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The Hemophilia Utilization Group Study: Cost of Out Patient, In Patient and Pharmaceutical Care*

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The main objective of the Hemophilia Utilization Group Study was to examine the cost of illness of persons with hemophilia A (PWH) treated in comprehensive hemophilia treatment centers (HTCs). Retrospective chart review of health services provided for 336 patients in five HTCs during 1995 were conducted to assess the utilization of health and pharmaceutical services for PWH. Costs were imputed from utilization data. The total annual cost of care was $139,102.10 (s.d. $304,033.80). The overall mean cost of total health care for HIV+ PWHs ($165,400, n = 114) was $40,000 per year more than the total cost of health care for HIV- patients. Although this difference is not significant it is consistent with estimates of annual per patient costs of $10,000 – $50,000 per year for HIV care. Adult PWHs consumed significantly ($p < .05$) more non-hemophilia medications, laboratory procedures, and diagnostic procedures, and fewer physician visits than children. For all patients in our sample using anti-hemophilic medication (n = 296) the proportion of factor VIII concentrate cost to the total cost of health care in 1995 was .72 increasing with the severity of factor VIII deficiency. The treatment of hemophilia is a costly, lifetime commitment on the part of the provider, payor and individual. An estimate of the cost of illness is vital to prioritize the delivery of care. Prospective studies following PWHs, to determine the relationship between treatment alternatives and outcomes are needed to better understand where cost can be contained without negatively impacting the quality of care.

Keywords: Cost, Hemophilia A, HIV disease, Pediatric

Hemophilia A (factor VIII deficiency) is a chronic disease caused by a sex-linked genetic disorder, the incidence of which is estimated at 1 per 5,000 males by recent studies.[1, 2] It results in numerous complications, including spontaneous and traumatic bleeding episodes that have life-threatening potential. Because treatment involves replacing factor VIII, hemophilia A requires a costly, lifetime commitment on the part of the provider, payer, and individual with

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hemophilia A. As a result, data on the cost of hemophilia care is needed in order to adequately plan for providing services for this population.

There have been few studies of the actual health care costs for patients with hemophilia A, and none of them are recent. The National Health Interview Survey estimated that the major cost for treatment of patients with hemophilia A is factor VIII concentrate (factor) which accounts for 75–80% of the cost of care[3] and is utilized by the majority of the hemophilia A population.[4] Goldsmith estimated that factor VIII concentrate costs were approximately $81,900 annually for an adult and $65,200 for a child in the early 1990's.[5] The type of factor infused, frequency of factor and the per unit cost of factor has changed throughout the past decade. Patients with hemophilia are now more likely to use recombinant factor and infuse prophyllactically than they were in the early 1990's. The average factor VIII concentrate costs range from $.60 –1.00 per unit of factor, for a total of $1,200-$2,000 per infusion of 2,000 units for the average 70 kilogram (150 pound) man.[3, 6] The number of infusions per year depends on whether factor VIII is infused on a prophylactic (scheduled several times per week) or on-demand (as needed to treat bleeding episodes) schedule. Factor usage can also vary by age. Younger children are increasingly being placed on prophylactic infusion schedules and because younger children are more likely to develop inhibitors to factor VIII concentrate they are more likely to be treated with immune tolerance. Additionally, many patients with hemophilia A contracted AIDS from factor VIII concentrate in the early 1980s, prior to the identification of blood products as a mode of transmission for HIV. HIV may have contributed to the increasing cost of care for persons with hemophilia (PWH).[5]

The methods used to examine costs of care for patients with hemophilia A have varied across studies and have covered only a limited range of health care services associated with the provision of care for patients with hemophilia A, usually including small samples of patients or estimating costs from clinical experience. For example, the schedule of factor VIII infusion (on-demand or prophylaxis) varies by study. As a result, previous results of cost estimates of hemophilia care vary widely. A rigorous assessment of the cost of illness in hemophilia has not been completed in over a decade. Methodologically improved estimates of the cost of illness may assist in policy decisions that ensure efficient provision of care to chronically ill patients.[5]

The main objective of this study was to examine the cost of illness for persons with hemophilia A, including the total health care resources used and the proportion of total healthcare costs that are due to factor VIII costs. First, we evaluated the total medical cost of illness for patients with hemophilia A and assessed whether the cost of illness for patients with hemophilia A differed between pediatric and adult populations and between patients with and without HIV infection. Second, we investigated the cost of care associated with factor VIII replacement therapy for persons with hemophilia A. Third, we assessed the difference in the factor VIII therapy (method and schedule of infusion, and type, brand and quantity of factor VIII concentrate infused) between pediatric and adult patients with hemophilia A and between patients with and without HIV disease.

