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Economic Burden of Illness among Persons with Hemophilia B from HUGS Vb: Examining the Association of Severity and Treatment Regimens with Costs and Annual Bleed Rates

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ABSTRACT

Objectives: To determine US societal burden of illness, including direct and indirect costs and annual bleed rate (ABR), for persons with hemophilia B (HB), a rare and debilitating genetic disorder, and to examine associations of hemophilia severity and treatment regimens with costs and ABR. **Methods:** From 2009 to 2014, the Hemophilia Utilization Group Studies Part Vb collected prospective data from 10 US hemophilia treatment centers. Participants with HB completed initial surveys on sociodemographic characteristics, clinical characteristics, and treatment patterns. During the 2-year follow-up, participants reported bleeding episodes, work absenteeism, and caregiver time quarterly. These data were used to calculate ABR and indirect costs. Direct costs were calculated using 1-year clinical chart records and 2-year dispensing records. **Results:** Of the 148 participants, 112 with complete medical records and one or more follow-up survey were included. Total mean annual per-person costs were $85,852 (median $20,160) for mild/moderate HB, $198,733 (median $147,891) for severe HB, and $140,240 (median $63,617) for all participants without inhibitors ($P < 0.0001$). Mean ABR for participants with severe HB on prophylaxis (5.5 ± 7.9 bleeds/y) was almost half that of those treated episodically. Clotting factor and indirect costs accounted for 85% and 9% of total costs, respectively. Compared with episodic treatment, prophylaxis use was associated with 2.5-fold higher clotting factor costs ($P < 0.01$), low but significantly more missed parental workdays ($P < 0.0001$) and clinician ($P < 0.001$) or nursing visits ($P < 0.0001$), less part-time employment and unemployment, and lower hospitalizations costs ($P = 0.17$) and ABR ($P < 0.0001$). **Conclusions:** HB is associated with high economic burden, primarily because of clotting factor costs. Nevertheless, prophylaxis treatment leads to clinical benefits and may reduce other nonfactor costs.

Keywords: burden of illness, economic outcome, prospective studies, rare diseases.

Introduction

Hemophilia is a rare congenital blood disorder that primarily affects males and causes potentially fatal internal bleeding in the brain and the gastrointestinal tract as well as frequent bleeding in joints and soft tissues [1,2] This disorder affects approximately 20,000 individuals in the United States. Hemophilia B (factor IX deficiency or HB) is much rarer than hemophilia A (factor VIII deficiency or HA), occurring in about 4,400 of these 20,000 US residents [3]. For individuals with hemophilia, acute bleeding episodes can occur spontaneously and after trauma or surgery. Repeated bleeding in joints may eventually lead to debilitating and painful chronic hemophilic arthropathy, limiting mobility [2,4].

Although there is no cure, hemophilia can be effectively managed by integrated teams who have expertise in diagnosis and management with clotting factor replacement therapy administered either after a bleeding episode (episodic or on-demand treatment) or regularly to prevent bleeding episodes (prophylaxis) [5–7]. People with mild or moderate hemophilia who bleed infrequently commonly use episodic treatment, which can control bleeding, relieve pain, and restore joint mobility, but cannot prevent arthropathy [8]. Prophylaxis results in fewer joint bleeds, delays the onset of arthropathy, and improves quality of life (QOL), and is currently considered optimal care for individuals with severe hemophilia who may bleed every 1 to 2 days [5,7,9–12].

The low prevalence of HB limits obtaining cohorts of sufficient size to robustly examine burden of illness associated with HB distinct from that specific to HA [13]. Because of individual variations in hemophilia severity, treatment regimens, and underlying therapeutic response, costs and outcomes can differ significantly in terms of bleeding rate, health care resource utilization, and QOL [12,14]. Prophylaxis compared with episodic treatment has been associated with lower bleeding rates across persons with HA and HB, but at the price of higher clotting factor

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costs [14,15]. The degree to which prophylaxis can improve outcomes to mitigate other hemophilia-related costs due to work productivity losses and health care services utilization and how the benefit of prophylaxis varies in HB remain unclear [13]. Furthermore, about 25% to 30% of individuals with HA and 3% to 5% of those with HB develop inhibitors (antidrug antibodies) to clotting factors [16]. These individuals require higher doses of clotting factors or other bypassing agents and can accrue annual costs more than 3 times higher than the costs for individuals without inhibitors [17].

Previous studies have estimated that 45% to 94% of total direct medical costs are due to clotting factor usage [15,18,19]. One French study of 126 individuals with HB found that the extra direct medical cost of prophylaxis versus episodic treatment was approximately $24,695 per bleeding episode prevented [15]. Although it remains unclear whether clotting factor consumption differs significantly between individuals with HA and HB, it is possible that persons with HA have more severe outcomes and could bear total costs different than those with HB [20,21]. Furthermore, approximately twice the amount of recombinant factor IX, which is used to treat HB, is generally required to achieve the same increase in normal circulating factor levels compared with recombinant factor VIII, which is used to treat HA. In addition, clotting factor is priced by the unit and so twice as much factor results in twice the cost for treatment. Thus, it is useful to obtain more comprehensive estimates of burden of illness by hemophilia type and other clinical subgroups.

