment of Hemophilia, along with the implementation of clotting factor replacement at home. This changed the quality of life of patients through early and continuous treatment, which prevented severe bleeding episodes and joint problems [7,8]. Unfortunately, a consequence of this life-saving treatment was the widespread contraction of blood-borne illnesses, particularly HIV and Hepatitis C, through contaminated blood donations [8]. As a result, increased screening processes for blood samples, as well as viral inactivators, made blood transfusions safer for patients with Hemophilia [7].

Before viable at home treatment methods were widely used, Hemophilia Treatment Centers specialized in providing emergent care to patients. With the invention of effective sustainable treatment methods, the centers started to provide specific, preventative, and long-term care through incorporating specialty practices such as orthopedics and hematology to help care for people with Hemophilia and the specific complications that arise from the disorder [7]. Specifically, the number of patients that underwent annual exams, with members from at least three different specialties, rose to 33% [9].

In 1977, Desmopressin was discovered to help produce more Factor VIII in patients, which revolutionized treatments because the primary methods, involving blood transfusions, posed risks to the patients of exposure to pathogens and were relatively expensive [7]. With the invention of Desmopressin, the cost of treatment diminished, and the risk of developing an illness due to exposure of contaminated blood decreased as well, but it was only effective in treating mild cases [7]. Today, the WHO considers the drug one of the most important treatments for mild bleeding disorders for patients with Hemophilia A [10]. One study focused on estimating the number of bleeding episodes Desmopressin could prevent. Worldwide, using data collected from societies of bleeding disorders, WFH-AGS 2023, and data from other studies, the researchers estimated 43,000 patients have mild cases and 38,000 have moderate cases [10]. Using data collected from other studies, 80% of patients with moderate Hemophilia and 25% with mild Hemophilia would respond to medication [10].

In the United States alone, it is estimated about 33,000 males have Hemophilia [9]. Specifically, Hemophilia A impacts 1 in every 5,000 births in the United States [10]. However, this number may be not accurate because less severe types of Hemophilia A, like moderate or mild, may evade diagnosis until later in life when an abnormal bleeding episode occurs. Typically, diagnosis of the disorder occurs at a young age, and Hemophilia A is more common than type B by 3 to 4 times [10]. Even though Hemophilia type A is more common in males, females can also present with the disorder. It is estimated 16% of moderate Hemophilia cases are females [11]. Hemophilia can occur in every race, however, there are some groups more at risk than others. In 2021, in the US, commonality of Hemophilia type A and B is as follows: "15.1 per 100,000" white males, "12.4 per 100,000" Black males, and "12.4 per 100,000" Hispanic males developed Hemophilia [11]. While it seems incidence in white males are higher, scientists still need to determine what the link is between race and the likelihood to develop Hemophilia before making a conclusion [11].

Hemophilia type A is caused by a deficiency in clotting Factor VIII; in most cases, the deficiency is due to a genetic mutation. The gene that controls the production of the factor is located on the X chromosome and is about 186 kb [12]. Hemophilia is inherited through sex linked chromosomes, specifically the X chromosome. Because of this, males are affected at a higher percentage than women [12]. This sex-based discrepancy is due to women having two X chromosomes (XX) while men have XY chromosomes. Transmission of Hemophilia is explained by carriers of the disorder, or individuals who possess the affected gene, but do not present with the illness. In the case of Hemophilia, women are carriers of the disorder because the mutated X chromosome is masked by the healthy X chromosome, whereas in males, if they inherit a defective X chromosome, the Y chromosome cannot compensate for the genetic error and cause Hemophilia [13].

For example, if a healthy female with two unaffected X chromosomes reproduces with an unaffected male, then their offspring would not be able to have Hemophilia, unless it was acquired [13]. Further, if a mother with one healthy X and one X mutated chromosome, reproduces with a healthy male, then their male children would have a 50% chance of developing Hemophilia because the mom donates either the healthy or the mutated X chromosome, while the father contributes unaffected genes [13]. Conversely, the female offspring would have a 50% chance of being carriers because they would inherit one healthy X chromosome and one abnormal X from her parents [13]. In another example, if a male with Hemophilia, one mutated X, has children with a carrier female, one healthy and one mutated X chromosome, then there is a 50% chance of their offspring, either daughter or son, having the disorder. If a Hemophilia male had offspring with a healthy female, their sons would not have Hemophilia, however, their daughters would be carriers for the gene, and they would have a chance to pass that off to their offspring [13]. In all, about 1 in 5,000 males are diagnosed with Hemophilia type A, however, while it is possible, women are not often diagnosed with the ailment [12]. The lower incidence is due to the lower probability of female offspring inheriting two mutated X chromosomes to present with the disease [13]. Inheriting a mutated X chromosome leads to abnormal clotting factor proteins created. In the case of Hemophilia Type A, a mutation will lead to a deficiency of Factor VIII.