METHODS

We conducted a retrospective chart review of health services provided to approximately 350 patients from January 1, 1995, to December 31, 1995 (index period), by five hemophilia Treatment Centers (HTCs) in California. Data were collected employing a standardized form. The collection form was designed to gather patient demographics and clinical information and was pilot-tested in a previous study. The project coor-

dinator interviewed a staff member at each participating HTC using the collection form and a study patient identification number assigned by the HTC. The staff member referred to the chart to provide the appropriate responses. To protect patient confidentiality, only the center staff member was unblinded to the identity of the patient. In an attempt to capture information not regularly recorded in the chart, such as phone contacts and psychosocial visits, the project coordinator interviewed key center staff including the physician, nurse, physician assistant and social worker. Data were collected for a total of 336 patients receiving treatment for at least 90% of their hemophilia care at one of three HTCs in Southern California and one of two HTCs in Northern California.

Patient Characteristics

Sociodemographic and clinical characteristics including age, weight, mode of factor administration, maintaining a self-infusion log, type of insurance, HIV status and hepatitis status were collected from the out-patient medical record. Physical activity level was assessed in two categories: the recreational (degree of involvement in strenuous sports activities) and occupational (level of physical activity required as part of daily occupational activities); each was scored as high, moderate, low, or none. Physical activity level data were collected from key center staff interviews and chart abstraction.

Utilization: Clinical Care

Utilization was measured for both reimbursed and non-reimbursed services, including the number and type of MD visits (regular or extended), nurses visits, phone contacts, genetic counseling, number of laboratory tests performed, psychosocial care, radiographic and electrophysiological testing, surgical care, dental care, physical therapy, occupational therapy, hemophilia related medication (factor VIII and other concentrates), HIV-related medications (anti-retrovirals, anti-fungals, medications for opportunistic infection prophylaxis and treatment of opportunistic infections), hepatitis-related medications and other medications (antibiotics, non-steroidal anti-inflammatories, analgesics, parenteral nutrition). Hospital utilization included the number of hospitalizations during the index period, length of stay for each hospitalization, the number of days in an intensive care unit, the number of days in rehabilitation, in-patient surgical procedures and the number of physician visits during the hospitalization.

Utilization: Pharmaceutical Care

Annual usage of factor VIII concentrate and other medications was abstracted from pharmacy records. The amount and type of factor dispensed was recorded in units and reported as total units dispensed during the index year. The amount of intravenous immunoglobulin and total parenteral nutrition used was recorded in grams. The number of hepatitis vaccines and other immunizations received during the index period was recorded. The quantity of anti-virals, anti-retrovirals, anti-fungals, antibiotics, non-steroidal antiinflammatories, analgesics, and other medications was recorded in weeks of oral therapy and weeks of IV antibiotic therapy. The type and quantity of durable medical equipment provided was also recorded.

Cost Measures: Clinical

Conceptually, we defined the cost of illness as the value of resources consumed. The components were the utilization of physician ambulatory visits, non-physician ambulatory visits, imaging, diagnostic, laboratory, psychosocial, hospital, and pharmaceutical usage. To assess

the total cost of medical resources used, each type of utilization was assessed separately.

To impute costs in this study, ambulatory services, including visits, procedures, imaging, diagnostic, and laboratory were costed using the Medicare Fee Schedule.[7] Appropriate Current Procedural Terminology (CPT) codes were assigned to each procedure. Laboratory, radiographic and electrophysiological procedures as listed in the medical record abstraction guide had multiple possible CPT codes. The CPT code used to assess costs was derived in a two-step procedure. First, the billing clerk at each of the five centers was interviewed to determine the CPT code used for each procedure at each of the five centers. Second, an expert panel of four hematologists providing care at the HTCs chose the CPT code that, on average, best represented each radiographic and electrophysiological test. Variation across patients for each procedure was determined.[8] For those procedures with variability across the physicians in applicable CPT codes, a weighted average of costs for the variable codes was calculated. The cost for each CPT code was computed by abstracting the appropriate relative value and dollar conversion value from the Medicare Fee Schedule Relative Value Units (RVUs).[9-12]

To calculate costs for physician ambulatory visits, the total number of regular ambulatory physician visits during the target period was calculated. This sum was multiplied by the Medicare charge for the associated CPT code. The same process was used to calculate the total number of extended physician visits. Ambulatory physician visit cost was the sum of the cost of total regular and total extended visits during the index period. The same methodology was employed to calculate the cost of non-physician ambulatory services. Total radiographic and electrophysiological costs were estimated by multiplying the associated Medicare charge for each diagnostic category by the total number of procedures for each category. The same methodology was employed to estimate imaging and laboratory costs.

