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Authors

Zhou, Zheng-Yi
Koerper, Marion A
Johnson, Kathleen A
et al.

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Original article

Burden of illness: direct and indirect costs among persons with hemophilia A in the United States

Zheng-Yi Zhou
University of Southern California, CA, USA

Marion A. Koerper
University of California, San Francisco, CA, USA

Kathleen A. Johnson
University of Southern California, CA, USA

Brenda Riske
University of Colorado Denver, CO, USA

Judith R. Baker
Center for Inherited Blood Disorders, CA, USA, and University of California, Los Angeles, CA, USA

Megan Ullman
University of Texas Health Sciences Center at Houston, TX, USA

Randall G. Curtis
Factor VIII Computing, Berkeley, CA, USA

Jiat-Ling Poon
Mimi Lou
Michael B. Nichol
University of Southern California, CA, USA

Address for correspondence:
Michael B. Nichol, PhD, Director, Graduate Programs in Health, Research Fellow, Leonard D. Schaeffer Center for Health Policy and Economics, Ralph and Goldy Lewis Hall 326, Los Angeles, CA 90089-0626, USA.
Tel.: (213) 740-2355;
mnichol@usc.edu

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Abstract

Objective:
To examine the direct and indirect costs of hemophilia care among persons with hemophilia A in the US.

Methods:
Observational data were obtained from HUGS-Va, a multi-center study from six federally supported hemophilia treatment centers (HTCs). Eligible individuals completed a standardized initial questionnaire and were followed regularly for 2 years to obtain information on work or school absenteeism, time spent arranging hemophilia care, and unpaid hemophilia-related support from caregivers. Data from 1-year healthcare utilization records and 2-year clotting factor dispensing records measured direct medical costs. Indirect costs were imputed using the human capital approach, which uses wages as a proxy measure of work time output.

Results:
A total of 222 patients with complete data were included in the analysis. Two-thirds had severe hemophilia and the mean age was 21.1 years. The use of prophylaxis in severe hemophilia patients is associated with statistically significant reduction in the numbers of emergency department (ED) visits and bleeding episodes compared with those who were treated episodically. From the societal perspective, mild hemophilia costs $59,101 (median: $7519) annually per person, $84,363 (median: $61,837) for moderate hemophilia, $201,471 (median: $143,431) for severe hemophilia using episodic treatment, and $301,392 (median: $286,198) for severe hemophilia receiving prophylaxis. Clotting factor contributed from 54% of total costs in mild hemophilia to a maximum of 94% for patients with severe hemophilia receiving prophylaxis.

Conclusion:
Hemophilia is a costly disorder not only because of its high medical expenses, but also due to the high indirect costs incurred.

Introduction

Hemophilia is a rare chronic congenital bleeding disorder affecting ~400,000 persons of all races worldwide, including 20,000 in the US[1]. Individuals with hemophilia are deficient in one of the blood clotting factor proteins, which impairs the body's ability to control bleeding. This study included persons with Factor VIII Deficiency or Hemophilia A. Severe hemophilia is characterized by spontaneous bleeding in joints, muscles, and other soft tissues, and in mild or moderate disease, bleeding related to traumatic or post-surgical bleeding. Repeated bleeding into joints may eventually lead to chronic hemophilic

arthropathy, chronic pain, loss of range of motion in joints, crippling musculoskeletal deformity, and disability[2].

Management of bleeding in hemophiliac patients includes use of clotting factor replacement therapy following a bleeding episode (episodic or on-demand treatment) or on a regular basis to prevent bleeding (prophylaxis). Prophylaxis instituted early in life has been shown to result in fewer joint bleeds, to delay the onset of arthropathy, and to improve quality of life[3–5]. Prophylaxis is currently considered standard care for individuals with severe hemophilia and recommended to be instituted prior to the onset of frequent bleeding in young children[6]. However, treatment with clotting factor is costly and places substantial economic burden on patients, their families, and healthcare systems.