Factor VIII, also known as antihemophilic factor, is synthesized by the liver, spleen, kidneys, and lymphatic tissues [14]. However, the

main synthesis occurs in the liver [14]. First, the gene containing the instructions to produce Factor VIII, is transcribed into mRNA, which encodes the amino acid sequence to create the protein, and the mRNA is translated into a protein by the ribosomes located in the rough Endoplasmic Reticulum [14]. Then, the synthesized Factor VIII goes to the lumen of the Endoplasmic Reticulum where it interacts with chaperone proteins, such as calnexin and calreticulin, which is then transported to the Golgi Body [14]. Once in the Golgi Body, the Factor VIII protein is further processed with different modifications such as proteolysis and sulfation of Tyrosine [14]. After additional modification, copper is used to bridge domains A1 and A3 to further stabilize the protein [14]. In Hemophilia type A, the altered gene on the X chromosome causes issues with transcribing and translating the gene (14). In other words, an altered DNA sequence causes the incorrect mRNA sequence, in turn, creating the mutated protein. The type of mutation determines the severity of Hemophilia. Severe Hemophilia is characterized by a drastic mutation that causes an entirely nonfunctional factor 8 or absence [15]. These mutations are known as null variants caused by inversion mutations, large deletions, and nonsense variants [15]. While moderate or mild hemophilia is caused by less drastic mutations like missense variations, known as non-null variants [15].

Through more recent research, scientists have uncovered specific genomic mutations that cause Hemophilia type A. For severe cases, an inversion between intron 22 and intron 1 is responsible [15]. Inversion mutations occur when a portion of a chromosome is removed, flipped, and reinserted in the genome [16]. In 4-10% of cases, an inversion from intron 1 moves it closer to the telomere region by 140 kb, causing a misfolded Factor protein [15]. The most common cause of Hemophilia A is an inversion of intron 22, located 500kb away from the Factor VIII gene [15]. Another known mutation that affects Factor VIII is in the taq1 operon, which contains the information required to produce the clotting factor [17]. Specifically, the mutation changes the amino acid from arginine (CGA) to a stop codon (TGA) or glutamine (CAA) [17]. The change in amino acids is detrimental to the production of an effectively functioning Factor VIII because when transcription of the mRNA takes place, converting mRNA to a protein, the change in the sequence can negatively, depending on the case, impact how the protein is made, either by early termination or substitution for another codon, changes the structure, and therefore the function, of the protein [17]. Another alteration of the genome that causes production of an ineffective clotting protein is a rare transposable element called L1, which inserts itself in exon 14 [17]. Transposable elements often move throughout the genome, inserting genetic information in other places of the genome, which can cause shifts in the reading frame of the ribosome, causing translational errors in mRNA to protein, and causes a structural change in the factor [17].

In rare cases, patients may present with Hemophilia with no genetic explanation, known as Acquired Hemophilia. The incidence of acquired hemophilia occurs for 1 per a million people annually [18]. However, the condition is often misdiagnosed, leading scientist to speculate a higher incidence than reported yearly [18]. Acquired cases have no genetic basis, and the condition occurs either due to another illness or idiopathically [19]. Additionally, the difficulty in diagnosis comes from the fact that the patient's condition may change rapidly. In other words, the condition of Hemophilia will develop later in life. Acquired Hemophilia develops because of mutations in the A2, A1, and C2 domains of the Factor VIII protein, which the autoantibodies of the patients bind to and deactivate the Factor VIII protein [20].