To calculate the cost of hospitalization, we abstracted the Medicare Diagnostic Related Group (DRG) for each hospital record. Inpatient services were costed using Medicare DRG payments.[13] DRG payments were geographically adjusted. Total inpatient costs included geographically adjusted DRG payment plus the cost of physician services.

Cost Measures: Pharmaceutical

Factor VIII concentrate, pharmaceutical and durable medical equipment costs were calculated through use of the "RedBook"[7] for wholesale prices of pharmaceuticals.[14] Since the cost per unit of factor VIII concentrate varied from $0.73 per unit to almost $2.00 per unit, the type of concentrate dispensed was included in the calculation.

The distribution of units of factor VIII received by the patients during the index period was graphed and was determined to be positively skewed with a mode of 0 (skew = 7.81). The literature reports costs for factor VIII concentrate specifically for those patients who utilize any anti-hemophilic medications. Therefore, we removed all patients who did not use any anti-hemophilic medication during 1995 for the purpose of comparison of costs with previous studies. A log transformation of the cost of hemophilia medication variable reduced the skewness of the distribution (skew = –1.14), and this transformed variable was used in multivariate subgroup analyses.

To calculate costs for total medical resources used during the index period, the total costs for physician ambulatory visits, non-physician ambulatory visits, hospitalizations, factor VIII concentrate, pharmaceuticals, electrophysiological studies, laboratory and imaging studies were summed.

ANALYSIS

Descriptive Statistics

Descriptive statistics calculated included patient characteristics, number and length of in-patient visits, number of outpatient visits, type and amount of pharmaceuticals filled, and type and amount of diagnostic, imaging and laboratory procedures. Severity of hemophilia was determined by percent of factor VIII deficiency (severe <1%, moderate 1–5%, and mild 6–50%). Severity classification for HIV was determined by CD4 count (>50, 50–100, 100–250, 250–500 and >500). Since the cohort of patients with hemophilia that contracted HIV from contaminated blood products was constrained within a narrow window of time (1981 through 1986, predominately prior to 1983), we did not use months/years HIV-positive as an independent variable.

Subgroup analysis

To analyze the differences between children and adults, we determined the mean utilization and cost for each dependent variable (factor usage, ambulatory physician utilization, ambulatory non-physician utilization, hospitalization and length of stay) for each subgroup (younger than 18 and 18 and older). Next, T-tests were used to identify significant ($p<0.05$) differences between the two groups. Similarly, we determined the mean utilization and costs for each dependent variable for patients with HIV disease and those without. Differences in utilization and costs between HIV-positive and HIV-negative groups were examined using t-tests.

Data transformation

The distribution of units of factor VIII received by the patients during the index period was graphed and was determined to be positively skewed with a mode of 0 (skew = 7.81). The literature reports costs for factor VIII concentrate specifically for those patients who utilize any anti-hemophilic medications. Therefore, we removed all patients who did not use any anti-hemophilic medication during 1995 for the purpose of comparison of costs with previous studies. Age and HIV subgroup comparisons were calculated with both parametric (comparison of means used for normally distributed data) and nonparametric (comparison of medians used for non-normally distributed data). There was no difference in findings between the parametric and nonparametric methods. Since mean comparisons are an acceptable analysis with a sample as large as ours the results of the parametric tests were used. Use of mean values facilitates both the comparison of our findings with previous studies and the interpretability of the results.

RESULTS

Patient Characteristics

Only a small proportion of our sample was female (1.5%) (Table I). Half were under 18 years of age and nearly 50% received public insurance (Medicaid, Medicare, California Children's Service or Genetically Handicapped Person Program). Nearly two-thirds of the patients were HIV positive.

