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PREVALENCE AND INCIDENCE OF HEMOPHILIA IN THE US

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Abstract

Hemophilia is a bleeding disorder that occurs because of deficiencies in coagulation proteins. The proteins involved are factor VIII and factor IX. Hemophilia A occurs when there is a deficiency of factor VIII. Hemophilia B, on the other hand, occurs when results when there is a deficiency of factor IX. Hemophilia affects normal blood clotting which is why bleeding is commonly reported in patients who live the disease. Another common problem reported in people with this disorder is joint problems including joint pain and arthropathy. Arthropathy occurs because bleeding is common in the joints. Bleeding in patients living with hemophilia can also happen in tissues and organs. Estimating the number affected by hemophilia in the US is difficult. However, results from epidemiological studies and surveillance data estimate the total number to be between 30,000 to 33,000. The incidence rate of hemophilia is 1 in every 5000 male births. Addressing the disorder is important because the disease is associated with a significant burden. Several comorbidities are associated with hemophilia. They are liver disease, overweight and obesity, and heart disease. Hemophilia is also associated with significant healthcare costs. Clotting factor replacement therapy and prophylaxis are the mainstay treatment strategies for treating hemophilia. Research has shown that the treatment strategies are effective in addressing hemophilia with lower risk of complications.

Keywords: hemophilia A, hemophilia B, factor VIII, factor IX, replacement therapy, prophylaxis.

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Introduction

Hemophilia is an inherited disorder that occurs from mutations in the genes which help with blood clot Hemophilia A (HA) and B (HB)occur when mutations occur in factor VIII and factor IXthe two proteins that are necessary for normal blood clotting.1 A patient has hemophilia if they have protein deficiency of both factors. Lack of blood clotting of factor VIII causes HA and lack of clotting factor IX results in HB.2 Patients who have hemophilia report prolonged and excessive bleeding. The bleeding normally occurs after trauma. Bleeding occurs in the organs, tissues, and joints after trauma and surgery.Hemophilia mainly presents in males. Although cases ofHA and HB are reported, HA is more common than HB. The incidence rate of HA is 1 in every 5000 male births while HB is 1 per 30,000 male births.3 Estimating people living with the disorder in the US is not easy. The lack of adequate surveillance and epidemiological data makes it difficult to estimate the exact data. However, a recent study has shown that the number could be between 30,000 and 33,000.4

Hemophilia manifests as bleeding that occurs after the affected patient experiences minor trauma.5 It can also present as a spontaneous bleed.5The severity of manifestation is proportional to the degree of residual factor level in the bloodor the age of the patient.6,2 The residual factor is vital in helping to classify hemophilia. For instance, patients that have a residual factor that is more than 5% to40% of factor activity of normal(0.05 to< 0.4IU/ml)which is classified as mild hemophilia have bleeding after significant trauma or surgery.5.6Patients who live with mild hemophilia rarely experience spontaneous bleeding. It is more common in patients who have moderate to severe hemophilia.Patients that present with 1% to5% of factor activity of normal(which is a clotting factor level of 0.01 to<0.05 IU/ml) have moderate hemophilia.5,6In these patients, bleeding occurs after trauma, injury, dental work or surgery. Some patients who have moderate hemophilia also experience recurrent joint bleeding. For patients that have a factor activity of less than 1% or clotting factorlevel of <0.01 IU/mL also classified as severe hemophilia, bleeding occurs spontaneously.5,6Patients who have severe hemophilia often report internal bleeding. In most instances, the

bleeding affects multiple organs.2 The patients can also present with joint pain. The joints also become swollen and inflamed which affects movement. The joints that are commonly affected are the knees, ankles, elbows, wrists, and hips.

Addressing hemophilia is vital because it is attributed to a significant burden of disease. Without adequate treatment, recurrent joint bleeding can lead to chronic debilitating joint disease.2 Hemophilia is also associated with significant risk of hemorrhage including intracranial hemorrhage in neonates.2 Intracranial hemorrhage can lead to permanent neurological sequelae. Hemorrhage associated with hemophilia can also lead to extracranial hemorrhage which is life-threatening. In addition to poor health outcomes, hemophilia is associated with significant healthcare costs.Patients who live with hemophilia require clotting factor replacement therapy on a regular basis after every bleeding episode to prevent the bleeding. Clotting factor replacement therapy is not a cheap treatment. Some researchers have estimated the total lifetime costs to be up to $21,086,607 for moderate and severe hemophilia.7Another study established that the annual treatment costs for mild hemophilia were$59,101 annually.8 For moderate and severe hemophilia, the cost of treatment annually was $201,471 and $301,392 respectively.8

Due to the significant burden of the disorder, it is important to examine the prevalence and incidence rates in the US. Estimating the prevalence and incidence is important for proper healthcare planning and resource allocation. It is also important to add to the existing data on the disease estimates. Therefore, the aim of this review is to examine the incidence and prevalence of hemophilia in the US. The review will also explore the burden of the disease and treatment strategies used in managing the condition.

