Transitioning of Care from Pediatric to Adult Providers Among Hemophilia Patients

by

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Abstract

Background: Individuals with hemophilia require lifelong specialized care. As the lifespan for individuals with hemophilia has increased, patients must transition from pediatric to adult providers. Research has shown that individuals with hemophilia face multiple barriers during this transition of care and have decreased prophylaxis regimen compliance which can have lifelong negative effects. In this study, we seek to determine the impact of transition of care on hemophilia patients who receive treatment at the Hemophilia Center of Western Pennsylvania (HCWP).

Methods: The medical records of a cohort of patients at the HCWP, aged 26 to 30, were reviewed from age 15 to their current age. Information was gathered about comprehensive visit compliance, bleeding events, and insurance coverage. Statistical analyses were performed using linear regression and summary statistics.

Results: 26 patients with hemophilia who were treated at the HCWP were included in this study. Statistical analysis did not provide evidence to suggest that there is a linear relationship between age and comprehensive visit compliance or age and bleeding events. 42.3% of the participants had at least one confirmed lapse in insurance during the time period studied.

Conclusions: The transition from pediatric to adult care providers in patients with hemophilia, treated at the HCWP, did not have an impact on comprehensive visit compliance or bleeding.

Lapses in health insurance coverage are a common problem for individuals with hemophilia after age 18. Further research is needed to determine effective interventions to increase comprehensive visit compliance at all ages and interventions to increase health insurance coverage of adults.

Public Health Significance: Comprehensive visit compliance is important for monitoring the health and treatment of individuals with hemophilia and helps to reduce healthcare costs.

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1.0 Introduction

The lifespan of individuals with hemophilia has greatly increased since the 1950s which has led to the need for comprehensive care of adults with this condition. This has created the need to transition patients from seeing pediatric specialists to adult specialists as they reach adulthood. The American Academy of Pediatrics policy statement, *A Consensus Statement on Health Care Transitions for Young Adults With Special Health Care Needs*, states that "the goal of transition in health care for young adults with special health care needs is to maximize lifelong functioning and potential through the provision of high-quality, developmentally appropriate health care services that continue uninterrupted as the individual moves from adolescence to adulthood."[1] This transition of care can be difficult for patients as it comes at a time of numerous life changes and the patient must take responsibility for his healthcare. Studies have shown that a difficult transition can result in decreased compliance and decline in quality of life and/or overall health for adolescents with chronic illness.[2] To try and address this transition for patients with hemophilia, the National Hemophilia Foundation published the *Transition Guidelines for People with Bleeding Disorders* in 2003. This document was developed to be used at Hemophilia Treatment Centers to help individuals with a bleeding disorder through many types of transitions including "acceptance of the bleeding disorder, self-care, progressing though school, vocational/career planning, moving to an adult center, starting a family, middle age and retirement."[2]

While there have been guidelines published outlining the transition of care in individuals with hemophilia, little research has been done to evaluate how patients are impacted by this transition. This study aims to examine the impact of this transition on patients with hemophilia who receive treatment at the Hemophilia Center of Western Pennsylvania (HCWP). We

investigated how this transition impacts patient care by studying their rates of bleeds, insurance coverage, and attendance at clinic before, during, and after this transition. We hypothesized that individuals will be negatively impacted by transitioning from pediatric to adult care. This study aimed to identify where efforts should be focused to improve the transition for patients with hemophilia as they reach adulthood. The specific aims of the study were to:

- Determine if there is a difference in rates of acute bleeding events in patients with hemophilia A or hemophilia B before, during, and after transitioning from pediatric to adult care providers
- Determine if there is a difference in attendance rates at clinic visits in patient with hemophilia A or hemophilia B before, during, and after transitioning from pediatric to adult care providers
- Characterize lapses in insurance coverage in patients with hemophilia A or hemophilia B before, during, and after transitioning from pediatric to adult care providers

This study was carried out by reviewing the electronic medical records of males age 26-30, diagnosed with hemophilia A or hemophilia B, who received treatment at the HCWP. We retrospectively examined medical records to record the number of acute bleeding events, annual comprehensive clinic attendance, and insurance coverage for before, during, and after transitioning from pediatric to adult care. We also collected additional information from the medical record including race, ethnicity, hemophilia type, hospitalizations, treatment, inhibitor development, and joint disease for use during statistical analysis.

2.0 Literature Review

2.1 Overview of Hemophilia

Hemophilia is an X-linked inherited coagulation disorder that is caused by pathogenic variants in clotting factor genes. Individuals with hemophilia A have pathogenic variants in the *F8* gene, which is responsible for making Factor VIII. Individuals with hemophilia B have pathogenic variants in the *F9* gene, which is responsible for making Factor IX. Hemophilia A prevalence in the United States is estimated at 1:6,500 live births.[3] The prevalence of hemophilia B is estimated at 1:30,000 live births, thus making hemophilia A about five times more prevalent than hemophilia B.[4] It is estimated that there are 20,000 individuals living with hemophilia in the United States.[5]

Hemophilia severity is classified by the measured factor concentration in the blood. Severe hemophilia is defined as <1% of normal factor concentration. Individuals with severe hemophilia typically have spontaneous bleeding into muscles and joints without an identifiable cause. Moderate hemophilia is defined as 1-5% of normal factor concentration. Individuals with moderate hemophilia typically have prolonged bleeding with minor trauma or surgery and occasional spontaneous bleeding. Mild hemophilia is defined as 5-<40% of normal factor concentration. Individuals with mild hemophilia rarely have spontaneous bleeding but have severe bleeding with major trauma or surgery.[6; 7]

Since hemophilia A and B are X-linked disorders, they typically affect males, while females are carriers. The expected mean clotting factor level in a female hemophilia carrier is 50% of the healthy population clotting factor level. Most female carriers are asymptomatic. Female carriers who have clotting factor levels that are 40-60% of the expected man clotting factor level

may have an increased bleeding tendency.[8] Approximately 30% of carrier females have clotting factor levels <40% which fall into the hemophilia range and may be symptomatic.[9; 10] In rare cases of significant non-random x-inactivation, carrier females may present with moderate to severe hemophilia.[8] There are also rare cases where females are compound heterozygotes and can present with any severity of hemophilia. Females who are found to have low clotting factor levels, and are symptomatic, should be characterized as having hemophilia and should be treated accordingly.[7]

2.1.1 Historical Overview

The history of hemophilia goes back to ancient times. The Talmud, a book of Jewish teachings from the second century AD, has the first mention of hemophilia. It states that boys who have had two brothers die from prolonged bleeding after circumcision should not be circumcised. Albucasis, a 12th century Arabic physician, was the first medical professional to describe a family whose males died from bleeding after minor injury.[11]

The first modern description of hemophilia was written by Philadelphian physician John Conrad Otto in 1803. He published "an account of an hemorrhagic disposition existing in certain families," but he did not yet use the term hemophilia.[12] He recognized many of the cardinal features of the disorder including that it was hereditary, affected mostly males, and was passed through a family by healthy females.[12] The term "haemophilia" first appeared in 1828 when Freidrish Hopff from the University of Zurich published an essay on the disease.[11]

Hemophilia is sometimes referred to as "the royal disease" due to its history of being found in European royalty. The Queen of England from 1837 to 1901, Queen Victoria, was a hemophilia B carrier.[13] Leopold, Queen Victoria's son, had the disease and had frequent hemorrhages.