Patients received factor concentrate through several delivery sources; about two-thirds self-infused factor VIII concentrate or were infused by a parent, and one-fifth infused prophylactically. Less than one-fifth of the patients in our sample did not use factor VIII concentrate during 1995. There were 61 (18%) patients who did not use any factor and 27 (8%) who did not use any type of anti-hemophilia medication during 1995. Of these patients, 10 had severe factor VIII deficiency, 7 were moderate and 44 were

mild. Three other anti-hemophilic medications (1-Deamino-8-D-arginine Vasopressin (DDAVP for injection), intranasal DDAVP (Simate™) and Epsilon Amino Caproic Acid (EACA)) were used by patients who did not use any factor VIII concentrate or as a supplement to infusion for those who did use factor VIII concentrate. DDAVP for injection was dispensed during 1995 to less than one-tenth of the patients in our sample, less than one-tenth of the patients received EACA, and less than one-twentieth received intranasal DDAVP. Less than 10% of our sample was on immune tolerance induction or maintenance therapy during the study year.

TABLE I Sample Characteristics (n = 336)

Variable	*Categories*	*N*	*Percent*
Patient Characteristics			
Age (dichotomized)	Under 18	170	50.7
	Over 18	166	49.3
Gender	Male	331	98.5
	Female	5	1.5
Educational Level	Not yet in school	33	9.8
	School age	142	42.3
	Didn't graduate HS	18	5.4
	HS graduate	58	17.3
	Some college	45	13.4
	College graduate	30	8.9
	M.S.	7	2.1
	Ph.D.	3	0.9
90% of hemophilia care at HTC	Yes	333	99.1
	No	3	0.9
HIV positive	Yes	220	65.5
	No	116	34.5
Primary insurance	Medi-Cal	128	38.1
	California Children's Service (CCS)	17	5.1
	Fee for service	52	15.5
	Genetically Handicapped Person Program (GHPP)	58	17.3
	HMO	37	11
	Medicare	22	6.5
	Other Public	1	0.3
	PPO	17	5.1
	Self-insured	4	1.2
Secondary insurance	Medi-Cal	10	3
	California Children's Service (CCS)	121	35.9
	Fee for service	9	2.7
	Genetically Handicapped Person Program	51	15.1

Variable	*Categories*	*N*	*Percent*
	(GHPP)		
	HMO	2	0.6
	Medicare	3	0 9
	Other public	1	0.3
	PPO	4	1.2
	Self-insured	0	0
	None	136	40.4
Factor deficiency	Mild	85	25.3
	Moderate	36	10.7
	Severe	168	50
	Severe + inhibitor	47	14
Arthropathy[a]	None	151	45.2
	Mild	91	27.2
	Moderate	67	20.1
	Severe/Disabling	25	7.5
History of inhibitor	No	283	84.2
	Yes	52	15.8
Inhibitor present during 1995	No	309	92.0
	Yes	27	8.0
Received immune	No	312	92.9
tolerance therapy during study year	Yes	24	7.1
Self-infuses	No	185	60.1
	Yes	123	39.9
Infuses at home by parent or self	No	113	33.6
	Yes	223	66.4
Infused at clinic or emergency room	No	239	70.9
	Yes	98	29.1
Infused through port or catheter	No	303	92.1
	Yes	26	7.9
Infuses prophylactically	No	249	80.3
	Yes	61	19.7
Keeps logs[b]	No	212	68.6
	Yes	97	31.4
Uses DDAVP for injection	No	306	91.1
	Yes	30	8 9
Uses EACA	No	306	91.1
	Yes	30	8.9
Uses intranasal DDAVP[b]	No	315	97.2
	Yes	7	2.8
Uses Recombinant factor VIII	No	256	75.2
	Yes	80	24.8
Uses high purity factor VIII	No	200	47.8
	Yes	136	42.2
Uses medium purity factor VIII	No	300	88.8
	Yes	36	11.2
Uses only intranasal or injectable DDAVP or EACA	No	318	95.8
	Yes	18	6.2
Uses activated PCC	No	320	95.2
	Yes	16	4.8

a. Rated by provider
b. All categories sum to less than the total sample size (n = 336) due to missing data for this variable.