Previous studies have estimated that 45–94% of the total direct medical costs for hemophilia are attributable to clotting factor use[7,8]. The study by Globe *et al.*[7] estimated the annual medical costs of hemophilia care in the US in 1995 at $139,102 (median: $55,330). Clotting factor consumption accounted for an average of 72% of total costs, ranging from 45% for mild hemophilia to 83% for severe hemophilia A[7]. In a 2004 study in Norway and Sweden, clotting factor consumption in prophylaxis was 2–3-times higher than that in episodic treatment, accounting for 94% vs 74% of total costs, respectively[8]. In addition, 25–30% of patients with severe hemophilia A and 4–6% with severe hemophilia B may develop antibodies (inhibitors) and require higher doses of clotting factors or other treatments[9], which result in even higher medical costs[10,11]. Affected individuals also incur considerable indirect costs, including lost productivity, costs for caregivers' unpaid time and hemophilic individuals' disability[12].

Given the high costs of clotting factor and the increasing use of prophylaxis, and new extended half-life factor concentrate, it is crucial to understand costs associated with hemophilia treatment from both payer and societal perspectives. Four recent studies have reported the annual healthcare costs among persons with hemophilia from the US payers' perspective[13–16]. Three studies were conducted using claims data of individuals covered by employer-sponsored insurance (ESI)[13,14,16], and one used a multi-state Medicaid database[15]. The average annual healthcare expenditure in 2008 for hemophilia was estimated to be $142,987 (median : $46,737) for individuals covered by Medicaid, and $155,136 (median : $73,548) among ESI enrollees[13,15]. However, using claims data to examine cost-of-illness has clear limitations. Clinical details, such as disease severity and treatment patterns, are not available in the claims. Moreover, inhibitor development was assumed only if bypassing agents were used. Thus, costs associated with disease severity could not be determined. In addition, none of these studies characterized indirect costs.

The Hemophilia Utilization Group Study part-Va (HUGS-Va) is a multi-center, prospective cohort study designed to examine the burden of illness among persons with hemophilia A at six federally-supported hemophilia treatment centers (HTCs) in the US[17]. The regionalized HTCs, a multi-disciplinary, team-based care delivery model, have been implemented in the US for several decades with goals to prevent orthopedic complications and to maximize the physical and psychological functioning and socioeconomic benefits for this rare disease population[18]. HTC care has been shown to be associated with lower mortality[19] and fewer bleed-related hospitalizations[20] compared with care obtained elsewhere. School absenteeism and high school graduation rates among HTC patients are comparable to those found in the general population[21]. Participants in HUGS-Va were followed up during a 2-year period to collect information on burden of illness of hemophilia, including self-reported barriers to care, health status, treatment patterns, healthcare utilization, clotting factor utilization, and lost productivity and caregivers' time. The present study, employing a societal perspective, examined the economic burden of hemophilia A in the US, including direct medical costs and indirect costs due to productivity loss for both patients and caregivers.

Patients and methods

Study design and data collection

Data were collected among patients from six HTCs located in racially and geographically diverse regions in the US (California-2 HTCs, Colorado, Indiana, Massachusetts, and Texas). The study methods and population baseline characteristics have previously been reported[17]. Persons with hemophilia A were eligible for this study if they met these inclusion criteria: (1) aged 2–64 years as of the date of initial interview; (2) factor VIII level $\leq$30%, with or without a history of inhibitor; (3) received at least 90% of their hemophilia care at an HTC; (4) obtained HTC care within 2 years prior to study enrollment; and (5) were English speaking. The University of Southern California (USC) served as the data co-ordinating center, and the study protocol was approved by the Institutional Review Board (IRB) of USC and by each participating HTC IRB.

A total of 329 participants (164 adults and 165 children) were recruited between July 2005 and July 2007. A baseline survey was completed at an initial patient interview to collect socio-demographic and clinical variables, comorbidities, treatment regimens, and self-reported health status. A periodic follow-up survey was administered each month in the first year and semi-annually in the second year to collect time lost from work for adult patients and caregivers, missed school, disability days, healthcare utilization, and outcomes of care.

The follow-up surveys were administered using an automated telephone system or a commercial online survey system, or were directly administered by clinicians via telephone interview.

In addition to patient surveys, standardized chart abstraction forms were used to capture data from clinical charts. Baseline clinical information collected included inhibitor status, hepatitis virus serology, and treatment regimen at the time of patient initial interview. During the first year, medical charts were reviewed for healthcare utilization, changes in treatment regimens, inhibitor development, and comorbidities. Dispensing data, including the brand and amount of factor or other hemophilia-related products, were collected in the 2-year follow-up period.

