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Characterization of Men with Hemophilia B and Factors Associated with Treatment Practices, Participating in the Community Counts Registry from 2014 to 2018.

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ABSTRACT

CHARACTERIZATION OF MEN WITH HEMOPHILIA B AND FACTORS ASSOCIATED WITH TREATMENT PRACTICES, PARTICIPATING IN THE COMMUNITY COUNTS REGISTRY FROM 2014-2018

By

FIONA M. BETHEA

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Hemophilia B is an inherited, X-linked, bleeding disorder caused by a mutation of the clotting factor 9 (FIX) gene. The mutation reduces the amount of FIX protein and results in spontaneous and trauma-related bleeding episodes. In 1994, approximately 2,800 men with hemophilia B (MWHB) were treated at hemophilia treatment centers (HTCs) in the United States (US). To date, studies examining health outcomes for MWHB in the US have not been compared across disease severities. Treatment of MWHB has become more complex with changes in prophylaxis practices in the US and the introduction of novel treatment products. Observational studies that describe health outcomes among MWHB and current treatment practices are important to inform future clinical practices. These cross-sectional analyses used data from MWHB enrolled in the Community Counts surveillance Registry (Registry) from 2014 to 2018. The first paper compared the sample of MWHB in the Registry to the population of MWHB who received treatment in HTCs and described the demographic, clinical factors, and health outcomes across disease severities. From 2014-2018, the population of MWHB who received care in HTCs included 4,816 MWHB, of which 2091 participated in the Registry. The second paper examined demographic, clinical factors, and health outcomes associated with treatment regimen, prophylaxis versus episodic; and used a marginal model. The final model included ethnicity, health insurance, history of a joint bleed, and interactions between severity by chronic pain as well as age by history of central venous access device utilization. The third paper examined demographic, clinical factors, and health outcomes associated with treatment product type utilization, standard half-life products versus extended half-life products, among MWHB on continuous prophylaxis; and used a marginal model. The final model included disease severity, enrollment year, HTC region, and percent of missed treatment dose. The second and third paper demonstrated that patient-level treatment outcomes were clustered by the HTCs where they received care. Future studies should examine the treatment dosage and frequency of administration of treatment products for MWHB on prophylaxis and replicate these studies for hemophilia A to determine if the factors associated with treatment are similar for all men with hemophilia.

CHARACTERIZATION OF MEN WITH HEMOPHILIA B AND FACTORS ASSOCIATED WITH TREATMENT PRACTICES, PARTICIPATING IN THE COMMUNITY COUNTS REGISTRY FROM 2014 TO 2018.

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APPROVAL PAGE

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Author's Statement Page

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Fiona Bethea

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CHAPTER 1

1.1 Hemophilia B

Hemophilia B (HB) is a bleeding disorder caused by a mutation of the clotting factor nine (FIX) gene and results in a lifelong bleeding tendency. The FIX gene is located on the X-chromosome and has an X-chromosomal inheritance pattern, although spontaneous mutations account for approximately 30% of men with HB (MWHB) who have no family history of the congenital bleeding disorder.[1] References to a bleeding disorder resembling hemophilia date back to the 2nd century AD and continued until the first published description of hemophilia and the inheritance pattern in 1803.[2] HB is also referred to as the 'royal disease' as it was demonstrated that Queen Victoria of England was a carrier who passed the disease onto several of her descendants in royal families in Germany, Spain, and Russia. Due to a similar clinical manifestation, it was not until 1952 that HB was differentiated from hemophilia A and termed the 'Christmas disease' after the first patient examined in detail.[3]

The mutation of the FIX gene reduces the factor activity level of the FIX protein, which is part of the intrinsic coagulation pathway.[4] In normal hemostasis plasma levels of FIX range from 50 to 150% and when a blood vessel is damaged, the blood vessels constricts, platelets adhere to the endothelial cells at the site of the injury and form a platelet plug. Clotting factors and platelets then seal the inside of the wound and form a fibrin clot. All together this forms a blood clot, the blood vessel typically heals within a few days and the blood clot dissolves.[5] However, in MWHB where the FIX clotting factor is decreased or absent, a mature fibrin clot does not form. The platelet plug forms and bleeding slows but without sufficient FIX, the fibrin clot cannot develop fully, and the platelet plug ultimately breaks down.[6] Bleeding resumes and the cycle of partial clotting and bleeding continues.

Disease severity is determined by the amount of endogenous FIX in the plasma, measured in international units per deciliter (IU/dl), in the absence of treatment. Severe HB is defined as less than 1% of normal FIX activity (0.01 IU/dl) and the clinical phenotype includes frequent spontaneous bleeding episodes, predominantly in the joints and muscles. However, it has been reported that 10 to 15% of persons with severe disease have a clinical phenotype that is more consistent with mild or moderate disease.[7] Moderate HB is defined as 1 to 5% FIX (0.01-0.05 IU/dl) and the phenotype consists of bleeding episodes predominantly due to injuries with some spontaneous bleeds. Mild HB is defined as 6 to 40% FIX (0.06-0.40 IU/dl) and bleeding episodes typically only occur after accidental trauma or invasive procedures.

1.2 Health Outcomes

Historically, chronic arthropathy has been the leading cause of morbidity for MWHB. Bleeding episodes in MWHB most frequently occur in joints, specifically synovial joints. Knees, elbows, ankles, shoulders, and wrists are the most commonly affected synovial joints.[8] Blood vessels in the synovial membrane break, spontaneously or due to injury, and blood fills the synovial space. Without treatment, pressure in the joint cavity stretches ligaments and tendons. Blood in the synovial space also leads to inflammation and angiogenesis, making the joint more likely to bleed, and also results in breaking down of smooth cartilage covering the ends of bones making them pitted. As the blood is removed from the cavity, ligaments and tendons become loose, resulting in a less stable joint. With repeated bleeding episodes, cartilage erodes, and joint destruction occurs. Overtime, permanent joint damage leads to chronic pain, restricted joint range of motion, and functional disability. Treatment for chronic arthropathy is limited to invasive joint procedures, such as synovectomy, joint replacement, or joint fusion, or corrective osteotomy, depending on the joint location and progression of joint disease.

1.3 Treatment History

Treatment of hemophilia has changed dramatically over the last century. In the early 1900's, the median life expectancy for men with hemophilia (MWH) with severe disease was 11.4 years.[9] In the 1930's, dilutions of snake venom were used to help blood clot in MWH and whole blood transfusions were used, which raised the life expectancy to 13 years. In the 1950's and early 1960's hospitalized MWH received transfusions of fresh frozen plasma and the life expectancy increased for severe patients to 20 years old.[9] However, the volume of plasma needed to stop bleeding episodes was extensive and patients were hospitalized for long periods of time, intracranial hemorrhages were fatal, and functional disability was profound. Dr. Judith Pool discovered that cryoprecipitate contained substantially higher amounts of factor proteins in a smaller volume of plasma and in the 1970's freeze-dried powered FIX concentrates could be produced by blood blank and stored at home. This reduced the time to infuse large quantities of FIX to more quickly form clots to stop bleeding episodes. This also allowed for 'self-infusion' in one's home, removing the need for all patients to get treatment at a hospital over the span of days or weeks. However, these plasma-derived products had to be pooled from tens of thousands of donors.

In 1983, it was documented that children with hemophilia were infected with human immunodeficiency virus (HIV) and their only exposure was to blood products. By the mid 1980's it was estimated that approximately half of the people with hemophilia were infected with HIV as a result of the contamination of the blood supply. In the Netherlands during the 1990's, HIV accounted for a quarter of all causes of death for MWH.[10] Prior to 1992, almost all MWH who received clotting factor concentrates became infected with hepatitis C virus (HCV).[11] After 1992, regulations mandated the blood supply was screened for HCV and advanced methods of

viral inactivation and purification techniques were implemented for plasma-derived treatment products. This reduced the risk of contracting these viruses from the blood supply. However, the impact of viral contamination in the blood supply was significant on morbidity and mortality rates for MWH.

The FIX gene was sequenced during the mid-1980's. This allowed pharmaceutical companies to develop synthetic factor products that were not plasma-derived. The first FIX recombinant product was approved by the federal drug administration (FDA) in 1997. The half-life of traditional FIX recombinant products is approximately 18 to 24 hours. In 2014, the first extended half-life (EHL) recombinant FIX treatment product was approved by the FDA. EHL treatment products have a mean half-life between 82-102 hours.[12] The half-life of treatment products have direct implications for treatment regimens for MWHB.

1.4 Treatment Regimen

The evolution of treatment products available has allowed for changes to the clinical management of MWH. Historically, treatment consisted of episodic care defined as the utilization of treatment products to stop a suspected or clinically evident bleeding episode. In the 1950's and 1960's, clinicians in Sweden and the Netherlands started to give regular infusions of anti-hemophilia globulin to severe hemophilia A patients to keep their patients above 1%.[13] In 1992, Nilsson *et al* reported that when prophylaxis, defined as utilization of treatment product to prevent bleeding episodes from occurring, was initiated early in severe patients and trough levels were kept above 1%, joint damage over time was significantly less.[13] Prophylaxis has been practiced in children with severe HB in Sweden since 1972, and became standard of care for MWH in many European countries as early as the 1970's.[13,14] The first randomized control trial examining joint health by treatment regimen of prophylaxis versus episodic care among men

with hemophilia A was published in 2007 in the United States.[15] Those evidence based findings confirmed observations from European countries regarding the effectiveness of prophylaxis. As a result, treatment regimens using prophylaxis for males with severe hemophilia A became more widely accepted in the US. However, the most recent examination of MWHB in the US demonstrated that between 1998 to 2011, the prevalence of prophylaxis usage was only 45% among severe MWHB and 25% among moderate MWHB.[16]

Adherence to prophylactic infusions has been identified as a strong barrier to the maintenance of prophylaxis. Novel EHL treatment products, which require significantly less infusions due to their increased half-life capacity, may eliminate a barrier to prophylaxis. It is likely that prophylaxis usage in the US has increased since the last published report from 2011.

1.5 Statement of purpose and summaries of studies.

Treatment of MWHB has become more complex with changes in prophylaxis practices in the US and the introduction of novel treatment products. Observational studies that describe health outcomes among MWHB and current treatment practices are important to inform future clinical practices. This dissertation focuses on characterizing the prevalence of health outcomes for MWHB across disease severities, the factors associated with treatment regimen, as well as the factors associated with treatment product type utilization among MWHB on continuous prophylaxis, from the Community Counts surveillance Registry (Registry) between 2014 to 2018.

Study 1.

The first paper compared the sample of MWHB from the Registry to the population of MWHB who receive care at federally funded hemophilia treatment centers from a separate dataset, the Community Counts Population Profile. It also described the demographic, clinical

factors, as well as the prevalence of health outcomes among MWHB at enrollment in the Registry across disease severities.

Study 2.

The second paper examined the demographic, clinical factors, and prevalence of health outcomes of MWHB associated with treatment regimen, prophylaxis versus episodic, at enrollment in the Registry. The paper evaluated if the outcome of treatment regimen was correlated among MWHB based on the hemophilia treatment center where they received treatment. Finally, it examined the demographic, clinical factors, and health outcomes, that were associated with the probability of the treatment regimen, prophylaxis versus episodic.

Study 3.

The third paper examined the demographic, clinical factors, and prevalence of health outcomes of MWHB associated with treatment product utilization, standard half-life versus extended half-life recombinant treatment products, at enrollment in the Registry. The paper evaluated if the outcome of treatment product type was correlated among MWHB based on the hemophilia treatment center where they receive treatment. Finally, it examined the demographic, clinical factors, and health outcomes, that were associated with the probability of the treatment product utilized at enrollment, standard half-life versus extended half-life products.

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CHAPTER 2.

Characteristics of Men with Hemophilia B in United States Hemophilia Treatment Centers and Demographic and Clinical Health Outcomes from 2014-2018.

Written for submission to Haemophilia

Introduction

Hemophilia B (HB) is an inherited, X-linked, recessive, bleeding disorder caused by a mutation of the clotting factor 9 (FIX) gene. The mutation of the FIX gene reduces the factor activity level of the FIX protein which is essential to the formation and maintenance of a stable clot.[1] This results in spontaneous and trauma-related bleeding episodes. These bleeding episodes predominantly occur in synovial joints. A single synovial joint bleed can make that joint more susceptible to future bleeds. Recurrent bleeding in joints results in chronic joint damage and potential loss of functionality. Over time chronic pain in a joint may require invasive joint procedures.

Treatment for men with hemophilia B (MWHB) predominantly comprises venous infusions of clotting factor IX replacement. Infused treatment products consist of plasma-derived, recombinant, and more recently extended half-life (EHL) FIX products. Despite the predominance of home treatment infusions for HB, emergency room visits and in-patient admissions for the treatment of severe bleeding episodes occur.

The leading cause of mortality and long-term disability for MWHB is an intracranial hemorrhage (ICH). Mortality is reported in approximately 15-20% of MWHB who experience an ICH.[2,3] ICH occurs more commonly among MWHB with severe disease during the first two years of life, however it has been reported in MWHB with mild and moderate disease.[2,4,5]

Using data from active surveillance of six states in the United States (US) from 1993-1994, Soucie *et al.* estimated the mean national incidence of hemophilia was 1 in 5032 live male births. This was projected to be 20,000 men with hemophilia (MWH) in the US, of which approximately 20% had HB.[6] It was also estimated that 70% of MWH were treated in federally funded hemophilia treatment centers (HTCs), representing the greatest catchment unit for MWH.[6]

From 1998 to 2011, the Centers for Disease Control and Prevention (CDC) established and maintained a national public health surveillance system of persons with bleeding disorders, the Universal Data Collection (UDC). Participants were identified and enrolled from 130 HTCs. UDC evaluated trends in treatment and health outcomes for MWH. Over the lifespan of the system, 3,785 MWHB were enrolled in UDC.[7] Their respective HTCs provided data pertaining to their clinical care and complications to CDC at annual intervals. While UDC represented one of the largest samples of MWHB worldwide, a limitation of the UDC system was that not all MWH who were treated in HTCs, enrolled in UDC. Data were not collected on the portion of MWH treated at the HTCs over the same time period who did not enroll, to fully quantify the population of MWH treated at HTCs. Without information on the number or characteristics of the overall hemophilia patient population treated at HTCs by year, the generalizability of the nonrandom UDC data sample could not be determined. Additionally, the UDC data were restricted to 2011 and changes in treatment practices over the last decade have likely had significant effect on health outcomes.

In collaboration with the American Thrombosis and Hemostasis Network and the US Hemophilia Treatment Center Network, CDC initiated a new hemophilia surveillance system, Community Counts.[8] Community Counts expands on the UDC surveillance activities and

consists of three components, HTC Population Profile, Community Counts Registry for Bleeding Disorders Surveillance (Registry), and Mortality. The HTC Population Profile was initiated in September 2011. Each HTC annually submits a de-identified Population Profile dataset with limited data pertaining to all patients treated for eligible bleeding disorders (MWH and other select bleeding disorders). As each HTC submits data on their total HB patient population, Population Profile is the most complete US national data collection system containing relevant demographic information for MWHB within the US national HTC network. Data collection for the Registry began in December 2013. The Registry collects more detailed clinical information from MWHB, than Population Profile, to describe epidemiologic characteristics, such as treatment, clinical factors, and health outcomes. The Registry is based on patient participation where patients provide authorization for inclusion and therefore represents a non-random sample of patients in the Population Profile. At enrollment into the Registry, HTCs complete an initial visit form. In subsequent years of participation, a subsequent visit form is completed.

To date, the majority of national cross-sectional studies describing the prevalence of health outcomes have focused solely on severe MWHB.[9,10] Few studies have described the prevalence of demographic and clinical outcomes across disease severities using a national dataset from the US. While it is established that worse health outcomes are more frequent amongst severe MWHB, the description of how that relates to moderate and mild patients has yet to be described.

In these analyses we used national data from Community Counts to describe the prevalence and characteristics of MWHB from 2014 to 2018 participating in the Community Counts Registry compared to the overall population of MWHB treated at HTCs from the Population Profile. We then described the demographic, clinical factors, and prevalence of health

outcomes among MWHB who participate in the Community Counts Registry across disease severities.

Methods

Data Collection

Data for both the Population Profile and the Registry datasets are collected from HTCs onto standardized data collection instruments by direct transfer from electronic report forms, manual transfer from patient charts to electronic and paper report forms, and patient interview. Form data with missing responses, that were not a result of a skip pattern, could not be submitted electronically. Data were sent without personal identifiers to a central CDC database. Community Counts was determined to be non-research by CDC and was approved by each participating HTC according to their institutional procedures.[8]

Design and Participants

This non-interventional retrospective cross-sectional analyses of Population Profile and Registry subjects included male patients with a primary diagnosis of HB and baseline factor activity level less than 40%,[11] who had an HTC visit during 2014 to 2018. For the Population Profile, where patients could have multiple visits to an HTC over the time period, the first year of visit was included. Data from Population Profile was restricted to the first visit during the time frame. Persons were excluded from analyses from the Registry sample who had multiple bleeding disorder diagnoses, had a history of a liver transplant, or had history of an inhibitor (see Figure 1, for sample size, based on these criteria). These additional exclusion criteria for the Registry were not collected in the Population Profile. Registry data from the Initial Visit form, collected at enrollment, were used for these analyses.