Recent studies have estimated the hemophilia-related burden of illness specifically in the United States [14,22–25]. Four studies calculated direct costs across both HA and HB from a payer's perspective using claims data [22–25]. Nevertheless, claims data lack detailed clinical and sociodemographic variables to identify hemophilia severity, treatment regimen, and inhibitor status and generally do not record information regarding work productivity or bleeding episodes. A 2015 study used prospective patient-reported outcomes and medical record extraction to calculate both direct and indirect costs and annual bleed rate (ABR) among 222 individuals with HA in the United States, revealing total mean annual per-person costs of $195,332 (median $139,571) in 2011 US dollars [14].

This study used prospective, longitudinal cohort data from the Hemophilia Utilization Group Studies Part Vb (HUGS Vb), a multicenter study designed to examine the burden of illness among persons with HB at federally supported hemophilia treatment centers (HTCs) in the United States. HTC care is a multidisciplinary, team-based care delivery model that aims to prevent orthopedic complications and maximize physical and psychological functioning as well as socioeconomic benefits [6].

The objective of this study was to determine societal burden of illness, including direct and indirect costs and ABR, for persons with HB in the United States and to examine associations of hemophilia severity and treatment regimens with costs and ABR.

Methods

Hemophilia Utilization Group Studies Part Vb

From 2009 to 2014, 10 HTCs collected prospective data on individuals with HB from 15 states (Arkansas, California, Colorado, Illinois, Indiana, Kansas, Massachusetts, Michigan, Mississippi, Montana, Ohio, South Dakota, Texas, Washington, and Wyoming) using the HUGS Vb protocol. All participants provided informed consent or assent. The inclusion criteria for the individuals were that they should be 1) aged between 2 and 64 years at initial interview; 2) diagnosis of factor IX deficiency of 30% or less, with or without history of inhibitors; 3) receiving at least 90% of hemophilia care from the HTC; 4) English- or Spanish-speaking; and 5) seen at the HTC within 2 years before the study's initiation. The protocol was approved by the institutional review board of the University of Southern California and of each participating HTC.

All adults 18 years or older or parents of pediatric participants younger than 18 years completed a baseline survey to collect information regarding sociodemographic characteristics, clinical characteristics, and treatment patterns. Participants or parents completed a follow-up survey quarterly over a 2-year study period (eight follow-up surveys) to track work or school absenteeism, unpaid hemophilia-related caregiver time, bleeding episodes, and health outcomes. ABR was annualized from the sum of participant-reported bleeding episodes.

Baseline clinical chart information included weight, inhibitor status, treatment patterns, and comorbidities collected from clinical chart abstraction. Follow-up clinical information regarding health care services utilization, changes in treatment pattern, inhibitor development, and new medical problems was abstracted monthly from clinical charts in the first year of the 2-year study period. Prescription data were collected monthly from dispensing records throughout the 2-year period.

Determination of Direct Costs

Each recorded instance of health care services utilization or drug dispensation was multiplied by the price associated with the service or product to estimate direct costs, which were adjusted to 2014 US dollars using the Consumer Price Index for medical care. Only patients with complete chart and dispensing records were included in the analysis.

Direct costs from clinical charts included all-cause hospitalizations, emergency room (ER) visits and outpatient services, and related units of clotting factor received. The length of stay (LOS) and primary diagnoses were used to calculate hospitalization costs. The average daily inpatient cost was obtained from the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project National Inpatient Sample average LOS and costs, on the basis of hospital-specific cost-to-charge ratios, for each *International Classification of Diseases, Ninth Revision*, code recorded [26]. The average cost of an ER visit was based on the Medical Expenditure Panel Survey statistical briefs [27].

Outpatient services included HTC visits (comprehensive, nursing, clinician, physical therapist, and social work/psychology), laboratory tests, and outpatient procedures. Comprehensive visits refer to annual multidisciplinary evaluations that involve the HTC team of specialists, nurses, and hematologists and include laboratory testing, assessment of treatment, and various training and counseling. Costs were estimated from the 2014 Medicare fee schedule, on the basis of Current Procedural Terminology codes [28]. A list of laboratory tests required during comprehensive visits, which varied by age, use of recombinant or plasma-derived clotting factor, and virological status, was summarized and reviewed by a hematologist previously [14].