Determination of healthcare costs

Direct hemophilia-related healthcare costs were determined by multiplying measured units of healthcare utilization by the representative unit price associated with each service, expressed in 2011 US dollars. Table 1 lists the data sources for the unit price associated with all healthcare services. Hemophilia treatments received outside HTCs and non-medical direct costs (e.g. transportation to a healthcare provider) were not considered.

Annual healthcare utilization was primarily obtained from medical charts. The number of hospital admissions, length of stay (LOS) and primary diagnosis recorded in the charts were used to calculate inpatient costs. Daily cost of inpatient stay was based on the Agency for Healthcare Research and Quality's (AHRQ's) Healthcare Cost and Utilization Project National Inpatient Sample (HCUP-NIS) average charges, retrieved from each event using the International Classification of Diseases, Ninth Revision (ICD-9) codes[22]. Charges were converted into inpatient costs by applying the coagulation disease-specific cost-to-charge ratio from Medicare Providers Analysis and Review (MedPAR)[23]. For those with missing diagnoses or self-reported inpatient stays without specifying the LOS (25.8% of all inpatient stays), median LOS and inpatient cost per day were used. The average cost of emergency department (ED) visits was based on the Medical Expenditure Panel Survey (MEPS) reports[24].

Outpatient costs consisted of HTC visits, laboratory tests, and outpatient procedures received at HTCs. HTC visits included annual multidisciplinary comprehensive visits as well as acute provider, physical therapy, and social work/psychology visits. Laboratory tests required during comprehensive visits vary by age, use of recombinant or plasma-derived clotting factor, and virological status. A list of laboratory tests was summarized and reviewed by an experienced hematologist, Dr Marion Koerper. The cost of outpatient visits and procedures and laboratory tests were estimated using the 2011 Medicare fee schedule, based on relative value unit scales assigned to each code determined by current procedural terminology (CPT)[25].

Annual factor utilization was calculated as the average of 2-year dispensing records. In addition, units of clotting factor received during ED visits, inpatient stays, and outpatient visits were also collected from the medical chart. Unit cost for clotting factors and bypassing agents were obtained from the payment allowance limit for Medicare Part B[26]. Wholesale acquisition costs were used to calculate the costs for hemophilia-related non-factor medications (i.e. desmopressin and aminocaproic acid)[27]. The annual number of bleeding episodes and indirect costs were calculated among participants who completed at least six follow-up surveys. Data were annualized using the actual number of follow-up days. Indirect costs were then imputed using the human capital approach[28], in which productivity loss was measured in terms of lost earnings of patients or caregivers, using wages as a proxy measure of the output of work time. Indirect costs included lost wages from missed work for those patients or parents who were employed, lost wages from working part-time or being unemployed due to hemophilia, and unpaid caregiver costs. Employment status was obtained from the initial patient survey. Missed work and unpaid caregiver hours due to hemophilia were calculated from patient follow-up surveys. Average hourly rate, including both wage and benefits, was obtained from the US Department of Labor Statistics[29]. The total employer compensation costs for civilian workers averaged $30.11 per hour

Table 1. Direct medical cost components.

Type	Cost data source(s)
Clotting factor and bypassing agent	Factor unit cost is estimated using average sales price from the payment allowance limit for Medicare Part B[26]
Healthcare service Comprehensive care Clinician visit Physical therapy Social worker Psychology	Cost for CPT code from the Medicare fee schedule relative value units[25] (RVUs)
Hospitalization	Based on the average cost for hospitalization with certain discharge diagnosis determined from Healthcare Cost and Utilization Project[22]. Adjusted by cost-to-charge ratio[23]
Emergency department	Medical Expenditure Panel Survey (MEPS) reports[30]
Outpatient procedure	Cost for CPT code from the Medicare fee schedule RVUs[25]
Lab test	Cost for CPT code from the Medicare fee schedule RVUs[26]
Other haemophilia-related medication(s)	Wholesale acquisition costs[27]

Table 2. Baseline characteristics.