Variables Assessed

We assessed several variables that were included in both the Population Profile and the Registry. These included disease severity, year of visit, year of birth, HTC region, race, ethnicity, primary health insurance status, history of hepatitis C virus (HCV), and history of human immunodeficiency virus (HIV). HTC region classification was based on the Health Resources Service Administration region classification and were anonymous per requirements of the Community Counts project review committee. For the Population Profile, where the full date of birth was not collected, age was calculated by subtracting the year of visit by the year of birth; whereas with the Registry, age at enrollment was calculated by subtracting the date of birth from the enrollment date. We then collapsed age at enrollment into six categories. History of HCV and HIV is defined as whether they had been diagnosed during their lifetime; an unknown response indicated the results were unknown, indeterminate or the patient had never been tested.

In the evaluation of Registry enrollment data, we examined a number of demographic characteristics and clinical outcomes. Participants with reported insurance as Medicaid, Medicare, Military Health Care, and state programs were coded as having government insurance. Participants with a highest education level of pre-elementary, primary or secondary, or GED or equivalent were coded as high school or lower; some college, technical school, 2-year college degree, and 4-year college degree were coded as college; and other was coded as unknown. Parent's highest education level was restricted to participants less than 18 years, per the survey instructions, and was coded the same as patients' highest education level. Patient employment status was restricted to participants 18 years or older. The location of where a participant received services from the HTC was defined as HTC service location. When this was reported as multiple locations (HTC primary location, HTC outreach clinic, and/or HTC telemedicine clinic) it was coded as a combination. Body mass index (BMI) for adult participants, 20 years and older,

was calculated as weight (kg) / height $(cm)^2$.[12] The BMI number was categorized as underweight if less than 18.5, normal if between 18.5 and 24.9, overweight if between 25 and 29.9, and obese if greater than 30.0. BMI percentile was calculated for participants between two years and nineteen years based on age, gender, height, and weight. The BMI percentile was categorized as underweight if less than the 5^{th} percentile, normal if between the 5^{th} and 85^{th} percentile, overweight if between the 85^{th} and 95^{th} percentile, and obese if equal to or greater than the 95^{th} percentile. Age at diagnosis was calculated by subtracting the date of birth from the date of diagnosis. Age at diagnosis could be a negative number up to 180 days prior to birth, because children can be diagnosed by amniocentesis between 15-20 weeks pregnant, approximately 175 days (0.48 year) prior to birth; age at diagnosis prior to 0.5 years were removed as outliers.

Treatment regimen at enrollment was collected on the data instrument as continuous prophylaxis, event-based prophylaxis, or episodic. Continuous prophylaxis was defined as the participant using any treatment product on a regular basis to prevent bleeding episodes and was expected to continue indefinitely. Event-based/short-term prophylaxis was defined as treatment either to prevent anticipated bleeds associated with an event or an activity on an intermittent basis, or to use any treatment product on a regular basis to prevent bleeds for an extended but not indefinite period of time. Episodic treatment was defined as treatment used solely to treat an active bleed episode.

Data Analyses

In these descriptive analyses, we compared demographic and clinical characteristics from MWHB in Population Profile dataset who met our eligibility criteria to MWHB in the Registry dataset who met our eligibility criteria, using frequency distributions. Statistical testing was not performed as the two samples are not independent of one another.

We further assessed demographic and clinical characteristics of MWHB in our Registry sample based on data at enrollment, by their disease severity, specifically mild, moderate or severe. Frequency distributions were used to summarize categorical variables and measures of central tendency and dispersion were used to summarize continuous variables. All analyses were conducted using SAS statistical software version 9.4 (SAS Institute, Cary, NC).

Results

The Population Profile dataset included 4,816 unique MWHB visited 140 HTCs (median 25 patients per HTC ranging from 1 to 248 patients, interquartile range (IQR) 13-42 patients), from 2014 to 2018. This resulted in 16,074 HTC annual visits over the five-year time frame (Figures 1, Table 1). The distribution of annual visits by disease severity were relatively uniform for each year of visit. Each year, the proportions of visits in the Population Profile for persons with HB with mild, moderate and severe HB were on average 26%, 42%, and 32% respectively.

Among the MWHB included in Population Profile from 2014 to 2018, 2091 MWHB from 133 HTCs (median 12 patients per HTC ranging from 1 to 166, (IQR 7-17 patients)) enrolled in the Community Counts Registry who met our inclusion criteria. This sample made up 43.4% of the Population Profile. Demographic and clinical variable proportions were similar for MWHB in the Population Profile compared to the Registry datasets using the full inclusion/exclusion criterion (Table 1). HTC region, disease severity, age at visit, race, ethnicity, primary insurance, history of HIV, history of HCV were not meaningfully different. Year of enrollment was the only variable that was substantially different between the Population Profile and the Registry sample. In 2014, 59% of MWHB in the Population Profile were treated at HTCs, and participants in the Registry were accrued on average 20% a year.

Demographic and clinical characteristics across disease severity from the Registry dataset are provided in tables 2, 3, and 4. The average age at Registry enrollment was 20.0 years and the proportions of persons with mild, moderate and severe HB were 24%, 40%, and 36% respectively. MWHB with moderate and mild disease severity accounted for 95% of uninsured participants. Among MWHB with a known history, the overall prevalence of ICH was 7%, the prevalence of HIV was 4%, the prevalence of HCV was 24%. Overall, 15% of MWHB had history of an invasive joint procedure and 17% had a history of using a central venous access device (CVAD). BMI was classified as overweight or obese for 54% of all participants. No history of a bleeding episode was reported by 4% of MWBH.

Race, ethnicity, employment status, BMI, family history of a congenital bleeding disorder, history of ICH, history of HCV, and history of invasive joint procedures differed by disease severity. Approximately half of Black or African American MWHB were severe with a quarter moderate and a quarter mild, where as a third of White MWHB were severe, a quarter were mild, and almost half were moderate. The majority of MWHB with Hispanic ethnicity were severe and approximately a fifth were moderate and a fifth were mild. Patient's employment status at enrollment was also comparatively different by disease severity. The majority of MWHB employed full time had moderate disease severity, whereas the majority of MWHB employed part-time and not employed had severe disease. Moderate MWHB had the highest proportions of overweight or obese participants and mild MWHB had the least proportions. Severe MWHB had the highest proportion who reported not having a family history of a congenital bleeding disorder, 56%, compared to mild (22%) and moderate (23%) MWHB. Among MWHB who had a history of ICH, HCV, and invasive joint procedures, approximately half were non-severe, moderate and mild MWHB.

Current treatment regimen was highly correlated with disease severity. Among severe MWHB 24% were using episodic therapy and 76% were using prophylaxis. Whereas event-based or continuous prophylaxis was used by 20% of men with moderate severity and by 10% of men with mild severity. The proportion of MWHB on event-based prophylaxis did not differ extensively by disease severity.

Overall, no history of a bleeding episode was reported for severe, moderate, and mild, disease severities as 17%, 44%, and 39% respectively. More than half of severe MWHB with no history of a joint bleed were 3 years of age or less at enrollment and 88% were less than 14 years old. However, only 1.4% of MWHB reported not having ever treated their bleeding disorder with any source of clotting factor, non-factor replacements, or antifibrinolytic. For all disease severities, the average age of the first bleeding episode occurred prior to the age of the first treatment episode.

The proportion of ICH was highest among MWHB with severe disease and lowest among MWHB with mild disease. However, participants with mild and moderate disease severity represented 47% of participants who had a history of ICH. History of using a central venous access device (CVAD) was reported by 27% of MWHB with moderate and 8% of MWHB with mild disease.

While the data collection instrument did not allow missing responses, a large proportion of dates of events were reported as unknown. For example, responses were unknown for 20% of participants for age at diagnosis (overall median 0.6 years ranging from -0.5 to 76.3 years), 29% for age at first bleed (overall median 1.3 years ranging from -0.5 to 70.3 years), 36% for age at first treatment (overall median 1.8 years ranging from -0.5 to 75.6 years), as well as 10% of the

number of treated bleeding events in the previous 12 months (overall median 1.0 ranging from 0.0 to 500).

Discussion

These data demonstrate that the cohort of MWHB who enrolled in the Community Counts Registry from 2014 to 2018 had characteristics similar to those of the population of MWHB treated in HTCs, during the same time period. The number of MWHB in the US has increased significantly since the national estimate from 1994. These analyses also demonstrated that only half of severe MWHB had a family history of the bleeding disorder and non-severe MWHB experience morbidity at an equal proportion to severe MWHB, for events such as ICH. And non-severe MWHB represent more than a quarter of MWHB whose treatment regimen is prophylaxis.

Soucie *et al* (1998) estimated approximately 2,800 MWHB were treated in US HTCs in 1994.[6] These analyses demonstrate that almost 5,000 MWHB were treated in US HTCs between 2014 to 2018. The difference in the populations treated in HTCs is not due to a difference in patient inclusion criteria between studies. Soucie *et al* limited inclusion to 30% and while the current estimate expands disease severity to 40%, this difference only accounts for 26 MWHB who had a baseline factor activity level between 31-40%. A potential important influence on the lower number of MWHB in the 1990's compared to more recently was the epidemic of hemophilia-treatment-related HIV and HCV exposure and consequent premature mortality that occurred in the 1990's. This effect was seen in other parts of the world as well. For example, the life expectancy for MWH in Italy between 1990-1999, was 64.0 years with 60% of mortality due to HIV. Life expectancy increased to 71.2 between the years of 2000-2007, and mortality due to HIV decreased to 17.6%.[13] Beyond a reduction in HIV-related mortality, it has been

hypothesized that in the US, the implementation of prophylactic care for patients with severe disease, has led to further gains in life expectancy. Additionally, the estimate that 70% of MWH are treated in HTCs may under represent the current proportion of patients treated at HTCs currently.

To date, few studies have examined ICH across disease severity for MWHB. These analyses demonstrated that non-severe MWHB experience a similar percentage of ICH as severe MWHB. The 7% overall prevalence of ICH among all MWHB with no history of an inhibitor, in all ages, is significantly higher than previously reported, although many previous studies of ICH included all MWH, precluding determination of the prevalence in MWHB.[14] A study in the US using UDC data from 1998-2008, found an ICH prevalence of 1.8%, however this sample included MWHB with a history of or current inhibitor, which is a known risk factor for ICH development, and therefore may overestimate the prevalance among MWHB without inhibitors.[2] An earlier study in the US using state-level data from 1993-1997 found an ICH prevalence of 2.0% however, this prevalence may have been lower because patients did not survive to later report their ICH history in surveillance programs.[15]

Surprisingly, we did see a difference in family history by disease severity. Among those with a no family history, approximately half were severe MWHB; and among those with a family history, the majority were moderate MWHB. No family history of a congenital bleeding disorder, where HB is the result of a spontaneous mutation, has been reported in approximately one-third of MWH.[16] Our analyses had a much lower overall proportion of MWHB with no known family history of HB at 17%. A known family history may be increased due to an increased number of women being diagnosed with hemophilia and as carriers or potentially that

with the improvements in treatment, couples with a history of hemophilia feel that if they conceive a child with hemophilia, it will be easier to manage.

In 2007 a randomized control trial in the US of severe MWH A demonstrated reduction of arthropathy by using prophylaxis treatment regimen compared to episodic.[17] In 2012, the World Federation of Hemophilia provided global guidelines for prophylactic therapy, indicating that short-term prophylaxis can interrupt repeated bleeding and is advised prior to engaging in physical activity; however specific guidelines for prophylactic care by disease severity were not provided.[18] In 2016 the Medical and Scientific Advisory Committee of the National Hemophilia Committee stated that prophylaxis should be used as optimal therapy for MWHB with severe disease.[19] Despite the recommendation, only 76% of severe MWHB were on prophylactic therapy at their Registry enrollment and public health promotion is needed to increase this proportion. However, the proportion has increased from previous estimates in the US from 1998-2011 with 45% of severe MWHB and in Canada the estimate from 2006 was 32% of severe HB patients were using prophylaxis.[20,21]

More importantly, the proportion of moderate MWHB using intermittent or continuous prophylaxis in our analyses was 20%, more than double previous estimates, and 10% of mild MWHB were using intermittent or continuous prophylaxis. Ullman *et al* reported that in the UDC from 1998-2011the prevalence of prophylaxis usage amongst moderates was 8%, and in Canada in 2006 was 5% of moderate and 1% of mild MWHB.[20,21] To our knowledge, no previous reports from US surveillance systems have documented prophylaxis among MWHB with mild disease.

Limitations

As noted, unknown data for ages at events related to diagnosis, bleeding, and treatment was substantial. Further work is needed to examine if this information is related to patients' age or associated with specific HTCs. For example, older patients may not recall this information and it may not be in their medical records if they have been treated at multiple institutions over the course of their lifetime. Or it could be measurement error, in that data coordinators at certain HTCs had difficulty capturing this information in the electronic health records and did not check with the patient to ascertain it.

Another limitation is that while these data are generalizable to patients being treated at federally funded HTCs, they may not be generalizable to the subset of patients treated by private practitioners or HTCs that are not federally funded. It has been hypothesized that clinical outcomes of patients being seen outside of HTCs may be different from those being seen within HTCs, if expense and lack of insurance are delaying care. However, previous reports of national data were limited to participants enrolled in UDC between 1998-2011, who were also seen at HTCs. Our analyses examined the prevalence of hemophilia-related health outcomes in MWHB during a more recent timeframe. Additionally, these analyses examined the prevalence of health outcomes across disease severity to better describe all MWHB as opposed to solely describing health outcomes of MWHB by a single disease severity.

Conclusion

The cohort of MWHB enrolled in the Community Counts Registry from 2014-2018 is representative of the population of MWHB treated in HTCs from Population Profile, during the same time period. These analyses demonstrated that there are almost 5000 MWHB being treated at HTCs, which is a significant increase from previous estimates, and almost half are enrolled in the Registry surveillance system. The proportion of non-severe MWHB who have experienced

an ICH have increased significantly from previous reports. Use of prophylaxis has increased, particularly among MWHB with moderate and mild disease. There are likely enough mild and moderate patients using prophylaxis to have disease severity included in statistical models of factors associated with prophylaxis. Since disease severity is likely to be the largest predictor of, and effect modifier of other clinical characteristics of prophylaxis, future research should include all disease severities.

Word Count: 3849

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Data Tables and Figures

Figure 1. Inclusion and Exclusion for Each Dataset

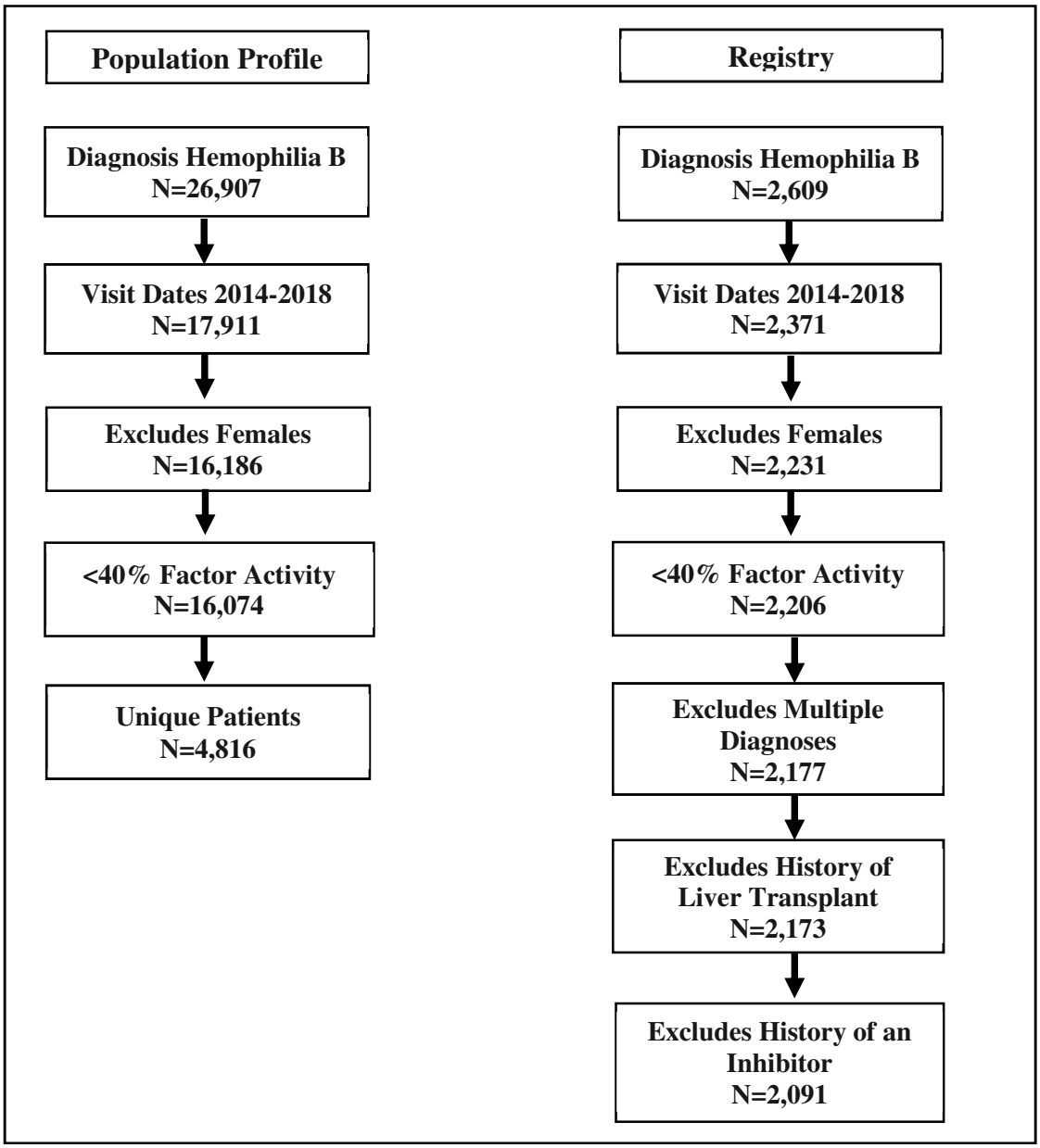

Table 1. Comparison of unique MWHB in the Population Profile compared to the Registry by demographic and clinical measures.