Annual medication costs were also included in direct costs and calculated using the average of 2-year dispensing records. The unit cost for clotting factors and bypassing agents was obtained from payment allowance limits for Medicare Part B [29]. All hospital-supplied factors recorded in the clinical charts were priced and added to health care services utilization costs. The Veterans Affairs Federal Supply Schedule was used to obtain the cost for aminocaproic acid [30].

Determination of Indirect Costs

The human capital approach was used to calculate indirect costs [31]. In this method, work productivity losses are estimated through lost earnings using wages as a proxy for work time

output. Indirect costs included lost wages due to days of work absenteeism among those employed and unpaid hemophilia-related caregiver time reported in participant- or parent-completed follow-up surveys as well as hemophilia-related part-time employment or unemployment reported in the baseline survey. Average civilian worker compensation obtained from the US Bureau of Labor Statistics was $31.96/h in 2014 and was multiplied by hours to value the indirect cost of work absenteeism days, hemophilia-related caregiver hours, and hemophilia-related part-time employment or unemployment [32]. Participants with at least one follow-up survey were included, and data were annualized using total follow-up days for each participant.

Statistical Analysis

Summary statistics were reported for all participants. Bivariate analyses were conducted to examine the associations of hemophilia severity and treatment regimen with outcome variables. The χ^2 statistic for categorical variables and the Kruskal-Wallis test for continuous variables were used to test groups for statistically significant differences. The χ^2 statistic for Poisson distributions was used to test for statistical significance in count data. All analyses were conducted using SAS statistical software, version 9.4 (SAS Institute, Cary, NC).

Results

Baseline Characteristics

Of the 148 recruited participants, 112 (75.7%) with complete chart and dispensing records and at least one follow-up survey were included. The 112 individuals completed an average of 6 (median 7) follow-up surveys with 21.4 (median 23.8) months of follow-up. Compared with excluded participants, included subjects were more likely to be children (55.4% vs. 33.3%; $P < 0.03$), have public or private health insurance only (48.2% vs. 2.8% or 39.3% vs. 22.2%; overall $P < 0.04$), and have severe disease (49.1% vs. 25%; $P < 0.02$) (Table 1). In addition, included subjects were more likely to have annual household income of more than $20,000 compared with excluded subjects (75.9% vs. 55.6%; $P < 0.01$). At the initial interview, two included participants had inhibitors to clotting factors.

The mean age of included participants was 22.1 ± 17.6 years, and almost half of the participants or parents (47.3%) were employed full-time (Table 1). As expected, only 3 out of 57 mild/moderate participants (5.3%) used prophylaxis compared with 31 out of 55 severe participants (56.4%). Furthermore, severe participants were more likely to be antibody-positive for the hepatitis C virus compared with mild/moderate participants (29.1% vs. 12.3%; $P < 0.03$) and have at least one comorbidity (34.5% vs. 24.6%; $P < 0.05$). Finally, severe participants compared with mild/moderate participants were more likely to have an annual household income of $20,000 or less (27.3% vs. 7.0%; $P < 0.01$) and slightly more likely to have more than 12 years of education (74.5% vs. 57.9%; $P = 0.06$).

Health Care Services Utilization, Dispensing, and Work Productivity Losses

During the 1-year clinical chart follow-up, 18 participants (16%) had at least one ER visit, and 7 (6.3%) had at least one hospitalization due to all causes. Overall, participants with severe HB using prophylaxis versus episodic treatment had more total ER visits in 1 year (12 vs. 1; $P < 0.04$) but fewer total hospitalizations (1 vs. 3; $P = 0.24$) with shorter mean LOS (1.5 vs. 6.3 days; $P = 0.09$ [Table 2]).

Severe participants compared with mild/moderate participants had significantly more nursing ($P < 0.0001$), clinician (doctor, nurse practitioner, or physician's assistant) ($P < 0.01$), and social work/psychology ($P < 0.03$) visits at the HTC (Table 2). The numbers of these types of HTC-related visits were generally low and also significantly higher among severe participants treated prophylactically versus episodically ($P < 0.0001$, $P < 0.001$, $P < 0.05$, respectively).

Furthermore, severe participants had significantly higher mean annual clotting factor dispensing measured by international units per kilogram of body weight (IU/kg) than mild/moderate participants ($P < 0.0001$) (Table 2). Prophylaxis users had significantly higher factor dispensing than episodic treatment users among severe participants (4945 [4184] vs. 1486 [1613]; $P < 0.01$).