Due to the typical presentation of genetic Hemophilia Type A, physicians may overlook Acquired Hemophilia as a cause of excessive bleeding. Unlike genetic Hemophilia Type A, stemming from alloantibodies, Acquired Hemophilia A stems from autoantibodies [20]. Specifically, in Acquired Hemophilia, the autoantibodies produce a quick reduction in Factor VIII, then slowly decrease the levels over time. Around 50% of acquired cases are of unknown origin, unrelated to medications or other diseases [20]. The other portion of cases is due to another disorder [21]. For instance, immune disorders, such as Rheumatoid Arthritis or lupus, increase the risk for developing AHA by potentially triggering the production of antibodies against Factor VIII [21]. Pregnancy may also put a patient at risk for AHA, however, the cause is unknown but is hypothesized to be related to immune system changes during gestation [21]. Other risk factors are related to cancer, pulmonary disorders, dermatological conditions, or drug interactions that can cause the development of AHA [19]. Often, elderly patients account for a higher proportion of cases, and Children are rarely impacted by the disorder [22]. However, it impacts all racial groups, and it has equal presentation in men and women, unlike genetic cases. Overall, Acquired Hemophilia occurs with 1.5 cases per million people per year [23].

Both Acquired and Genetic Hemophilia Type A present similarly in all patients; severity depends on the mutation or progression of the disorder. Some general symptoms of hemophilia include: nosebleeds, excessive menstrual bleeding, bleeding that persists for long periods after injury, easy bruising, blood in joints, blood in urine, or blood in stool [24]. While some cases may not present obviously, there are symptoms parents and healthcare professionals should look for in their child to determine if they need to be tested for Hemophilia. If healthcare professionals or the parents notice prolonged bleeding well after a venipuncture, circumcision, or bleeding on the head after delivery, there may be a reason to test for Hemophilia Type A [25].

Another sign of Hemophilia that parents can catch early is unusual bruising [25]. Typically, patients aware of a family history are more observant of symptoms and will have frequent doctor visits [13]. In fact, it is recommended for patients to receive testing if a family history of Hemophilia is present [24]. For females with a family history of Hemophilia, physicians will recommend testing to determine if they are a carrier, or if they have any clotting deficiencies [26]. Depending on the severity of the disorder, diagnosis may occur in early childhood, but mild or moderate cases may present later in life [27]. Specifically, acquired cases may also develop later in life due to triggers such as surgery [17]. Unfortunately, there is no specific symptomatology to diagnose a patient with Hemophilia rather than other bleeding disorders, let alone the type of Hemophilia present. Additionally, symptomology for all bleeding disorders is similar, so Physicians will not only consider Hemophilia as a potential cause. Rather, there are a multitude of differential diagnoses, including Ehlers-Danlos syndrome, Von Willebrand, or Platelet disorders [27]. As a result, a physician needs to order comprehensive testing to determine the diagnosis and the specific clotting factor deficiency.

To rule out a differential diagnosis, a Physician may consider if the patient has any risk factors that increase the likelihood of developing Hemophilia. Risk factors essentially explain who is more likely to develop Hemophilia [28]. For instance, Males are at a higher risk of developing the disorder due to lacking a second X chromosome [28]. Therefore, patients presenting with these risks are a more likely candidate for Hemophilia.

Before testing, it is important for physicians to learn the most common presentation of the illness. Mostly, severe cases are more noticeable with young children, as the parents may notice abnormalities right away, and healthcare professionals will notice prolonged bleeding after circumcision [25]. Physicians may also consider patient testimonials to determine the severity of Hemophilia present. For instance, if an adult is complaining of bleeding severely without injury, has blood in muscles, or joints then the physician should consider severe Hemophilia A as a probable cause [29]. Moderate Hemophilia usually causes bleeding after injury [29]. Mild Hemophilia essentially triggers bleeding episodes after severe events like surgery, serious injury, or even tooth extractions [29]. Therefore, the physician's next steps are to assess for Hemophilia or an alternative diagnosis. If the patients have Hemophilia, it is also important that physicians test for which factor is not produced at an effective rate and how much less it is being produced compared to the standard.

In the case of Acquired Hemophilia, symptomology is similar; however, there is no genetic component that clearly points to Hemophilia causing unexplained bleeding episodes. Often, clinicians will see the condition as rare, so it may go undiagnosed for years. Most cases are idiopathic in nature, but the patient will notice spontaneous bleeding episodes in the muscles, joints, gastrointestinal tract among other symptoms [20]. In this case, without a family history, there could potentially be other disorders that present the same way as Acquired Hemophilia, so testing is also needed to rule out other causes [20]. In other words, physicians need to keep an open mind when testing for causes that present similarly to Hemophilia A but still not discount it as a cause of symptoms in their patient.