Characteristic	Population Profile HB (N=4816) N (%)	Initial Registry visit HB (n=2091) N (%)
Disease Severity		
Severe	1533 (31.8)	754 (36.1)
Moderate	2017 (41.9)	827 (39.6)
Mild	1266 (26.3)	510 (24.4)
Year of Visit		
2014	2834 (58.9)	482 (23.0)
2015	787 (16.3)	481 (23.0)
2016	491 (10.2)	473 (22.6)
2017	372 (7.7)	357 (17.1)
2018	332 (6.9)	298 (14.3)
HTC Region		
A	966 (20.1)	468 (22.4)
B	707 (14.7)	245 (11.7)
C	622 (12.9)	213 (10.2)
D	482 (10.0)	188 (9.0)
E	503 (10.4)	257 (12.3)
F	421 (8.7)	229 (11.0)
G	702 (14.6)	359 (17.2)
H	413 (8.6)	133 (6.3)
Enrollment Age (in years)		
<3	634 (13.2)	155 (7.4)
3-12	878 (20.3)	493 (23.6)
13-19	684 (14.2)	390 (18.7)
20-30	824 (17.1)	305 (14.6)
31-45	721 (15.0)	301 (14.4)
46+	975 (20.2)	447 (21.4)
Race		
White	4151 (86.2)	1757 (84.0)
Black or African American	420 (8.7)	202 (9.7)
Asian	129 (2.7)	62 (3.0)
Other / Unknown	116 (2.4)	70 (3.3)
Ethnicity		
Hispanic/Latino/Spanish origin	491 (10.2)	206 (9.9)
Not Hispanic/Latino/Spanish origin	4270 (88.7)	1859 (88.9)
Unknown	55 (1.1)	26 (1.2)
Primary Health Insurance Status		
Insured	4168 (86.5)	1904 (91.1)
Not Insured	605 (12.6)	175 (8.4)
Unknown	43 (0.9)	10 (0.5)
History of HCV Infection		
Yes	923 (19.2)	466 (22.3)
No	3204 (66.5)	1492 (71.3)
Unknown	689 (14.3)	133 (6.4)
History of HIV Infection		
Yes	174 (3.6)	79 (3.8)
No	3851 (80.0)	1856 (88.7)
Unknown	791 (16.4)	156 (7.5)

Column percentages.

Table 2. Comparison of MWHB demographic characteristics in the Registry by disease severity.

	Disease Severity			
	Severe (N=754)	**Moderate** (n=827)	**Mild** (n=510)	**Total** (n=2091)
Characteristic	N (%)	N (%)	N (%)	N
Year of Enrollment				
2014	207 (43.0)	161 (33.4)	114 (23.6)	482
2015	182 (37.8)	193 (40.1)	106 (22.0)	481
2016	156 (33.0)	218 (46.1)	99 (20.9)	473
2017	122 (34.2)	134 (37.5)	101 (28.3)	357
2018	87 (29.2)	121 (40.6)	90 (30.2)	298
HTC Region				
A	117 (25.0)	249 (53.2)	102 (21.8)	468
B	87 (35.5)	88 (35.9)	70 (28.6)	245
C	77 (36.2)	81 (38.0)	55 (25.8)	213
D	64 (34.0)	87 (46.3)	37 (19.7)	188
E	119 (46.3)	78 (30.4)	60 (23.4)	257
F	81 (35.4)	93 (40.6)	55 (24.0)	229
G	132 (36.7)	127 (35.4)	100 (27.9)	359
H	77 (58.3)	24 (18.2)	31 (23.5)	132
Enrollment Age (in years)				
<3	81 (52.2)	55 (35.5)	19 (12.3)	155
3-12	186 (37.7)	195 (39.5)	112 (22.3)	493
13-19	130 (33.3)	168 (43.1)	92 (23.6)	390
20-30	120 (39.3)	111 (36.4)	74 (24.3)	305
31-45	117 (38.9)	120 (39.9)	64 (21.2)	301
>=46	120 (26.9)	178 (39.8)	149 (33.3)	447
Race				
White	577 (32.8)	739 (42.1)	441 (25.1)	1757
Black or African American	108 (53.5)	45 (22.3)	49 (24.3)	202
Asian	39 (62.9)	14 (22.6)	9 (14.5)	62
Other	30 (42.9)	29 (41.4)	11 (15.7)	70
Ethnicity				
Hispanic/Latino/Spanish origin	125 (60.7)	43 (20.9)	38 (18.4)	206
Not Hispanic/Latino/Spanish origin	624 (33.6)	770 (41.4)	465 (25.0)	1859
Unknown	5 (19.2)	14 (53.9)	7 (26.9)	26
Patient Highest Education Completed				
High school or Lower	482 (34.9)	586 (42.5)	312 (22.6)	1380
Some college	203 (41.6)	163 (33.4)	122 (25.0)	488
Advanced degree	37 (33.0)	45 (40.2)	30 (26.8)	112
Unknown	32 (28.8)	33 (29.7)	46 (41.4)	111
Parent Highest Education Completed (Patients' <=18 years of age)				
High school or Lower	81 (32.5)	126 (50.6)	42 (16.9)	249
Some college	128 (41.4)	118 (38.2)	63 (20.4)	309
Advanced degree	34 (40.5)	25 (29.8)	25 (29.8)	84
Unknown	100 (39.4)	97 (38.2)	57 (22.4)	254
Patient Employment Status (Patients' <=18 years of age)				
Full-Time	175 (27.3)	289 (45.1)	177 (27.6)	641
Part-Time	47 (41.2)	37 (32.5)	30 (26.3)	114
Not employed	179 (43.9)	125 (30.6)	104 (25.5)	408
Unknown	10 (35.7)	7 (25.0)	11 (39.3)	28

Row Percentages

Table 3. Comparison of MWHB clinical characteristics in the Registry by disease severity.

	Disease Severity			
	Severe (N=754)	**Moderate** (n=827)	**Mild** (n=510)	**Total** (n=2091)
Characteristic	N (%)	N (%)	N (%)	N
Health Insurance Type				
Commercial	391 (36.8)	398 (37.5)	273 (25.7)	1062
Government	325 (43.1)	256 (34.0)	173 (22.9)	754
Other	28 (28.6)	41 (41.8)	29 (29.6)	98
Uninsured	8 (4.6)	132 (75.4)	35 (20.0)	175
Family History Bleeding disorder				
Yes	525 (32.1)	710 (43.4)	401 (24.5)	1636
No	190 (55.7)	77 (22.6)	74 (21.7)	341
Unknown	39 (34.2)	40 (35.1)	35 (30.7)	114
Body Mass Index*				
Underweight	17 (36.2)	23 (48.9)	7 (14.9)	47
Normal weight	311 (37.4)	332 (39.9)	189 (22.7)	832
Overweight	170 (35.3)	184 (38.2)	128 (26.6)	482
Obese	185 (34.2)	201 (37.2)	155 (28.6)	541
HTC Location				
Primary HTC	703 (38.2)	668 (36.3)	468 (25.6)	1839
Outreach Clinic	36 (17.4)	134 (64.7)	37 (17.9)	207
Combination	15 (34.1)	23 (54.6)	5 (11.4)	44
History of HIV				
Yes	59 (74.7)	12 (15.2)	8 (10.1)	79
No	655 (35.3)	753 (40.6)	448 (24.1)	1856
Unknown	40 (25.6)	62 (39.7)	54 (34.6)	156
History of HCV				
Yes	240 (51.5)	165 (35.4)	61 (13.1)	466
No	478 (32.0)	612 (41.0)	402 (26.9)	1492
Unknown	36 (27.1)	50 (37.6)	47 (35.3)	133
History of Intracranial Hemorrhage				
Yes	79 (54.1)	47 (32.2)	20 (13.7)	146
No	641 (34.1)	760 (40.4)	479 (25.5)	1880
Unknown	34 (52.3)	20 (30.8)	11 (16.9)	65
History of CVAD Usage				
Yes	227 (64.7)	95 (27.1)	29 (8.3)	351
No	499 (29.8)	708 (42.3)	467 (27.9)	1674
Unknown	28 (42.4)	24 (36.4)	14 (21.2)	66
History of Joint Bleed				
Yes	607 (47.9)	462 (36.5)	198 (15.6)	1267
No	136 (17.4)	334 (44.1)	301 (38.5)	781
Unknown	11 (25.6)	21 (48.8)	11 (25.6)	43
First Joint Bleed Age				
<3 years	194 (76.1)	52 (20.4)	9 (3.5)	255
3-6 years	110 (57.0)	66 (34.2)	17 (8.8)	193
>6 years	49 (16.3)	156 (51.8)	96 (31.9)	301
Unknown	253 (48.9)	188 (36.4)	76 (14.7)	517
History of Invasive Joint Procedure				
Yes	161 (51.3)	95 (30.3)	58 (18.5)	314
No	575 (33.1)	718 (41.3)	446 (25.6)	1739
Unknown	18 (47.4)	14 (36.8)	6 (15.8)	38
Current Treatment Regimen				
Episodic	185 (14.1)	662 (50.6)	461 (35.2)	1308
Event-based prophylaxis	35 (36.8)	37 (39.0)	23 (24.2)	95
Continuous prophylaxis	534 (77.7)	127 (18.5)	26 (3.8)	671

*Missing n=189

Table 4. Comparison of MWHB clinical characteristics in the Registry by disease severity.

	Disease Severity								
	Severe (N=754)			**Moderate** (n=827)			**Mild** (n=510)		
Characteristic	M	IQR	Range	M	IQR	Range	M	IQR	Range
Age at Diagnosis (yrs)*	0.1	0.0-1.1	-0.5-63.4	0.9	0.0-9.4	-0.3-64.8	5.1	0.0-17.1	-0.2-76.3
Age at First Bleed (yrs)**	0.4	0.0-1.2	-0.5-35.7	1.8	0.6-5.6	-0.5-70.3	5.2	1.7-10.8	-0.2-66.2
Age at First Treatment (yrs)***	0.6	0.0-1.5	-0.5-35.7	2.4	0.9-8.6	-0.4-58.6	7.5	2.3-17.7	-0.2-75.6
Number Treated Bleeds Previous Year****	2.5	1.0-6.0	0.0-500.0	1.0	0.0-3.0	0.0-160.0	0.0	0.0-1.0	0.0-26.0

M = median; IQR = Interquartile Range; *Unknown n=410; **unknown n=602; ***Unknown n=758; ****unknown n=219

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CHAPTER 3.

Evaluation of Factors Associated with Prophylaxis Treatment Regimen among Men with Hemophilia B Participating in the Community Counts Registry from 2014-2018.

Written for submission to Haemophilia

Introduction

Hemophilia B (HB) is an X-linked congenital bleeding disorder caused by a genetic mutation of the factor IX (FIX) gene which results in spontaneous and trauma-related bleeding. HB affects approximately 5,000 men in the United States (US) treated in federally funded hemophilia treatment centers (HTCs).[1] Treatment goals for men with hemophilia B (MWHB) in the US include the effective management and prevention of bleeding episodes to reduce arthropathy and life-threatening bleeds, such as intracranial hemorrhage (ICH), as well as improving the overall health and quality of life.[2] Clinical management of men with hemophilia (MWH) generally involves episodic or prophylactic treatment regimens. Episodic care is defined as treatment product usage to control a clinically evident bleeding episode. Prophylactic care is defined as treatment product usage on a continuous or intermittent basis to prevent bleeding episodes.

Prophylactic treatment has been practiced in children with severe HB in Sweden since 1972.[3] Despite the insufficient plasma derived factor concentrate availability at times and long intervals between doses, they found significant improvements in joint health outcomes. Patients with severe disease on prophylaxis had joint function that resembled patients with moderate disease.[3] In the US, the current National Hemophilia Foundation Medical And Scientific Advisory Council (MASAC) recommends that healthcare providers use continuous prophylactic treatment regimens as optimal therapy for persons with severe hemophilia B.[2] Globally, the

World Federation of Hemophilia does not provide specific guidelines for prophylactic care for moderate and mild MWHB.[4] MWHB with mild and moderate disease severity comprise approximately two-thirds of MWHB treated in federally funded HTCs, yet there are currently no standardized US or global recommendations or guidelines for their optimal therapy.[1]

Hemophilia is a rare disorder. In the US, HB accounts for an estimated 1 in 20,000 male births in the US and an estimated 1 in 50,000 male births in Europe.[5] Achieving sample sizes of MWHB to perform randomized controlled trials, to develop evidence-based standardized treatment practices have been challenging. To date, the majority of hemophilia treatment guidelines, such as implementing prophylaxis as standard of care for men with severe HB, have been based on research studies composed of MWH A and applied to MWHB since the disorder manifests in similar ways.[6,7,8] In the absence of randomized controlled trials of MWHB and limited treatment guidelines, observational studies that describe current treatment practices and health outcomes among MWHB are important to inform the hemophilia community of current clinical practices.

Previous studies examining characteristics of MWH using prophylaxis versus episodic treatment regimens used logistic regression modeling. A fundamental assumption of logistic regression is the independence of observations. However, this assumption is violated if data are clustered. One type of clustered data is if individuals are sampled within sites, such as HTCs, where the site is the cluster. Several studies have previously suggested that hemophilia treatment practices vary by HTCs.[9] If treatment regimen is correlated among MWHB based on the HTC where they receive treatment, then to accurately assess the probability of treatment in various subgroups of MWHB, one must incorporate into the model the variation in the outcome at the

HTC level. In addition to conventional regression coefficients to account for the multilevel nature of the data.

Marginal models that use generalized estimating equations (GEE) are a type of generalized linear model methodology that allow for correlated outcome observations due to clusters. Marginal models using GEE have been proven to be effective and appropriate when the outcome measures are binary, patient-level covariates are the analytic interest, there are a large number of clusters and varying numbers of observations in each cluster.[10,11,12] Marginal models estimate population averaged probabilities, that account for the clustering effects, to allow inferences to the population.[13]

We hypothesize that treatment regimens for MWHB are not independent and are better modeled as a hierarchical structure of MWHB, providers, and HTCs; with the assumption that the dependent variable, treatment regimen, is correlated between groups of MWHB, who are nested within providers at clusters of HTCs. We hypothesized that an intraclass correlation coefficient (ICC) greater than 5%, which LeBreton and Senter (2008) have proposed represents a small to medium effect, is sufficient to demonstrate clustering.[14]

Using a large national sample, the Community Counts Registry for Bleeding Disorders Surveillance project (Registry) from 2014-2018, this analyses (i) examines the demographic and clinical factors of MWHB associated with treatment regimen, (ii) evaluates if treatment regimen is correlated among MWHB based on the HTC where they receive treatment, and (iii) examines the demographic and clinical factors that are associated with the probability of the treatment regimen practiced at enrollment, prophylaxis versus episodic.