Baseline characteristics[a]	Included ($n=222$)	Excluded ($n=107$)	p Value
Age, mean (SD)	21.1 (14.9)	22.5 (15.7)	0.4788
Older than 18 years, *n* (%)	112 (50.5)	52 (48.6)	0.7529
Hemophilia severity, *n* (%)			
Mild	45 (20.3)	37 (34.6)	0.0049
Moderate	31 (14.0)	5 (4.7)	0.0114
Severe	146 (65.8)	65 (60.7)	0.3740
Employment status, *n* (%)[b,c]			
Full-Time	97 (43.7)	53 (49.5)	0.3192
Part-Time	54 (24.3)	20 (18.7)	0.2517
Not Employed	71 (32.0)	34 (31.8)	0.9700
Married/with a partner, (%)[b]	125 (56.3)	68 (63.6)	0.2112
Education: >12 years, *N* (%)[b]	160 (72.1)	66 (61.7)	0.0569
Household income: >$20,000, *n* (%)[b,c]	173 (77.9)	83 (77.6)	0.9417
Race/Ethnicity, *n* (%)[c]			
White/Non-Hispanic	161 (72.5)	52 (48.6)	<0.0001
Black/Non-Hispanic	11 (5.0)	5 (4.7)	0.9113
Hispanic	26 (11.7)	33 (30.8)	<0.0001
Other[d]	24 (10.8)	17 (15.9)	0.1915
Health insurance, *n* (%)[c]			
No insurance	6 (2.7)	6 (5.6)	0.1880
Partial-year insurance coverage	13 (5.9)	6 (5.6)	0.9279
Full-year insurance coverage	196 (88.3)	94 (87.9)	0.9084
Comorbidities, *n* (%)			
HIV/AIDS	31 (27.7)	13 (25.5)	0.7704
HCV	78 (72.9)	35 (70.0)	0.7065
Use prophylaxis, *n* (%)	97 (43.7)	47 (43.9)	0.9684
Current inhibitors, *n* (%)	8 (3.6)	5 (4.7)	0.6409

Abbreviations: SD: standard deviation; HIV/AIDS: human-immunodeficiency-virus and acquired immune deficiency syndrome; HCV: hepatitis C virus
[a]Chi-square tests were used for comparisons of categorical variables. Wilcoxon signed-rank tests were used for comparisons of continuous variables.
[b]For patient or parent if patient age <18 years.
[c]Data do not add up to $n=329$ because of missing data.
[d]Other races include American Indian, Alaska Native, Asian/Pacific Islander and others.

worked in 2011. Full-time work was assumed to be 40 hours per week, and part-time work was assumed to be 20 hours per week.

Statistical analysis

Descriptive statistics were performed for all participants grouped by hemophilia severity or age. Comparisons among groups were calculated using chi-square statistic for discrete variables and Wilcoxon Rank-Sum test or Kruskal-Wallis test for continuous variables. All analyses were performed using SAS version 9.2 statistical software (SAS Institute, Cary, NC).

Results

Baseline characteristics

Among the 329 HUGS-Va participants recruited during 2005–2007, a total of 222 (67.4%) participants with at least six periodic follow-up surveys and complete medical charts and dispensing records were included in the cost analysis. The remaining participants had either less than six follow-up surveys ($n=93$) or missing medical charts and dispensing records ($n=9$) or both ($n=5$) and were excluded. On average, participants in the analysis completed 10 follow-up surveys; the mean follow-up time was 12 months. The baseline characteristics of the 222 patients included in the analysis and the 107 patients excluded because of missing follow-up data are shown in Table 2. Included participants had very similar baseline characteristics compared to those excluded with regard to demographics and clinical characteristics. However, the included cohort comprised fewer patients with mild hemophilia (20.3% vs 34.6%, $p=0.0049$) and more patients with moderate hemophilia (14.0% vs 4.7%, $p=0.0114$). In addition, discrepancies were found in participants' race and ethnicity. A larger percentage of those included vs excluded were White (72.5% vs 48.6%, $p<0.0001$) and a smaller percentage of those included vs excluded were Hispanic (11.7% vs 30.8%, $p<0.0001$).

