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# Historical and Current Management of Hemophilia: A Focus on Inhibitor Development and Treatment in Severe Hemophilia A

Julia Colling
*Augsburg University*

# Historical and Current Management of Hemophilia: A Focus on Inhibitor Development and Treatment in Severe Hemophilia A

Julia Colling, PA-S

Advisor: Skye Peltier, MPH, PA-C

**INTRODUCTION:**

Hemophilia is a congenital X-linked bleeding disorder that results from a deficiency of one of two coagulation factors. The majority of individuals with hemophilia are deficient in factor VIII (FVIII), known as hemophilia A. A smaller subset is deficient in factor IX (FIX), known as hemophilia B. Hemophilia A affects 1 in 5,000 male births, whereas hemophilia B affects 1 in 30,000 male births.[1] There is wide variation in disease severity amongst individuals with hemophilia. Approximately 60% are affected by the severe form, defined as factor levels of less than 1%. Another 15% are affected by the moderate form (factor levels of 1-5%), and the remaining 25% are affected by the mild form (factor levels of 6-30%).[2] Individuals with milder forms of hemophilia may only experience significant bleeding episodes following an injury or other external stimuli. Individuals with more severe forms experience spontaneous bleeding episodes, often into their joint spaces, known as hemarthrosis.[2] Hemarthrosis can progress to debilitating arthropathies, most commonly in the ankles, knees, and elbows.[3] However, bleeding does not only affect the joint spaces. Bleeding can occur in any tissue or organ, and although musculoskeletal bleeding is characteristic of hemophilia, epistaxis and bleeding of the mucus membranes is also common.[4]

**BACKGROUND:**

Although evidence of hemophilia exists in writings dating back to the second century AD, the first modern description is credited to American physician Dr. John Conrad Otto in 1803. Otto wrote of an inheritable bleeding disorder in which males were affected and transmission occurred via unaffected females.[5] For over one hundred years following Otto's description, the disorder continued to be studied by physicians all over the world. Many different theories regarding the pathophysiology of hemophilia were proposed and subsequently disproven. The year 1937 marked a turning point in our understanding of hemophilia. In 1937, Harvard physicians Arthur J. Patek and F.H.L. Taylor discovered that they could temporarily shorten coagulation times in patients with hemophilia by adding a substance extracted from plasma that they eventually called "anti-hemophilic globulin".[1, 2] In 1944, Alfredo Pavlovsky, a doctor in Buenos Aires, discovered that the blood from one individual with hemophilia could temporarily correct the coagulation defect of another individual with hemophilia. He had unintentionally stumbled upon two patients with different deficiencies, one with a FVIII deficiency, and the other with a FIX deficiency[1]. These deficiencies were later termed hemophilia A and hemophilia B, respectively. The culmination of these

discoveries, among others, led to our current pathophysiologic understanding of hemophilia and set the stage for research that would lead to hemophilia treatments.

Prior to the 1950s, the only treatment available for bleeding episodes in patients with hemophilia was whole blood transfusion. It wasn't until the late 1950s that hospitals and treatment centers began transfusing fresh frozen plasma. However, these products did not contain enough FVIII or FIX to stop severe bleeding, and most individuals with hemophilia died of internal hemorrhage in childhood or early adulthood.[1] By the end of 1960, the life expectancy for individuals with severe hemophilia was less than 20 years.[2] In 1965, Judith Graham Pool, a researcher at Stanford University, discovered that when bags of fresh frozen plasma were thawed slowly, an insoluble cryoprecipitate settled out of the solution.[1,5,6] This cryoprecipitate was subsequently found to contain the majority of the fibrinogen, factor VIII, factor XIII, von Willebrand factor (vWF), and fibronectin that was originally dispersed within the fresh frozen plasma.[7] This discovery revolutionized hemophilia treatment as it allowed for adequate amounts of factor to be infused in much smaller volumes. This led to an improved ability to control severe bleeding and made surgery a possibility for patients with hemophilia.[1] Not long after Pool's discovery, scientists began to isolate factor from cryoprecipitate using various fractionation and purification techniques. By 1970, freeze dried factor concentrates were made available for individuals with hemophilia, allowing them to self-infuse their factor products in the comfort of their own homes.[3,6]