Methods

Dataset

The Registry has been conducted since December 2013 and is a collaboration between the Centers for Disease Control and Prevention (CDC), the American Thrombosis and Hemostasis Network, and the US Hemophilia Treatment Center Network. The structure and organization of Community Counts have been previously described.[1,7] In brief, the Registry includes standardized data on clinical outcomes among persons with bleeding disorders who receive comprehensive care at federally-funded HTCs throughout the US. Patients (or parents of minor patients) are asked to provide authorization for enrollment and inclusion of their data in the Registry. For each participating patient, the HTC collects and submits to the Registry detailed clinical information from the patient's enrollment to the HTC and thereafter from the patient's annual visits; data collection includes demographic characteristics, health characteristics, bleeding disorder treatments, and complications associated with the patient's bleeding disorder or treatment. Data from the from the initial visit form, completed at enrollment, were used for these analyses.

Design and Participants

The design was a non-interventional retrospective cross-sectional analysis. Inclusion criterion included MWHB with a completed initial visit form between 2014 to 2018 who had a baseline factor activity level less than 40%. Exclusion criterion included MWHB with multiple bleeding disorder diagnoses (n=29), history of a liver transplant (n=4), or a history of an inhibitor (n=82). History of an inhibitor was defined as having a date the inhibitor was detected, two inhibitor titers identified on separate dates >=2.0 Bethesda units, or one inhibitor titer >=2.0 Bethesda units and indication of inhibitor treatment, such as immune tolerance induction or treatment with bypassing agents (*CDC unpublished).*

Variables Assessed

The dependent variable was treatment regimen at the time of enrollment, defined as episodic or prophylaxis. In the Registry, episodic treatment regimen was defined as the use of treatment product only for the treatment of extant bleeds. The prophylaxis treatment regimen included both event-based/short term/intermittent prophylaxis and continuous prophylaxis. In the Registry, event-based/short term/intermittent prophylaxis was defined as use of treatment product to prevent anticipated bleeds associated with a medical/dental event or an activity on an intermittent basis, repeatedly over a short period of time; or treatment on a regular basis to prevent any and all bleeds for an extended period of time, but not indefinitely. Continuous prophylaxis was defined as the use of treatment product on a regular basis to prevent any and all bleeds and is expected to continue over an indefinite period of time.

We assessed a number of demographic characteristics and clinical outcomes hypothesized to be associated with the treatment regimen. Participants with endogenous FIX activity of <1% were classified as severe, 1-5% as moderate, and 6-40% as mild.[15] To increase the power to analyze multiple covariates and interaction effects in the model, we collapsed moderate and mild patients into a category as non-severe. HTC region classification was based on the Health Resources Service Administration region classification and were anonymous per requirements of the Community Counts project review committee. Age at enrollment was calculated by subtracting the date of visit by the date of birth. We then categorized enrollment age, with the youngest category including children less than or equal to three years of age. History of Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) were defined according to whether the participants had been diagnosed during their lifetime; the unknown response category included results unknown, indeterminate test results, or the patient had never been tested.

Participants with reported insurance as Medicaid, Medicare, Military Health Care, and state programs were coded as having government insurance. Participants with a highest education level of pre-elementary, primary or secondary, or GED or equivalent were coded as high school or lower; and some college, technical school, 2-year college degree, and 4-year college degree were coded as college; and other was coded as unknown. Parent's highest education level was restricted to participants less than 18 years, per the survey instructions, and was coded the same as participants' highest education level. Patient employment status was restricted to participants 18 years or older. The location of where a participant received services, defined as HTC service location, was reported as multiple locations (HTC primary location, HTC outreach clinic, HTC telemedicine clinic), this was coded as combination. Body mass index (BMI) for participants, 20 years and older, was calculated as weight (kg) / height $(cm)^2$.[16] The BMI number was categorized as underweight if less than 18.5, normal if between 18.5 and 24.9, overweight if between 25 and 29.9, and obese if greater than 30.0. BMI percentile was calculated for participants between two years and nineteen years based on age, gender, height, and weight. The BMI percentile was categorized as underweight if less than the 5^{th} percentile, normal if between the 5^{th} and 85^{th} percentile, overweight if between the 85^{th} and 95^{th} percentile, and obese if equal to or greater than the 95^{th} percentile.

Data Analyses

We conducted descriptive analyses to assess demographic and clinical characteristics of our study population according to treatment regimen at enrollment. Measures of central tendency and dispersion were used to summarize continuous variables and frequency distributions were used to summarize categorical variables. Chi-Square tests of association were performed to test

for association between categorical variables. We tested for differences in location of continuous variables using the Mann-Whitney U test. A significance level of 0.05 was used.

To estimate factors associated with treatment regimen, we used marginal models and parameters were estimated with generalized estimating equations (GEE). This estimation method adjusts the standard errors, to account for correlated data within HTC. The outcome measure of treatment regimen was used with a binomial probability distribution and a logit link function to predict the probability of prophylaxis, as a linear function of demographic and clinical predictors. An exchangeable correlation structure was used. Prior to modeling, independent variables with responses of "unknown" or "other" were set to missing. Missing responses for variables included in the model were minimal and assumed to be missing at random.

Model Selection

It was determined a-priori to not include variables in the model with high proportions of unknown responses (>20% of all responses) and a high correlation with other independent variables, specifically: age at diagnosis, age at first bleeding event, and age at first treated bleeding event. It was also determined a-priori to include disease severity and primary health insurance in the model, regardless of statistical significance, due to contextual and clinical significance.

Independent variables with significant bivariate associations, using chi-square tests, were considered for inclusion in the model. For those variables, a two-fold approach using the magnitude of the bivariate odds ratios (not presented) as well as the evaluation of the quasi-likelihood (QIC-u) under the independence model criterion goodness of fit test statistics were used. We also examined interaction effects. Statistical modeling was performed with the PROC GENMOD SAS procedure.

To quantify the effect of clustering we estimated the intraclass correlation coefficient (ICC) for a multilevel logistic model, using the final multivariable model.[13] The ICC was used to determine the proportion of variance accounted for by the HTC level. This modeling was performed with the GLIMMIX SAS procedure.

Data in the model are presented as adjusted odds ratios with 95% confidence intervals and p-values for the Wald test. We interpreted the exponentiated β regression coefficients (odds ratios) as the odds a characteristic is present versus absent when modeling the logit of the dependent variable, prophylaxis versus episodic treatment regimen. Statistical significance was set a priori for two-sided test values at α=.05. All analyses were conducted using SAS statistical software version 9.4 (SAS Institute, Cary, NC).

Results

Descriptive Statistics

Our sample contained 2090 MWHB from 133 HTCs. Overall, 37.4% were on a prophylactic treatment regimen at enrollment in the Registry (table 1). We observed a wide variation in the treatment regimen for persons with severe HB by HTC. Figure 1 presents the variation by HTC in the proportion of MWHB with severe disease who received prophylaxis at enrollment in the Registry. Of the 123 HTCs that treated one or more MWHB with severe disease, the following had severe HB patients who were treating with prophylaxis: 4% of HTCs had none, 1.6% had been 1-25% of their patients, 11.4% had between 26-50% of their patients, 26.8% had 51-75% of their patients, 17.2% had 76-99% of their patients, and 39.0% had 100% of their severe HB patients using prophylaxis.

Overall, 42.0% of all disease severities and 81.9% of severe children 20 years or younger at enrollment were utilizing prophylaxis. However, among children less than or equal to 3 years

of age at enrollment, 35.8% of all disease severities and 60.7% of severe HB, were on prophylaxis. Prophylaxis usage among non-severe MWHB increased from 16.8% in moderate and 6.1% in mild patients in 2014 to 26.4% in moderates and 10.0% in mild patients in 2018. The proportion of white MWHB using prophylaxis (34.2%) was significantly lower than the proportion of Black or African American (54.5%) and Asian (64.5%) using a prophylactic treatment regimen. This trend was also seen in the variable ethnicity, the proportion of MWHB who identified as Hispanic/Latino/Spanish origin treating with prophylaxis was significantly higher (62.6%) than MWHB who did not identify with this ethnicity (34.8%). Treatment regimen was not significantly associated with parents' highest education level or and history of emergency room (ER) visits in the previous year.

Among MWHB with a history of an intracranial hemorrhage (ICH), 41.8% were using episodic therapy at enrollment (table 2). More MWHB who did not have a family history of hemophilia were using prophylaxis (52.1%) than those who did have a family history (34.3%). The proportion of MWHB using prophylaxis at enrollment did not change significantly from 2014 to 2018. The average age at enrollment, age at diagnosis, age at first joint bleed, age at first treatment were all significantly lower for MWHB on prophylaxis compared to episodic treatment (table 3).

Multivariable Associations

Table 4 presents the multivariable analyses from the final model which included disease severity, enrollment age, ethnicity, primary health insurance, history of a CVAD, history of a joint bleed, and chronic pain in the previous 12 months. In addition, a significant interaction was found between disease severity and history of chronic pain as well as between age at enrollment and history of a CVAD. After controlling for disease severity only, the following covariates were

no longer significantly associated with treatment regimen: participants' race, history of an invasive joint procedure, history of HIV, history of HCV, HTC region, patient's education level, BMI, patient employment, family history of a bleeding disorder, location of HTC services, and inpatient admission in previous 12 months.

In the multivariable model, after adjusting for the other variables in the model, we found that MWHB with severe disease and a history of chronic pain were 16.4 times more likely to be treating with prophylaxis, then MWHB with non-severe disease who had no history of chronic pain. MWHB between the ages of 13 to 20 years at enrollment who had a history of CVAD usage were 39.7 times more likely to be treating with prophylaxis then MWHB greater then 45 years old at enrollment who did not have a history of CVAD usage. The odds ratio for children less than 3 years of age being treated with prophylaxis compared to MWHB greater than 46 years old was not significant on its own; however, when examining the interaction effect of children less than 3 years of age with a history of CVAD compared to 46 years and older with no history of CVAD usage, the odds of currently treating with prophylaxis increased to 22.7 and was significant. After adjusting for the other variables in the model, MWHB with a history of a joint bleed were 3.4 times more likely to currently treat with prophylaxis than MWHB with no history. The odds of uninsured MWHB were 0.4 times less likely to be treating with prophylaxis compared to MWHB with commercial insurance.

Using the final model, the ICC was 10%. This was double the hypothesized value of 5%. This reaffirms that patient-level observations for treatment regimen (episodic vs prophylaxis) are more similar within HTCs then patient level observations for treatment regimen from different HTCs.

Discussion

A large number of publications have demonstrated the benefits of prophylaxis for men with hemophilia with severe disease in the last decade. Our analyses found that among children less than or equal to 20 years of age, 82% of children with severe HB were utilizing prophylaxis. This is a significant increase from estimates from 1998 to 2011 which reported 35% of children less than or equal to 19 years of age were treated with prophylaxis.[17] A 2017 study demonstrated that prophylaxis usage in severe MWHB was only effective in preventing loss of joint motion if initiated prior to 4 years of age.[17] We observed that only 61% of children less than three years with severe HB were treated with prophylaxis at enrollment. Additional health promotion work targeted to parents of children younger than 4 years of age and providers to increase prophylaxis among that age group may be beneficial.

While the goal of prophylaxis has historically been to maintain a factor level greater than 1%,[3] more recent studies have demonstrated that maintaining baseline factor activity levels at 12-15% or above are required for full protection from spontaneous bleeds.[18,19] This indicates that MWHB with moderate disease with factor activity between 1-5%, and MWHB with mild disease with factor activity levels great than 5%, could greatly benefit from prophylaxis.

Previous studies examining prophylaxis usage in the US have largely excluded MWHB with mild and moderate disease. However, we observed that MWHB with mild and moderate disease represent over a quarter of the MWHB who are using prophylaxis. While we originally intended to keep disease severity in distinct categories in the multivariable regression model, the confidence intervals were very wide due to the low samples size of mild patients on prophylaxis. To obtain more precise estimates of predictors and since neither moderate or mild MWHB have standardized treatment guidelines regarding prophylaxis, we collapsed mild and moderate into a single category. We chose not to exclude mild patients because we demonstrated that mild

patients are using prophylaxis and excluding MWHB with non-severe disease from these analyses would create a subgroup analysis, which has been demonstrated to have a number of limitations.[20]

We observed that there was an increase in prophylactic treatment among non-severe patients over time, but surprisingly there was not a significant change in the overall prophylaxis usage over time from 2014 to 2018. We had hypothesized that the introduction of three FDA-approved novel extended half-life treatment products during our analyses time period would have increased the proportion of participants on prophylaxis. One of the greatest barriers to providers prescribing and MWHB utilizing prophylaxis, is adherence to frequent venous injections of treatment products, particularly among infants when venous access can be problematic. Utilization of extended half-life treatment products significantly reduces the number of required infusions to maintain the benefits of prophylaxis. However, with the introduction of novel treatment products that minimize a significant barrier to prophylaxis during the analyses time period, we did not see a significant change in prophylaxis usage between 2014 to 2018. The lack of difference between years of enrollment on treatment regimen was not attributed to significant differences in patients' enrollment by disease severity, as MWHB with severe disease remained constant during the same time period.[1] The confidence intervals were wide, which was likely due to small sample sizes.

These data provide strong evidence that treatment regimens for MWHB are strongly clustered by their HTCs using qualitative (figure 1) and quantitative assessment (ICC). LeBreton and Senter (2008) have proposed that an ICC of 5% represents a small to medium effect.[14] After adjusting for all patient-level demographic and clinical parameters in the full model in our

analyses, 10.1% of the observed variance in patients' treatment regimen was due to systematic differences between HTC, compared to the total variance in treatment regimen.

To our knowledge, only one national study has been performed in the US examining predictors for treatment regimen for MWHB, Ullman et al (2017). They examined predictors for prophylaxis from MWHB with severe and moderate disease collected via the Universal Data Collection (UDC). The UDC was the surveillance project from 1998-2011, prior to the initiation of Community Counts. However, there were several limitations to this study. Ullman et al. excluded MWHB with mild severity, the UDC did not collect information on patients <2 years of age therefore this age group was excluded, and only presented bivariate associations with odds ratios for the outcome of episodic versus prophylaxis treatment and did not build a full model that controlled for covariates.[21] In addition, the wide time frame of this study likely skewed results as the first randomized control trial demonstrating the effects of prophylaxis versus episodic therapy was published in 2007.[7]

Clinical management of MWH remains challenging in the U.S. due to a number of factors. MASAC recommends that healthcare providers determine optimal care for individuals with hemophilia based on their individual disease severity, patient pharmacokinetics, number and severity of lifetime bleeding episodes, history of prescribed treatment regimen, treatment product utilized, and potential for bleeding episodes due to injury from physical activities.[2] However, these analyses demonstrate that after accounting for HTC clustering effects, there are other specific patient-level demographic and clinical characteristics that predict the likelihood for MWHB to utilize prophylaxis, such as history of CVAD usage, chronic pain, and ethnicity. Additionally, in these analyses, disease severity was a conditional effect while the overall effect was the sum of disease severity plus the interaction between disease severity and chronic pain.

Cost of care is significant for MWH and may also influence treatment regimen. A recent evaluation of direct costs to patients determined that median annual cost of prophylactic care for men with severe HB was $208,999 compared to $95,353 for episodic treatment regimens.[22] The cost of treatment has likely increased, as extended half-life treatment products were not available at the time of those analyses. Yet notably, while presence of insurance was significant over lack of insurance, type of insurance, government compared to commercial or other compared to commercial, was not a significant factor in determining treatment regimen during this time period. And other patient-level socioeconomic factors, such as patients' highest education level, parent's highest education level, and patient employment after adjusting for disease severity, were not significant. Patient-level socioeconomic factors may no longer be a consideration regarding treatment regimens for MWHB.

Limitations

There are several limitations to this study. Most notably is the temporality of effects for the factors associated with prophylaxis usage. The outcome was current treatment regimen practiced at enrollment and not at the initiation of prophylactic treatment. A CVAD is commonly used with repeated bleeding events as well as the initiation of prophylaxis, particularly amongst young children. The authors attempted to control for this by including the interaction term of CVAD by age. In addition, it has been reported that patients will start and stop and restart prophylaxis over their lifetime; therefore, initiation of prophylaxis is not always a one-time occurrence, and the purpose of this study was not to ascertain changes in treatment. The other main limitation is that these data are cross sectional in nature and while the sample has been demonstrated to be comparable to the population of MWHB treated in Population Profile at HTCs, it is unknown if this outcome is also generalizable to that population.

Conclusion

The proportion of individuals utilizing prophylaxis remained stable from 2014-2018, there were no significant differences by year at enrollment in Community Counts. We evaluated a potential association between a number of demographic and clinical factors and treatment regimen. We observed that history of a joint bleed, health insurance, ethnicity, and the interaction between enrollment age and history of CVAD usage, as well as the interaction between severity and chronic pain were the most significant factors associated with treatment regimen. In these analyses, we provided strong evidence that treatment regimens for MWHB are strongly clustered by their HTCs. Thus, future studies assessing treatment practices need to consider the possibility of clustering by HTC and if present, use appropriate statistical methods, such as multilevel or marginal modeling methodology. Future studies should also examine the type of treatment product for MWHB who are on continuous prophylaxis, to examine trends in product type after the introduction of the novel extended half-life treatment products.