Prevalence and Incidence of Hemophilia in the US

Identifying the exact number affected by the disorder in the US is difficult because of the limited data and surveillance on the disease. Estimates show that the disease affects between 30,000 and 33,000 people.4 The current surveillance reports by the CDC show that people served in hemophilia treatment centers (HTCs) between 2015 and 2018 was15,859 for HA and 4,948 for HB putting the total number at 20,807.9 The data also showed that patients who were recorded in community count patient registry between 2015 and 2018 to be 7811 for HA and 2095 for HB.9 These estimates correspond with total estimates for hemophilia as reported by Soucie et al.4 Therefore, the average number affected by hemophilia in the US is between 30,000 and 33,000.

The prevalence rates of hemophilia in the US vary with the most affected being males. Soucie et al. reported about 12 cases per 100,000 males for hemophilia A and 3.7 cases per 100,000 for hemophilia B.4The prevalence of hemophilia varied significantly across states. The variations ranged from 1.1. per 100,000 to 18.8 per 100,000 for hemophilia A and 0.7 per 100,000 to 10.4 per 100,000 for hemophilia B.9 With regard to factor deficiency level, the number affected varied with those with severe hemophilia A accounting for the highest number at 7597 according to HTC data.9People affected by moderate hemophilia was 2,601 while mild hemophilia accounted for 5,418.9 The unknown cases was approximately 243. For hemophilia B, thepatients who have severeform of the disease was estimated to be 1,340 according to HTC data. In the patients' community registries,the number was significantly lower at 763. The number who had moderate and mild hemophilia according to HTC data was 1797 and 1742 respectively.9

When it came to state variation, the Northeastern and Midwestern states accounted for the highest numbers. As such, the highest prevalence rates were reported in states such as Vermont, Maine, Iowa, New Hampshire, West Virginia, and Pennsylvania for HA.4 For HB, the prevalence rates were highest in Iowa, Indiana, Ohio, West Virginia, Maine, and Pennsylvania. When it came to incidence, there was 1 case per 5617 male births for HA and 1 per 19,283 male births for HB.4

The study also highlighted hemophilia distribution by race. Hemophilia was more prevalent among whites than other races. Whites were overrepresented in the data accounting for 81% vs. 72.4%. This was significantly higher than in Hispanics at 16% vs. 16.3%, blacks at 11.2% vs. 12.6% and Asians at 3.6% vs.4.8%.4 The findings were similar to a previous study that showed that the prevalence of hemophilia was higher among whites than any other race. According to the study, the prevalence of hemophilia was 13.2 cases per 100,000 among whites, 11.5 per 100,000 among Hispanics, and 11.0 per 100,000 among African American males.10 The high prevalence rates of hemophilia among white males have also been reported by CDC surveillance data. According to the data, hemophilia was more prevalent in whites compared to other races. Both the HTC and patients' registry data showed that HA was higher in white males at 12,371 and 6,078 respectively.9 Lower numbers were reported among Black males at 1803 and 950 and Hispanics at 2994 and 1286 respectively.9 Other races also accounted for lower numbers. The high prevalence rates of hemophilia among white males could be as a result of high representation among this population in clinical trials and surveillance data. A recent study by Fedewa et al.showed that the percentage of white participants was higher in 66 trials at 65.8% compared to 22.8% for Asian, 5.1% for Hispanics, and 3.9% for Blacks.11

In terms of hemophilia distribution by age, individuals aged between 12 and 44 were the most affected. Soucie et al.reported a higher number of hemophilia cases among individuals aged 12 to 19 with 3839 affected.4 The second group that recorded a high number of cases were people aged 20 to 29 at 3670.4 Data from the HTCs showed that the highest population affected by hemophilia A were individuals aged between 20 to 44 at 5901 cases.9 This

population was also the most affected according to community counts patient registry with the number of cases recorded being 2699. Among individuals aged 11 to 19, the number of cases recorded was 3553 in the HTC and 1999 in the patient registries.9 A similar pattern was reported for HB with the most affected groups being individuals aged 11 to 19 and 20 to 44.9