Hemophilia B was passed on to the Russian, Spanish, and German royal families, by Queen Victoria's daughters, Alice and Beatrice.[14]

The cause of hemophilia was not found until the late 1930s. The original theory was that the bleeding tendency in hemophilia was due to fragile blood vessels and platelets were thought to be a likely cause. In 1937, scientists at Harvard, Patek and Taylor, discovered anti-hemophilia globulin, a substance that could be extracted from plasma which could correct the coagulation defect in hemophilia. Another big breakthrough came from the scientist Pavlosky from Buenos Aires in 1944. He discovered that hemophilia was two separate diseases, hemophilia A and B. He found that transferring blood from one hemophilia patient, to another hemophilia patient, would correct the coagulation defect after he happened upon patients with different factor deficiencies. Both of these discoveries would be fundamental in the future diagnosis and treatment of hemophilia.[15]

In the 1950s and 1960s, hemophilia was treated with whole blood or fresh plasma transfusions. These transfusions did not contain enough factor VIII or factor IX to stop severe bleeding. Since severe bleeding still occurred, those with severe hemophilia died in childhood or early adulthood.[15] This lifespan was an improvement from before treatment with transfusion, as previously children with hemophilia rarely survived past the first decade.[16] In 1964, Judith Pool discovered that the fraction cryoprecipitated from plasma contained large amounts of factor VIII.[17] This cryoprecipitate revolutionized treatment for hemophilia. Treatment with rather small volumes, could now control severe bleeding and allow hemostatic control for major surgeries.[15]

Even after this discovery, modern management of hemophilia did not begin until the 1970s. The 1970s saw the "increased availability of lyophilized plasma concentrates of coagulation factors and the widespread adoption of home replacement therapy which led to the early control

of hemorrhages and the reduction of musculoskeletal damage typical of untreated or poorly treated patients."[15] Also, Sweden began the use of primary prophylaxis, with the goal of preventing bleeding episodes and reducing the impact of arthropathy.[18] As the need for emergency treatment lessened, hemophilia treatment centers began to focus more on comprehensive care from a multidisciplinary team. Patients began to more frequently have elective surgeries, most commonly orthopedic operations to correct musculoskeletal abnormalities from poorly treated bleeds. In 1977, the drug desmopressin was discovered as a treatment for mild hemophilia A. This treatment helped reduce the need for plasma-derived products and lowered treatment costs for patients with mild hemophilia A.[19]

Unfortunately, the "golden age" of hemophilia treatment of the 1970s came to an end in the early 1980s. During this time, 60-70% of individuals with severe hemophilia became infected with human immunodeficiency virus (HIV) because factor concentrates, generated from pooled plasma derived from thousands of individuals, were contaminated with the virus. For the same reason, during this time, almost all patients with hemophilia were infected with hepatitis C if they received factor concentrates.[20] Plasma from thousands of donors was used to manufacture factor concentrates, and there was no screening or viral inactivation of donated blood products in place. Many individuals suffered from sequelae of these infections and there was a great need for the safe treatment of hemophilia. To control the spread of infection, viral inactivation techniques were developed and implemented in plasma-derived factor concentrate production. Additionally, there were methods adopted, such as nucleic acid testing, to screen blood donation for viruses. As a result of these changes, there has not been transmission of HIV or hepatitis viruses in plasma-derived factor concentrates since the late 1980s; however the fear of possible transmission of new or unknown pathogens in blood products remains.[15]

While the hemophilia community was suffering the devastating impacts of these blood-borne infections, great scientific advancements were made for hemophilia treatment. In 1982, the *F9* gene was cloned for the first time. Cloning of the *F8* gene came soon after in 1984. The cloning of these genes allowed for the industrial production of recombinant factor VIII and IX.[21] The first report of clinical efficacy of recombinant factor in two hemophilia A patients was published in 1989.[22] Recombinant factor went on to become widely used to treat patients with hemophilia. Steps have also been taken during manufacturing to increase the safety of recombinant factor products through improved protein purification, avoidance of all human or animal proteins, and additional viral inactivation.[23]

The widespread availability of safe factor replacements and implementation of prophylactic treatment of patients with hemophilia has enabled patients to maintain near normal lifestyles.[24] Additionally, great progress has been made in the treatment of blood-borne viral infections such as antiretroviral treatment for HIV and combined ribavirin and α-interferon treatment for hepatitis C. All of this together has helped the hemophilia population by reducing morbidity and improving quality of life.[25] The life expectancy of individuals with hemophilia, without viral infection, has greatly increased and is expected to be similar to that of the general population.[26]

2.1.2 Molecular Genetics

Hemophilia A is caused by pathogenic variants in the *F8* gene located at Xq28. The *F8* gene is 186 kb long and has 26 exons.[27] About 43-45% of individuals with severe hemophilia A have an intron 22 inversion in *F8*. About 2-5% of individuals with severe hemophilia A are found to have an intron 1 inversion.[28] Almost all nonsense and frameshift pathogenic variants cause a

severe hemophilia A phenotype. Splice site variants most commonly result in a severe hemophilia A phenotype but can also be found in individuals with moderate or mild disease. Less than 20% of individuals with severe hemophilia A have a missense mutation while missense mutations are found in almost all cases of mild or moderate hemophilia A.[9] It is estimated that about 60% of individuals with hemophilia A have a family history of the disease and the other 40% are sporadic cases. Of the sporadic cases, 90% of the mutations occurred in the affected individual's parents or grandparents.[29] In about 5% of cases of hemophilia A, a pathogenic variant cannot be identified in the *F8* gene.[30]

Hemophilia B is caused by mutations in the *F9* gene located at Xq27. The *F9* gene spans 34 kb and has 8 exons.[31] Over 1,000 mutations have been identified in *F9* to cause hemophilia B. Over 70% of the reported pathogenic variants are point mutations and 16% are deletions. The remaining reported mutations are duplications, insertions, and combinations of insertions and deletions.[32; 33] There have also been a few reports of large rearrangements in *F9* that cause hemophilia B.[34] Nonsense mutations, large deletions, and most frameshift mutations usually cause severe hemophilia B. Missense mutations can result in mild, moderate, or severe disease depending on the location of the specific nucleotide substitution.[35] Some mutations that cause mild disease, such as c.1025C>T, have unusually high frequencies in certain populations, such as the Amish, due to the founder effect. It is estimated that 20-30% of cases of mild hemophilia B are due to founder effect mutations.[36] It is estimated that up to 50% of cases of hemophilia Bare *de novo*, and the individual has no family history of disease.[10] In families with sporadic hemophilia, 10% of cases are cause by somatic mosaicism. This can be difficult to detect and makes it hard to determine recurrence risks for a family.[37]

There is a rare subtype of hemophilia B called hemophilia B Leyden. Individuals present as hemophilia B in childhood, with low levels of Factor IX. After puberty their Factor IX levels begin to rise, and they often become asymptomatic.[38] This rise in Factor IX activity is associated with increased androgen receptor and growth-factor activity.[39] Point mutations in the promoter of *F9* cause Hemophilia B Leyden.[40] As of 2013, more than 80 families have been identified to be affected by hemophilia B Leyden.[41]

An individual's genotype can help determine their risk of inhibitor development. Individuals who have molecular defects that result in the complete absence of factor protein (i.e. large deletions, inversions, and nonsense mutations) have a higher likelihood to develop inhibitor than those who have a molecular defect that has some residual factor protein present (i.e. missense and splice site mutations).[42] Individuals with an inversion of intron 22 in F8, the most common mutation that causes severe hemophilia A, are known to have a 20-30% risk of developing inhibitors.[9] Individuals with a complete deletion of *F9* are at a 50% risk of developing inhibitors while those with frame shift or nonsense mutations in *F9* have a 20% risk.[43] For those with missense mutations in *F9*, the risk for inhibitor development is almost zero.[6]

2.2 Care for Individuals with Hemophilia

2.2.1 Comprehensive Hemophilia Treatment Centers

In 1975, the United States Congress established funding to create a national network of Hemophilia Diagnostic and Treatment Centers.[44] Each of these centers had a blood bank, a coagulation laboratory, and a multidisciplinary hemophilia treatment team.[45] There are currently

141 federally funded hemophilia treatment centers (HTCs) across the United States that have expanded to provide comprehensive care to individuals with many different inherited bleeding disorders, including hemophilia. HTCs in the United States are separated into eight geographic regions: MidAtlantic, New England, Great Lakes, Southeast, Northern States, Mountain States, Great Plains, and Western States. HTCs provide physical, emotional, psychological, educational, financial, and vocational support to their patients. The diverse care team at a HTC typically includes "hematologists, pediatricians, nurses, social workers, physical therapists, orthopedists, and dentists."[46] HTCs fulfill the American Academy of Pediatrics recommendations that children with special health care needs should have a medical home which is defined as care that is "accessible, continuous, comprehensive, family centered, coordinated, and compassionate."[47]