In all, there are many diagnostic tests that physicians can perform to check the presence of Hemophilia. The first test a physician may order is a complete blood count, or CBC. The CBC procedure is a common way for physicians to determine morphological abnormalities in the blood [30]. The patient will have their blood drawn by a medical professional using a purple-top tube containing EDTA to prevent clotting [30]. Then, a peripheral blood smear is created and examined under a microscope to look at the state of red blood cells, platelets, white blood cells, hemoglobin, and hematocrit levels [30]. In patients with Hemophilia, the CBC ranges may appear normal, but in most severe cases, the RBC, hemoglobin, or hematocrit levels may be low which might indicate prolonged bleeding in the patient [30]. Another way physicians can test for Hemophilia is through the PTT Assay, or Partial Thromboplastin Time Test which allows Physicians to see how long it takes blood to clot [31].

The test takes the patient's plasma and the reagent, incubates them together, then calcium chloride is added into the sample to initiate clotting [6,31]. Typically, a physician will suspect Hemophilia as a cause when the blood sample takes more than 35 seconds to clot [6]. This test measures how well Factors VIII, IX, XI, and XII aid in clotting [31]. However, high values can also indicate an autoimmune disease, a vitamin K deficiency, liver disease, or VWD [6,31]. Since the test does not account for the specific cause of the decreased clotting efficiency, more testing is required. However, it does provide the Physician with evidence of a potential clotting disorder. In conjunction, a Prothrombin Timed Test will be performed to more specifically observe deficiencies in clotting factors. This test will measure how well clotting factors such as fibrogen, factor V, factor VII, factor X, and prothrombin are performing [31]. Similarly, a Fibrinogen test may be used when patients present with symptoms of difficulty clotting, or their PT and PTT test are not normal [30]. Essentially, Fibrinogen is produced by the liver and aids in blood clotting [33]. If a patient has abnormal PT and PTT, the next step is to test for Fibrinogen levels to rule out a deficiency. If results are outside the 200 to 400 milligram per deciliter range, then a clotting disorder is possible [33]. While these tests may point to the patient having difficulty in forming a blood clot, it is not specific enough to determine the classification of Hemophilia is present. The next step for a physician after determining whether the patient has a difficulty in forming blood clots, is to order a clotting factor test, to determine which of the clotting factors are inhibited (34). If the results show that Factor VIII is ineffective, then the patient may have Hemophilia Type A [34].

While there are accurate forms of testing for Hemophilia type A, women still face barriers in diagnoses. Since women are labeled as carriers, it gives the perception that Hemophilia cannot impact both genders, and women can only spread the disorder [35]. Underdiagnosis also stems from overlooked symptoms, such as heavy menstrual bleeding, and underrepresentation in clinical trials (35). Therefore, more research and education are needed to increase access to diagnoses and treatments for women when it pertains to Hemophilia.

Once the physician has determined through testing that the patient has Hemophilia Type A, they choose a treatment specific to the disorder. The most common treatment for Hemophilia Type A is the administration of clotting Factor VIII [28]. The new factor is either donated or is a recombinant factor created in the lab [28]. While both produce the same result, 75% of patients use a recombinant factor to help with blood clotting due to a decreased risk of contamination [35]. Patients receive the recombinant factor through an infusion, and the severity of Hemophilia determines how often they receive treatment [35]. While administering a clotting factor does stop bleeding episodes, there are major drawbacks, such as a Shortt half-life [36]. Therefore, IV injection is necessary to quickly deliver new clotting factors to the patient [36]. In situations where clotting factor replacement is used as a preventative measure, like in surgical settings, it is necessary to receive infusions 3 times a week [36]. In recent years, there have been advancements to extend the half-life of this therapy. One method involves Pegylation which adds polyethylene glycol around the Factor VIII protein to prevent quick degradation in the body from the immune system and kidneys [36, 37]. While effective, it only reduces the amount of treatment Hemophiliac A patients receive by 30%, so the patients would receive two instead of three infusions [36]. Another drawback of this treatment is the development of inhibitors due to the patient's own immune system function [36].