Word Count: 4153

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Data Tables and Figures

Figure 1. Proportion of participants with severe hemophilia B using a prophylaxis treatment regimen in the Registry by HTC.

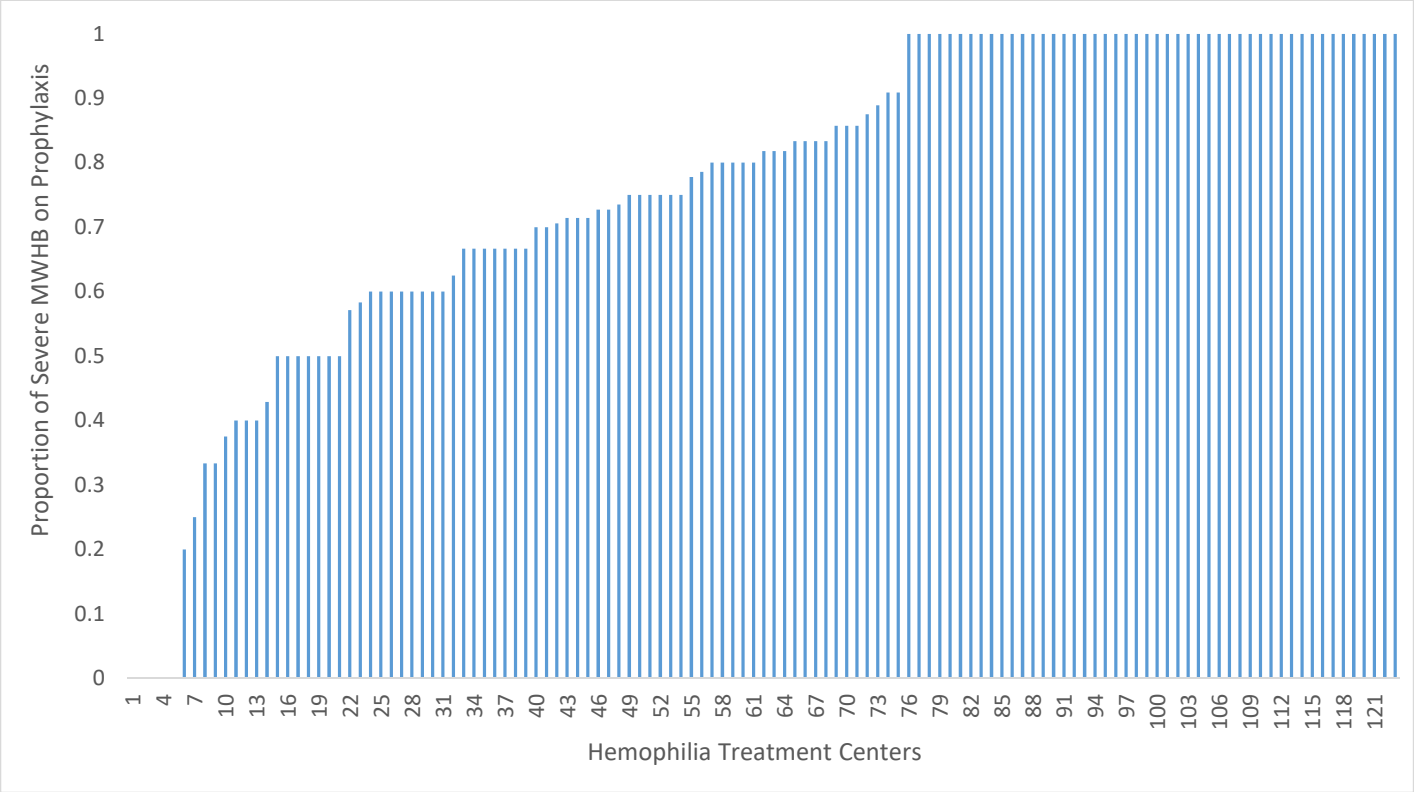

Table 1. MWHB demographic characteristics and association with treatment regimen at Registry enrollment.

	Treatment Regimen			
	Episodic (N = 1308)	**Prophylaxis** (N = 782)	**Total** (N=2090)	**P-value**
Characteristic	N (%)	N (%)	N	
Severity				
Severe	185 (24.5)	569 (75.5)	754	<0.0001
Moderate	662 (80.1)	164 (19.9)	826	
Mild	461 (90.4)	49 (9.6)	510	
Year of Enrollment				
2014	299 (62.0)	183 (38.0)	482	0.9461
2015	300 (62.5)	180 (37.5)	480	
2016	203 (64.1)	170 (35.9)	473	
2017	219 (61.3)	138 (38.7)	357	
2018	187 (62.7)	111 (37.3)	298	
Age at Enrollment (yrs)				
<=3	136 (64.1)	76 (35.9)	212	<0.0001
4–12	246 (56.4)	190 (43.6)	436	
13–20	220 (56.4)	170 (43.6)	390	
21-30	175 (57.4)	130 (42.6)	305	
30-45	201 (66.8)	100 (33.2)	301	
>=46	330 (74.0)	116 (26.0)	446	
HTC Region				
A	349 (74.6)	119 (25.4)	468	<0.0001
B	140 (57.1)	105 (42.9)	245	
C	132 (62.0)	81 (38.0)	213	
D	110 (58.5)	78 (41.5)	188	
E	146 (57.0)	110 (43.0)	256	
F	150 (65.5)	79 (34.5)	229	
G	231 (64.3)	128 (35.7)	359	
H	50 (37.9)	82 (62.1)	132	
Race				
White	1155 (65.8)	601 (34.2)	1756	<0.0001
Black or African American	92 (45.5)	110 (54.5)	202	
Asian	22 (35.5)	40 (64.5)	61	
Other	39 (55.7)	31 (44.3)	70	
Ethnicity				
Hispanic/Latino/Spanish origin	77 (37.4)	129 (62.6)	206	<0.0001
Not Hispanic/Latino/Spanish origin	1211 (65.2)	647 (34.8)	1858	
Unknown	20 (76.9)	6 (23.1)	26	
Patient Highest Education Completed				
High school or Lower	868 (62.9)	512 (37.1)	1380	0.0218
Some college	286 (58.6)	202 (41.4)	488	
Advanced degree	72 (64.9)	39 (35.1)	111	
Other	82 (73.9)	29 (26.1)	111	
Parent Highest Education Completed *(Patients' <18 years of age)*				
High school or Lower	149 (59.8)	100 (40.2)	249	0.4360
Some college	167 (54.1)	142 (45.9)	309	
Advanced degree	52 (61.9)	32 (38.1)	84	
Other	145 (57.1)	109 (42.9)	254	
Patient Employment Status *(18 years and older)*				
Full-Time	459 (71.7)	181 (28.3)	640	<0.0001
Part-Time	72 (63.2)	42 (36.8)	114	
Not Employed	237 (58.1)	171 (41.9)	408	

Other	23 (82.1)	5 (17.9)	28

Table 2. MWHB clinical characteristics and association with treatment regimen at Registry enrollment.

	Treatment Regimen			
	Episodic (N = 1283)	**Prophylaxis** (N = 765)	**Total** (N=2048)	**P-value**
Characteristic	N (%)	N (%)		
Primary Health Insurance				
Commercial	654 (61.6)	408 (38.4)	1062	<0.0001
Government	429 (56.9)	325 (43.1)	754	
Uninsured	166 (94.9)	9 (5.1)	175	
Other	59 (60.8)	38 (39.2)	97	
Family History Congenital				
Yes	1075 (65.7)	561 (34.3)	1636	<0.0001
No	163 (47.9)	177 (52.1)	340	
Unknown	70 (61.4)	44 (38.5)	114	
Body Mass Index				
Underweight	29 (61.7)	18 (38.3)	47	0.0008
Normal weight	478 (57.5)	354 (42.5)	832	
Overweight	310 (64.3)	172 (35.7)	482	
Obese	347 (64.3)	193 (35.7)	540	
HTC Location				
Primary HTC	1113 (60.6)	725 (39.4)	1838	<0.0001
Outreach Clinic	164 (79.2)	43 (20.8)	207	
Combination	30 (68.2)	14 (31.8)	44	
History of HCV Infection				
Yes	257 (55.3)	208 (44.7)	465	<0.0001
No	952 (63.8)	540 (36.2)	1492	
Unknown	99 (74.4)	34 (25.6)	133	
History of HIV Infection				
Yes	30 (38.5)	48 (61.5)	78	<0.0001
No	1160 (62.5)	696 (37.5)	1856	
Unknown	118 (75.6)	38 (24.4)	156	
History of ICH				
Yes	61 (41.8)	85 (58.2)	146	<0.0001
No	1212 (64.5)	667 (35.5)	1879	
Unknown	35 (53.9)	30 (46.1)	65	
History of CVAD				
Yes	86 (24.5)	265 (75.5)	351	<0.0001
No	1188 (71.0)	485 (29.0)	1673	
Unknown	34 (51.5)	32 (48.5)	66	
Joint Bleed History				
Yes	623 (49.2)	643 (50.8)	1266	<0.0001
No	654 (83.7)	127 (16.3)	781	
Unknown	31 (72.1)	12 (27.9)	43	
First Joint Bleed Age				
<3 years	63 (24.7)	192 (75.3)	255	<0.0001
3-6 years	73 (37.8)	120 (62.2)	193	
>6 years	219 (72.8)	82 (27.2)	301	
Unknown	268 (51.9)	248 (48.1)	516	
Invasive Joint Procedure History				
Yes	160 (51.0)	154 (49.0)	314	<0.0001
No	1128 (64.9)	610 (35.1)	1738	
Unknown	20 (52.6)	18 (47.4)	38	
Chronic Pain in previous year				
Yes	205 (45.5)	246 (54.5)	451	<0.0001
No	1071 (67.7)	510 (32.3)	1581	
Unknown	32 (55.2)	26 (44.8)	58	

Emergency Room Visit in previous year				
Yes	310 (61.1)	197 (38.9)	507	0.7006
No	984 (63.0)	578 (37.0)	1562	
Unknown	14 (66.7)	7 (33.3)	21	
Inpatient Admission in previous year				
Yes	108 (51.7)	101 (48.3)	209	0.0024
No	1189 (63.9)	673 (36.1)	1862	
Unknown	11 (57.9)	8 (42.1)	19	

Table 3. MWHB clinical characteristics and association with treatment regimen at Registry enrollment.

	Treatment Regimen						P-value
	Episodic (N = 1283)			Prophylaxis (N = 765)			
Characteristic	M	IQR	Range	M	IQR	Range	
Age at Diagnosis (yrs)*	1.3	0.0-11.2	-0.5-76.3	0.3	0.0-1.9	-0.4-64.8	<0.0001
Age at First Bleed (yrs)**	2.7	0.7-7.6	-0.5-70.3	0.5	0.0-1.3	-0.5-37.2	<0.0001
Age at First Treatment (yrs)***	3.8	1.1-11.8	-0.4-75.6	0.7	0.1-2.0	-0.5-45.0	<0.0001
Number of Treated Bleeds In Previous 12 months ****	1.0	0.0-2.0	0.0-500.0	2.0	1.0-5.0	0.0-100.0	<0.0001

M = median; IQR = Interquartile Range, *Missing n=410; **Missing n=601; *** n=757 ; ****Missing n=218

Table 4. Multivariable Factors Associated with a Prophylaxis Treatment Regimen using GEE Prediction Model

Characteristics	OR	95% CI	P-value
Ethnicity			
Hispanic/Latino/Spanish	1.7	(1.2-2.5)	0.0060
Not Hispanic/Latino/Spanish	reference		-
Primary Health Insurance			
Commercial	reference		-
Government	1.0	(0.7-1.3)	0.9606
Uninsured	0.4	(0.2-0.9)	0.0262
Other	1.3	(0.6-2.7)	0.4646
History of Joint Bleed Event			
Yes	3.7	(2.6-5.4)	<0.0001
No	reference		-
Severity by Chronic Pain			
Severe by Present Chronic Pain	14.4	(9.2-22.3)	0.0014
Non-severe by Absent Chronic Pain	reference		
Enrollment Age by CVAD usage			
<=3 years by CVAD (yes)	22.0	(5.5-88.2)	0.0014
4–12 years by CVAD (yes)	34.9	(14.4-84.9)	0.0002
13–20 years by CVAD (yes)	18.1	(7.6-43.4)	0.0160
21-30 years by CVAD (yes)	6.9	(2.6-18.6)	0.3729
30-45 years by CVAD (yes)	1.0	(0.4-3.0)	0.0806
>= 46 years by CVAD (no)	reference		-

OR=odds ratio. CI = confidence interval. GEE = generalized estimating equations.

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CHAPTER 4.

Evaluation of Factors Associated with Extended Half-Life Product Utilization for Men with Hemophilia B Participating in the Community Counts Registry from 2014-2018

Written for submission to Haemophilia

Introduction

Treatment of men with hemophilia B (MWHB) primarily consists of factor 9 protein replacement therapy. However, the types of replacement therapy products available and clinical management of MWHB in the United States (US) have evolved over time. Infused protein replacement therapy typically includes three types of treatment products, plasma-derived, since the late 1960's, traditional recombinant, since the mid 1980's, and extended half-life recombinant, first approved by the FDA in 2014. In the last six years there has been a dramatic change in the treatment products available to MWHB. Between 1992 and 1997, there were two plasma-derived and one traditional recombinant product approved by the FDA. Between 1998 and 2012 no products were approved. Between 2013 and 2018, there have been six products approved by the FDA; one plasma-derived, two traditional recombinant, and three extended half-life (EHL) recombinant treatment products.

Current clinical recommendations, from the Medical and Scientific Advisory Council of the National Hemophilia Foundation, are that MWHB in the US use recombinant products for treatment, as plasma-derived products still have a theoretical risk for viral transmission.[1] No product-related viral seroconversions have been documented in the US in over a decade. However, plasma-derived products have a documented risk of transmission of Parvovirus B19 and a theoretical risk of transmission of Creutzfeld-Jakob disease.[2,3]

The goal of prophylaxis has historically been to maintain a trough level of baseline factor activity above 1%, to keep a severe patient in the moderate level (1-5%) and reduce or even eliminate spontaneous bleeding episodes.[4] However, it has been demonstrated that to prevent joint damage, a trough level of 12-15% or potentially greater is required for full protection against bleeding events.[5,6] Therefore, joint damage in MWHB with moderate severity and some with mild severity, could be significantly reduced through a prophylaxis treatment regimen.

Prior to the approval of EHL treatment products, the World Federation of Hemophilia recommended that MWHB on prophylaxis with severe disease use standard half-life (SHL) treatment products (plasma-derived or recombinant) and infuse twice a week.[4] Twice weekly infusions are required to maintain severe MWH above 1% because SHL products have a half-life of 20-25 hours, although individual variability in pharmacokinetics exists.[5] However, these frequent venous injections of SHL products have been documented as a significant barrier to adherence in maintaining a prophylactic treatment regimen.[7] Initiating prophylaxis prior to the age of three has been demonstrated to have the largest impact for MWH with severe disease on reducing joint damage. However, frequent weekly infusions are challenging among infants and toddlers, resulting in the need for a central venous access device (CVAD) which can increase the likelihood of infection.

New EHL products for hemophilia B have two to three times greater half-lives compared to SHL products.[5] This dramatically increases the intervals between infusions, reducing the frequency of venous infusions to approximately every seven to fourteen days.[5] It has been hypothesized that this decrease in weekly infusions for prophylactic treatment regimens will have a large impact in improving patient treatment adherence and remove many of the challenges in implementing prophylaxis in young children.

However, treatment costs for prophylaxis increase significantly with EHL products compared to SHL products.[8] A recent evaluation of direct costs to patients determined that the median annual cost of prophylactic care for men with severe HB was $208,999 compared to $95,353 for patients on episodic treatment regimens.[9] And treatment costs for EHL treatment products have been estimated to be double the expenditures of SHL treatment products.[8] Therefore patient-level socioeconomic factors, such as employment status and health insurance utilization likely remain a consideration for healthcare providers in their prescribed treatment.