The Hemophilia Center of Western Pennsylvania (HCWP) is a state and federally funded HTC. HCWP is one of the sixteen HTCs that are located in the MidAtlantic region. It is one of the first established in 1975, after receiving federal funding. In 2001, HCWP established a clotting factor program through the federal 340B Drug Pricing Program. Through this program, clotting factor is purchased at a discounted Public Service rate and then used to fulfill patient factor prescriptions. The revenue generated from this program goes to support patient care and has allowed HCWP to expand its comprehensive care services.[48] The care team at HCWP consists of pediatric and adult hematologists, nurses, social workers, a physical therapist, and a genetic counselor. Dr. Margaret Ragni has been a director of HCWP since 1988.[49]

The HCWP has also actively participated in research since it was established. The center has a wide range of research endeavors available, from observational studies to NIH and pharmaceutical-sponsored drug trials and gene therapy studies.[50]

Patients who receive care at HCWP are recommended to have a yearly comprehensive evaluation where they are seen by members of the care team. This visit typically includes meeting with a hematologist, nurse, physical therapist, social worker, and insurance specialist. The appointment typically consists of a review of medical history, current medications, and upcoming elective surgical procedures. A physical exam is performed along with laboratory studies, and an assessment of thrombotic events and associated complications. Patients are also evaluated by the physical therapist and speak with the social worker and insurance specialist.[51]

2.2.2 Prevention, Management, and Treatment

Physical activity is encouraged in individuals with hemophilia, but with some restrictions. Non-contact sports are encouraged while high contact and collision sports should be avoided due to the risk of life-threatening bleeding that can be associated with injuries. During physical activity, target joints, or joints that experience frequent bleeding, should be protected with braces or splints. Individuals that chose to participate in physical activities that carry a higher risk of injury should prophylactically administer clotting factor prior to the activity.[7]

The goal of treatment for hemophilia is to replace the missing clotting protein to prevent bleeds and in turn prevent long-term complications associated with hemophilia. Clotting factors come in two different types: plasma-derived and recombinant. Plasma-derived factor is derived from human plasma from human blood donations. Human blood carries a risk of transmitting infectious viruses such as hepatitis and HIV. Recombinant factor is artificially created in a lab and does not contain components derived from human blood, and therefore does not carry the same infectious risks.

There are a number of recombinant forms of factor VIII that have FDA approval to treat hemophilia A. These include Helixate, Reombinate, Kogenate, Advate, ReFacto, Elocate, and Xyntha. There are four plasma-derived factor VIII products available for the treatment of hemophilia A which are Monarc-M, Monoclate-P, Hemofil, and Koate-DVI.

In 2017, the FDA approved Hemlibra (Emicizumab-KXWH), a bispecific antibody, for the treatment of hemophilia A. This medication is unique in its mechanism and that it is approved for the treatment of individuals with inhibitors. Hemlibra mimics factor VIII by binding to both activated factor IX and factor X which helps the blood to clot normally. Hemlibra prophylaxis safety and efficacy was evaluated in the HAVEN 1 trial. This was a Phase 3, open-label, multicenter, randomized trial that included 109 patients with hemophilia A who had inhibitors. In this trial, patients who received Hemlibra prophylaxis had an 87% reduction in annual bleed rate compared to those only given on-demand bypassing agents.[52]

Individuals with mild hemophilia A also have the option of being treated with desmopressin (DDAVP) or antifibrinolytics (aminocaproic acid or tranexamic acid). DDAVP is a synthetic agent that is a derivative of vasopressin. This medication works by raising the level of factor VIII in the plasma and stopping bleeding. DDAVP can be administered via IV or nasal spray. Antifibrinolytics are medications that work by slowing clotting factor breakdown in the blood.

There are also a number of recombinant forms of factor IX that have FDA approval for the treatment of hemophilia B. These include BeneFIX, Rixubis, Ixinity, Alprolix, Idelvion, and Rebinyn. AlphaNine SD and Mononine are the two factor IX plasma-derived concentrates currently on the market.

There are two main categories of factor replacement, episodic and prophylactic. Episodic, or "on demand" treatment, means that an individual only treats with factor replacement when there is clinically evident bleeding.[7] Episodic treatment requires skill to evaluate the symptoms of a bleed and treat in a timely fashion.[53] Prophylactic treatment means an individual treats with factor replacement on a consistent schedule to prevent anticipated bleeding.[7] Prophylactic treatment can reduce the anxiety and alarm around physical trauma but this treatment regime carries ongoing psychological and organizational burdens.[53] Prophylaxis has been shown to prevent bleeds and joint destruction which is important to preserve musculoskeletal function. Prophylactic treatment is useful in patients whose factor levels are less than 1 IU/dl (1%).[7] There are no clear recommendations regarding how long patients should remain on prophylactic treatment.[54]

Home therapy for patients with hemophilia is preferred. Home therapy allows for individuals to treat bleeds immediately which results in decreased dysfunction, pain, and long-term disability.[55] Home therapy also improves quality of life by giving individuals the flexibility to participate in physical activities and travel. Individuals who treat at home also miss less days of school/work and have greater employment stability.[56] Home therapy needs to be done under the supervision of a comprehensive care team and can begin once an individual, and family, has been educated and trained about the treatment.[57] Home therapy can even be initiated in young children as long as there is adequate venous access and trained family members. Some young children require an implanted venous access device to make administering treatment feasible.[58]

2.2.3 Complications of Hemophilia

A number of complications can occur in patients with hemophilia, especially in those not receiving adequate treatment. Repeated bleeding into joints with inadequate treatment can lead to

loss of function from muscle atrophy, loss of motion, joint deformity, pain, and contractures in the first or second decade of life.[59] Chronic hemophilic arthropathy is the name used for this joint deterioration. This "process is set in motion by the immediate effects of blood on the articular cartilage during hemarthrosis and reinforced by persistent chronic synovitis and recurrent hemarthroses, resulting in irreversible damage."[7] With advancing cartilage loss, chronic hemophilic arthropathy leads to the development of muscle atrophy, angular deformities, and secondary soft tissue contractures. Chronic hemophilic arthropathy can be extremely painful and often requires ongoing treatment. The treatment used for chronic hemophilic arthropathy depends on the individual's symptoms and stage of the condition. Typically, conservative techniques such as bracing, mobility, aids, and physiotherapy are used to manage the condition first. If conservative management techniques fail, surgical intervention may be needed.[7]

Another musculoskeletal complication in hemophilia is synovitis. Synovitis is when the synovium of a joint becomes inflamed, hyperemic, and extremely friable after acute hemarthrosis. If acute synovitis is not treated, then it can result in repeated joint bleeds.[59] A musculoskeletal complication that is unique to hemophilia is the development of pseudotumors which can be limb and life-threatening. Pseudotumors develop from an inadequately treated soft tissue bleed, typically in muscle adjacent to bone. If untreated, pseudotumors can grow very large, put pressure on adjacent neurovascular structures, cause fractures, and lead to the development of a fistula through the overlying skin.[7]

In the current treatment era, the most severe treatment-related complication is inhibitor development in individuals with hemophilia.[7] Inhibitors refers to IgG antibodies that neutralize clotting factors. Inhibitors cause treatment with replacement factor to be impossible because the inhibitory antibody blocks and clears the infused factor. Thus, it is recommended that all

individuals be screened for the presence of inhibitors.[7] Development of inhibitors is more common in hemophilia A compared to hemophilia B. Approximately 20-30% of individuals with severe hemophilia A and 5-10% of individuals with mild or moderate hemophilia A will develop inhibitors in their lifetime.[60] Comparatively, less than 5% of individual with hemophilia B develop inhibitors in their lifetime.[6] It is important to note that up to 50% of individuals with hemophilia B and inhibitors have severe allergic reactions, including anaphylaxis, when factor IX is administered. Due to this complication, individuals with hemophilia B should be given factor IX concentrates in a clinic or hospital setting for their first 10-20 treatments in case of an allergic reaction.[61] Inhibitors in individuals with severe hemophilia A can be eradicated using immune tolerance induction therapy. Experience with this therapy is limited in hemophilia B and can cause other complications so immunosuppressive therapies can be considered in these individuals.[62; 63]

Another complication of hemophilia, albeit more historically, is risk of contracting transfusion-transmitted infections. Before the availability of recombinant factor, plasma-derived factor was widely used, which carries the risk of infection. Many individuals with hemophilia contracted HIV and/or a form of hepatitis by receiving plasma-derived clotting factor. Individuals that contract one of these infections also have to deal with the complications associated with these viruses and require special treatments.