One recent development for the treatment of Hemophilia type A is Emicizumab. The drug is a monoclonal antibody that mimics Factor VIII by facilitating the combination of Factor IX and X [38]. One benefit of the treatment is the drug is not impacted by inhibitors because it does not share any genetic similarities [38]. Additionally, Emicizumab has a longer half-life which significantly decreases the number of injections patients receive, reducing the amount to potentially one time a week (36,38). While a promising advancement, Emicizumab is expensive and is largely useful for preventing bleeding episodes. In a recent literature review published using clinical trials from 2017-2022, researchers demonstrated Emicizumab, despite age, inhibitor presence, or severity, contributed to less annualized bleeding overall and had minimal adverse side effects [36].

Another drug is DDAVP, which acts like the hormone vasopressin and helps stop bleeding episodes in patients with mild cases of Hemophilia A [28]. The exact mechanism is unknown. It is hypothesized that Desmopressin either stimulates the release of Factor VIII from the producing cells or protects from degradation by stimulating endothelial cells to produce VWF [38]. Von Willebrand factor is a glycoprotein, and it functions is to protect factor VIII from degradation [38]. Since DDAVP increases the amount of VWF in the blood, the amount of functional factor VIII also is present in large quantities [38]. DDAVP can be administered through an injection or a nasal spray, which is a major advantage because it decreases cost and increases access to treatment for patients [39]. However, it cannot be used to treat all severity levels of Hemophilia A because the drug enhances the body's existing supply of Factor VIII [38]. Therefore, if the patient has a severe case of Hemophilia A, there is not enough factor VIII naturally produced from the body.

Experimentally, SerpinPC is assessed for its ability to effectively stop bleeding through inhibiting the inactivation of prothrombinase which generates thrombin. When thrombomodulin binds with thrombin, affinity increases for protein C [40]. This complex will bind with EPCR which will allow for Protein C to undergo a conformational change, where the active site is exposed [40]. Once Protein C is active, it will cleave factor V, inhibiting prothrombinase activity [40]. This drug specifically targets Activated Protein C which inhibits thrombin production. SerpinPC is utilized to deactivate APC, therefore, allowing more time for thrombin to be produced from prothrombinase [41]. Since the drug is specific to originally Activated Protein C, it irreversibly binds to the protein and ceases its function. Essentially, it prevents the degradation of thrombin [41].

Other forms of treatment for Hemophilia type A do not involve injections, rather some treatments can promote clotting and healing on wounds that the patient has sustained. For example, Fibrin sealants are used at the surface of the wounds to initiate and promote clotting [42]. Essentially, fibrin, naturally, is produced by the liver as fibrinogen [44]. Once a wound is present, thrombin converts fibrinogen to fibrin, which then bundles together, pulling platelets to the site, causing a clot [43]. As previously mentioned, patients with Hemophilia Type A do not produce enough, or any factor VIII, which results in clotting difficulties; therefore, it is beneficial to aid the body as much as possible to properly form clots. Specifically, the sealant contains both artificial and natural factors like thrombin, human fibrinogen, and virus-inactivated XIII, which all either are involved in, or mimic, the natural pathway the with which the body clots [42]. This is commonly used in dental surgeries with patients with Hemophilia to promote clotting [42].

For patients with Acquired Hemophilia A, treatments are usually very similar to those who have genetic Hemophilia A. Using replacements for factor VIII does help tremendously with clotting in the most severe cases. Another treatment consideration for this is immunosuppressants [42]. In cases of mild Hemophilia A, the use of immunosuppressants, instead of clotting replacement, remits 60-80% of cases of the acquired condition [42]. Suppressing the immune system in patients will allow for more factor VIII to circulate in the body by preventing autoantibody inhibition of the protein. Often, immunotherapies are used in conjunction with other treatments like rituximab, which inhibits the CD20 antigen, which creates the autoantibodies [44]. Recently, scientists have discovered that a specific regimen of drugs has shown promise in the treatment of Acquired cases. The cyDRI regimen uses cyclophosphamide, rituximab, and dexamethasone in interval doses and has proven not only effective at suppressing patients' immune responses against factor VIII, but it also has a low toxicity profile [44].