Although estimating the people who are affected by hemophilia is challenging because of the lack of surveillance data, recent surveillance and epidemiological data can help to give a rough estimate. The estimates are between 30,000 and 33,000 people with an incidence rate of 1 in 5000 male births. Hemophilia is mostly attributed to the family history of the disease with two-thirds of cases reported being inherited from family.12Hemophilia is also commonly reported in males. CDC surveillance data reported that 14,285 males were affected by the disease compared to 1,574 females. Similarly, for HB, more males were affected by the disease compared to females at 4,296 and 652 respectively.9 Addressing hemophilia is important because of the burden attributed to the disease. Individuals affected report poor outcomes with bleeding, pain, and joint disease contributing to poor quality of life. Individuals with hemophilia are also likely to report more comorbidities than the general population including liver disease, heart disease, arthritis, HIV/AIDS, hepatitis C, and obesity/overweight. Continued surveillance can help to address the burden of the disease.

The Burden of Hemophilia

Joint disease is one of the complications of hemophilia. It is reported in severe hemophilia but can also occur in patients who live with moderate hemophilia. Joint disease occurs as a result of recurrent bleeding into joints.13 This bleeding leads to inflammation and destroys joints resulting in a condition that is known as arthropathy.14Hemophilia mostly affects knee joints, elbows, ankles, shoulders, and wrists. Individuals that have arthropathy are likely to reported increased levels of joint pain. They are also likely to report joint problems and reduced range of movement in the joints. In a study involving 141 young men aged 18 to 34 years, 90% reported being affected by joint pain.15 The scope of pain varied. For instance, some participants reported pain only when they had a joint hemorrhage while others reported pain sometimes, most of the time, and at all times.15 The first episodes of joint bleeding usually occur at around two years of age. Failing to treat the bleeding adequately increases the individual's risk of developing arthropathy by the time they turn 20.14 Recurrent bleeding into joints leads to chronic synovitis. Consequently, it results in damage to both cartilage and bone.16 Without proper treatment, patients develop pain, swelling, and reduced range of motion. Recurrent bleeding can also lead to degenerative arthritis in patients who live with hemophilia. It can also affect the bone growth and limb length.14Patients who experience recurrent bleeding and without treatment are also at a prolonged risk of developing osteoporosis.17Joint problems resulting from hemophilia significantly affect a patient's quality of life. Other than pain, it can lead to loss of employment, absenteeism from school, and lower quality of life.15,18Therefore, addressing joint problems associated with hemophilia is vital to improving a patient's quality of life.

Pain is one of the most reported symptoms in patients who have hemophilia. It affects about two-thirds of patients with the disease with a cohort study comprising 141 patients showing that 90% were affected by joint pain.15 An additional survey established that 32 to 50% of hemophilia patients experienced chronic pain.19Pain in hemophilia patients is attributed to joint bleeding and joint degeneration such as arthropathy.20According to Curtis et al. up to 33% of patients who experienced joint pain had a joint hemorrhage.15 Addressing pain attributed to hemophilia is important. Pain significantly affects the quality of life. It contributes to physical inactivity which increases the risk of obesity, overweight, and cardiovascular disease. Pain also affects the social aspect of a patient's life. Patients who have pain may find it difficult to socialize, work, or be productive. A study by Siddiqi et al. established that the disability-adjusted life years (DALY) resulting from hemophilia was 110,095.21

Overweight/ obesity is another complication of hemophilia. Obesity and overweight carry a significant burden for patients who live with hemophilia.22The high burden of obesity and overweight in patients who have hemophilia is attributed to reduced mobility because of joint pain, joint inflammation, and other joint problems.23Hemophilia is also attributed to reduced range of motion which affects mobility in this population. The prevalence of overweight and obesity in young adults with hemophilia is rising. A study by Curtis et al. established that nearly half (47.5%) of the 141-population cohort were either obese or overweight.15Overweight and obesity have significant implications for people affected by hemophilia. In addition to reducing range of motion, being overweight and obese affects the ability of individuals to use home infusion and self-infusion.24The inability to use these treatments can lead to delayed treatment of bleeds which can increase the risk of complications such as arthropathy. Research has shown that excess body weight increases the rate at which an individual develops joint mobility loss more so in the lower limbs.25 Addressing obesity and overweight in patients who live the disorder is important because of the impact it has on health. It contributes to a significant health burden, particularly the risk of developing joint problems and mobility loss.