The Community Counts Registry provides a unique opportunity to evaluate treatment product utilization trends for MWHB and examine factors associated with the uptake of EHL products among MWHB. An evaluation of MWHB participating in Community Counts demonstrated that treatment regimen, prophylaxis versus episodic, was clustered by HTC; where treatment regimen was correlated between groups of MWHB, who were nested within providers in clusters of HTCs.[10] We hypothesized that the outcomes of treatment product type used among MWHB on continuous prophylaxis are also correlated between groups of MWHB who are nested within providers at HTCs. We hypothesized that an intraclass correlation coefficient (ICC) greater than 5%, which represents a small to medium effect of clustering, would demonstrate clustering in our sample. In these analyses, we used national data from MWHB using continuous prophylaxis, participating in the Community Counts Registry at their enrollment between 2014 to 2018, to describe their treatment product type. We further examined the demographic and clinical factors as well as history of health outcomes associated with the probability of using an EHL products compared to SHL products at Registry enrollment for participants on continuous prophylaxis.

Methods

Design and Participants

We conducted a non-interventional retrospective cross-sectional analysis of the initial visit form data from the Community Counts Registry, completed at enrollment. Participants included male patients with a primary diagnosis of HB, a baseline factor activity level less than 40%, who were enrolled in the Registry between 2014 to 2018, and whose treatment regimen was continuous prophylaxis at enrollment. Participants were excluded from the analyses who had multiple bleeding disorder diagnoses, a history of a liver transplant, or had a history of an inhibitor. MWHB whose treatment regimen at enrollment was listed as episodic or intermittent prophylaxis were excluded as the enrollment form did not capture the treatment product at enrollment for these treatment regimens. Participants were also excluded from analyses if their treatment product could not be categorized. This consisted of 32 participants. Participants were excluded for the following reasons: 2 patients who otherwise met inclusion criteria, including lack of inhibitor, were reported as using bypass agents; 1 participant was listed as using investigational product which could not categorized; and the treatment product was unknown for 29 participants.

Variables Assessed

The outcome variable was the treatment product type, SHL or EHL. Plasma derived and recombinant products were categorized as SHL because they had an average half-life of 24 hours or less. Plasma derived FIX products included AlphaNine SD™, Mononine™, Profilnine SD™, Konyne 80™, Proplex T™, and Bebulin™. Traditional recombinant products included Benefix™, Ixinity™, and Rixibus™. Products were categorized as EHL if they had a terminal-phase half-life of greater than 24 hours and included Alprolix™, Idelvion™, and Rebinyn™.

While Rebinyn™ is not approved by the US Food and Drug Administration for routine use for prophylaxis, it is an extended half-life product and was reported as the treatment product for continuous prophylaxis, so it was included in the analyses.

We assessed a number of demographic characteristics. HTC region classification was based on the Health Resources Service Administration region classification and reported as anonymous per requirements of the Community Counts project review committee. Age at enrollment was calculated by subtracting the enrollment date from the date of birth. We then collapsed enrollment age into six categories. Patients with a highest education level of pre-elementary, primary or secondary, or GED or equivalent were coded as high school or lower; of some college, technical school, 2-year college degree, and 4-year college degree, and advanced were coded as college or higher; and unknown and other were coded as other. Patient employment status was restricted to participants 18 years or older. Parent's highest education level was restricted to participants less than 18 years, per the data collection instruments' instructions, and was coded the same as patients' highest education level.

We assessed a number of clinical characteristics. Participants with endogenous FIX activity of <1% were classified as severe, 1 to 5% as moderate, and 6 to 40% as mild.[11] To increase the power to analyze multiple covariates and potential interaction effects in the model, we collapsed moderate and mild patients into a category defined as non-severe. Participants with insurance reported as Medicaid, Medicare, Military Health Care, and state programs were coded as having government insurance. The most recent weight and heights were reported and BMI was calculated as weight (kg) / height (cm).[12] BMI was calculated for participants between 2 and 19 years using the CDC definition for an adolescent and for participants 20 years and above using the CDC definition for an adult.[12] The BMI number was categorized as underweight if

<18.5, normal if 18.5-24.9, overweight >25 and <=29.9, and obese if >30.0. The location of where a participant received services from an HTC was defined as HTC service location, and multiple locations (HTC primary location, HTC outreach clinic, HTC telemedicine clinic), were coded as combination. History of hepatitis C virus (HCV) and human immunodeficiency virus (HIV) were defined as whether they had been diagnosed during their lifetime; an unknown response included if the results were unknown, indeterminate or the patient had never been tested. First joint bleed age and the age prophylaxis was initiated were collected in multiple formats; as a date, age in days, months, or years, or an approximate date with the categories of <3, 3-6, >6 years of age. To standardize the age for these variables we collapsed all data into categories. The data collection instrument question of the approximate percent of doses missed for continuous prophylaxis in the last 12 months, an indicator of adherence, was defined as percent of missed doses; 10-20% and 21-50% were collapsed into a category of 10-50%. Children can be diagnosed by amniocentesis between 15-20 weeks pregnant, 175 days prior to birth, so a negative number for age at diagnosis was not considered to be an error (0.5 years). The number of days the participant missed from school or work due to his bleeding disorder was defined as the number of days missed.

Data Analyses

We conducted descriptive statistics for demographic and clinical characteristics in the Registry dataset with the binary outcome of product type utilized at enrollment. Measures of central tendency and dispersion were used to summarize continuous variables and frequency distributions were used to summarize categorical variables. Chi-Square tests of association were performed to test for association between categorical variables. We tested for median differences for continuous variables using the Mann-Whitney U test.

We used marginal models and parameters were estimated with generalized estimating equations (GEE). This estimation methods adjusts the standard errors, to account for correlated data within HTC. The outcome measure of product type was used with a binomial probability distribution and a logit link function to predict the probability of an EHL treatment product, as a linear function of demographic and clinical predictors. An exchangeable correlation structure was used. Prior to modeling, independent variables with responses of "unknown" or "other" were set to missing. Missing responses were minimal and assumed to be missing at random.

Model Selection

It was determined a-priori to include disease severity in the model, regardless of statistical significance, due to contextual and clinical significance. Independent variables with significant bivariate associations (p-value <0.05) using chi-square tests, were considered for inclusion in the multivariable model. For those variables, a two-fold approach using the magnitude of the bivariate odds ratios (not presented) as well as the evaluation of the quasi-likelihood under (QIC-u) the independence model criterion goodness of fit test statistics was used. We also examined interaction effects. Statistical modeling was completed with the PROC GENMOD SAS procedure. To quantify the effect of clustering we estimated the intraclass correlation coefficient (ICC) for a multilevel logistic model, using the final multivariable model.[13] The ICC was used to determine the proportion of variance accounted for by the HTC level. This modeling was performed with the PROC GLIMMIX SAS procedure.

Data in the model are presented as adjusted odds ratios with 95% confidence intervals and p-values for the Wald test. We interpreted the exponentiated β regression coefficients (odds ratios) as the odds a characteristic was present for categorical data, given the likelihood of an EHL product at enrollment versus a SHL product for each independent variable. Statistical

significance was set a priori for two-sided test values at α=.05. All analyses were conducted using SAS statistical software version 9.4 (SAS Institute, Cary, NC).

Results

Our sample contained 655 MWHB from 121 HTCs who were using a continuous prophylaxis treatment regimen at enrollment. SHL products were used by 60.9% of MWHB (39 participants used plasma-derived (5.9%), 360 participants used recombinant (55.0%)) and 39.1% were using EHL products.

In these analyses we observed a wide variation in the treatment practices for MWHB by HTC. Figure 1 presents the variation of EHL treatment product usage among the 513 severe MWHB on continuous prophylaxis by the 116 HTCs where they received treatment. We further examined variation by year of enrollment (figure 2). Between 2014 and 2018, the proportion of patients using EHL at HTCs increased. In 2014, 134 severe MWHB were enrolled at 52 HTCs and 14.2% were treating with EHL products. Among these HTCs with severe MWHB, 76.9% of HTCs had no patients using EHL products, 11.5% of HTCs had between 1-49% of patients using EHL products, 3.8% had between 50-99% of patients using EHL products, and 7.7% had 100% of their patients using EHL products. In 2015, 129 severe MWHB were enrolled at 59 HTCs and 31.0% were treating with EHL products. Among these HTCs with severe MWHB, 55.9% of HTCs had no patients using EHL products, 11.9% had between 1-49% of patients using EHL products, 10.2% had between 50-99% of patients using EHL products, and 22.0% had 100% of their patients using EHL products. In 2016, 102 severe MWHB were enrolled at 55 HTCs and 34.3% of MWHB were treating with EHL products. Among these HTCs with severe MWHB, 52.7% of HTCs had no patients using EHL products, 12.7% had between 1-49% of patients

using EHL products, 12.7% had between 50-99% of patients using EHL products, and 21.8% had 100% of their patients using EHL products. In 2017, 84 severe MWHB were enrolled at 50 HTCs and overall 54.8% of MWHB were treating with EHL products. Among these HTCs with severe MWHB, 30.0% of HTCs had no patients using EHL products, 4.0% had between 1-49% of patients using EHL products, 3.0% had between 50-99% of patients using EHL products, and 36.0% had 100% of their patients using EHL products. In 2018, 64 severe MWHB were enrolled at 39 HTCs and 65.6% of MWHB were treating with EHL products. Among these HTCs with severe MWHB, 30.8% of HTCs had no patients using EHL products, 0.0% had between 1-49% of patients using EHL products, 15.4% had between 50-99% of patients using EHL products, and 53.8% had 100% of their patients using EHL products.

Year of enrollment, disease severity, HTC region, percent missed doses for continuous prophylaxis in the previous year, age at first treatment, and the number of treated bleeding events in the previous 12 months were significantly associated with product type (tables 1, 2, and 3). The number of MWHB enrolled in 2018 using EHL products was significantly higher than MWHB enrolled in 2014. EHL products were used most commonly by MWHB with mild disease (65.2%) compared to MWHB with severe disease (35.5%). Product utilization was evenly distributed between SHL and EHL products for MWHB with moderate disease, 50.4% and 49.6%, respectively. Significant differences were observed between the eight HTC regions. The percent of missed doses for the continuous prophylaxis treatment regimen in the previous year was lowest among MWHB who were using EHL treatment products at enrollment. The number of treated bleeds in the previous twelve months was significantly lower among patients on EHL treatment products. All of the other variables examined were not associated with treatment product type.

Multivariable Associations

Table 4 presents the multivariable analysis from the final model which included disease severity, year of enrollment, HTC region, and percent of missed doses. Age by disease severity was not associated with the product outcome. After adjusting for disease severity and year of enrollment, the number of treated bleeds in the previous 12 months and patient's highest education level were no longer significantly associated with treatment product type. In the multivariable model, adjusting for other variables, the odds of MWHB with severe disease were 0.6 times less likely to be treated with EHL products compared to SHL products (aOR 0.6, CI 0.4-0.9) then non-severe MWHB. The strongest factor associated with product usage was year of enrollment. Compared to MWHB enrolled in 2014, there was a steady increase in utilization of EHL products each year. MWHB enrolled in 2018 were 9.4 times more likely to be treated with an EHL product than participants enrolled in 2014, after adjusting for the other variables in the model. We found that MWHB treated in HTCs in regions A, F, and G were significantly more likely to be treating with EHL products compared to SHL products for MWHB in region E (aOR 4.6 CI 1.7-12.5, aOR 3.3 CI 1.4-7.8, and aOR 3.8 CI 1.5-9.5 respectively). Use of EHL products was significantly associated with an improvement in the decreased in the number of missed doses, as MWHB who missed less than 10% of their prescribed doses were 4.3 times more likely to be using EHL products, than MWHB who missed greater than 50% of their prescribed doses.

We did not find any significant interaction effects with our covariates. We examined a potential interaction between year of enrollment and HTC region as well as reported missed doses, however the sample size was too low to detect a difference and provided cell sizes too small for the algorithm to converge. We examined an interaction between year of enrollment and severity, however the interaction was not significant and not presented in the final model. We did

not find significant interactions between severity and HTC region or missed dose. Overall, the confidence intervals for many of the estimations were wide in the adjusted model, this lack of precision was also likely due to small sample sizes in the adjusted model. Using the covariates in the final model, the ICC was 14.9%.

Discussion

In this study, we observed a wide variation in the product type used at Registry enrollment for MWHB (figure 1), even after stratifying by year of enrollment (figure 2). It appears that while some HTCs were early adopters of EHL products in 2014, in 2018 none of the severe MWHB in 29% of HTCs were utilizing this treatment product type. Between 2014 to 2018, 20% of HTCs had between 75% to 100% of their severe MWHB participants on EHL products at enrollment; and similarly, 20% of HTCs had no severe MWHB using that treatment product type.

Additionally, while we hypothesized that a number of patient-level factors would be associated with treatment product type, they were not; only two patient-level factors, severity and percent of missed doses for continuous prophylaxis were significantly associated with the outcome. The lack of patient-level factors and significance of regional differences could be construed as additional evidence that the decision to utilize EHL products came more strongly from provider-related factors, and those provider-related factors were different based on clustering at HTCs. The ICC of 15% reaffirms that patient-level observations for treatment product type for continuous prophylaxis (EHL versus SHL) are more similar within HTCs, than patient level observations for treatment product type from different HTCs.

Year of enrollment was the strongest factors associated with utilizing EHL treatment product types and while there were HTC differences, this still demonstrates significant uptake of

this new treatment product category between 2014 to 2018. EHL treatment products were marketed to reduce the number of required infusions and were believed to likely improve adherence. EHL treatment products were demonstrated to be significantly associated with reduced percentage of missed doses for continuous prophylaxis in the previous 12 months.

We hypothesized that since MWHB with severe disease in the Registry were on a prophylaxis treatment regimen significantly more during this time period compared to mild and moderate MWHB,[10] that they would also be utilizing EHL treatment products significantly more than moderate or mild patients. Severe MWHB would have a greater incentive to utilize the EHL products to reduce the number of infusions for their prophylactic regimen. Interestingly, the data demonstrated that the odds of MWHB with non-severe disease utilizing EHL products was two times the odds of MWHB with severe disease.

There are a few potential reasons for severe MWHB treating with EHL products less than often than non-severe patients. Severe MWHB whose prophylactic treatment regimen with SHL were adequately preventing bleeding episode may have preferred not to switch to an unknown novel product. Another likely reason is the perceived risk of inhibitor development, the greatest adverse event to treatment, which occurs most often in MWHB with severe disease. The Federal Drug Administration has regulations about inhibitor development for clinical trials of hemophilia treatment products, and all treatment products included in these analyses were approved by FDA as of 2018. However, sample sizes in clinical trials are low, samples of patients tend to be skewed to those with the least inhibitor development risk, and there are no formal requirements for pharmaceutical companies to monitor their treatment products for inhibitor development post-market. Some providers may have been reticent to have their severe patients switch to

utilizing extended half-life treatment products until there was more data about the potential immunogenicity of the specific products.

In addition, product switching was hypothesized in the 1990's as a potential risk factor for inhibitor development. Many studies have since been published demonstrating that product switching does not significantly increase risk of inhibitor development.[14,15,16,17] However, a study in 2013 examining barriers to product switching among MWH and caregivers, identified that 57% of MWH still believed switching treatment products significantly increased the likelihood of inhibitor development.[14] The same study also performed a qualitative assessment of providers beliefs about the risk of inhibitor development associated with product switching was that while not evidence based, many provider in clinical practice still avoid product switching because of the fear of inhibitor development.[14] It is likely that provider and patient reluctance to switch treatment products to EHL treatment products in our analyses was due to concern about inhibitor development for severe MWHB, despite strong evidence that product switching is not a risk factor for inhibitor development.

It is possible that non-severe patients were twice as likely to use an EHL product than severe patients because prophylaxis with EHL become more appealing than the burden of prophylaxis with SHL products. Prophylaxis usage increased among non-severe patients between 2014 to 2018 and this increase may be due to the introduction of EHL products.[10] For non-severe patients the burden with SHL products may have outweighed the benefits of a prophylactic treatment regimen. However, EHL products provided an option that reduced the burden of infusions and made a continuous prophylactic treatment regimen more appealing to non-severe patients. This could explain the increase in prophylaxis usage and increased use of EHL products among non-severe MWHB.

Our study had several notable limitations. This was a retrospective analysis and not a randomized control trial, therefore these results may not be generalizable. It was previously documented that about half of MWHB being treated in HTCs (Population Profile) were enrolled in the Community Counts Registry and that some clinical and demographic characteristics of MWHB in the Registry were not significantly different. However, Population Profile does not collect information on treatment regimen or treatment product utilization. Since we utilized a sample of MWHB who were on continuous prophylaxis at enrollment which cannot be compared to all MWHB being treated in HTCs on continuous prophylaxis, these analyses may not be generalizable to all MWHB being treated in HTCs. In addition, there is potentially a temporality bias. While we know the treatment products used for continuous prophylaxis as of the participants' enrollment into the Registry, since this was a cross-sectional analyses we did not examine prospective data on adherence among patients switching from SHL to EHL products. Future studies could prospectively evaluate adherence among MWHB who change product utilization from SHL to EHL, using a multi-level model.