Initially, the ability to mass-produce and infuse concentrated factor products offered individuals with hemophilia the promise of longer, higher quality lives. However, in the early 1980s, approximately ten years after the release of concentrated factor products, a frightening truth was brought to light. Due to nearly non-existent donor screening protocols and the pooling of plasma from thousands of donors, 60-70% of individuals that received factor products contracted the HIV virus. Furthermore, nearly 100% of them contracted the hepatitis C virus.[1] Thousands of patients died due to the complications of receiving contaminated factor products.[6] These products, which originally offered hope to so many individuals, destroyed lives, tore apart families, and sparked numerous controversies across the globe. In response to this horrific tragedy, donor screening protocols and viral inactivation techniques were developed.[1,5] In 1981, Haemate® P, the first pasteurized concentrate of FVIII/vWF, was introduced in Germany. The pasteurization method used in the manufacturing process of Haemate® P successfully inactivated both the HIV virus and the hepatitis C virus. Following the development of Haemate® P, various other inactivation techniques were successfully developed, including heat and solvent-detergent treatments. By the end of the 1980s, all factor products were produced using the aforementioned techniques.[5]

In addition to the development of inactivation techniques, the FVIII gene was successfully cloned for the first time in 1984, eventually leading to the development and licensure of recombinant human FVIII (rFVIII) in 1992.[3] Five years later, recombinant human FIX (rFIX) also became widely available for use.[2] These factor replacement products were not only completely safe from viral transmission, they also made factor products more widely available. Though originally pioneered decades earlier, using factor products for primary prophylaxis became much more of a common practice in the United States during the 1990s, likely due in large part to the newly established safety and availability of these products.[2,5] Today, primary prophylaxis is the standard of care for severe hemophilia in the United States, as well as in the majority of other developed countries. Primary prophylaxis largely prevents bleeding episodes and joint disease related to hemarthrosis.

Though the medical community should never seek to forget the thousands of lives affected by contaminated factor products, the issue of unsafe products is almost entirely ameliorated in the present day. With this behind us, the focus has shifted to other issues currently affecting the hemophilia community. Current concerns include increasing the availability of factor products in underdeveloped countries, increasing the half-life of our current factor products, treating hemophilia patients with inhibitors, and finally, finding a cure for hemophilia.[3] I will focus largely on inhibitor development in severe hemophilia A, including pathophysiology, proposed risk factors, and current available treatments.

**METHODS:**

In July of 2018, I spent seven days at a summer camp for children with hemophilia and other chronic bleeding disorders. Not only did I have the opportunity to learn from many experts in the field, I was also able to get a glimpse of the day to day management of hemophilia, as well as gain an understanding of how this disease has the potential to impact quality of life. The camp check-in process at the beginning of the week offered me my first glimpse into the daily lives of these patients. The campers arrived alongside their parents, wearing medical alert bracelets and carrying large boxes or coolers filled with factor products and/or other medications that they would undoubtedly need over the course of the week. One camper arrived in a wheelchair due to a recent joint bleed. Some others were unable to make it entirely due to recent severe bleeds or hospitalizations. Every morning, campers filed into the health center after breakfast for their prophylactic therapy, a practice that for many occurs triweekly. I observed young children, some no older than eight, learn self-infusion, a life-long skill that nearly all patients with severe hemophilia must

acquire. I was taken aback by the comradery amongst the campers, as well as the encouragement and mentorship they offered one another while learning self-infusion. However, despite regular prophylaxis, bleeding remains a concern. Many campers spent a lot of time in the health center, be it for their third nosebleed of the day, a hard fall from a game of capture the flag, or simply to rest and ice achy joints that had been previously damaged by hemarthrosis. Some campers were restricted from participating in more intense camp activities due to recent injuries or bleeds. Though at camp this may be a minor inconvenience, back at home, it may result in missed days at school or work. Furthermore, bleeds may result in significant arthropathies and permanent joint damage. It was humbling and inspiring to witness the bravery and adaptability of so many young people with hemophilia, and it was a joy to see how advancements in medicine have allowed these children to thrive at a level that was impossible in years prior. However, bleeding remains a common occurrence in many with hemophilia, and though none of the children at camp had inhibitors at the time (some had been successfully treated with ITI), one can imagine how this would have complicated things further.