Additionally, people with hemophilia are at a high risk of developing liver disease. Research has shown that the risk of liver disease is significantly higher among patients who hemophilia than in general population.26 Different factors are attributed to the increased risk of liver disease in this population.Renal bleeding is one of the risk factors for liver disease.27Other risk factors for liver disease in

patients who have hemophilia are renal obstruction which occurs after treatment of a bleed with an antifibrinolytic agent and infections such as hepatitis and HIV.28HIV and hepatitis C occur from blood transfusions and are common among individuals living with hemophilia who received plasma-derived concentrates before the availability of virally inactivated products beforethe mid-1980s.28,29Other risk factors that increased the risk of liver disease in this population were using drugs that had nephrotoxic potential such as antibiotics, antifungals, and antiretroviral drugs that are mostly used by people living with HIV. Addressing renal disease in people living with hemophilia is important because of the high risk of progressing to end-stage liver disease.

The burden of hemophilia can also be established based on the cost of treating the disease.30,31 Hemophilia is mainly treated using clotting factor replacement therapy. The therapy is expensive with one study estimating the lifetime cost of treating the disease to be up to $21,086,607.7 For severe hemophilia, life-long prophylaxis with a standard half-life (SHL) or extended half-life products are used for treatment. These products are given every two to three days or 7 to 14 days. The estimated life cost for EHL was $22,987,483.7 Another study estimated the annual cost of treating severe hemophilia to be $201,471 per person. For mild and moderate hemophilia, the estimated cost was $59,101 and $59,101 respectively.8 For patients receiving prophylaxis, the estimated cost was $301,392.8

Addressing hemophilia is important because of the associated health and cost burden. Furthermore, the pain associated with hemophilia can result in poor quality of life. Different treatment strategies that are used for hemophilia are discussed in detail below.

Treatment Strategies

Treatment for hemophilia has advanced significantly from the first type of treatment which comprised of direct blood transfusion in 1840 and fresh frozen plasma in the 1950s and 60s.2 Today, the mainstay treatment for hemophilia is replacement therapy which is done to attain adequate hemostasis. Immediate replacement therapy is done using high-dose clotting factor concentrate (CFC). It is done either using factor VIII or IX. Treatment is infused on demand at the time of bleeding. Although the dose of infusion depends on the severity of the bleed,Mehta et al. recommend that the dose should be 50 IU/kg body weight for factor VIII or 100 to 120 IU/kg for factor IX.5 Prothrombin complex concentrate can be given if factor IX concentrate is not available.

In addition to clotting factor replacement therapy another strategy that is used for treating hemophilia is prophylaxis. Prophylaxis is done using an intravenous injection of factor concentrate.32,33,34The treatment is mainly done to control bleeding and prevent deterioration of the joints. Unlike replacement therapy which is infused after every bleeding episode, primary prophylaxis is a long-term treatment that is done two to three times per week. The treatment begins at a young age below two years before a patient develops joint disease. Secondary prophylaxis begins after the onset of joint disease.5 Prophylaxis dose is administered every 2 to 3 times per week as a dose of 25–40 IU/kg.2 Although prophylactic therapy is effective in controlling joint bleeding, the early initiation presents a challenge. The frequent venous access that is done using a central venous access device increases the risk of infection, sepsis, and thrombosis especially when the infusion is done at home.2 Another challenge that comes with using prophylaxis as a treatment method is that less than half of adults continue with the therapy.35,36Considering prophylaxis is a mainstay treatment for hemophilia, it is important to address the challenges associated with the treatment. Addressing the challenges attributed to prophylactic therapy can improve outcomes for patients who live with hemophilia.

Conclusion

Hemophilia is ableeding disorder that occurs because of deficiencies in coagulation proteins factor VIII and factor IX. The deficiency affects normal blood clotting. Deficiency of factor VIII results in hemophilia A while deficiency of factor IX results in hemophilia B. Bleeding and joint problems are the main presenting problems in people with hemophilia. The bleeding occurs after trauma or surgery. It normally occurs in joints, tissues, and organs. Hemophilia is more common in males. In the US, approximately 33,000 people have hemophilia. The incidence rate is 1 in every 5000 male births. Addressing hemophilia is vital because it contributes to a significant burden of disease. In addition to bleeding and joint problems, hemophilia increases the risk of liver disease, heart disease, overweight and obesity. Hemophilia is also associated with a significant amount of pain which can affect the patient's quality of life. Clotting factor replacement therapy and prophylaxis are the main treatment strategies that are used in treating hemophilia.

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