2.3 Transition of Care From Pediatric to Adult Care Providers

Health care transition is defined as the of changing from a pediatric to adult health care model care. In recent years, this transition of care has become a significant issue due to an aging population. Over 90% of individuals with severe disabilities are now living into adulthood and

need continuation of appropriate healthcare services, which are often more complex.[64] Health care transition has been a growing area of research and a number of policy statements have been published that address how it should be performed.

In 2002, the American Academy of Family Physicians, American Academy of Pediatrics, and American College of Physicians-American Society of Internal Medicine published a joint policy statement about the transition of care for young adults with chronic health conditions. This outlined that "the goal of transition in health care for young adults with special health care needs is to maximize lifelong functioning and potential through the provision of high-quality, developmentally appropriate health care services that continue uninterrupted as the individual moves from adolescence to adulthood."[1] The organizations supporting this statement wanted all primary care and subspecialty physicians who work with young adults with special health care needs to have a better understanding of transition. Specifically they wanted physicians to "1) understand the rationale for transition from child-oriented to adult oriented health care; 2) have the knowledge and skills to facilitate the process; and 3) know if, how, and when transfer of care is indicated."[1] The statement emphasizes the importance that individuals receive developmentally appropriate care from a physician trained in the medical care of adults.

The statement also goes on to detail six steps to ensure the transition to adult-oriented health care is successful for this patient population. The first step indicates that all patients should have an identified health care professional that can assume responsibility for their health care as they reach adulthood. The next step is that physicians and medical residents receive training on how to "provide developmentally appropriate health care transition services to young people with special health care needs."[1] The third step addresses the development of a medical summary that is up-to-date for each patient that can provide a knowledge base for all health care professionals

involved in a patient's care. Next, a written health care transition plan should be created with the patient and family that details what health care services are needed, who will provide the services, and how the services will be paid for. There should be a minimum of annual plan updates. The fifth step outlines that all patients with special health care needs should be cared for following the same guidelines for primary and preventative care that are used for all adolescents and young adults, but it should be recognized that these individuals may need more resources and services. The final step indicates that continuous health care coverage should be ensured throughout adolescence and adulthood.[1]

In 2011, the same organizations updated their policy statement about transition, and expanded it to include youth without special health concerns.[65] Shortly after, the "Six Core Elements of Health Care Transition" was developed as a structured process that can be customized to different situations and applied to many different transition of care models. Three different version of the Six Core Elements have been created: for pediatric practices, for adult practices, and for clinicians who care for individuals throughout their lifespan. Additionally, two process measurement tools and a feedback measurement tool have been developed to evaluate the Six Core Elements. All of the Six Core Elements of Health Care Transition information is available for public access on gottransition.org. This resource also outlines a recommended health care transition timeline.

Following the updated policy statement, a study was done to evaluate what proportion of the United States youth, ages 12 to 17, were receiving transition planning. This study surveyed the parents and/or caregivers of 20,708 youth to determine if transition planning occurred. The survey evaluated transition planning by asking about the following elements: 1) if the health care provider discussed the change to an adult healthcare provider, 2) if the health care provider helped the youth

gain self-care skills or helped them understand the health care changes at age 18, and 3) if the youth had time alone with the health care provider during the last preventive care visit. Individuals that met all three of the outlined measurements were said to meet the overall transition measure. The researchers found that "17% of youth with special health care needs and 14% of youth without special health care needs met the overall transition measure."[66] After this study was published, an updated policy statement was published in 2018 which includes more practice-based quality improvement guidance.[67]

2.3.1 Challenges During Transition of Care

As research related to transition expands, more adverse effects of transition have been revealed. Individuals who lacked a structed health care transition have shown higher rates of medical complications,[68] discontinuity of care,[69] problems with treatment and medication compliance,[70] higher hospital and emergency department use,[71] and higher costs of medical care.[72]

Another growing area of research has investigated the barriers to an effective transition. One of the largest barriers to transition that patients and families cite is the fear of leaving their pediatric clinicians for a new physician and possibly new health care system.[73] Another barrier is inadequate planning for the transition, especially in individuals without special health care needs. A 2017 study showed that youth with special health care needs had higher levels of transition readiness which included completing more medical tasks independently, with less parent involvement, compared to their peers without chronic medical conditions.[74] System difficulties such as finding specialized adult clinicians, transferring medical records, and insurance coverage are other barriers that have been reported by patients and families.[73]

Health care providers have noted some of the same barriers to transition such as lack of communication between pediatric and adult physicians and between health care systems. Another barrier is limitations in training. Specifically, limited training in pediatric-onset conditions, caring for adult patients who are reliant on their caregivers, and adolescent development and behavior. Pediatric clinicians often cite the lack of adult clinicians willing to treat patients with pediatric-onset conditions as a barrier.[75] Adult clinicians note that they need improved infrastructure in the form of care coordination and community resources to care for individuals with pediatric-onset conditions.[76]

2.3.2 Challenges During Transition of Care in Patients with Hemophilia

In addition to the normal challenges that can be experienced during the period between adolescence and adulthood, patients with hemophilia have added challenges due to their disease. During this time, patients usually have to adapt their lifestyle due to hemophilia, transition their care from pediatric to adult care services, and eventually take full responsibility for management of their hemophilia. Taking full responsibility for hemophilia management includes many aspects including self-infusions, ordering supplies, attending clinic appointments, maintaining treatment adherence, and navigating the insurance system.[77]

A Scandinavian survey investigated the transition of hemophilia management from parent to child. They found that age 14 was the average age that patients take over responsibility for their treatment, but at age 17.2 years, almost 25% of participants needed help from their parents for their hemophilia-related care. This finding suggests that parents of individuals with hemophilia often play a role in medical management, even after age 18.

This same study also looked at treatment compliance. They reported that 41% of the hemophilia patients, aged 13 to 25, did not follow their prophylaxis regimen as prescribed.[77] Poor prophylaxis compliance has been seen in other research. An international survey of 147 hemophilia treatment centers showed a significant decrease in prophylaxis adherence between age groups. In the 0-12 age group, 59% of patients had over 90% prophylaxis adherence compared to 13% with this level of adherence in the 13-18 age group and 6% in the 19-28 age group. The health care providers survey cited multiple reason for decreased compliance including: "inability to understand potential benefits, denial, poor venous access, lack of parent/family commitment, interference with lifestyle, teenage rebellion, and lack of time."[78] Decreased prophylaxis adherence in adolescence has the potential to lead to recurrent joint bleeds, which impact lifelong medical complications and quality of life.

2.3.3 Transition Recommendations in Hemophilia

In the early 2000s, the National Hemophilia Foundation created the "Transition Task Force" to develop transition guidelines that could be used with children who have bleeding disorders by the HTC care team. The task force succeeded in developing transition guidelines for members of the healthcare team such as nurses, physicians, physical therapists, social workers, and genetic counselors who provide care for patients with bleeding disorders. The developed transition guidelines are age-specific and address items from birth to 18 years of age. The goals and objectives at each age group are divided into five sections: social support, health and lifestyle, educational/vocational/financial planning, self-advocacy and self-esteem, and independent health care behaviors. Each goal/objective has listed strategies for the health care providers to use to meet

the goal. The Transition Task Force also developed review questions for each age group included in the transition guidelines.