Hemophilia severity and treatment regimen were also associated with different work productivity losses (Table 2). Severe hemophilia compared with mild/moderate hemophilia was associated with significantly more days of parental work absenteeism ($P < 0.01$) and hours of caregiver time ($P < 0.0001$), but there was no statistically significant difference between participant work absenteeism ($P = 0.17$). On average, severe adult participants lost 5.2 ± 5.5 days of work productivity annually and parents of severe pediatric participants lost 1.6 ± 3.5 days, of which 3.5 ± 4.5 and 1.2 ± 2.8 days were due to hemophilia, respectively. Among mild/moderate participants, adults lost 5.8 ± 9.5 days annually and parents of pediatric participants lost 0.9 ± 3.6 days, of which 3.2 ± 7.5 and 0.5 ± 1.5 days were due to hemophilia, respectively. Compared with those treated prophylactically, more severe adult participants or parents of severe pediatric participants treated episodically were unemployed (12.5% vs. 6.5%; $P = 0.44$) or employed part-time because of hemophilia (12.5% vs. 3.2%; $P = 0.19$), but prophylaxis was associated with more missed parental workdays ($P < 0.0001$).

Bleeding Episodes

Table 2 presents mean ABR for participants by severity and also by treatment regimen among those with severe HB. Overall mean ABR was 5.2 ± 6.7 (median 2.5). Severe participants compared with mild/moderate participants had more than 2 times higher ABR ($P < 0.0001$). Episodic treatment users had significantly higher ABR than prophylaxis users in severe (9 ± 7 vs. 5.5 ± 7.9; $P < 0.0001$) and mild/moderate participants (3.6 ± 5.2 vs. 1 ± 1.3; $P < 0.03$).

Direct and Indirect Costs

Mean annual total (direct plus indirect) costs per participant without inhibitors (N = 110) was $140,240 (median $63,617) (Table 3). Clotting factor costs accounted for an average 85% (median 98%) of total costs and 92% (median 99%) of direct costs. Indirect costs accounted for 9% (median 0%) of total costs, whereas lost wages from unemployment or part-time employment accounted for 96% of indirect costs for those who were underemployed (n = 11). Mean total costs for mild/moderate and severe participants without inhibitors were $85,852 (median $20,160) and $198,733 (median $142,891), respectively ($P < 0.0001$) (Table 3). Among participants with inhibitors (n = 2), mean direct and indirect costs were $1,424,364 and $34,638, respectively.

Costs by Participant Subgroups

Severe versus mild/moderate participants had higher indirect costs (mean [median] $8,421 [$204] vs. $4,416 [$0]; $P = 0.11$) and direct costs ($190,312 [$141,879] vs. $81,435 [$19,146]; $P < 0.0001$) (Table 3). Prophylaxis versus episodic treatment for severe participants was associated with lower indirect costs ($6,477 [$408] vs. $10,957 [$131]; $P = 0.96$) but significantly higher direct costs

Table 1 – Baseline characteristics among persons with HB.

Variables	Excluded (n = 36)*	Included (n = 112)*	P value†	Hemophilia severity, included participants		
				Mild/moderate (n = 57)	Severe (n = 55)	P value†
Sociodemographic characteristics						
Age (y), mean ± SD	27.6 ± 17.5	22.1 ± 17.6	0.05	21.9 ± 16.7	22.4 ± 18.6	0.77
Adult, n (%)			<0.03			0.83
Child (2–<18 y)	12 (33.3)	62 (55.4)		31 (54.4)	31 (56.4)	
Adult (≥18 y)	24 (66.7)	50 (44.6)		25 (43.9)	24 (43.6)	
Sex, male, n (%)	35 (97.2)	111 (99.1)	0.39	57 (100)	54 (98.2)	0.31
Race/Ethnicity n (%)			0.70			<0.02
White, non-Hispanic	27 (75)	70 (62.5)		37 (64.9)	33 (60)	
African American, non-Hispanic	1 (2.8)	8 (7.1)		2 (3.5)	6 (10.9)	
Hispanic	4 (11.1)	18 (16.1)		6 (10.5)	12 (21.8)	
Asian Pacific Islander	1 (2.8)	5 (4.5)		2 (3.5)	3 (5.5)	
Other‡	3 (8.3)	11 (9.8)		10 (17.5)	1 (1.8)	
Employment status,§,‖ n (%)			0.37			0.43
Full-time	14 (38.9)	53 (47.3)		27 (47.4)	26 (47.3)	
Part-time	7 (19.4)	15 (13.4)		7 (12.3)	8 (14.5)	
Not employed	15 (41.7)	38 (33.9)		22 (38.6)	16 (29.1)	
Retired	0 (0)	5 (4.5)		1 (1.8)	4 (7.3)	
Married/with partner,§ n (%)	20 (55.6)	77 (68.8)	0.11	42 (73.7)	35 (63.6)	0.24
Education >12 y,§ n (%)	25 (69.4)	74 (66.1)	0.71	33 (57.9)	41 (74.5)	0.06
Income,§,‖ n (%)			<0.01			<0.04
≤$20,000	14 (38.9)	19 (17)		4 (7)	15 (27.3)	
$20,001–$40,000	2 (5.6)	29 (25.9)		17 (29.8)	12 (21.8)	
$40,001–$75,000	4 (11.1)	24 (21.4)		15 (26.3)	9 (16.4)	
≥$75,001	14 (38.9)	32 (28.6)		17 (29.8)	15 (27.3)	
Insurance type,‖ n (%)			<0.04			0.29
Public	1 (2.8)	54 (48.2)		29 (50.9)	25 (45.5)	
Private	8 (22.2)	44 (39.3)		21 (36.8)	23 (41.8)	
Both public and private	22 (61.1)	10 (8.9)		4 (7)	6 (10.9)	
No insurance	4 (11.1)	3 (2.7)		3 (5.3)	0 (0)	
Clinical characteristics						
Using prophylaxis, n (%)	6 (16.7)	34 (30.4)	0.11	3 (5.3)	31 (56.4)	<0.0001
Comorbidities, n (%)						
≥1 comorbidities	13 (36.1)	33 (29.5)	0.89	14 (24.6)	19 (34.5)	<0.05
HIV/AIDS	2 (5.6)	4 (3.6)	0.60	1 (1.8)	3 (5.5)	0.29
HCV	8 (22.2)	23 (20.5)	0.83	7 (12.3)	16 (29.1)	<0.03
Severity, n (%)			<0.02			–
Mild/moderate	27 (75)	57 (50.9)		–	–	
Severe	9 (25)	55 (49.1)		–	–	