Conclusion

These data provide strong evidence that treatment product type for MWHB is strongly clustered by the HTC where they are treated. MWHB started using novel extended half-life treatment products compared to traditional recombinant and plasma-derived products significantly more between 2014 and 2018. MWHB with severe disease were significantly less likely to use EHL treatment product types than non-severe patients and this finding should be examined further to elucidate the barriers to switching among MWHB and providers. As expected, the proportion of missed infusion doses was significantly less among MWHB on EHL treatment products compared to traditional products. Future evaluation of treatment practices

with the outcome of treatment product type used for continuous prophylaxis, should examine outcome clustering by HTC and if present, multilevel or marginal modeling methodology should be employed. Future analyses should also examine variations in the dose of factor administered and the frequency at which treatment is administered for MWHB using continuous prophylaxis who participate in Community Counts.

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Data Tables and Figures

Figure 1. Overall proportion of participants with severe Hemophilia B using Extended Half-life treatment products in the Registry by HTC.

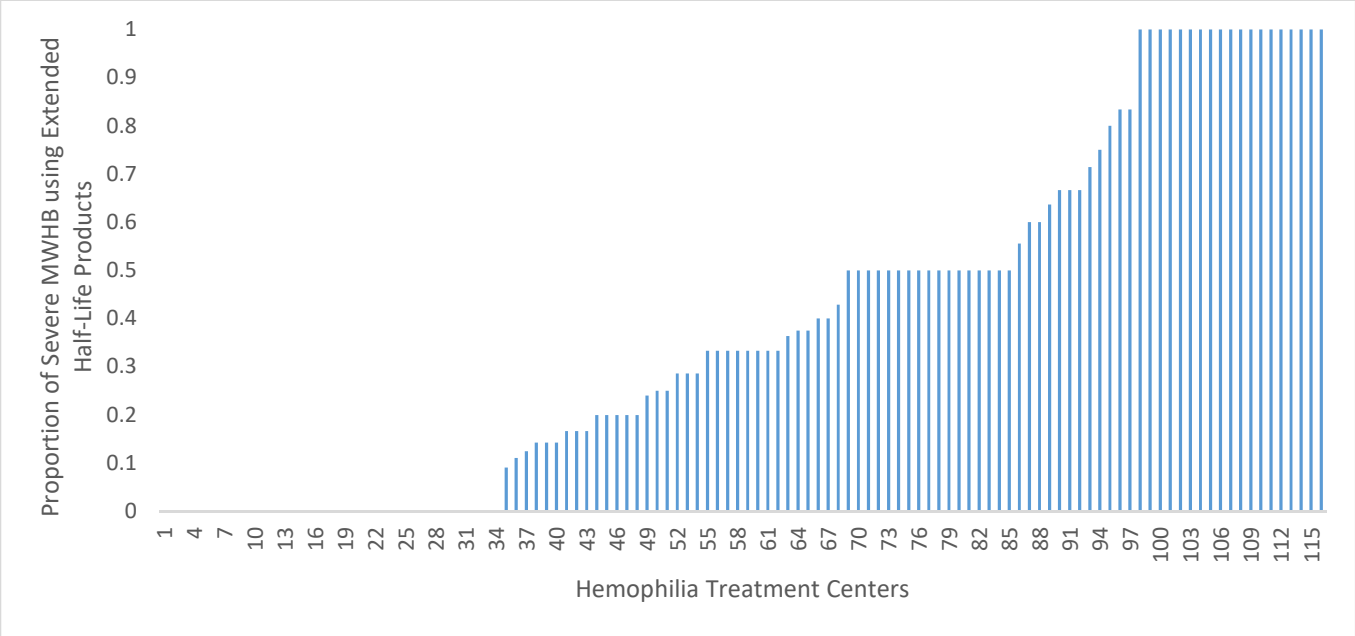

Figure 2A. Proportion of participants with severe Hemophilia B using Extended Half-life treatment products in the Registry by HTC and Enrollment Year in 2014.

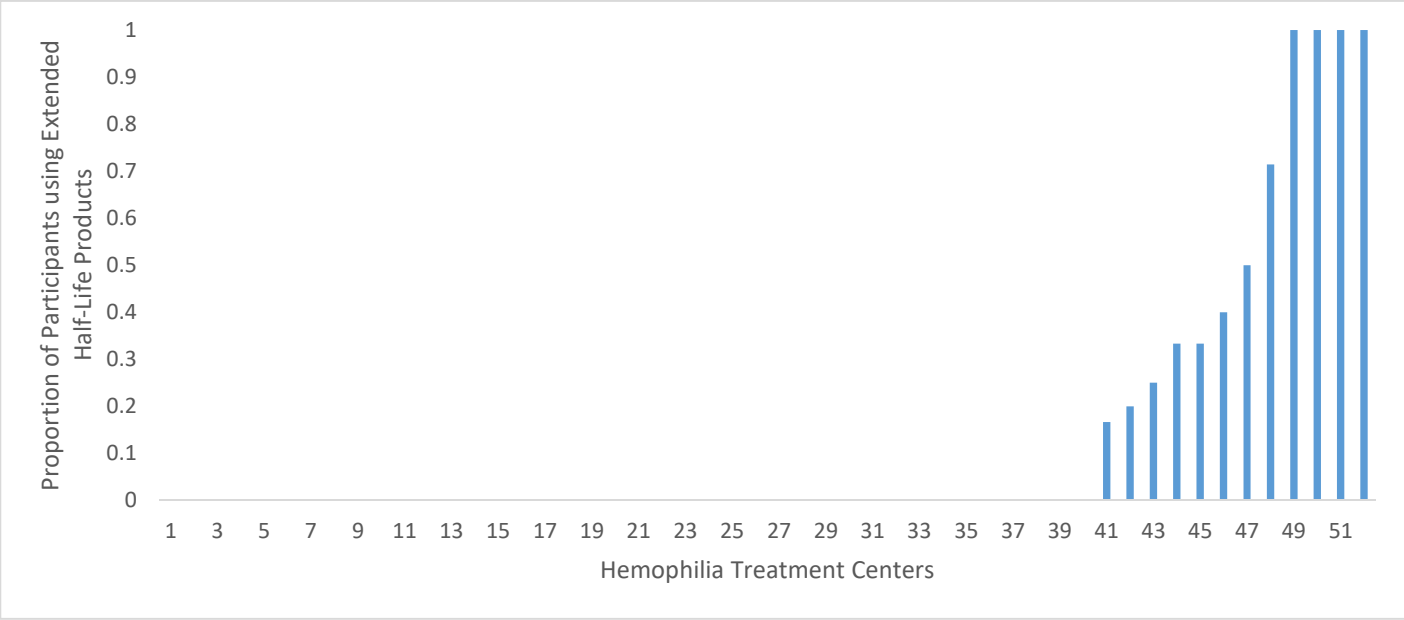

Figure 2B. Proportion of participants with severe Hemophilia B using Extended Half-life treatment products in the Registry by HTC and Enrollment Year in 2015.

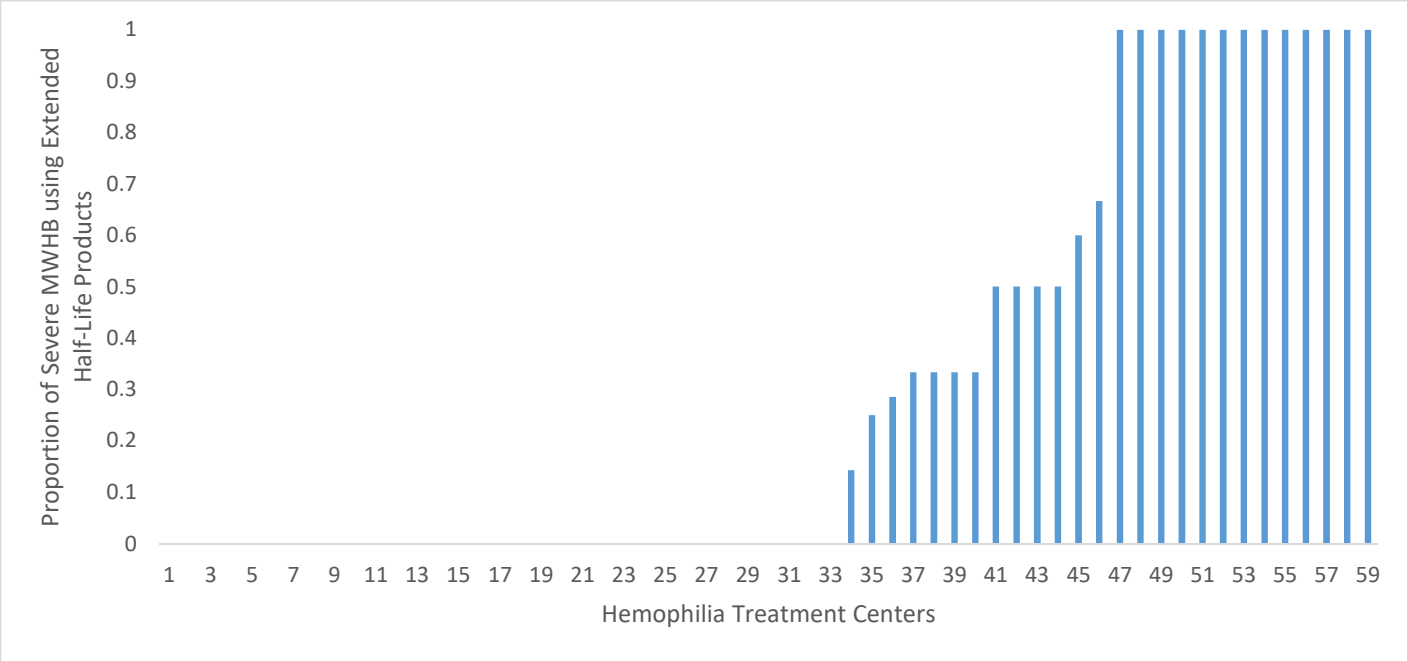

Figure 2C. Proportion of participants with severe Hemophilia B using Extended Half-life treatment products in the Registry by HTC and Enrollment Year in 2016.

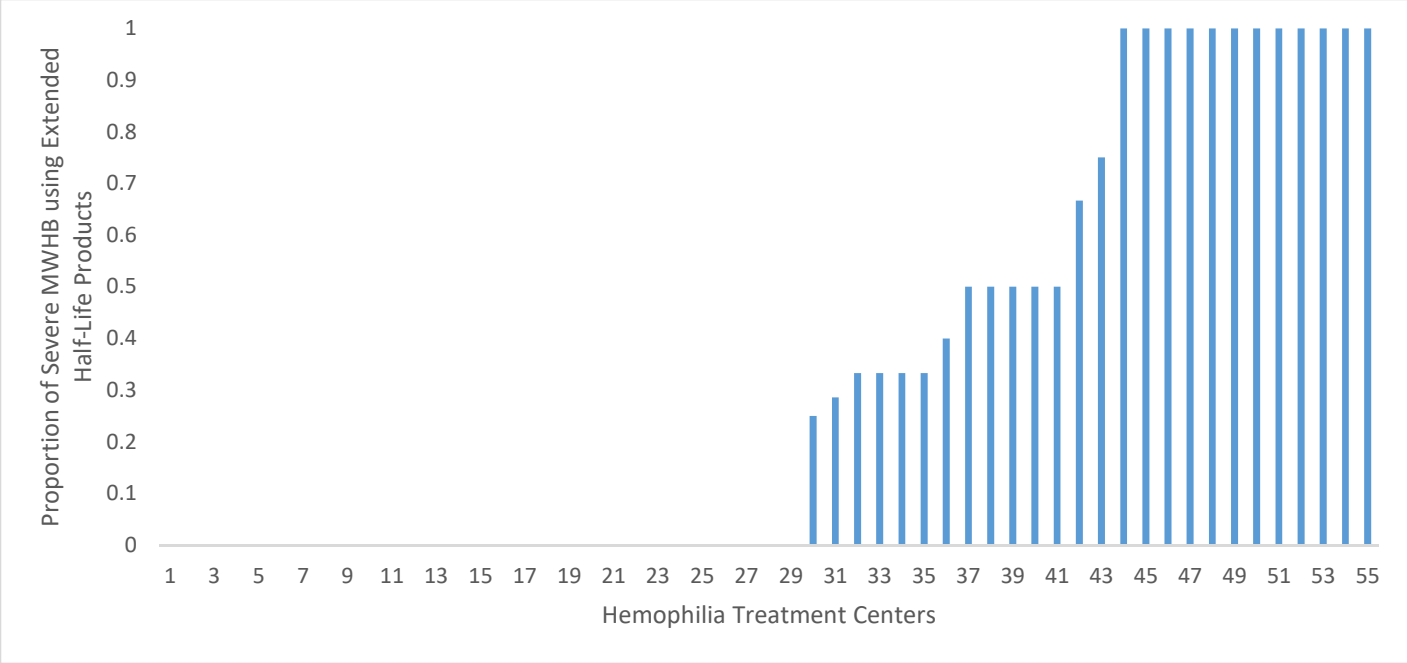

Figure 2D. Proportion of participants with severe Hemophilia B using Extended Half-life treatment products in the Registry by HTC and Enrollment Year in 2017.

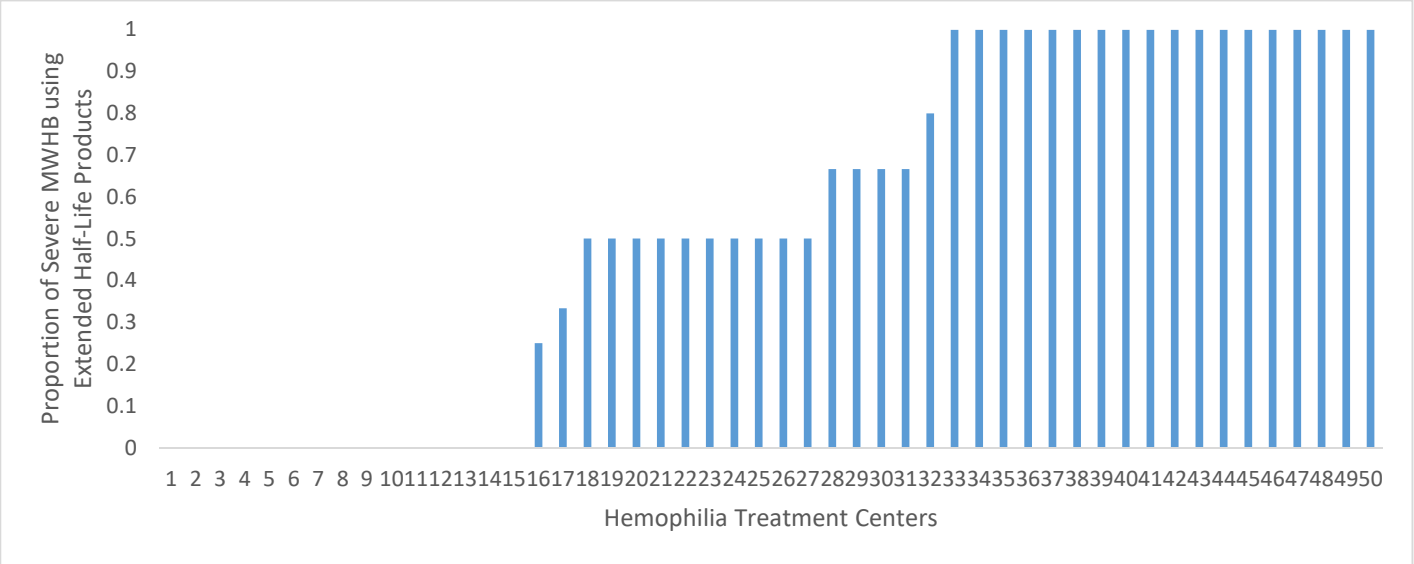

Figure 2E. Proportion of participants with severe Hemophilia B using Extended Half-life treatment products in the Registry by HTC and Enrollment Year in 2018.