In 2012, transition recommendations were published in the journal *Haemophilia.* These recommendations divide the lifespan into six age categories: infancy, toddler years, early school years, middle school years, teen years, and adulthood. The recommendations outline the medical and psychosocial transitional issues for each age category. This paper encourages a "well-developed transition plan from birth to adulthood" that "facilitates the necessary change from total dependence on caregivers to complete independence by the time one reaches 18 years of age."[79] During the teen years, it is recommended that individuals with hemophilia become fully independent in their care, which includes ordering, mixing and self-administering factor. It is also recommended that the health care team reviews bleed recognition and early treatment along with an emphasis on continuing prophylactic treatment. The main psychosocial aspects of transition during the teen years are the disclosure of the disease to others and the shift of responsibility from parent(s)/guardian(s) to the patient. It is recommended that the healthcare team help patients navigate through the consideration of when and how to disclose their diagnosis to friends and significant others. This article highlights that the main medical challenges in adulthood are the decision to continue or discontinue prophylaxis, the management of joint disease and other complications, and finding an appropriate primary care physician. During adulthood, the challenge of disclosure continues as well as appropriate career choice.[79]

3.0 Manuscript

3.1 Background

Hemophilia is an X-linked inherited coagulation disorder. Hemophilia A is the result of Factor VIII deficiency, and hemophilia B is the result of Factor IX deficiency. These deficiencies are caused by pathogenic variants in *F8* and *F9*, respectively. The prevalence of hemophilia A is estimated at 1:6,500 live male births, and the prevalence of hemophilia B is estimated at 1:30,000 live male births in the United States.[3; 4] Hemophilia severity is classified based on the factor concentration in the blood and symptoms differ based on severity. Individuals with severe hemophilia (less than 1% factor level) typically have spontaneous bleeding into joints and muscles, while individuals with moderate hemophilia (1 to 5% factor level) have occasional spontaneous bleeding and prolonged bleeding with minor trauma. Individuals with mild hemophilia (greater than 5% factor level) usually only have severe bleeding with major trauma.[6]

Originally, hemophilia was treated with blood transfusions and then with cryoprecipitated factor from plasma. In the 1980s, recombinant factor products began to be manufactured and have become the mainstay of hemophilia treatment.[21] The goal of hemophilia treatment is to replace the missing clotting factor to treat and prevent bleeds and complications associated with hemophilia. Individuals may receive episodic treatment, where they only use factor replacement when there is evident bleeding. Others receive prophylactic treatment, where they administer factor replacement on a consistent schedule to prevent anticipated bleeding.[7] The treatment advancements of recombinant factor and prophylactic treatment, have led to an improved quality of life and reduced

morbidity in the hemophilia population.[25] The life expectancy of individuals with hemophilia has greatly increased and is expected to be similar to the general population.[26]

While the life expectancy of individuals with hemophilia has increased, there are still several complications that may occur. Individuals may develop a "target joint," or a joint where they experience recurrent episodes of hemarthrosis, which can result in permanent damage to the joint and hemophilic arthropathy. Hemophilic arthropathy typically develops in the second decade of life. This can result in secondary muscle atrophy, soft tissue contractures, and angular deformities of the joint which can be extremely painful.[7]

Inhibitor development is another major complication and refers to the development of IgG antibodies that neutralize clotting factors. This can lead to increased bleeding, as factor replacement is no longer effective. Approximately 20-30% of individuals with severe hemophilia A and approximately 5-10% of individuals with mild or moderate hemophilia A develop inhibitors in their lifetime.[60] Less than 5% of individuals with hemophilia B develop inhibitors in their lifetime.[6]

Individuals with hemophilia require specialized lifelong care. In 1975, the United States developed a national network of Hemophilia Diagnostic and Treatment Centers for the care of individuals with hemophilia.[44] The Hemophilia Center Western Pennsylvania (HCWP) is one of the 141 federally funded hemophilia treatment centers. The HCWP provides physical, emotional, psychological, educational, financial, and vocational supports to its patients with a diverse team of care providers including pediatric and adult hematologists, nurses, social workers, a physical therapist, and a genetic counselor. Individuals with hemophilia, cared for by HCWP, are recommended to have yearly comprehensive clinic visits. These visits typically include meeting

with multiple members of the care team including a hematologist, nurse, physical therapy, social worker, genetic counselor, and insurance specialist.

Now that individuals with hemophilia have an expected normal lifespan, they must transition from being seen by pediatric to adult health care providers. At the HCWP, patients continue to be seen at the same clinic location, but they transition from a pediatric to an adult hematologist. Additionally, as patients age into adulthood, they need to take over full responsibility for the management of their condition. This includes many aspects such as self-infusion, ordering supplies, attending clinic appointments, maintaining treatment adherence, and navigating the insurance system.[77] Previous research about the transition of care in individuals with hemophilia has found decreased prophylaxis adherence during this period. Additionally, research has found that parents often play a role in medical management of their child's hemophilia after age 18.[77]

Overall, research about transition of care in hemophilia is limited. In this study we aim to evaluate the impact of transition of care from pediatric to adult health care providers in patients with hemophilia who are treated at the HCWP. This study specifically focused on how comprehensive visit compliance and bleeding events are impacted by transition of care while also assessing lapses in insurance coverage.

3.2 Methods

The participants for this study were chosen from the pool of adult patients diagnosed with hemophilia A or hemophilia B who are cared for at the Hemophilia Center of Western Pennsylvania (HCWP). The participant population included male patients ranging from age 26 to age 30, as of October 1, 2019, and currently being cared for HCWP. Participants of this age were

included as they are of a post-transition of care age and have had access to similar treatment products and clinical care guidelines. Participants were excluded if they had not received at least 5 consecutive years of treatment at the HCWP. Male participants with all severities of hemophilia were included in the study.

3.2.1 Data Collection

The data were collected from electronic and paper medical records and coded. Data were collected starting at age 15 for each participant. If participants, were not yet enrolled in the HCWP program when age 15, data was recorded from the year they became patients at HCWP. Demographics including sex, age, and ethnicity were collected. Previous laboratory studies were used to determine hemophilia type and severity. Individuals with <1% factor activity were classified as severe. Moderate disease was classified as individuals with 1-5% factor activity. Those with >5% factor activity were classified as mild.

Each participant's medical record was evaluated to ascertain any lapses in insurance. A participant was said to have a confirmed lapse in insurance if any nursing note or social work note said that the patient either had no insurance coverage or had a period of time where they did not have coverage. Additionally, when the patient registration noted they were self-pay, they were said to have no insurance at this time.

Joint disease complications and inhibitor development was determined for each participant. Joint disease status was determined by the presence of a target joint or hemophilia arthropathy recorded in any comprehensive visit or physical therapy note, from age 15 to 30. To determine inhibitor development at any point, Bethesda inhibitor titer results were used, as well as

comprehensive visit notes that mentioned inhibitor or a history of inhibitor that had previously been tolerized.

Comprehensive visit compliance was determined for every age, beginning at age 15 or when they became patients at HCWP. Comprehensive visit compliance was not determined for the current age of each patient, as they still have time to complete this annual comprehensive visit for their current age. Patients who had a yearly comprehensive appointment at HCWP were recorded as being compliant. Additionally, the presence of bleeding, including joint and soft-tissue bleeding, was determined for each age. Bleeding was determined by looking at comprehensive visit notes, physical therapy notes, and patient calls to HWCP about bleeding. If any of these sources of medical information mentioned the presence of traumatic or non-traumatic bleeding, then it was recorded as bleeding for that year.

3.2.2 Statistical Analysis

Descriptive statistics were conducted to determine the average age of participants, rates of hemophilia type and severity, lapses in insurance coverage, joint disease and inhibitor rates. These were calculated using Microsoft Excel. Two sample t-tests with equal variances were done to determine if joint disease or inhibitor development varied based on hemophilia severity. The same statistical analysis was performed to see if joint disease or inhibitor varied based on hemophilia type. All t-tests were performed using StataSE 15.

For ages 15 through 29, the proportion of participants that were compliant with comprehensive visits and the proportion of participants that had bleeding were calculated. Using these proportions, linear regression analyses were performed to assess the linear relationship

between age and comprehensive visit compliance and age and bleeding events. These analyses were performed using StataSE 15.

This study was approved by the University of Pittsburgh IRB. A copy of the approval can be found in Appendix A.

3.3 Results

3.3.1 Participant Demographics and Disease Characteristics

A total 40 male patients with hemophilia, aged 26-30 years old, were being treated at HCWP as of October 1, 2019. Only 26 of these patients had at least 5 consecutive years of treatment at HCWP and were included in this study. Fourteen patients were excluded because they had recently established care at the HCWP and had not been under the care of the HCWP for at least 5 years. The mean age of the 26 participants was 27.73 years. Nine (34.6%) of the participants had hemophilia B while the other 17 (65.4%) had hemophilia A. Fourteen (53.8%) of the participants had hemophilia that was categorized as severe and the other 12 (46.2%) had hemophilia that was categorized as mild or moderate. The ethnicity of 23 of the participants was classified as white; the other 3 ethnicities were classified as African American, Hispanic, and other.