Data source: Hemophilia Utilization Group Study Part Vb (HUGS Vb).

HB, hemophilia B; HCV, hepatitis C virus.

* A total of 148 participants were recruited, with 112 having at least one follow-up patient survey, and complete follow-up clinician chart records and dispensing records.

† Any P values of <0.05 indicate that variables differ significantly on the basis of the χ^2 statistic for categorical variables and the Kruskal-Wallis test for continuous variables.

‡ Other races/ethnicities include American Indian or Alaskan Native and others.

§ Applies to participants ≥18 y old, or parents of participants 2–<18 y old.

‖ Does not add up to total sample because of missing data.

($256,775 [$205,575] vs. $103,630 [$63,765]; $P < 0.01$), largely because of greater factor consumption.

The costs of hospitalizations and ER visits accounted for most nonfactor health care services utilization costs across subgroups (Fig. 1). Severe versus mild/moderate participants had significantly higher HTC visit costs (mean [median] $243 [$187] vs. $139 [$111]; $P < 0.04$) and laboratory test costs ($225 [160] vs. $113 [$107]; $P < 0.01$). In severe participants, prophylaxis compared with episodic treatment was associated with lower hospitalization costs ($68 [$0] vs. $5389 [$0]; $P = 0.17$) and significantly higher HTC visit costs ($325 [$223] vs. $135 [$111]; $P < 0.03$). Lost wages from part-time employment or unemployment because of hemophilia accounted for most of the indirect costs across subgroups (Fig. 2), and differences were not statistically significant.

Discussion

Data from HUGS Vb were used to examine annual hemophilia-related burden of illness for individuals with HB in the United

Table 2 – Annual health care resource utilization, work productivity loss, and bleeding episodes among individuals with HB.