Among the 222 patients in the analysis cohort, the mean age was 21.1 (standard deviation (SD): 14.9) years, and more than 50% were adults. The proportions of persons with mild, moderate, and severe hemophilia were 20.3%, 14.0%, and 65.8%, respectively; 43.7% were treated prophylactically. Less than half (43.7%) of patients or parents of patients less than 18 years were employed

full-time; 27.8% were employed part-time, and 33.8% were unemployed due to hemophilia. Among adults, 72.9% were antibody-positive for the hepatitis C virus (HCV), and 27.7% were human-immunodeficiency-virus (HIV) positive. At recruitment, eight patients (3.6%) had current antibodies or inhibitors to clotting factor, and two patients developed inhibitors during the 2-year follow-up period.

Study period direct resource use, medically related absenteeism, and bleeding episodes

Overall, 34.2% of patients with hemophilia A had at least one ED visit, and 19.4% had at least one hospitalization. The mean length of hospital stay for those who were hospitalized ($n = 43$) was 5.5 (SD = 5.9) days each year. The average annual school absenteeism for children age 5–17 years was 7.3 (SD = 14.4) school days, with 5.0 (SD = 10.9) missed days specifically due to hemophilia. Parents missed 3.2 (SD = 9.5) days from work annually due to their child's hemophilia. Among adults, average annual school/work absenteeism was 16.0 (SD = 42.1) days, with 14.5 (SD = 41.8) days specifically due to hemophilia. On average, children experienced 6.3 (SD = 7.8) bleeding episodes annually, and adults had 15.5 (SD = 14.9) episodes. The annual number of bleeding episodes and number of days missed from school or work by hemophilia severity are presented in Table 3.

The annual healthcare resource utilization and number of bleeding events were further compared between patients with severe hemophilia who infused clotting factor prophylactically vs episodically (Figure 1). The mean number of ED visits was 0.4 (SD = 0.9) for prophylaxis compared with 1.0 (SD = 1.8) for patients receiving episodic treatment ($p = 0.0127$). Fourteen patients (16.3%) on prophylaxis vs 12 patients (23.5%) on episodic treatment were hospitalized. Among those who were hospitalized, the average number of hospital days per patient-year was 3.9 days for patients treated prophylactically and 7.8 days for those on episodic treatment ($p = 0.0895$). The annual number of bleeding episodes for those who infused factor prophylactically was half the number than those who infused episodically (9.4 vs 19.6, $p < 0.0001$).

Cost

The mean direct medical costs for all patients without inhibitors ($n = 212$) were $185,256 (median = $113,857), and mean indirect costs were $10,076 (median = $233). Clotting factor accounted for 92% of total direct medical costs and 80% of total costs. The direct medical costs, indirect costs, and total costs by hemophilia severity and treatment patterns are presented in Table 4. The mean annual direct costs per patient for persons with mild and moderate hemophilia were $53,907 (median = $5863) and $75,320 (median = $32,687), respectively. In persons with severe hemophilia, the mean annual direct medical costs were $184,518 (median = $125,385) and $292,525 (median = $272,892) for those receiving episodic vs prophylactic treatment ($p = 0.009$). Annual hemophilia-related indirect costs for the same groups were $5195 for mild, $9043 for moderate, $16,952 for severe on episodic treatment, and $8867 for severe on prophylaxis. From the societal perspective, mild hemophilia cost $59,101 (median = $7519) annually per person, $84,363 (median = $61,837) for moderate hemophilia, $201,471 (median = $143,431) for severe hemophilia using episodic treatment, and $301,392 (median = $286,198) for severe hemophilia receiving prophylaxis. Clotting factor contributed from 54% of total costs in mild hemophilia to a maximum of 94% for patients with severe hemophilia receiving prophylaxis.

The mean annual total, indirect, direct medical, and factor costs per person per year for adults and children are described in Figure 2. The total direct and indirect costs for children and adults with hemophilia were $160,003 (median = $104,075) and $230,662 (median = $154,964), respectively. Lost wages from working part-time or being unemployed due to hemophilia are the major drivers of total indirect costs of hemophilia. The annual indirect costs associated with productivity loss for parents

Table 3. Average annual medically related absenteeism and number of bleeding episodes by age and hemophilia severity ($n = 222$).