All the participants were receiving either recombinant factor or Hemlibra as treatment throughout the time period studied. Only one participant was documented to have received human blood products during the time period studied. The administration of human blood products to this participant was due to a serious traumatic injury.

Table 1: Participant demographics and disease characteristics

PARTICIPANT DEMOGRAPHICS			
26 Individuals age 26-30 (mean age 27.73 years)			
Hemophilia Type			
Hemophilia A		Hemophilia B	
17 (65.4%)		9 (34.6%)	
Severity			
Severe		Mild/Moderate	
14 (53.8%)		12 (46.2%)	
Ethnicity			
White	African American	Hispanic	Other
23 (88.5%)	1 (3.8%)	1 (3.8%)	1 (3.8%)

3.3.2 Insurance

Medical records were reviewed to determine insurance coverage from age 15 to age 30. Based on the medical records reviewed, eleven (42.3%) of the 26 participants were found to have at least one confirmed lapse in insurance coverage during this age period. All of the confirmed lapses occurred after age 18 in this cohort.

3.3.3 Joint Disease and Inhibitor

Medical records were used to assess the presence of joint disease. Seventeen (65.4%) participants had documented joint disease. The presence or history of inhibitor was evaluated through review of medical records. Five (19.2%) participants were found to have inhibitor. All participants in this study that had inhibitor had hemophilia A. A two-sample t-test with equal

variances was used to evaluate the relationship between joint disease and hemophilia severity. No difference was found in joint disease with severe hemophilia compared to those with mild/moderate hemophilia (p-value=0.36). A two-sample t-test with equal variances was also used to evaluate if inhibitor development varied by severity of hemophilia. No difference was found in inhibitor development with severe hemophilia compared to those with mild/moderate hemophilia (p-value=0.21).

The same statistical analyses were performed to evaluate the relationships between joint disease and hemophilia type, as well as inhibitor development and hemophilia type. No difference was found in joint disease with hemophilia A compared to hemophilia B (p-value=0.44). A statistically significant difference was found with inhibitor development by hemophilia type (p-value=0.02). A correlation analysis was done between joint disease and inhibitor development. The Pearson correlation coefficient was 0.355 with a p-value of 0.08. We do not have evidence to suggest that there is a correlation between joint disease and inhibitor development in this study.

Table 2: Inhibitor and joint disease status

Inhibitor 5/26 (19.2%)	
Hemophilia A	Hemophilia B
5/17 (29.4%)	0/9 (0%)
Severe	Mild/Moderate
4/14 (28.6%)	1/12 (8.3%
Joint Disease 17/26 (65.4%)	
Hemophilia A	Hemophilia B
12/17 (70.6%)	5/9 (55.6%)
Severe	Mild/Moderate
8/14 (47.1%)	9/12 (75%)

3.3.4 Age, Comprehensive Visit Compliance, and Bleeding

Yearly comprehensive visit compliance and presence of bleeds were determined for each participant from age 15, or when they became patients at HCWP. Visit compliance and bleeds were not determined for their current year of age, as the full calendar year has not been completed for these measures. The proportion of participants who were compliant with their comprehensive visit was calculated for each age from 15 to 29. A linear regression analysis was performed to evaluate the relationship between age and comprehensive visit compliance. The estimated slope was found to be -0.004 with a confidence interval from -0.02 to 0.012. This means that for every 1 year increase in age, there was a 0.004 decrease in the proportion of participants with comprehensive visit compliance. The p-value for this analysis was 0.59, so this result was not statistically significant. Based on this analysis, we do not have evidence to suggest that age has a linear relationship with comprehensive visit compliance in this study.

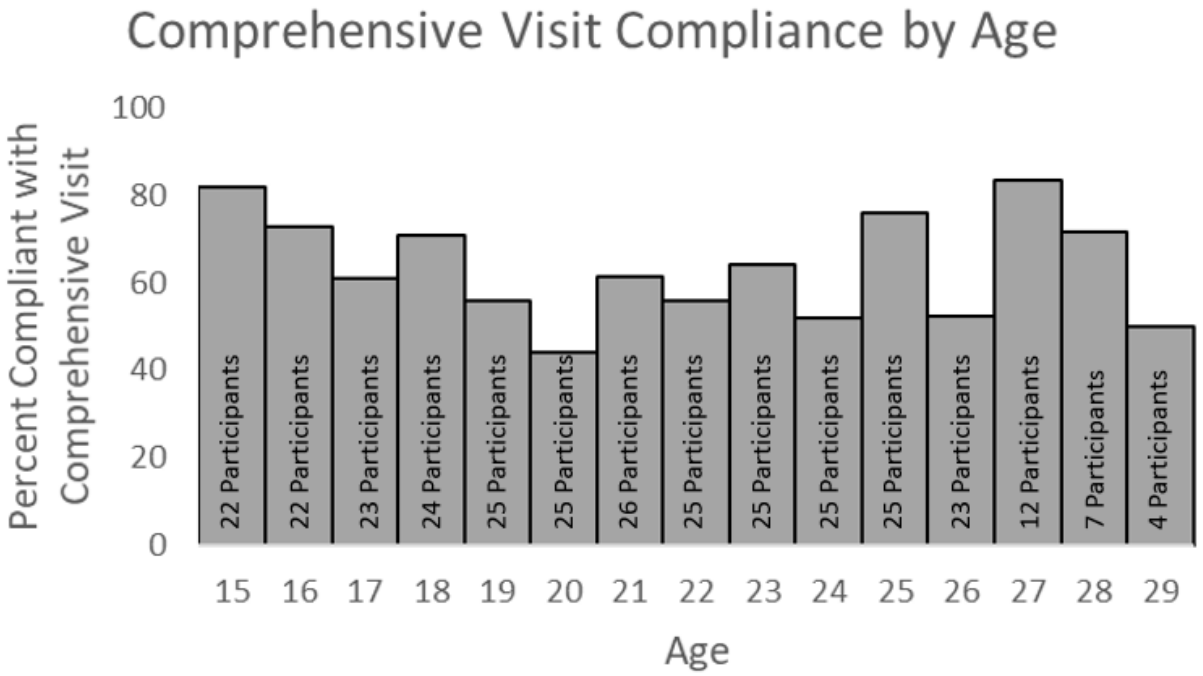

Figure 1: Comprehensive visit compliance by age

The proportion of participants that had bleeding each year was calculated for each age from 15 to 29. A linear regression analysis was performed to evaluate the relationship between age and bleeding. The estimated slope was found to be 0.00011 with a confidence interval of -0.0145 to 0.0148. This means that for every 1 year increase in age, there was a 0.00011 increase in the proportion of participants with bleeding. The p-value for this analysis was 0.987, so this result was not statistically significant. Based on this analysis, we do not have evidence to suggest that age has a linear relationship with bleeding in this study.