TABLE II Ambulatory and In-patient Resource Costs (n = 336)

Variable	*Mean*	*SD*	*Median*	*Proportion of Total Health Care Costs*
Cost for all physician and allied health encounters	$1,268.60	$1472.50	$802	0.009
Cost for all durable medical equipment	$30.90	$155.50	$0	<0.001
Cost for all radiographic and electro-physiological testing	$135.20	$292.20	$0	0.001
Cost for all laboratory testing[a]	$558.00	$842.50	$270	0.004
Cost for all anti-hemophilia medication	$130,438.60	$300,992.00	$46,179	0.938
Cost for all other medication	$3,972.44	$12432.30	$48	0.029
Cost for all HIV-related medication	$3,359.10	$11953.60	$0	0.024
Total emergency room costs	$176.90	$420.90	$0	0.001
Total hospital costs (including 1 day hospitalisation)	$2,369.20	$7027.50	$0	0.017
Total health care costs (including in-patient, out-patient, emergency room and medication)	$139,102.10	$304,034.00	$55,330	1.000

a. Utilization of laboratory tests was divided into six separate categories: 1) general lab (CBC with differential, urinalysis, other), 2) coagulation studies (factor level, inhibitor screen, inhibitor titer, PTT/PT, and other), 3) chemistry studies (single tests, chemistry panel, and other panel), 4) immunology (hepatitis test, hepatitis panel, QUIG's, antibody titers, other), 5) bacteriology (blood culture, other culture, other), and 6) HIV (T-cells, B2M, P24 antigen, and other).

Costs: Clinical Care

The mean total estimated (and standard deviation) cost for health care for the year was $139,102.10 (304,033.80) (Table II). The mean total cost for all encounters, including both physician and non-physician services were $1,268.60 (1,472.50) for the one-year period in 1995 (index period). The mean cost for all laboratory testing during the year, $558.00 (842.50), was almost four times greater than the mean cost for all radiographic and electrophysiological testing during the year, $135.20 (292.20). This was because nearly 90% of the patients in our sample received multiple laboratory tests during the year, while only about half of the patients in our sample had a radiographic test, electrophysiological test, imaging test or procedure during the year. The mean hospital costs for the year were $2,369.20 (7,027.50), while the mean emergency room costs for the year were lower, $176.90 (420.90). The recorded prescriptions for durable medical equipment were small (0.3 units of equipment [1.4]), resulting in a comparatively low mean cost of $30.90 (155.50) for the year.

Costs: Pharmaceutical Care

The mean cost for anti-hemophilia medication during the index year was $130,438.60 (300,922.20) and accounted for the greatest proportion of total health care costs (Table II). As expected, this cost was significantly greater ($F = 22.04$, $p < 0.001$) for patients with severe hemophilia ($114,906.30) and those with a history of inhibitor to factor VIII ($433,238.09) compared to those with moderate ($84,742.96) and mild factor VIII deficiency ($24,23.28). Of the 215 patients with severe factor VIII deficiency, hemophilia medication costs were five times greater for patients receiving immune tolerance therapy (ITT) during 1995 ($651,996, n = 22) compared to those without ITT treatment during the study year ($125,365, n=179). For all patients in our sample using anti-hemophilic medications (n = 296), the proportion of factor cost to total cost of health care in 1995 was 0.72. The proportion of factor cost to total cost of health care was the highest for patients with severe factor VIII deficiency compared to those with mild or moderate factor VIII deficiencies. The proportion was

similar for patients with severe hemophilia A (0.83 [0.23]) and patients with a history of inhibitor to factor VIII concentrate (0.86 [0.29]). As expected, the proportion of anti-hemophilic factor costs to total health costs was lower for patients with moderate hemophilia A (0.70 [0.39]) and mild hemophilia A (0.45 [0.43]). There was no significant difference in total health care costs or the cost of hemophilia related medication between severe factor VIII deficient patients administering factor on a prophylactic schedule ($196,411, n=53) compared to an on demand administration ($181,527, n=145). HIV- related medication ($2,141.42 [5,344.44]) accounted for the majority of non-hemophilia medication costs, $3,972.44 (12,432.32).

Subgroup Analysis: HIV Positive Compared to HIV Negative

Although costs did not differ significantly overall between HIV positive and HIV negative patients, costs were higher overall for HIV positive patients with more severe disease as measured by CD4 count. Patients with CD4 counts less than 100 accrued the highest mean costs ($307,526.40). The cost of total health care for the subset of HIV-positive patients decreased as CD4 count increased. HIV-positive patients utilized somewhat more services than HIV-negative patients across all resource categories. However, the mix of treatments appeared to differ between the two groups. Only three out of the nine categories of resource use were significantly different by HIV exposure status. Physician encounter costs ($p < .005$), laboratory costs ($p < .0001$) and radiographic and electrophysiological costs ($p < .001$) were significantly higher for HIV-positive patients. There was not a significant difference in the mean yearly cost of factor between the two groups (SERO-positive $148,580, SERO-negative $120,440).