One effective method for Acquired Hemophilia is recombinant factor VIII, otherwise known as porcine rpVIII, which is a slightly altered factor VIII [45]. This treatment works by binding to platelets and VWF in the bloodstream, which helps with clotting. In all, this treatment is 86% effective at stopping bleeding episodes in patients with Acquired Hemophilia; however, scientists still need to do more research on the impact that inhibitors have on the treatment, and the maximum number of inhibitors present before the treatment stops working [45]. Another treatment recommended for acquired Hemophilia A patients is the use of Activated Prothrombin Complex Concentrate. In the United States, the use of Factor Eight Inhibitor Bypassing Activity, FEIBA, which stops inhibitors using other available clotting factors [45]. In cases where this has been used, it has an 86% success rate in patients with Acquired Hemophilia [45].

One form of experimental treatment that is promising is gene therapy. The goal of gene therapy is to cure the disorder by replacing the defective gene with the correct sequence to produce a functional factor VIII [44]. Since Hemophilia A is caused by a single mutation, and a minor correction of 10% is needed to show improvement in symptoms, it proves a viable candidate for gene therapy [45]. One method scientists have attempted to deliver the correct genetic information is via a vector, using an adeno–associated virus, in which a scientist injects a recombinant plasmid containing the gene encoding factor VIII into the patient [44]. The virus will insert its DNA into the host, or the patient's, cells, which are then translated and transcribed into fully functional factor VIII [44]. The use of AAV5 did increase levels of Factor VIII in patients and decreased the need for other treatments; however, the impact diminished after one year [46]. While gene therapy is helpful for long-term management of the disorder, using adeno viral vectors has the potential to trigger an immune response in some patients [45]. In some cases, patients did not respond to immunosuppressive therapy and completely lost Factor VIII expression [45]. Currently, there are clinical trials in the beginning phases that show promising results for future use. Even with treatment options available that do help alleviate the symptoms of the disorder, there is still a need for more research to address the current obstacles patients face. One major issue with current treatment is that about 1 in 5 patients will develop resistance to treatment [43]. Typically, resistance to treatment through antibody development occurs through numerous treatments, if the patient is Black or Hispanic, or if there is a family history of inhibitor development [43]. Even without these risk factors, it is important that patients with Hemophilia Type A get tested every year for resistance, as it diminishes the effectiveness of treatment in ceasing bleeding episodes [43]. Another problem with the current Hemophilia treatments is the lack of longevity. In the study mentioned, using viral vectors to deliver clotting factors, some issues they observed were that the expression of the clotting factors declined over time, so while the treatments lasted longer than existing methods to replace and introduce clotting factors, the patients still needed to come back to the medical office to receive another injection [26]. According to the scientists, the decline is due to immunological responses that rapidly degrade the vectors [26]. In other words, the patient's immune system eventually recognized these vectors as foreign and removed them from the body. Also, most clotting factor replacements have half-lives and degrade eventually in the body [26]. Unfortunately, people with

more severe cases of Hemophilia type A need constant treatment to clot normally, and the degradation of the medicine increases the need for treatment over time [26]. Overall, it is expensive to receive treatment constantly, and if the patient has been given the responsibility of self-administering, then giving them a more permanent solution would decrease the potential of missing a dose and relieve patient responsibility.

Another problem with current Hemophilia Type A treatment, is the significant cost to the patient. In the US, on average, the treatment cost about 150,000 to 300,000 dollars per year, [48]. Unfortunately, this statistical cost does not account for the need for some to obtain continuous treatment or if there is complication with treatment and need for missing activities like work or school [48]. While some Medicare programs will cover the cost, it is still significantly expensive for those who do not qualify for Medicare, or if their insurance will not cover the cost of the medication [48].

In addition, using live human plasma donations, as seen in the fibrin sealants, poses some risks to the individual affected with Hemophilia [49]. Since some treatments for Hemophilia rely on certain factors of human blood from donations, careless mistakes could cause catastrophic consequences. Using these methods of treatment puts the patient at risk for potential infections from contaminated plasma which could give the patient another lifelong illness that may be fatal. Additionally, treatment for Acquired Hemophilia A also involves human plasma donations using APCs which use human plasma, therefore, there is a slight risk for this population with cross-contamination [49].