To build upon the information I gained during this experience, I turned to the literature to learn more about the occurrence and treatment of inhibitors in severe hemophilia A. To find articles, I used the following resources: PubMed, Academic Search Premier, DynaMed, the New England Journal of Medicine, UpToDate, the National Hemophilia Foundation, and the European Association for Haemophilia and Allied Disorders. I included the following search terms: hemophilia, history of hemophilia, hemophilia treatments, hemophilia with inhibitors, neutralizing antibodies in hemophilia A, hemophilia A with inhibitors, severe hemophilia A, severe hemophilia A with inhibitors, risk factors for inhibitor development, treatment of inhibitors in hemophilia, recombinant factor eight products, plasma-derived factor eight products, factor eight inhibitor bypassing agents, and emicizumab.

## DISCUSSION:

### Inhibitor Development:

Inhibitors are FVIII-specific IgG alloantibodies that develop as a result of an immune response against infused FVIII. Once in the bloodstream, inhibitors bind to FVIII in such a way to disrupt the formation of the FVIII-FIX complex, thus inhibiting thrombin generation and preventing proper coagulation.[8] This complication renders FVIII replacement therapies ineffective and predisposes patients to an increased risk of morbidity and mortality. Inhibitor development is not only the most problematic complication facing

the world of hemophilia treatment today, it is also the most expensive.[9] The annual cost of treating hemophilia with inhibitors is more than three times greater than that of treating hemophilia without inhibitors. According to Guh et al., in the United States, hemophilia with inhibitors costs approximately $446,945 per patient annually, with some patients requiring more than $1,000,000 annually. Compare that to cost of hemophilia without inhibitors, which was found to be approximately $124,700 per patient annually.[10,11]

The immune response to infused FVIII involves both humoral and cell-mediated immunity. In short, FVIII is engulfed by antigen presenting cells (APCs) and FVIII-specific antigens are then presented on the major histocompatibility class II complexes (MHCII). The antigens are then detected by T-cell receptors on CD4+ helper T-cells, leading to their activation and proliferation into FVIII-specific effector and memory T cells. Simultaneously, the activated helper T-cells directly bind to B cells. This binding leads to further activation of the T-cells, resulting in the release of specific cytokines that are involved in upregulating the immune system and promoting B cell proliferation and differentiation into FVIII-specific effector and memory B cells. Furthermore, this binding provokes the release of FVIII-specific antibodies.[12] Specifically, these FVIII-specific antibodies are IgG alloantibodies that typically bind to either the A2 or C2 domain of FVIII and disrupt the formation of the FVIII-FIX complex, thus inhibiting thrombin generation.[8] After the initial immune response, the presence of FVIII specific memory T and memory B cells results in the hastening of subsequent immune responses against FVIII, a process known as anamnesis.

Though individuals with severe hemophilia A are the most likely subset to develop an inhibitor, the majority of these individuals are unaffected by this complication. Inhibitors develop in ~30% of patients with severe hemophilia A. In these patients, the onset of inhibitor development typically occurs within the first 50 days of exposure to FVIII. Conversely, in patients with non-severe hemophilia A that are only exposed to FVIII intermittently, the incidence of inhibitor development increases with each subsequent exposure, with the incidence reaching >15% after >125 exposures.[13] The reason that an immune response occurs in some individuals as opposed to others is largely misunderstood. Countless studies have found that the development of inhibitors is multifactorial, with both genetic (non-modifiable) and environmental (modifiable) risk factors involved. Well established risk factors for inhibitor development include the severity of hemophilia, intensity of early FVIII exposure, concurrent immune system activation/environmental stressor (trauma, surgery, vaccination, infection, etc.), family history of inhibitors, and use of on-demand therapy over prophylactic therapy.[4,8] Perhaps the two most prominent risk factors for inhibitor development include patient genetics and the type of FVIII product used.

Hemophilia A, by definition, is a genetic disease involving mutation(s) of the factor VIII gene. However, there is wide variation amongst individuals regarding the type(s) of mutations present. Interestingly, one of the largest predictors of inhibitor development is the genetic profile of the patient.[14] Overall, the presence of large insertions/deletions spanning more than one domain and nonsense mutations of the light chain are associated with the highest risk of inhibitor development. Mutations of intermediate risk include large insertion/deletions spanning a single domain, nonsense mutations of the heavy chain, intron-22 inversion, and intron-1 inversions. Mutations with lesser risk of inhibitor development include small insertions/deletions, missense mutations, and splice site mutations.[12]