Variables	Total (N = 112)*	Hemophilia severity			Treatment regimen, severe hemophilia only		
		Mild/ moderate (n = 57)	Severe (n = 55)	P value†	Episodic (n = 24)	Prophylactic (n = 31)	P value†
Annual health care service utilization, mean ± SD (no. of visits/person/y)‡							
Comprehensive visits	1 ± 0.8	0.8 ± 0.8	1.2 ± 0.8	0.11	1 ± 0.9	1.3 ± 0.8	0.53
Nursing visits	0.8 ± 4.8	0.4 ± 0.7	1.3 ± 6.9	<0.0001	0.3 ± 0.7	2 ± 9.1	<0.0001
Other clinician (MD/PA/NP) visits	0.5 ± 1.1	0.3 ± 0.6	0.6 ± 1.5	<0.01	0.1 ± 0.4	1.1 ± 1.8	<0.001
Physical therapist visits	0.2 ± 0.7	0.2 ± 0.6	0.3 ± 0.8	0.07	0 ± 0	0.6 ± 1	–
Social work/psychology visits	0.2 ± 0.6	0.1 ± 0.4	0.3 ± 0.8	<0.03	0.1 ± 0.5	0.5 ± 1	<0.05
ER visits	0.2 ± 0.6	0.2 ± 0.5	0.2 ± 0.7	0.93	0 ± 0.2	0.4 ± 0.8	<0.04
Hospitalizations	0.1 ± 0.2	0.1 ± 0.2	0.1 ± 0.3	0.67	0.1 ± 0.3	0 ± 0.2	0.24
Length of stay (days/patient/y)§	3.9 ± 3.5	2.3 ± 0.6	5.1 ± 4.4	0.07	6.3 ± 4.5	1.5 (–)	0.09
Outpatient procedures	0.1 ± 0.3	0.1 ± 0.3	0 ± 0.2	0.19	0.1 ± 0.3	0 ± 0	–
Annual clotting factor dispensed, mean ± SD (IU/kg body weight/y)‖	2372 ± 3392	1299 ± 2597	3548 ± 3775	<0.0001	1486 ± 1613	4945 ± 4184	<0.01
Employment status due to hemophilia, n (%)¶							
Employed part-time	4 (3.6)	0 (0)	4 (7.3)	<0.04	3 (12.5)	1 (3.2)	0.19
Unemployed	8 (7.1)	3 (5.3)	5 (9.1)	0.43	3 (12.5)	2 (6.5)	0.44
Missed days of work, mean ± SD							
Missed days due to all reasons, parent#	1.3 ± 3.5	0.9 ± 3.6	1.6 ± 3.5	<0.01	0.7 ± 1.8	2.3 ± 4.3	<0.0001
Missed days due to HB, parent#	0.9 ± 2.2	0.5 ± 1.5	1.2 ± 2.8	<0.001	0.5 ± 1.3	1.7 ± 3.5	<0.001
Missed days due to all reasons, participant**	5.5 ± 7.8	5.8 ± 9.5	5.2 ± 5.5	0.17	4.7 ± 4.6	5.6 ± 6.1	0.15
Missed days due to HB, participant**	3.6 ± 6	3.8 ± 7.1	3.5 ± 4.5	0.34	3.6 ± 4.8	3.4 ± 4.4	0.756
Unpaid caregiver hours, mean ± SD	6.5 ± 25.1	3.2 ± 7.5	9.8 ± 34.8	<0.0001	10 ± 42.6	9.7 ± 28.1	0.71
ABR, mean ± SD	5.2 ± 6.7	3.5 ± 5.1	7.1 ± 7.7	<0.0001	9 ± 7	5.5 ± 7.9	<0.0001

Data source: Hemophilia Utilization Group Study Part Vb.

ABR, annual bleed rate; ER, emergency room; HB, hemophilia B; IU, international unit; MD, doctor of medicine; NP, nurse practitioner; PA, physician's assistant.

* Includes all participants with (n = 2) and without (n = 110) inhibitors.

† Any *P* values of <0.05 indicate that variables differ significantly on the basis of the χ^2 statistic for categorical variables and Poisson-distributed count data and the Kruskal-Wallis test for continuous variables.

‡ Visits refer to in-person visits.

§ Applies only to participants with hospital stays (n = 7).

‖ Three participants with missing weight data were excluded. Inhibitor-related bypassing agent dispensations were excluded. Participants with inhibitors did not have clotting factor dispensation in addition to bypassing agents.

¶ Full-time work was assumed to be 40 h/wk, and part-time work was assumed to be 20 h/wk.

Parents of pediatric participants aged 2–<18 y (mild/moderate, n = 31; severe, n = 30).

** Adult participants aged ≥18 y (mild/moderate, n = 26; severe, n = 23).

States. Although a similar analysis has been done for HA, studies evaluating hemophilia-related costs from a societal perspective with detailed information on patient characteristics and bleeding patterns are scarce, especially in HB [14]. Polack et al. [15] used French national health insurance data from 126 subjects with HB to calculate mean annual per-person medical costs of approximately $104,459 ± $90,828 and mean ABR of 3.57 ± 6.55, but did not estimate indirect costs other than travel time to the clinic, and followed-up for only 1 year [15]. Other recent studies evaluating HA- and HB-related costs from US payers' perspectives relied on claims databases that lack detailed patient information [22–25].

These results evaluate the economic and clinical impact of HB, separate from HA, on both patients and society. HB is a costly disorder with lower ABR and annual per-person costs compared with estimates for HA [14]. In addition, this study found generally low health care resource utilization among patients with HB in terms of outpatient and ER visits and hospitalizations, as well as

Table 3 – Annual per-person HB-related costs (in 2014 US dollars).