Another notable issue is the ongoing debate on the amount of clotting factor needed to stop bleeding episodes. Due to the size of the gene, there are many different levels and causes of Hemophilia type A. Therefore, there is no magic number that is given to patients to fully stop the bleeding. For years, scientists have debated the amount of clotting factor needed to prevent bleeding in spontaneous cases of Hemophilia A. Initially, it was recommended that increasing the clotting factor by 1% is enough to stop the bleeding, however, with further research it is estimated that raising the clotting factor anywhere from 3 to 5% is the most effective [50]. Now, some researchers are saying a 12% increase is what is most needed in patients with Hemophilia Type A [50]. Therefore, more research into the disorder itself is needed, as now with the current knowledge, it is unclear how much clotting factor is needed to stop spontaneous bleeding in severe cases. It is a possibility that scientists may have a wide range in the percentage to increase the clotting factor, since there is a wide variety of causes and cases of Hemophilia. Therefore, it may be more beneficial to do more research into other methods of treatment that can be more easily individualized, like gene therapy.

Gene therapy does show promise and seems a straightforward, effective treatment for patients with Hemophilia A. Still, scientists have problems to address before becoming widely available. One problem is addressing informed consent. For the therapy to become approved for widespread use, it must pass several clinical trials. Some have drawn attention to lack of understanding from participants of the potential risks of gene therapy [47]. With gene therapy there is the potential the patient loses all ability to naturally produce factor VIII which may require immunosuppression, and the unpredictable results need to be thoroughly discussed with patients [47]. There are also questions on how the cost compares of implementing gene therapy, especially in countries with a universal healthcare system, to the benefits [47].

While there are treatments that patients can receive that are given via a medical professional, there are other ways patients can manage Hemophilia Type A at home without the use of medication. Typically, a healthcare professional will recommend preventative measures to prevent a bleeding emergency from occurring as well as administering treatments at home. This allows for a decrease cost of treatment, by decreasing the amount of time spent in a hospital and decrease in serious complications from the bleeding episodes [50]. Patients that have access to at home treatment also saw an increase in quality of life via administering at home IV treatments of Factor VIII [50].

While there are ways to live with Hemophilia type A, there are many complications that arise with having this disorder. Specifically, women and men need slightly different considerations when living with Hemophilia Type A. Since the condition is passed on through the X chromosome many women do not have Hemophilia Type A, therefore, it is important that women get genetically tested for the condition as they could pass it on to their child [26]. Even if the woman carries a gene for Hemophilia Type A, they could still present with some of the symptoms of the disease, such as decreased clotting. Consequently, they are more at risk for complications from severe bleeding during childbirth, C-sections, or surgeries [26]. A physician will also need to take special consideration of carriers of Hemophilia A during pregnancy. While the body will naturally produce Factor VIII, and other clotting proteins, in excess to prepare for delivery, the increase is only temporary, and these women are at an increased risk for postpartum hemorrhage [52]. Typically, these patients will see a Hematologist along with their Obstetrician to receive the proper treatment before labor. DDAVP will be given by 36 weeks if the patients clotting factors are below 50%, and the use of factor replacement therapy for weeks postpartum may be necessary [52].

Along with the mother, an important consideration is the presence of Hemophilia Type A in the newborn child. If no proper testing is done by the physician beforehand, certain procedures can put the infant at risk. It is recommended that in babies with Hemophilia avoid circumcision as lack of clotting factor, in this case factor VIII, causes this to be a dangerous procedure, especially since the infants are often not diagnosed until after the procedure occurs [26]. More pressingly, the most common complication in infants is brain bleeding. Newborns with carrier mothers are at an increased risk of Intracranial Hemorrhage [52]. Presently, there is no known advantage of a C-section delivery versus a standard vaginal delivery in preventing an ICH, however, brain bleeds are more likely prevented when a physician knows the mother is a carrier for Hemophilia [52].