Whether or not the use of recombinant FVIII products (rFVIII) as opposed to plasma-derived factor VIII products (pFVIII) increases the chance of inhibitor development has been widely debated. Ex vivo studies have demonstrated that von Willebrand factor (vWF), which is present in pFVIII but not in rFVIII, does play a protective role against inhibitor development. The proposed mechanism being that vWF is involved in the prevention of the endocytosis of FVIII by dendritic cells and the uptake of FVIII by antigen presenting cells. Furthermore, vWF competes with a subset of inhibitors for binding sites on the C2 domain of FVIII.[3] Despite these ex vivo studies, multiple observational and retrospective studies have failed to find an increased risk of inhibitor development with the use of rFVIII. Recently, a study intended to settle this ongoing debate was designed. The Survey of Inhibitors in Plasma-Products Exposed Toddlers (SIPPET) was the first randomized clinical trial that compared plasma-derived and recombinant factor products. The SIPPET trial included patients with severe hemophilia A under the age of 6 that were previously untreated with any FVIII products. The previously untreated patients (PUPs) were divided into two groups: 125 patients received pFVIII, and 126 patients received rFVIII. Both groups were then followed and monitored for inhibitor development. Of the 125 patients in the pFVIII group, 26.8% developed inhibitors within fifty days of exposure. Of the 126 patients in the rFVIII group, 44.5% developed inhibitors within fifty days of exposure. The authors concluded that the rFVIII group had an 87% higher risk of inhibitor development than the pFVIII group.[15] Despite the authors' conclusions, several factors must be taken into consideration. First, the recombinant factor products used in this trial were all produced from hamster-cell cultures. This is not representative of all of the current recombinant factor products available, such as those produced from human embryonic kidney cells (HEK) or those with extended half-lives.[15,16] Second, because the trial only included PUPs with less than fifty days of exposure to FVIII, its results may not apply to those who have already been exposed to FVIII for more than fifty days.[16] Finally, despite the lower incidence of inhibitor development in the pFVIII group, 26.8% of these patients still developed inhibitors, suggesting that other

factors must be at play.

Current Treatment Options:

The most widely used tool for quantifying inhibitors is the Bethesda Assay. Using this tool, inhibitor titers are measured in Bethesda Units (BU) per milliliter. One BU is defined as the amount of plasma inhibitor per milliliter that results in 50% residual Factor VIII activity. Patients with titers of <5 BU are considered to have low titer inhibitors, whereas patients with titers of ≥5 BU are considered to have high titer inhibitors. Generally speaking, high titer inhibitors are increasingly difficult to treat.[17]

Immune tolerance induction (ITI) is considered the standard of care for hemophilia patients with inhibitors. ITI involves frequent exposures to high dose FVIII over several months to years. This is done in an effort to induce tolerance via the proposed mechanisms of T-cell overstimulation and exhaustion, inhibition of FVIII specific B memory cells, and the formation of anti-idiotypic antibodies.[17] If ITI is successful, patients are able to resume the use of standard FVIII products, thus reducing costs and decreasing morbidity and mortality. The success rate of ITI is approximately 59-86% in patients with severe hemophilia A with an inhibitor.[3] Much like vFW may play a role in preventing inhibitor development, it has been suggested that it may also play a role in increasing the success rate of ITI. However, studies investigating whether or not the use of pfVIII as opposed to rfVIII in ITI increases the likelihood of successful eradication of the inhibitor are largely inconclusive at this time.[1]

For the subset of patients in which ITI is unsuccessful, the inhibitor remains, and alternative treatments will likely be needed to achieve hemostasis. Congenital hemophilia patients can typically achieve hemostasis when FVIII levels reach 10-15% of what is considered normal in healthy populations. Though seemingly a small percentage, it is nearly impossible to achieve in patients with high alloantibody titers (≥5 BU).[8] Thus, these patients may require bypassing agents, either as prophylaxis or on-demand therapy. Two bypassing agents are available, both of which have similar efficacies overall. However, patients respond to each agent on an individual basis, and therefore failure of one agent warrants trial of another. Factor Eight Inhibitor Bypassing Agent (FEIBA) contains plasma-derived FII (prothrombin), FIX, FX, & FVIIa. It works primarily as an activated prothrombin concentrate (aPCC) that negates the requirement for FVIII in achieving hemostasis.[8] However, FEIBA holds a potential risk for anamnesis of the inhibitor due to trace amounts of FVIII that may still be present in this plasma-derived product. Furthermore, FEIBA requires large infusion volumes.[4,17] Another option is Recombinant Factor VIIa (rFVII) (NovoSeven®). Activated FVII has the ability to directly activate platelet-bound FX, which itself is a

hemostatic agent. Because it is a recombinant agent, rFVIIa does not pose any risk of anamnesis. However, due to its short half-life, treatment with rFVIIa may require frequent infusions to achieve hemostasis, sometimes up to every 2 hours.[4] A disadvantage of both FEIBA and rFVIIa is the absence of reliable biomarkers to correlate with therapeutic dosing or treatment efficacy. This poses a number of risks, including the risk of thrombosis.[17]