	Children			*p* Value	Adults			*p* Value
	Mild ($n = 22$)	Moderate ($n = 17$)	Severe ($n = 71$)		Mild ($n = 23$)	Moderate ($n = 14$)	Severe ($n = 75$)	
Annual missed work/school days								
All causes	5.3 (8.9)	6.5 (11.3)	8.0 (16.3)	0.3394	6.2 (10.1)	5.6 (12.6)	21.0 (50.2)	0.4109
Due to hemophilia	3.3 (7.5)	4.7 (8.7)	5.6 (12.2)	0.1785	4.7 (9.2)	4.3 (11.6)	19.4 (49.9)	0.7208
Parents' missed work days due to child's hemophilia	3.6 (8.8)	3.2 (8.9)	3.1 (10.0)	0.9719	–	–	–	–
Annual number of bleeding episodes	4.1 (6.9)	9.1 (8.2)	6.4 (7.9)	0.0085	4.5 (10.0)	8.6 (11.8)	20.2 (14.5)	<0.0001

Events were annualized and reported as mean (standard deviation). Wilcoxon signed-rank tests were used for the comparisons.

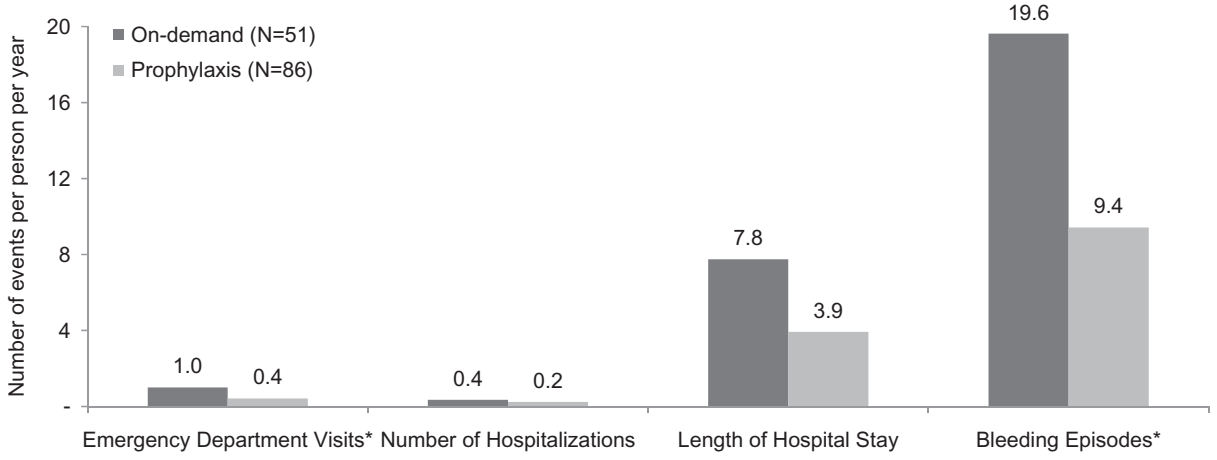

Figure 1. Average healthcare resource utilization and bleeding episodes among patients with severe haemophilia. Persons with inhibitors ($n = 10$) were excluded. Length of hospital stay only applies to patients who were hospitalized ($n = 26$). *Statistically significant differences at $p < 0.05$ were observed between patients who used a clotting factor on demand vs prophylactically.

of children with hemophilia were $7858. For adults, the total annual indirect costs were $12,993, with 96.6% attributable to the productivity loss of patients themselves. Among the 10 patients with current inhibitors, the mean direct medical costs and indirect costs were $978,955 (median = $554,916) and $21,325 (median = $10,541), respectively. On average, 82% of total costs were due to the use of bypassing agents and clotting factors.

Discussion

The present study provides a prospective observational study period to estimate the burden of illness in the hemophilia A population in the US. Several retrospective studies have reported the direct medical costs of hemophilia in the US[7,13–16], but most of these investigations were limited to descriptions of healthcare insurance claims databases[13–16]. However, costs of hemophilia are driven mainly by the clinical manifestations of the disease. Lack of clinical information in claims databases makes it difficult to determine the costs of illness by hemophilia severity level, inhibitor status, and clotting factor replacement patterns. An earlier study using a retrospective chart review was conducted nearly two decades ago[7], before the evidence basis for prophylaxis in children was firmly established and affected treatment patterns, and prior to the discovery of HIV anti-retroviral therapy, which affected the number of hospitalizations for the proportion of people with hemophilia infected via contaminated blood products. Using a prospective study design, our study confirms and updates previous findings by reporting healthcare utilization and costs and by taking into account the indirect costs, which have not been previously studied in the US.