Children with Hemophilia also require special consideration due to lack of understanding of severity, and lack of approved treatments. Parents of children that are diagnosed with Hemophilia A should use protective equipment such as ensuring children are wearing helmets or knee pads to protect from injury [53]. They should also monitor infants and toddlers when they are walking, to ensure that they do not fall and injure themselves, and they should ensure all sharp corners are covered. Using seatbelts on highchairs and in the car can prevent injury to the child which can trigger a bleeding episode [53]. Obviously, sharp objects should be kept away from the child because one small accidental nick can cause a severe bleeding episode. When dealing with children that have Hemophilia, the best way to ensure the child's safety is to be aware of their environment and always be on the lookout for bleeding episodes and unexplained bruising [53]. This also is the parent's responsibility to ensure any other people that must

supervise the child should be aware of the disorder and its risks. Another good strategy is to get the child a medical ID bracelet or necklace which lets strangers, and first responders, known in an emergency of their child's condition [54]. While certain drugs, like Emicizumab, are approved in children with Hemophilia A, scientists need to further research the effectiveness to prevent bleeding episodes during and after minor surgical procedures [54]. Often with surgical procedures, physicians need to ensure that the child's clotting factors are observed, and the parents are educated on strict guidelines to present to the hospital Post-op with complications [54].

In all, there is still more research to be done that can more effectively, cheaply, and safely treat Hemophilia type A. While technological advances have made most of the treatments today safer, there is still a risk when getting plasma-based treatments or blood transfusions. Therefore, it is important that physicians educate their patients about their condition, and the potential risks that come with it. It is also important for physicians to emphasize the importance of testing for genetic abnormalities, and it is imperative physicians do not discount a potentially Hemophilic case because it may be rare or less common. One major improvement that needs to happen in the healthcare world is making sure all future healthcare professionals have an open mind and account for all variables. As missing a diagnosis of Hemophilia A in men, women, or children can have catastrophic consequences that may cost them their life. Hopefully, gene therapy will become a viable option for patients with Hemophilia A, which would provide a safer, and more permanent, alternative treatment to cure Hemophilia A for all patients and increase their quality of life.

Summary

Hemophilia type A is a genetic disorder caused by a mutation in the X chromosome which causes the blood not to clot due to the deficiency in Factor VIII. There are multiple different kinds of Hemophilia, but they are differentiated by the clotting factor that is not being produced by the patient's body. Due to the inheritance pattern, it is more prevalent in males than females, because two X chromosomes block the presentation of Hemophilia A. Another way patients can develop Hemophilia A is called acquired Hemophilia since there is no genetic explanation for the deficiency in Factor VIII. For most, Hemophilia A is detected early at birth, due to prior genetic testing or through circumcision in males, which will present with prolonged bleeding. In other cases, especially with acquired Hemophilia cases and women, despite presenting with symptoms, may not be diagnosed for months or years. Individuals may come into the hospital complaining of unexplained bleeding episodes, bruising, or joint pain which should point the physician to test for Hemophilia; however, many physicians still retain the idea that women or people without a genetic basis, cannot develop Hemophilia but this thought is untrue. There are also multiple different kinds of Hemophilia, as well as differential diagnosis that may present in a similar nature to Hemophilia, but they are differentiated if a clotting factor that is not being produced by the patient's body, and what clotting factor is not being reproduced in the body. The physician will order numerous tests to show if the patient's blood shows a difficulty clotting, through the PT and APTT tests, as well as identifying what kind of clotting factors are missing. If the healthcare professional finds that the patient's blood takes longer to clot, and they are missing Factor VIII protein, then the patient has Hemophilia A. The next step is providing a treatment to prevent bleeding episodes. Common treatments include reintroducing the Factor VIII through medications like Emicizumab which is a imitator for Factor VIII, or DDAVP which stimulates an increased production of factor 8. Another treatment includes a fibrin sealant, which is commonly used for dental procedures, that promotes clotting to reduce bleeding after surgery. However, most of these treatments are temporary and individuals often develop inhibitors which decrease the effectiveness of treatment. One experimental treatment that shows promise is gene therapy, where a vector is used to insert the correct mRNA into cells to produce the correct factor 8 protein. This solves the problems of contamination of plasma, longevity, and effectiveness of treatment because this may completely cure the illness with one application. After making a treatment plan, physicians need to educate patients on how to live with the disorder which mainly emphasizes vigilance, in themselves or others affected, in identifying bleeding episodes to get early treatment. In all, the life expectancy of patients with Hemophilia A, as long as they receive treatment will live a normal life, but they may still present with complications like development of inhibitors, chronic joint pain/ deterioration, and living a very careful life, therefore, physicians need to research more into the disorder in order to provide a cure.

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