Annual costs, mean ± SD (median)	Total (N = 110)*	Hemophilia severity			Treatment regimen, severe hemophilia only		
		Mild/moderate (n = 57)	Severe (n = 53)	P value†	Episodic (n = 23)	Prophylactic (n = 30)	P value†
Total costs (direct + indirect)	140,240 ± 170,392 (63,617)	85,852 ± 20,160 (20,160)	198,733 ± 178,246 (147,891)	<0.0001	114,577 ± 90,336 (95,353)	263,253 ± 202,128 (208,999)	<0.01
Total direct costs	133,894 ± 167,768 (51,814)	51,435 ± 137,459 (19,146)	190,312 ± 137,459 (141,879)	<0.0001	103,620 ± 90,256 (63,765)	256,775 ± 203,391 (205,575)	<0.01
Health care services utilization costs‡	2,303 ± 8,508 (438)	1,439 ± 3,548 (250)	3,231 ± 11,682 (500)	0.10	6,122 ± 17,453 (500)	1,015 ± 1,381 (500)	0.54
Clotting factor costs§	131,574 ± 167,606 (51,205)	79,974 ± 137,097 (18,927)	187,070 ± 180,514 (131,837)	<0.0001	97,490 ± 88,570 (62,658)	255,747 ± 203,062 (205,085)	<0.01
Total indirect costs‖	6,346 ± 17,296 (159)	4,416 ± 14,977 (0)	8,421 ± 19,417 (204)	0.11	10,957 ± 21,544 (131)	6,477 ± 17,747 (408)	0.96
Factor costs as proportion of total costs	0.85 ± 0.27 (0.98)	0.86 ± 0.25 (0.96)	0.86 ± 0.29 (0.99)	0.15	0.82 ± 0.3 (0.98)	0.87 ± 0.28 (0.99)	0.10

Data source: Hemophilia Utilization Group Study Part Vb.

ER, emergency room; HTC, hemophilia treatment center.

* Excludes participants with inhibitors (n = 2).

† Any *P* values of <0.05 indicate that costs differ significantly on the basis of the Kruskal-Wallis test.

‡ Includes HTC visits, laboratory tests, ER visits, hospitalizations, and outpatient procedures.

§ Cost of nonfactor hemophilia-related medication (aminocaproic acid) was also included in direct costs.

‖ Includes lost wages from part-time or unemployment due to hemophilia, lost wages from missed work due to all reasons, and unpaid caregiver time. Full-time work was assumed to be 40 h/wk and part-time work was assumed to be 20 h/wk.

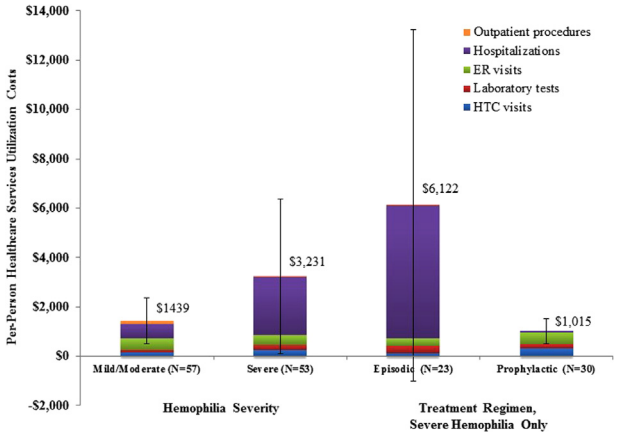

Fig. 1 – Mean annual nonfactor health care services utilization costs by HB severity and treatment regimen. This excludes participants with inhibitors (n = 2). Numeric labels above bars represent total mean per-person health care services utilization costs. Error bars represent 95% confidence intervals for total per-person health care services utilization costs. ER, emergency room; HB, hemophilia B; HTC, hemophilia treatment center.

low parental work absenteeism even considering the prevalence of prophylaxis use and comorbidities in this study sample. Low ER and hospitalization and parental work absenteeism were also estimated in the study from Zhou et al. [14] among patients with HA, although those results in HA are somewhat higher than results reported in this study of HB. Nevertheless, further comparisons of economic and clinical outcomes specific to HB versus HA should be made cautiously, because different patient populations and enrollment, data collection, and analysis methods from multiple studies may limit the comparability of separate study results.

Subgroup analyses from HUGS Vb showed that severe HB is associated with more work productivity losses among parents of pediatric patients, higher direct costs, and more bleeds compared with mild/moderate HB, as expected. Among those with severe HB, treating prophylactically versus episodically is associated with lower ABR, at the price of significantly higher direct costs, primarily because of higher clotting factor consumption. Among these individuals, prophylaxis use was also associated with more HTC-related visits and missed parental workdays, presumably because of the need for more monitoring and assistance with frequent factor infusions, care related to the higher prevalence of comorbidities, and also potential selection bias in that patients with poorly managed severe HB or who have a higher bleeding frequency tend to use prophylactic treatment. There is some preliminary evidence of cost savings through fewer hospitalizations with shorter LOS and more full-time employment compared with episodic treatment use. These savings, however, do not fully offset higher factor costs because these other costs are generally low compared with factor costs across all subgroups. Although cost and bleeding patterns among clinical subgroups in HUGS Vb are similar to those found in HA, a direct comparison of economic and clinical outcomes is still needed to evaluate differences between HA and HB. Interesting differences in health care services utilization and nonfactor costs between clinical subgroups should also be further examined to better understand the main drivers of economic burden of illness.