In general, the cost of factor for 1995 for patients with HIV was significantly ($p < 0.05$) greater compared to patients who were HIV-negative, regardless of the degree of factor VIII deficiency (Table III). However, patients with moderate hemophilia A had an inverse relationship (ns). (Note: the HIV-positive subgroups for mild, moderate and severe plus inhibitor categories were very small. This made the comparison less stable than the comparison in the severe hemophilia A subgroup). In 1995 the mean cost of factor VIII concentrate for a patient with severe hemophilia A who was HIV-positive was $129,138 compared to $96,522 for an HIV-negative patient.

TABLE III 1995 Factor Utilization and Costs by Severity of Hemophilia and HIV Status

Severity of Hemophilia	*HIV Status*	*n*	*Proportion of patients in the total sample*	*Mean Total Factor[a] (Units of Factor)*	*Mean Total Factor Cost[ab]*	*Mean Total Anti-Hemophilia Medication Cost[ac]*	*Mean Total Annual Health Care Costs*
Mild	Neg	70	0.22	19,202	$ 21,941	$ 22,214	$25,232
	Pos	14	0.04	38,123	$ 34,291	$ 34,329	$42,052
Moderate	Neg	33	0.10	86,658	$ 88,087	$ 88,178	$90,558
	Pos	3	0.01	39,573	$ 46,696	$ 46,957	$53,440
Severe	Neg	69	0.21	98,783	$ 96,522	$ 96,548	$101,115
	Pos	89	0.28	141,283	$ 129,135	$129,138	$147,790
Severe with inhibitor	Neg	35	0.11	333,804	$ 394,424	$394,429	$405,119
	Pos	8	0.02	667,063	$ 603,027	$603,027	$619,080

a. Using two-way Anova mean difference between severity levels is significant.
b. Using two-way Anova mean difference between HIV status categories is significant.
c. Total factor includes only factor VIII concentrate while total anti-hemophilia medication includes factor VIII concentrate, intranasal or injectable DDAVP, EACA and activated prothrombin complex concentrate.

TABLE IV 1995 Factor Utilization and Costs by Severity of Hemophilia and Age Category (n = 321)

Severity of Hemophilia	*Age*	*n*	*Proportion of patients in the total sample*	*Mean Total Annual Units Factor*	*Mean Total Annual Factor Cost*[a]	*Moan Total Annual Anti-Hemophilia Medication Cosy*[ab]	*Mean Total Annual Health Care Costs*
Mild	Adult	36	0.10	19,008	$ 18,017	$ 18,197	$ 22,182
	Child	48	0.15	24,614	$ 28,485	$ 28,760	$ 32,579
Moderate	Adult	17	0.10	97,734	$ 89,932	$ 90,038	$ 93,573
	Child	19	0.10	74,683	$ 79,900	$ 80,005	$ 81,999
Severe	Adult	94	0.30	133,345	$ 122,388	$ 122,392	$ 137,419
	Child	64	0.20	107,122	$ 103,882	$ 103,911	$ 112,885
Severe with inhibitor	Adult	16	0.05	411,367	$ 471,442	$ 471,442	$ 478,269
	Child	27	0.10	386,585	$ 410,592	$ 410,598	$ 425,937

a. Using two-way Anova, mean difference between severity levels is significant.
b. Total factor includes only factor VIII concentrate, while total anti-hemophilia medication includes factor VIII concentrate, intranasal or injectable DDAVP, EACA and activated prothrombin complex concentrate.

Subgroup Analysis: Adults Compared to Children

Total health care costs in 1995 did not differ significantly by age or HIV status. Adults had significantly higher mean costs of non-hemophilia related medication (adult $6,220 and pediatric $1,710, $p < .0001$), laboratory testing (adults $990 and pediatrics $330, $p < 0.001$), and radiographic and electrophysiological testing (adults $220 and pediatrics $90, $p < 0.001$). There was not a significant difference in the mean yearly cost of factor between the two groups (adults $130,268.32 and pediatrics $130,614.17, $p = 0.99$). Although the cost of physician encounters was not different for pediatrics ($500), compared to adults ($490), the cost of total encounters (child $1,430, adult $1,100) and allied health care encounters (child $950, adult $620) was significantly higher for children compared to adults ($p < 0.05$).