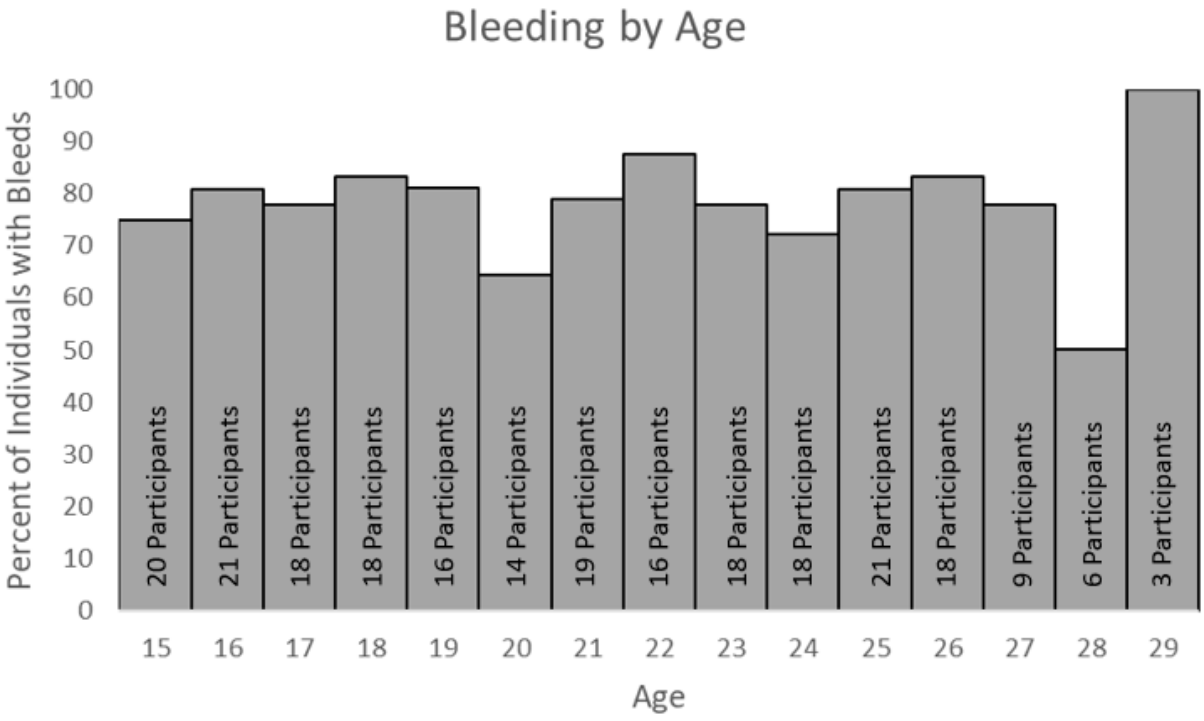

Figure 2: Bleeding by age

3.4 Discussion

3.4.1 Insurance

In this study, we identified that many individuals with hemophilia have lapses in their insurance coverage. Specifically, we found that 42.3% of the participants had lapses in insurance, all of which were after age 18. In Pennsylvania, all children can get insurance coverage, the type of coverage depends on a family's income, which is likely why insurance lapses occurred only after age 18. Children can either receive health insurance through the Children's Health Insurance Program (CHIP) or medical assistance. Once a child turns 19, they are no longer eligible to be

covered by CHIP. Individuals may also have lapses in their insurance when they turn 26 and can no longer be covered under their parent's health insurance.

We found a higher rate in lapses in insurance coverage compared to what has been reported in the literature. In 2015, a study was published that examined the demographics, comorbidities, and health status of young adults with hemophilia in the United States. This study included 141 men aged 18-35 years old who received care at hemophilia treatment centers between 2005 and 2013. They found that the uninsured rate in their cohort was 9.9% which is lower than the uninsured rate of the general United States adult population.[80]

3.4.2 Joint Disease and Inhibitor

This study did not find a significant difference in joint disease between severe hemophilia and mild/moderate hemophilia. This was an unexpected result. Previous research has shown that as factor activity decreases, the number of joint bleeds increase. This means that those with severe disease have higher rates of joint bleeds which increases their likelihood of developing joint disease. Based on this, we expected to see a difference in joint disease present between hemophilia severity.[81] We may not have observed this difference because joint disease development can be influenced by other factors such as prophylactic or episodic therapy, age, and weight which were not taken into account in this analysis.

In this study, we found that there was not a significant difference in joint disease between hemophilia A and hemophilia B, which is in contrast to what has been reported in the literature. Other studies in the literature have investigated the differences in the need for joint arthroplasty between types of hemophilia. These studies used joint arthroplasty as an indirect measure of joint arthropathy, as severe cases of arthropathy often require arthroplasty. In these studies, individuals

with hemophilia A underwent about three times more joint arthroplasties than those with hemophilia B. This finding has been consistent across multiple nationalities.[82] We may not have observed this finding because we were measuring the presence of any severity joint disease, rather than focusing on severe joint disease that requires arthroplasty.

Additionally, we found that there was not a significant difference in inhibitor development between individuals with severe hemophilia compared to those with mild/moderate hemophilia. This finding contradicts other studies that have evaluated inhibitor development and disease severity. Other studies have found that rates of inhibitor development are lower among individuals with mild or moderate hemophilia compared to those with severe hemophilia. Inhibitors are thought to be more common in individuals with severe hemophilia because these individuals are more likely to have no or truncated protein. Comparatively, individuals with mild or moderate disease are tend to have trace amounts of protein which can result in immune tolerization.[83] This difference may not have been observed in our study due to our small sample size.

As we expected, we found that there was a significant difference in inhibitor development between the types of hemophilia with 29.4% of individuals with hemophilia A developing inhibitors compared to 0% of individuals with hemophilia B. This finding was expected as numerous studies have shown that inhibitor development is more common in individuals with hemophilia A than hemophilia B. Specifically, about 30% of individuals with severe hemophilia A are expected to develop inhibitors compared to up to 5% of individuals with severe hemophilia B.[83]

3.4.3 Age, Comprehensive Visit Compliance, and Bleeding

Hemophilia is a lifelong hematologic condition that requires continual care throughout an individual's lifespan. This study was done to investigate the impact of the transition of care from pediatric to adult care providers in a cohort of males that receive treatment at the HCWP. Previous studies have shown that this transition has a negative impact on prophylaxis compliance, but no studies have investigated the impact on clinic attendance or the presence of bleeding.[78]

This study focused on a cohort of males age 26-30 and looked retrospectively at their medical records from an age before transition to their current age at the time of the study. We did not find a linear relationship between age and bleeding. Previous research has shown that prophylaxis regimen compliance decreases when an individual is transitioning care.[77] Based on this previous research, we would have predicted bleeding to increase with age as prophylaxis compliance has been shown to decrease. We may not have seen this trend because we were studying a cohort that included individuals with a mix of episodic and prophylactic treatment. Additionally, this trend may not have been observed due to the small sample size in this study.

We did not find linear relationship between age and comprehensive visit compliance in our cohort. While there is not a relationship, comprehensive visit compliance is lower than the HCWP goals for their patients. Ideally, all individuals should be seen annually for their comprehensive visit. Previous research has shown that individuals that attend less than one visit per year at a hemophilia treatment center have higher rates of emergency department visits and hospitalizations compared to patients that never missed appointments.[84] This means that poor comprehensive visit compliance can result in more complications for patients with potentially life long impacts.

3.4.4 Limitations

Several limitations exist in this study. One of the limitations is that the data were collected retrospectively using electronic and paper medical records. Only information included in the medical records was able to be collected. The medical records contained a number of gaps in information that were collected. For instance, HCWP used an electronic medical record system called Medinotes from 2009 to 2014. Medinotes only contained the comprehensive visit notes, and some social work and physical therapy notes. Medinotes did not contain other information that Centricity and the paper medical records contained such as factor prescriptions, phone call records, and registration information. This resulted in some gaps of information about insurance coverage.

Another limitation is small sample size. This study only had 26 participants, which is relatively small. Additionally, not all of the participants were patients at HCWP from age 15. This combined with the gaps in data, means that not every age had data on all 26 participants, making the sample size at each age even smaller.

Fourteen patients, age 26-30, were excluded from this study as they did not have at least five consecutive years of treatment at the HCWP. Since 35% of the total male hemophilia patients age 26-30 at the HCWP were excluded in this study, this sample may not be representative of the entire HCWP hemophilia patient population.

3.4.5 Future Studies

Previous studies have found the adherence to prophylactic therapy decreases as individuals age into adolescence and into adulthood. A decrease in prophylactic therapy can lead to increases in bleeding, which can result in long-term joint damage. Our study did not specifically evaluate

treatment adherence to either episodic or prophylactic treatment. A future avenue of research would be to evaluate the impact of transition from pediatric to adult care providers on treatment adherence. This would also allow additional analyses to assess the relationship between changes in treatment adherence and bleeding episodes.

Future research could focus on identifying barriers to clinic attendance at HCWP as patients age into adulthood. This could be done by surveying patients at the hemophilia center to determine the existing barriers to clinic attendance. There is a paucity of literature on this topic and this new information should help to identify and characterize barriers; then new interventions can be established to attempt to minimize these barriers, improve clinic attendance, medical adherence and quality of life.