ABR observed in HUGS Vb is higher than what has been reported in clinical trials of individuals with severe or moderately severe HB and by Polack et al. [15,33,34]. Nevertheless, there is other evidence of frequent patient- or clinician-reported bleeding episodes despite clotting factor therapy from studies that captured outcomes in routine clinical practice [14,35,36]. Despite the effectiveness of clotting factor treatment regimens observed in highly regulated clinical trial environments, the results suggest that individuals using prophylactic treatments will still experience bleeding episodes in routine clinical practice.

Combined, the total US societal cost to treat these 112 patients with HB from HUGS Vb would be $15.5 million annually. This sample represents 2% to 3% of the individuals with HB receiving care at an HTC [37]. Given that clotting factor usage accounts for 85% of total costs and prophylaxis may lead to fewer hospitalizations, more full-time employment, and lower indirect costs, additional studies may enhance our understanding of the cost-effectiveness of individual treatment decisions. Furthermore, the degree to which reduced ABR and hospitalizations provide long-term nonmonetary benefits to patients, in terms of joint health, QOL, and caregiver burden, has yet to be fully assessed in prospective longitudinal studies of HB. Previous studies have shown that hemophilia leads to impaired QOL among children and adults with HA or HB, as well as their caregivers. In addition, treatment effectiveness, in terms of reduced ABR, is associated with significant QOL improvements [34,38]. As such, the results of this study on economic burden should be also interpreted in light of growing evidence demonstrating the potential impact of treatment regimen on social costs through improved QOL. Combined with future studies that assess the long-term impact of clotting factor treatment regimens, the current results can shed light on opportunities to personalize treatment of HB for optimal outcomes beyond reduction in ABR.

Study Limitations

This study has a few limitations that emphasize the need for future studies. First, the results rely on patient-reported data, which may be subject to recall, social response, or other biases. In addition, no adherence data are available to corroborate the clotting factor usage suggested by dispensing records. Second, analyses by subgroups were not based on patients randomized to prophylaxis or episodic treatment. Because multivariate analyses were limited by the skewed nature of medical costs and the small

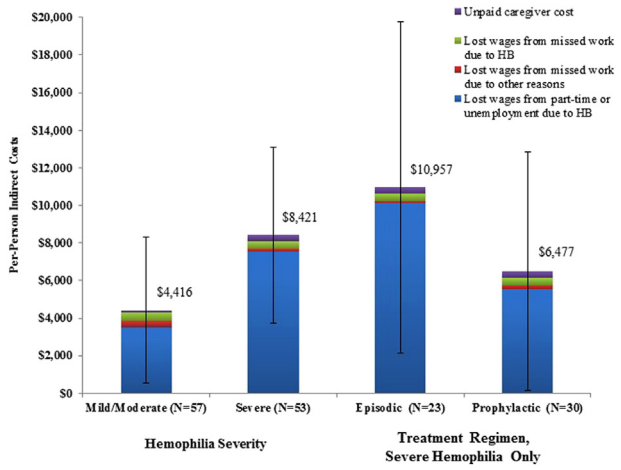

Fig. 2 – Mean annual indirect costs by HB severity and treatment regimen. This excludes participants with inhibitors (n = 2). Numeric labels above bars represent total mean per-person indirect costs. Error bars represent 95% confidence intervals for total per-person indirect costs. HB, hemophilia B.

sample size of subjects with complete covariate information, potential selection bias should be factored into interpretations of the comparisons between treatment regimens. Third, 36 participants without complete follow-ups, who tended to be children with severe HB from poorer households, were excluded. As such, these individuals may have different access to health care and social resources compared with included subjects and may face disparities in health outcomes that could bias results. Finally, this study examined males receiving care at 10 of 141 HTCs in the United States, potentially limiting the generalizability of the results to the entire US HB population. In 2010, about 70% of the US HB population was treated at HTCs, and it is unclear whether individuals treated at HTCs are different from those treated elsewhere [37]. In addition, any costs for hemophilia-related care received outside the HTCs or HTC-affiliated hospitals were not fully captured by the HUGS Vb survey forms.

Conclusions

HB is associated with high total costs and surprisingly high ABR in routine clinical practice in the United States. This is the first study to examine the burden of illness for the US HB population, and the results demonstrated significant associations of hemophilia severity and treatment regimens with costs and ABR. Overall, indirect and health care services utilization costs were low compared with clotting factor costs. Severe versus mild/moderate HB and prophylaxis versus episodic treatment use in severe HB were significantly associated with more HTC-related visits and missed parental workdays. Although frequent prophylactic infusions may necessitate more HTC visits and work absenteeism, evidence of lower hospitalization costs, more full-time employment, and lower ABR suggests potential long-term benefits to prophylaxis use for HB compared with episodic treatment use. Future studies should evaluate how individualized treatment regimens and other patient characteristics impact factor use and ABR and should assess the long-term impact of these findings on joint health and overall patient well-being.

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