Since factor concentrate is prescribed per kilogram of body weight, larger patients, given equal expression of their hemophilia A, were expected to utilize a greater amount of factor VIII concentrate. For patients with severe hemophilia A, the mean total units of factor VIII concentrate dispensed per year for an adult was 133,345 compared to 107,122 units on average for children under 18 years of age (Table IV). For both children and adults, patients with inhibitors to factor VIII concentrate used four times more factor, 411,367 units on average for adults and 386,585 units on average for children ($p < 0.05$). As expected, the amount of factor used per year increased with the level of severity of hemophilia A. A similar trend was evident in the cost of factor per year. The costs were also greater for adults compared to children for patients with all levels of severity of hemophilia A, except those with mild hemophilia A.

DISCUSSION

In this study we examined the cost of illness among a cohort of persons with hemophilia A being treated at 42% (5 out of 12) of all Hemophilia Treatment Centers (HTCs) in California. Providing efficient services to beneficiaries with chronic diseases, like hemophilia A, requires information concerning the cost of care for the disease and identification of factors that predict greater or less than average costs for the specific group of beneficiaries.

There are four important findings from this study. First, we demonstrated the high cost of the treatment of hemophilia A. Second, higher costs were associated with a greater severity of hemophilia A. Third, the cost of illness is higher for patients with hemophilia A who also have advanced HIV infection. And finally, we determined the association of costs and age.

We have estimated the mean cost of care for patients with varying levels of severity of hemophilia A, including anti-hemophilia medication costs, out-patient, diagnostic, emergency room and hospital costs. Our sample consisted of 336 patients, representing twenty-seven percent (27%) of the hemophilia A patients registered at HTCs in the federal Region IX (California, Hawaii and Nevada) in the United States. The average total annual health care cost was nearly $140,000 per patient in this sample. The annual per patient cost for other chronic diseases ranges from $10,000 for HIV combination therapy to $35,000 for multiple sclerosis.[13, 15] The cost of care, excluding the costs of hemophilia A medication was over $8,000 which is more than twice as much as the 1996 per capita cost of health care in the United States ($3,700).[16]

People with hemophilia A have been reliant on clotting factor concentrates that were derived from blood products. Products manufactured from human blood in the 1980s were contaminated with HIV and other viruses. These blood-derived products (or plasma-based products) compounded the health care resource needs of PWH. In our study HIV-positive patients were more resource intensive for total physician encounters, non-hemophilia medication, laboratory testing, radiographic testing and electrophysiological procedures. The frequency and breadth of services for HIV positive patients was dependent on the severity of factor deficiency and whether the patient with HIV had immunological, infectious, hematological, or oncological complications or risks because of poor immunity or dysregulated immunity associated with HIV. In our study, patients with HIV infection used more factor VIII. To reduce the theoretical risk of continued antigenic stimulation in patients with hemophilia A who were HIV-infected, there was a greater likelihood that these patients were prescribed a recombinant factor VIII concentrate rather than a high purity plasma-derived factor VIII concentrate. These recombinant products were procured at a higher cost per unit. Furthermore costs were higher for HIV positive patients with lower CD4 counts similar to findings in other studies.[17]

The similarity in costs for children compared to adults poses an interesting issue: we do not know if this is a function of similar usage across all ages for similar reasons. For instance, both children and adults might have had an equal number of bleeding episodes and required an equal number of infusions to treat each of these episodes. On the other hand, different uses across different users might aggregate to a similar total. For example, children have more frequent accidental injury related bleeds and are more likely to use factor prophylactically (volume of factor used is three times greater compared to an on-demand schedule) while adults have more arthropathy related bleeds and are large so require more units per bleeding episode for treatment. In our study 59% of those on prophylaxis were children and 25% of the children in our study were on prophylaxis compared to on demand. Another possible reason for the apparent increased consumption of factor concentrate in children is that children are more likely to demonstrate inhibitors to factor VIII and therefore be placed on immune tolerance induction (ITI). Eighty-two percent (82%) of those on ITI in our study were children, representing 11% of the total children in our study). Thus, the similarity in cost of illness between adults and children is likely to be masking differences in the underlying parameters for resource utilization. This may be a result of the changing approaches to hemophilia A treatment over time.