Insurance coverage is another important issue that should be further studied. This study found that 43.2% (11/26) of the participants had at least one confirmed lapse in insurance coverage. Insurance coverage is needed by most individuals to help pay for their hemophilia-related medical expenses such as factor prescriptions, clinic visits, and laboratory studies. Further research could evaluate the specific barriers that patients experience when losing and obtaining insurance coverage. Through identification of these barriers, interventions can be developed to try and improve insurance coverage in this population. Improved insurance coverage has the possibility of increasing comprehensive clinic adherence, medication adherence, and decreased rates of hemophilia complications such as joint disease.

3.4.6 Lessons Learned

Through the data collection of this study, we gained insight about the medical records at the HCWP. The major lesson learned was that there is a lack of standardization in the physician's

comprehensive visit notes. When formulating this study, we planned to determine the number of bleeding episodes participants had annually, as well as their treatment compliance. Once medical record review began, it was discovered that collecting this detailed level of data would not be possible, mainly because this information was not consistently included in the physicians' notes. Some of the physician notes included information about whether a patient experienced any bleeding events in the past year, but often vague terms were used, such as "some bleeds," or "occasional bleeding events." This terminology conveys that bleeding is present, it but does not quantify the amount of bleeding that took place. Additionally, the physician notes often did not differentiate between joint and soft tissue bleeds. This is an important differentiation to include, as these different bleed types result in different complications.

The physician's notes rarely included information about the patient's treatment compliance. A patient's treatment compliance can be estimated based on talking with the patient, the presence of bleeds, and factor replacement usage. The new electronic medical record system used by the HCWP includes information about when a patient refills their factor prescription, so a physician can use this data as a proxy for treatment compliance. Having information about treatment compliance could be helpful for all members of the care team to be aware of and could be a beneficial variable to look at in future studies.

3.5 Conclusion

This study adds to the body of research regarding the impact of transition of care from pediatric to adult providers in the hemophilia population. It offers insight about how comprehensive visit compliance and bleeding is impacted. In this small study, we found that age

did not have an impact on comprehensive visit compliance and bleeding. Additionally, this study showed that many of the patients with hemophilia have lapses of health insurance coverage over the age of 18. Further research could help determine effective ways to improve comprehensive visit attendance and health insurance coverage.

4.0 Significance to Genetic Counseling and Public Health

One of the three core functions of public health is assessment. This is defined as the monitoring and diagnosing of health problems in the community. HCWP uses annual comprehensive clinic visits to monitor the health of individuals with hemophilia. This study did not find an association between age and comprehensive visit compliance, but the study did show that comprehensive visit compliance is less than ideal at all ages at the HCWP, averaging only 63.5%. Comprehensive visits are important in ensuring patients are receiving an adequate replacement factor dosage which is critical for the effective treatment or prevention of bleeds. Additionally, these appointments allow the healthcare team to identify a variety of complications of hemophilia such as inhibitor development and hemophilic arthropathy. Often during these comprehensive visits patients meet with social workers to evaluate how they are coping with their diagnosis and help them navigate other difficulties that may come with hemophilia such as insurance coverage and getting appropriate accommodations that may be needed at school or work.

One complication that is important to identify early is hemophilic arthropathy as it can have major impacts on the quality of life of individuals with hemophilia. Hemophilia arthropathy can be very painful and cause joint contractures/deformity which can interfere with daily activities. This can also result in individuals with hemophilia missing work and school. Individuals are evaluated for hemophilic arthropathy at their annual comprehensive visits in order to identify and treat early and prevent progression. When hemophilic arthropathy is identified at an early stage, conservative treatments can be used to try and manage the pain and maintain function of the joint. If conservative measures fail, then individuals may require surgical interventions to manage the

arthropathy.[7] Surgical interventions are often more costly to the healthcare system and require additional time of work and/or school for recovery.

Individuals with hemophilia usually have their inhibitor levels checked at their annual comprehensive clinic visits. It is important for inhibitor development to be identified and treated in a timely manner. When inhibitor develops, individuals no longer respond to their replacement factor, and may even have an anaphylactic reaction to the factor. This can cause individuals to have more frequent bleeding which increases the risk of severe complications. Determining ways to increase comprehensive visit compliance has the possibility of improving the long-term health of individuals with hemophilia and reduce the health care costs of hemophilia treatment.

The assessment of individuals with hemophilia through comprehensive visits is also important in decreasing healthcare costs associated with hemophilia. A previous study evaluated non-attendance among patients at hemophilia treatment centers from 2010-2014. They found the individuals who attended less than one visit per year had higher rates of emergency department visits and hospitalizations compared to patients that never missed appointments.[84] These increases in emergency department visits and hospitalizations increases the healthcare costs for these patients which can be a cost to the patient and society. It is estimated that one third of patients with hemophilia are covered by Medicaid which means the care is funded by the state.[85]

The costs of treatment associated with hemophilia is a huge burden economically for patients, healthcare systems, and society as a whole. It is estimated that the mean healthcare costs for a patient with hemophilia, with the absence of inhibitors, is $140,000 per year. Over 80% of this direct expenditure is the cost of factor replacement therapy. The costs of treatment for hemophilia with the presence of inhibitor can be five times greater than treatment without inhibitor.

Additionally, patients with inhibitor are more likely to visit the emergency department and more likely to require inpatient hospital stays.[85]

An essential service of public health is educating individuals about their health issues. The National Hemophilia Foundation Transition Guidelines recommend that all individuals with hemophilia, or who are carriers of hemophilia, understand the implications of the diagnosis between ages 16 to 18. This should include education about how hemophilia is inherited. During the transition years, patients may be begin thinking about having children and should be aware of the inheritance risks. Patients with hemophilia should be educated that all of their daughters will be obligate carriers of hemophilia and that 30% of carrier females are symptomatic. They should know that they cannot pass on hemophilia to any male children. It is important for patients to be aware of these risks prior to having children in case it would impact their reproductive decisions. This study revealed that age does not appear to have an impact on comprehensive clinic attendance, but overall attendance is lower than the HCWP would like. Knowing that comprehensive visit attendance is low it may be beneficial to determine alternate methods for genetic counselors to provide this information to patients that fail to attend their comprehensive visits.

The genetic counselor at the HCWP plays an integral role in the care of patients with hemophilia. Other hemophilia treatment centers also have genetic counselors as a part of their comprehensive care team. These genetic counselors are involved in many aspects of hemophilia patient care including genetic testing, carrier testing, reproductive counseling, and education about hemophilia. This study showed transition did not have an impact on comprehensive visit compliance, but overall visit attendance is lower than desired. Additionally, this study found that 65.4% of the cohort have joint disease. These are important areas where genetic counselors can

work with patients to educate them on the importance of comprehensive visit compliance as well as proper treatment adherence to help prevent the development of joint disease.

Appendix IRB Approvals

University of Pittsburgh
Institutional Review Board

Human Research Protection Office
3500 Fifth Avenue, Suite 106
Pittsburgh, PA 15213
Tel (412) 383-1480
www.hrpo.pitt.edu

APPROVAL OF SUBMISSION (Exempt)

Date:	October 4, 2019
IRB:	STUDY19090169
PI:	frederico xavier
Title:	Transitioning of care from pediatric to adult providers among hemophilia patients
Funding:	None

The Institutional Review Board reviewed and approved the above referenced study. The study may begin as outlined in the University of Pittsburgh approved application and documents.

Approval Documentation

Review type:	Initial Study
Approval Date:	10/4/2019
Exempt Category:	(4) Secondary research on data or specimens (no consent required)

Determinations:	• Waiver of HIPAA authorization
Approved Documents:	• HRP-723 - WORKSHEET - Exemption_Secondary Data.Specimens_Version_0.01.docx, Category: IRB Protocol;

As the Principal Investigator, you are responsible for the conduct of the research and to ensure accurate documentation, protocol compliance, reporting of possibly study-related adverse events and unanticipated problems involving risk to participants or others. The HRPO Reportable Events policy, Chapter 17, is available at http://www.hrpo.pitt.edu/.

Clinical research being conducted in an UPMC facility cannot begin until fiscal approval is received from the UPMC Office of Sponsored Programs and Research Support (OSPARS).

If you have any questions, please contact the University of Pittsburgh IRB Coordinator, Teresa McKaveney.

Please take a moment to complete our Satisfaction Survey as we appreciate your feedback.

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