The newest drug on the scene, emicizumab (HEMLIBRA®), was approved for use in late 2017. Emicizumab is a recombinant, humanized bispecific monoclonal antibody. It functions by binding FIX and factor X on a phospholipid membrane, therefore eliminating the need for the cofactor function of FVIII. Because emicizumab and FVIII are structurally dissimilar, emicizumab is not neutralized by inhibitors or acted on by physiologic regulatory proteins.[4,18] The initial phase III study of emicizumab included patients with inhibitors using bypassing agents for either primary prophylaxis or on-demand therapy. Following weekly subcutaneous injections of emicizumab, the study demonstrated a 79% bleed reduction for patients previously on bypassing agent prophylaxis, and an 87% bleed reduction for patients previously using bypassing agents for on-demand therapy.[18] Despite these efficacious results, there still exists some major concerns regarding the drug. Due to its binding characteristics, any amount of emicizumab in the plasma, even small nontherapeutic levels, will correct the activated partial thromboplastin time (aPTT). This renders the aPTT an inaccurate monitoring tool. Furthermore, it renders all assays based upon the aPTT, such as the Bethesda assay, inaccurate as well.[4] Without accurate tools of measure, monitoring efficacy and determining therapeutic dosing becomes increasingly difficult. Furthermore, four serious adverse events of thrombosis have occurred with emicizumab use. These include 2 cases of microangiopathy, 1 case of cavernous sinus thrombosis, and 1 case of skin necrosis-superficial thrombophlebitis. However, all of these events occurred when emicizumab was used in combination with multiple infusions of aPCC. Both cases of microangiopathy resolved after aPCC was stopped and neither required anticoagulation.[18]

**CONCLUSION**:

Reflecting on the history of hemophilia and the progression of hemophilia treatment, it is difficult to imagine that only sixty years ago, whole blood transfusion was the only treatment available, and the life expectancy of individuals with hemophilia was under twenty years. It is almost more difficult to believe that just over forty years ago, the tragedy of contaminated blood products was brought to light, and that many of the individuals that received those blood products are still affected today. Fortunately, the safety and

efficacy of factor products in the present day has given individuals with the disease a life expectancy similar to that of healthy unaffected individuals. Unfortunately, as hemophilia treatments have evolved, so too has the disease. The development of inhibitors remains the most challenging and expensive complication in the treatment of hemophilia today.

Moving forward, further research involving the prevention of inhibitor development is essential. Though evidence suggests that plasma-derived products may be less immunogenic, there simply is not enough availability of these products to treat all individuals with hemophilia. However, given the current evidence, providers can take steps to identify high risk individuals, and tailor treatments accordingly. Patients with high risk genetic defects and/or other multiple non-modifiable risk factors should be considered candidates for plasma-derived products. In addition, the research surrounding pFVIII and rFVIII products should be shared with patients and families, thus allowing them to make informed decisions.

For individuals with established inhibitors, immune tolerance induction should remain first line management due to its high potential to eradicate the inhibitor completely, thus reducing costs and improving morbidity and mortality. Furthermore, it allows for the preservation of the role of FVIII within the body, which may do more than science has yet discovered.

Though immune tolerance induction is effective in the majority of inhibitor patients, it does not eradicate all inhibitors. For that reason, research surrounding bypassing agents and novel agents such as emicizumab must continue. Though current research has demonstrated high efficacy amongst these products, they are expensive and not without safety concerns. Furthermore, there are no reliable biomarkers by which to monitor and dose these medications.

Despite numerous recent advancements, medicine has not yet been able to achieve hemostasis with the use of exogenous products in a completely safe and effective manner. Though we may never be able to master the intricacies of this complex mechanism, given what is at stake, it is important that this effort continues.

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