In our sample, there was an association between older age and the presence and severity

of arthropathy. Adults were more likely to have arthropathy compared to children. Adults also had more severe arthropathy than children. Over 75% of the study patients with moderate or severe arthropathy were adults. Currently, the evolving approach to care is to prevent orthopedic complications in children by treating prophylactically. In light of this trend, we would expect to see a decreasing need for factor VIII concentrate in the adult population over time for treatment of arthropathy-related bleeds. Although we would expect to see a greater proportion of adults on prophylactic administration of factor VIII concentrate (raising the proportional cost of care for factor VIII replacement therapy), we would expect the hospitalization, surgical, procedure and diagnostic costs related to arthropathy to decrease in the future. If the current early, aggressive factor concentrate therapy, including prophylaxis in children, maintains joint integrity, we would expect fewer adult patients with arthropathy as this current cohort of children ages toward adulthood. This trend would decrease the number of orthopedic surgeries and related testing and therapy, although the annual cost of such care appears to be greater than on-demand administration.[18] The cross sectional nature of the current study does identify trends that support this explanation, however, it does not allow us to test this hypothesis. Future studies should aim to determine the association between patient characteristics, clinical characteristics, and approaches to treatment and outcomes of care for PWHs, emphasizing methodologies to measure the clinical benefits of approaches to care such as prophylaxis.

Most treatment protocols with a goal of prophylaxis aim at keeping a minimum level of factor VIII in the blood of over 1%.[19] A recent study of ten severe factor VIII deficient children demonstrated that lower doses of recombinant factor VIII concentrate were needed to achieve this minimal level compared to high purity factor VIII concentrate.[20] Some clinicians believe that with this approach, fewer units of higher cost concentrate are needed. The increasing trend in treatment is to prescribe recombinant factor VIII concentrates. Although the costs per unit of recombinant concentrates are more, utilization of fewer units of this concentrate may result in a net cost savings. This scenario highlights the need to identify more explicit parameters for prescribing factor VIII concentrate. We found a positive association between the use of recombinant factor VIII concentrates and annual usage of factor VIII concentrate. Nevertheless, we cannot infer causality from our data since we do not know why certain patients were prescribed recombinant, high purity or medium purity products and our 1995 data under-estimates the current amount of recombinant products prescribed.

There were other limitations with our study. First, as in all studies using DRG methodology to estimate hospital costs we were not able to account for variations in the length of hospital stay which decreased the accuracy of our cost estimates. However, the mean length of stay for our sample per DRG category was similar to national estimates. Second, health care services from providers not affiliated with the HTC are not incorporated into the cost estimates, resulting in a possible under-reporting of total health care costs during the target period. An additional limitation was that HIV infection was the only blood borne viral disease assessed in this study. Although the present plasma derived factor concentrates are from smaller pools of donors and treated with various methods of viral attenuation, the risk still remains of transmission of blood borne viral diseases such as hepatitis and HIV.[21]Although, the contamination of blood with HIV has been well recognized over the last decade, hepatitis will have the possibility of causing greater illness and cost in PWHs. Future studies are needed to determine the impact of hepatitis on utilization of hemophilia care. A glimmer of hope for the use of additional treatment modalities was raised by a recent Phase I clinical trial of adeno-associated viral gene trans-

fer in several patients with Hemophilia B.[22] How the future use of resources for hemophilia management will be impacted by gene therapy modalities is yet to be determined.

A comprehensive continuum of care in comprehensive HTCs has been the standard mechanism for delivery of care for over two decades for patients with hemophilia A. Comprehensive care has been demonstrated to provide superior outcomes for patients with hemophilia A compared to care from independent physicians.[23] Inadequate funding threatens to fragment hemophilia care delivery. Provision of care for patients with chronic diseases under a capitated system must insure that reimbursement rates are sufficient to provide comprehensive care.[24] The findings of our study help to identify these utilization needs in this population and serve as a model for estimates of the cost of illness for other chronic diseases. Further studies that identify the reasons for specific clinical treatment choices and assess the outcomes of these treatment decisions are needed to better understand where costs can be contained without negatively impacting the quality of care in an environment of rapid technological advancements with concomitant increases in costs.

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