This economic analysis estimated the cost of illness for persons with all severities of hemophilia A, considering clotting factor costs, non-factor drug costs, healthcare utilization costs, and patients' and caregivers' indirect costs. Management of severe hemophilia A in particular incurs high costs, primarily due to the cost of clotting factor. In our sample of patients from six federally supported HTCs, the total annual direct and indirect cost was $195,332 per person, with ~80% attributable to clotting factor use. The direct medical cost, excluding the cost of clotting factor, was $6857 per person, almost double the 2010 per-person healthcare expenditure among Americans aged under 65 ($3866)[30]. Approximately 25–30% of patients with severe hemophilia A develop factor inhibitors[9], which further exacerbates the treatment costs[10]. Furthermore, hemophilia is associated with school absenteeism among children, which may affect their academic performance. Hemophilia A is also associated with considerable indirect costs, mainly due to functional disability of adult patients and under-employment of parents of affected children with hemophilia. The total burden of illness to society was estimated to be $51 million annually among the 222 patients in our study, representing ~1% of individuals with hemophilia receiving care at HTCs in the US[31].

Optimal management of hemophilia care requires an understanding of the burden of illness associated with different treatment strategies. Our results show that use of prophylaxis in severe hemophilia patients is associated with reduction in the numbers of ED visits and bleeding episodes compared with those who were treated episodically. Prophylaxis treatment among persons with severe hemophilia not only leads to significantly lower medical costs other than clotting factor, but may also reduce indirect costs, although the latter is not statistically significant. On the other hand, the clotting factor consumption

Table 4. Average hemophilia-related costs per person per year by hemophilia severity and treatment patterns.

12-month costs[a]	Total ($n = 212$)	Mild ($n = 44$)	Moderate ($n = 31$)	Severe ($n = 137$)	
				On-demand ($n = 51$)	Prophylaxis ($n = 86$)
Total direct costs[b,c]	185,257 [113,857] (190,621)	53,907 [5863] (140,080)	75,320 [32,687] (121,600)	184,518 [125,385] (160,758)	292,525 [272,892] (186,739)
Clotting factor costs[b,c]	178,400 [107,319] (188,588)	47,649 [5501] (137,489)	70,438 [32,391] (116,855)	170,037 [118,259] (151,846)	289,172 [272,236] (186,502)
Average percent attributable to total costs[b,c]	0.80	0.54	0.74	0.84	0.94
Other medical costs[c]	6857 [878] (22,451)	6258 [605] (11,875)	4882 [1000] (9154)	14,481 [1502] (41,881)	3353 [500] (8352)
Total indirect costs	10,076 [233] (20,773)	5195 [0] (16,877)	9043 [0] (21,439)	16,952 [301] (26,068)	8867 [376] (17,959)
Total costs (direct + indirect)[b,c]	195,332 [139,571] (194,179)	59,101 [7519] (149,369)	84,363 [61,837] (121,433)	201,471 [143,431] (164,377)	301,392 [286,198] (188,977)

[a]Costs were reported as mean [median] (standard deviation) during the 12-month period. All costs were inflated to 2011 US dollars. Direct costs were inflated using the CPI for Medical Care. Indirect costs were inflated using average hourly compensation data from the Bureau of Labor Statistics. Costs for persons with inhibitors ($n = 10$) were not reported in the table.
[b]Statistically significant differences at $p < 0.05$ were observed among the mild, moderate and severe groups.
[c]Statistically significant differences at $p < 0.05$ were observed between patients who used clotting factor on demand vs prophylactically.

among prophylaxis users was 1.7-fold higher than that among those using episodic treatment. Although the reduced direct other medical costs and indirect costs are insufficient to offset increases in factor costs, non-monetary benefits to the patient in terms of improvements in quality of life and joint outcomes should also be considered when assessing the benefits of prophylaxis[3].

Several limitations must be considered in interpreting the results of this study. This is a study looking only at costs in hemophilia A and cannot be generalized to hemophilia B, the other most frequently occurring clotting factor deficiency.