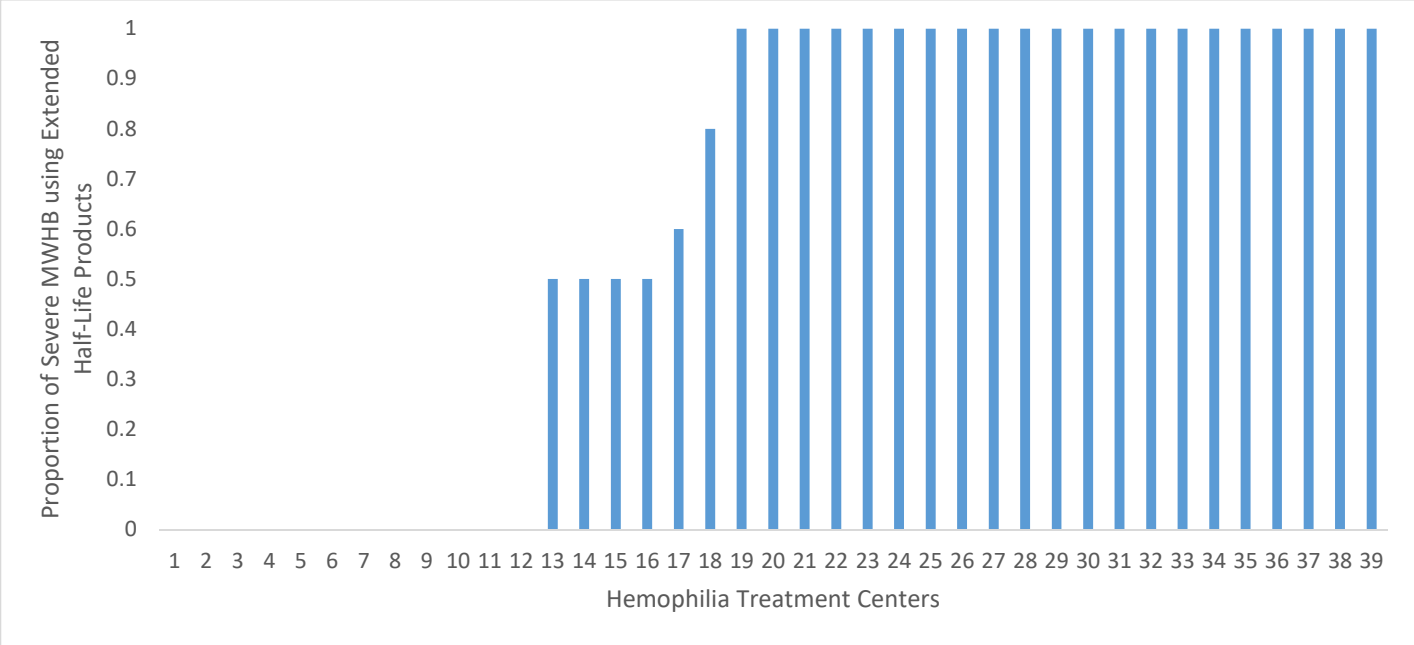

Table 1. Association between MWHB demographic characteristics and product type at Registry enrollment.

	Product Type			
	SHL (n=399)	**EHL** (n=256)	**Total** (n=655)	**P-value**
Characteristic	N (%)	N (%)	N (%)	
Year of Visit				
2014	133 (86.4)	21 (13.6)	154	<0.0001
2015	110 (68.3)	51 (31.7)	161	
2016	85 (60.7)	55 (39.3)	140	
2017	44 (37.9)	72 (62.1)	116	
2018	27 (32.1)	57 (67.9)	84	
HTC Region				
A	49 (51.6)	46 (48.4)	95	0.0005
B	60 (66.7)	30 (33.3)	90	
C	48 (68.6)	22 (31.4)	70	
D	33 (51.6)	31 (48.4)	64	
E	69 (78.4)	19 (21.6)	88	
F	34 (50.7)	33 (49.3)	67	
G	70 (63.1)	41 (36.9)	111	
H	36 (51.4)	34 (48.6)	70	
Age at Enrollment (in years)				
<=3	41 (59.4)	28 (40.6)	69	0.3888
4-12	108 (61.7)	67 (38.3)	175	
13-20	88 (61.5)	55 (38.5)	143	
21-29	67 (67.0)	33 (33.0)	100	
30-45	40 (50.6)	39 (49.4)	79	
>=46	55 (61.8)	34 (38.2)	89	
Race				
White	303 (60.5)	198 (39.5)	501	0.6309
Black or African American	63 (64.9)	34 (35.1)	97	
Other	33 (57.9)	24 (42.1)	57	
Ethnicity				
Hispanic/Latino/Spanish origin	75 (67.6)	36 (32.4)	111	0.1119
Not Hispanic/Latino/Spanish origin	320 (59.5)	218 (40.5)	538	
Patient Highest Education Completed				
High school or Lower	278 (63.0)	163 (37.0)	441	0.1558
Some College or Higher	105 (55.3)	85 (44.7)	190	
Other	16 (66.7)	8 (33.3)	24	
Patient Employment Status *(18 years and older)*				
Full-Time	77 (55.4)	62 (44.6)	139	0.1675
Part-Time	19 (52.8)	17 (47.2)	36	
Not Employed	867 (65.4)	46 (35.6)	133	
Parent Highest Education Completed *(<18 years old)*				
High school or Lower	49 (57.6)	36 (42.4)	85	0.7105
Some college	81 (61.4)	51 (38.6)	132	
Advanced degree	19 (63.3)	11 (36.7)	30	
Other	64 (66.0)	33 (34.0)	97	

SHL = standard half-life ; EHL= extended half-life

Table 2. Association between MWHB clinical characteristics and product type at Registry enrollment.

	Product Type			
	SHL (n=399)	**EHL** (n=256)	**Total** (n=655)	**P-value**
Characteristic	N (%)	N(%)	N(%)	
Severity				
Severe	331 (64.5)	182 (35.5)	513	0.0006
Moderate	60 (50.4)	59 (49.6)	119	
Mild	8 (34.8)	15 (65.2)	23	
Health Insurance Type				
Commercial	215 (61.1)	137 (38.9)	352	0.8008
Government	165 (61.8)	102 (38.2)	267	
Other	19 (55.9)	15 (44.1)	34	
Family History				
Yes	273 (58.6)	193 (41.4)	466	0.1532
No	102 (67.1)	50 (32.9)	152	
Unknown	24 (64.9)	13 (35.1)	37	
BMI				
Underweight	6 (37.5)	10 (62.5)	16	0.1203
Normal weight	197 (64.8)	107 (35.2)	304	
Overweight	79 (58.5)	56 (41.5)	135	
Obese	98 (60.9)	63 (39.1)	161	
HTC Location				
Primary HTC	367 (60.4)	241 (39.6)	608	0.2958
Combination	32 (68.1)	15 (31.9)	47	
History of HIV				
Yes	21 (60.0)	14 (40.0)	35	0.7254
No	357 (60.6)	232 (39.4)	589	
Unknown	21 (67.7)	10 (32.3)	31	
History of HCV				
Yes	107 (63.7)	61 (36.3)	168	0.5856
No	275 (59.6)	186 (40.4)	461	
Unknown	17 (65.4)	9 (34.6)	26	
History of ICH				
Yes	45 (57.7)	33 (42.3)	78	0.1956
No	336 (60.6)	218 (39.4)	554	
Unknown	18 (78.3)	5 (21.7)	23	
History of CVAD Usage				
Yes	144 (60.8)	93 (39.2)	237	0.9980
No	241 (61.0)	154 (39.0)	395	
Unknown	14 (60.9)	9 (39.1)	23	
Joint Bleed History				
Yes	341 (61.9)	210 (38.1)	551	0.2159
No	53 (55.2)	43 (44.8)	96	
First Joint Bleed Age				
<3 years	119 (67.2)	58 (32.8)	177	0.2104
3-6 years	67 (64.4)	37 (35.6)	104	
>6 years	33 (56.9)	25 (43.1)	58	
Unknown	122 (57.8)	89 (42.2)	211	
Age Prophylaxis Initiated				
<3 years	129 (61.7)	80 (38.3)	209	0.0558
3-6 years	61 (72.6)	23 (27.4)	84	
>6 years	129 (60.0)	86 (40.0)	215	
Unknown	80 (54.4)	67 (45.6)	147	
History of Invasive Joint Procedure				
Yes	74 (58.7)	52 (41.3)	126	0.6222

No	316 (61.1)	201 (38.9)	517	
Chronic Pain 12 months				
Yes	125 (62.5)	75 (37.5)	200	0.5644
No	260 (59.8)	175 (40.2)	435	
Unknown	14 (70.0)	6 (30.0)	20	
ER Visit 12 months				
Yes	103 (61.7)	64 (38.3)	167	0.8393
No	293 (60.8)	189 (39.2)	482	
Inpatient Admission 12 months				
Yes	49 (57.6)	36 (42.3)	85	0.5022
No	346 (61.5)	217 (38.5)	563	
Missed dose				
<10%	243 (57.0)	183 (43.0)	426	0.0008
10-50%	64 (71.1)	26 (28.9)	90	
>50%	26 (89.7)	3 (10.3)	29	
Unknown	66 (60.0)	44 (40.0)	110	
Joint Bleeds 12 months				
2 or more bleeds into large joints	180 (63.4)	104 (36.6)	284	0.3533
0 or 1 bleed total in large joints	134 (60.9)	86 (39.1)	220	
Unknown	85 (56.3)	66 (43.7)	151	

ICH = intracranial hemorrhage; CVAD= central venous access device; SHL = standard half-life ; EHL=extended half life

Table 3. Association between MWHB clinical characteristics and product type at Registry enrollment.

	SHL (n=399)			EHL (n=256)			
Characteristic	M	IQR	Range	M	IQR	Range	p-value
Age at Diagnosis (yrs)*	0.1	0.0-0.9	-0.4-63.4	0.3	0.0-1.6	-0.1-55.1	0.0574
Age at First Bleed (yrs)**	0.4	0.0-1.1	-0.5-30.2	0.5	0.0-1.1	-0.4-37.2	0.5239
Age at First Treatment (yrs)****	0.5	0.0-1.3	-0.5-39.7	0.8	0.2-2.3	-0.4-37.4	0.0080
Number of Treated Bleeds In Previous 12 months*****	3.0	1.0-6.0	0.0-100.0	2.0	0.0-4.0	0.0-100.0	0.0128
Number of days missed******	0.0	0.0-2.0	0.0-365.0	0.0	0.0-2.5	0.0-115.0	0.2567

M = median; SD = standard deviation; * n=127 missing; **n=161 missing; ***n=499 ****n=222 missing; *****n=85; ******n=261 missing; SHL=standard half-life ; EHL=extended half-life

Table 4. Multivariable Factors Associated with of Extended Half-life Recombinant Treatment Product Utilization for Continuous Prophylaxis using GEE Prediction Model

Characteristic	OR	95% CI	P-value
Severity			
Severe	0.6	0.4 – 0.9	0.0097
Non-severe	reference	-	-
Year of Enrollment			
2014	reference	-	-
2015	2.7	1.4 – 5.6	0.0054
2016	3.3	1.5 – 7.1	0.0028
2017	7.7	3.6 – 16.3	<0.0001
2018	9.4	3.9 – 22.6	<0.0001
HTC Region			
A	4.6	1.7 – 12.5	0.0031
B	2.0	0.8 – 4.9	0.1186
C	2.1	0.9 – 4.9	0.0994
D	2.1	0.8 – 5.4	0.1141
E	reference	-	-
F	3.3	1.4 – 7.8	0.0078
G	2.5	0.9 – 6.8	0.0743
H	3.8	1.5 – 9.5	0.0053
Missed Dose			
<10%	4.3	1.4 – 13.1	0.0115
10-50%	2.4	0.7 – 8.0	0.1548
>50%	reference	-	-

OR=odds ratio. CI = confidence interval. GEE = generalized estimating equations.

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CHAPTER 5.

Hemophilia B (HB) treatment practices have evolved significantly in the last decade and will likely continue to evolve significantly with the anticipated gene therapy. There are currently nine FIX gene therapies in phase 1,2, or 3 clinical trials. However, if genetic therapies are approved by Federal Drug Administration (FDA), it is unclear if all disease severities will have access to this new therapeutic strategy or the potential financial costs to patients associated with this treatment. While clinical trials continue, it is important to characterize and identify predictors of current treatment regimen and treatment product utilization for men with HB (MWHB). Our analyses examined MWHB from their enrollment into the United States national surveillance program, the Community Counts Registry, from 2014 to 2018.

The first paper focused on assessing the generalizability of the MWHB participating in the Community Counts surveillance Registry to the population of MWHB being treated at HTCs between 2014 to 2018 from the Community Counts Population Profile. We found that the sample of MWHB in the Registry were remarkably similar to MWHB who were treated in HTCs based on a number of demographic and clinical characteristics. In addition, we found that the previous publication estimating the prevalence of HB being treated in US HTCs of approximately 2,800 MWHB, which has been cited by 322 peer-reviewed journal articles with the most recent in 2019, is no longer representative of the current HB population. As our analyses found that almost 5,000 MWHB were being treated in HTCs between 2014 to 2018. We then presented the demographic and clinical characteristics and prevalence of health outcomes for our sample across disease severities. To date, the majority of published articles on hemophilia B, have either examined samples of both men with hemophilia (MWH) A and B, or focused on health outcomes among one disease severity, predominately MWHB with severe disease. The assumption was

that moderates and mild MWHB do not experience the same level of morbidity or mortality as severe MWHB. Our analyses demonstrated that among MWHB who had a history of intracranial hemorrhage, the most life-threatening bleed, 47% were non-severe patients compared to 53% who were severe. In addition, while clinical guidelines for MWHB with severe disease recommend prophylaxis treatment regimen, our analyses demonstrated that 24% were still using episodic therapy; and among MWHB using prophylaxis, more than a quarter had moderate or mild disease severity. These analyses highlight that future studies should include all disease severities and not exclude moderate or mild patients, as these subgroups experience morbidity associated with their disorder, and are being treated with prophylaxis. Prophylaxis is no longer being utilized solely among severe patients.

The second paper focused on examining the association between hypothesized demographic and clinical characteristics as well as health outcomes against the treatment regimen used by the Community Counts Registry participants at enrollment. We observed that the following patient-level factors were the most significant factors associated with prophylaxis versus episodic treatment regimen: ethnicity, health insurance, history of a joint bleed, the interaction between enrollment age and history of CVAD usage, as well as the interaction between severity and chronic pain. We provided strong evidence that treatment regimen for MWHB were strongly clustered by their HTCs. In addition, despite the introduction of extended half-life recombinant treatment products, which remove a significant barrier to prophylaxis usage – the reduction in venous infusions to maintain trough level, prophylaxis usage remained stable between 2014 to 2018.

The third paper focused on examining the association between hypothesized demographic and clinical characteristics as well as health outcomes for MWHB on continuous prophylaxis

against the treatment product type utilized by Community Counts Registry participants at enrollment. We found that disease severity, year of enrollment, HTC region, and adherence to missed doses were the most significant factors associated with using extended half-life recombinant treatment products compared to recombinant and plasma-derived treatment products. MWHB with severe disease were significantly less likely to use the novel products compared to MWHB with moderate and mild disease. And adherence to prophylactic treatment regimens were more significantly associated with extended half-life treatment products compared to traditional products. We also provided strong evidence that FIX treatment product type for MWHB were strongly clustered by their HTCs.

While it is largely accepted that clinical management of hemophilia requires individualized medicine to account for patient's pharmacokinetic, pharmacodynamic, the genetic mutation type, disease severity, perceived adherence, and other factors in determining a patients' treatment regimen and product type. These analyses provide strong evidence that in addition to patient-level factors, there is a second level influence of the HTC for treatment practices. Traditional analytic methods of binary treatment outcomes among MWHB, such as logistic regression, are likely no longer appropriate. In Community Counts, data on hematologists practicing at HTCs are not collected and the providers at each HTC may not have remained stable during our time frame. We used HTCs as the second level effect, which may be a proxy indicator for providers. Future studies should examine the multilevel framework of treatment practice, examining factors associated with the HTC that may influence the random effect on treatment practice. These HTC level effects could be based on the type of population the HTC sees (pediatric, adult, or mixed), the number of patients an HTC treats, the number of hematologists and supportive staff such as nurses, laboratory on site, etc. In addition, future

studies should examine if treatment practices for MWH A are also clustered by HTC, to determine if this is occurring among all MWH.

Health education and promotion directed to HTC providers and MWHB are likely needed to increase prophylaxis usage among children less than three years of age, since if prophylaxis is initiated in this age group the potential for joint damage can be significantly reduced. Future research should be done to examine the mild and moderate patients being put on prophylaxis to determine if standardized evidence-based clinical guidelines can be developed for non-severe MWHB. Ultimately the goal of public health and clinical management of MWHB is to reduce morbidity and mortality and promote a quality of life that is in accordance with individuals who do not struggle with chronic conditions.

APPENDIX – Acronyms

HB - Hemophilia B

HA – Hemophilia A

MWH - Men with hemophilia

MWHB - Men with hemophilia B

FIX - factor nine

IU/dl - units per deciliter

CDC – Centers for Control and Prevention

Registry - Community Counts surveillance Registry

Population Profile – Community Counts HTC Population Profile

UDC – Universal Data Collection system

FDA - Federal Drug Administration

ICH – intracranial hemorrhage

CVAD – central venous access device

HIV - Human immunodeficiency virus

HCV - Hepatitis C virus

BMI – body mass index

EHL - extended half-life

SHL - standard half-life

HTC - hemophilia treatment center

MASAC – National Hemophilia Foundation Medical and Scientific Advisory Council

GEE – generalized estimating equations

ICC – intraclass correlation coefficient