Second, this cohort of hemophilia A patients included a higher proportion of patients with severe disease compared with the proportion in the US reported by the CDC's Universal Data Collection (UDC) Project (65.2% vs 52.9%)[31]. Furthermore, our cohort included patients who received care in the network of more than 130 federally supported HTCs; the results, therefore, are applicable only to those individuals receiving HTC care. Based on the 2010 US census data, there are nearly 14,000 males with hemophilia A and B (Factor IX deficiency) receiving care through the nationwide HTC network, which represents ~70% of the 20,000 males with hemophilia in the US[32,33]. The 30% of patients receiving care elsewhere are likely to have milder conditions, and, therefore, their outcomes may be different than those found in this study cohort.

These differences in outcomes may explain why the mean annual direct medical costs in our study are higher compared with those reported in the Medicaid or commercially insured population. However, the economic burden for patients with each level of hemophilic severity is detailed in our study, so some comparisons may still be made.

Third, our study may under-estimate healthcare utilization and costs because hemophilia-related healthcare utilization outside the HTCs or HTC-affiliated hospitals was not fully captured in the chart review and patient follow-up surveys due to limited data access.

Fourth, patients were not randomly assigned to receive prophylaxis or on-demand treatment, and multivariate analysis to account for selection bias was not conducted due to the small sample size. Potential selection bias should be considered when interpreting the results comparing two treatment strategies.

Fifth, employment status was collected only during the patients' initial interview. Therefore, changes in employment status may affect the calculation of indirect costs. Finally, around one-third of the initial HUGS population was lost to follow-up during the 2-year study period and, therefore, were not included in this burden of illness study sample. However, most demographic and clinical characteristics for patients who were included in our study were not statistically different from those excluded. We assume

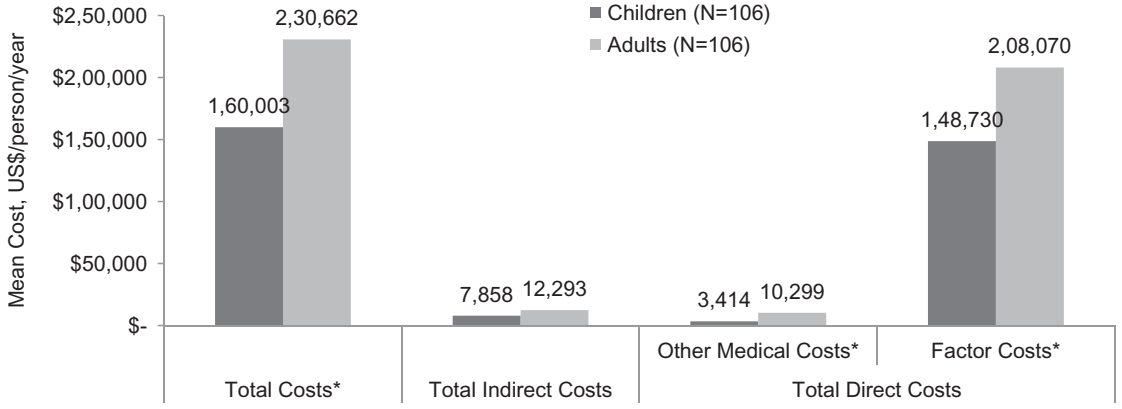

Figure 2. Average hemophilia-related costs per person per year by age group.
Costs were reported as mean in 2011 US dollars. Costs for persons with inhibitors ($n = 10$) were excluded. *Statistically significant differences at $p < 0.05$ were observed between children and adults.

the attrition is random and, thus, may not lead to a substantial bias.

In conclusion, hemophilia is a costly disorder, not only because of its high medical expenses, but also due to the high indirect costs incurred. Lost wages from working part-time or being unemployed due to hemophilia are the major drivers of total indirect costs. Among patients with severe hemophilia, prophylaxis is associated with fewer bleeding episodes, lower medical costs other than for clotting factor, and lower indirect costs compared with episodic treatment. Further studies that identify factors associated with increased healthcare utilization will advance our understanding of the economic impact of this condition. These studies should also consider the long-term economic and non-economic repercussions of missing work or school due to hemophilia in quantifying the burden of illness in this population.

Transparency

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