

Descriptive epidemiology of hereditary angioedema hospitalizations in the United States, 2004–2007

Marya D. Zilberberg, M.D., M.P.H.,^{1,2} Brian H. Nathanson, Ph.D.,³ Thomas Jacobsen, Pharm.D., M.S.,⁴ and Glenn Tillotson, Ph.D.⁴

ABSTRACT

Hereditary angioedema (HAE) is a rare inherited disorder of complement factor C1 inhibitor. There are ~6000 HAE cases in the United States, nearly one-half of whom suffer a monthly exacerbation. Little is known about hospital use patterns by patients with HAE attacks in the United States. This study was designed to examine burden, epidemiology, and outcomes of hospitalizations among HAE patients. We evaluated epidemiology, resource use, and discharge destinations of HAE (ICD-9-CM code 277.6) hospitalizations within the NIS, part of Agency's for Healthcare Research and Quality Healthcare Costs and Utilization Project in 2004 through 2007. There were 10,125 hospitalizations with HAE, of which 3216 (31.8%) had HAE as the principal diagnosis (HAE-PD). Two-thirds of all HAE hospitalizations were among women, and 60% were white. Hypertension was the most common comorbidity (26.9%, all HAE, and 28.0%, HAE-PD). Mortality was 1.4% in HAE and 0.3% in the HAE-PD group. Mean hospital length of stay (3.7, 95% CI 3.0–4.4 days vs. 5.0, 95% CI 4.6–5.4 days) and costs (\$4,760, 95% CI \$3,612–\$5,907 vs. \$8,383, 95% CI \$7,432–\$9,334) were lower in HAE-PD than in the HAE cohort. Although >80% in each group were discharged home routinely, 15.9% of HAE and 4.9% of HAE-PD required either home health care or a transfer to another short-term hospital or a skilled nursing facility. HAE hospitalization volume is substantial. Because diagnostic uncertainty is likely, HAE and its related resource use may be underestimated. HAE prevention strategies need to be examined in the context of these outcomes.

(Allergy Asthma Proc 32:248–254, 2011; doi: 10.2500/aap.2011.32.3452)

Hereditary angioedema (HAE) is a rare inherited deficiency or dysfunction of the complement factor C1 inhibitor. It generally manifests late in the first or early in the second decade of life as recurrent episodes of mucosal angioedema, affecting the skin and gastrointestinal and respiratory tracts.¹ The reported prevalence of HAE ranges from 1 case per 50,000 to 1 per 150,000 population.^{2,3} Mortality without treatment is reported to approach 30% resulting from laryngeal edema and asphyxiation.¹

In the United States the estimated number of cases of HAE is on the order of 6000. It has been reported that nearly one-half of all patients afflicted with HAE suffer a monthly exacerbation, and another 40% have 6–11 attacks annually.⁴ Little is known about hospital use patterns by patients with HAE attacks in the United States. A recent study reported HAE hospitalization

epidemiology and outcomes based on the aggregate data from the Agency's for Healthcare Research and Quality Nationwide Inpatient Sample (NIS).⁵ According to this study, in 2007 there were 1691 HAE-related hospitalizations with HAE as the principal diagnosis (PD) in 46.0%. Together, HAE-PD and angioedema (AE) PD hospitalizations accrued 35,000 hospital days and hospital costs of \$63 million annually.

Given that hospital costs are responsible for approximately one-third of the U.S. national health care expenditures,⁶ optimization of hospital care is an attractive target for cost containment efforts. Furthermore, to understand the quality of care provided to specific populations, it is first imperative to describe the types of services provided, to target potential improvements in those services. Because the HAE population is small, to the best of our knowledge, there are no studies examining in detail hospital services use and outcomes in this population. To this end, we conducted a retrospective descriptive cohort study of individual hospitalization data available from the NIS of all HAE-related hospitalizations in the United States for the years 2004 through 2007.

METHODS

We evaluated the volume, characteristics, and resource use associated with hospitalizations in the United States with HAE within the NIS database, combining data for the years 2004 through 2007. NIS was

From the ¹University of Massachusetts, Amherst, Massachusetts, ²EviMed Research Group, LLC, Goshen, Massachusetts, ³OptiStatim, LLC, Longmeadow, Massachusetts, and ⁴ViroPharma, Inc., Exton, Pennsylvania

Supported by ViroPharma, Inc., Exton, PA

M. Zilberberg is a consultant to ViroPharma, Inc.; M. Zilberberg's company, EviMed Research Group, LLC, received a research grant from ViroPharma, Inc., to support this study; B. Nathanson's company, OptiStatim, LLC, received compensation from EviMed Research Group, LLC, to conduct this study; T. Jacobsen and G. Tillotson are employees and stockholders of ViroPharma, Inc.

Address correspondence and reprint requests to Marya Zilberberg, M.D., M.P.H., PO Box 303, Goshen, MA 01032

E-mail address: evimedgroup@gmail.com

Copyright © 2011, OceanSide Publications, Inc., U.S.A.

Table 1 Hereditary angioedema (HAE) discharge characteristics

	HAE All (<i>n</i> = 10,125)		HAE-PD (<i>n</i> = 3216)	
	<i>n</i>	%	<i>n</i>	%
Age group, yr				
<1	320	3.16%	23	0.72%
1–17	1018	10.05%	227	7.08%
18–44	4111	40.60%	1959	61.07%
45–64	3379	33.37%	880	27.43%
65–84	1211	11.96%	111	3.46%
≥85	86	0.85%	7	0.22%
Mean (95% CI) age for patients >1 yr, yr	42.3 (40.7, 44.0)		37.8 (35.4, 40.2)	
Gender				
Male	3609	35.64%	809	25.22%
Female	6486	64.06%	2369	73.85%
Race				
White	6057	59.82%	1678	52.31%
Black	606	5.99%	300	9.35%
Hispanic	631	6.23%	306	9.54%
Asian/Pacific Islander	82	0.81%	24	0.75%
Native American	10	0.10%	0	0.00%
Other	163	1.61%	85	2.65%
Not provided/missing	2575	25.43%	816	25.44%
Primary payor				
Medicare	2775	27.41%	658	20.51%
Medicaid	2070	20.44%	828	25.81%
Private including HMO	4243	41.91%	1262	39.34%
Self-pay	452	4.46%	208	6.48%
No charge	19	0.19%	19	0.59%
Other	561	5.54%	234	7.29%
Missing/unknown	4	0.04%	0	0.00%
Admission source				
ER	5445	53.78%	2016	62.84%
Another hospital	418	4.13%	58	1.81%
Another facility	99	0.98%	9	0.28%
Court/law enforcement	10	0.10%	0	0.00%
Routine/birth/other	3934	38.85%	909	28.34%
Missing/unknown	219	2.16%	126	3.93%
Elective admission				
Yes	1900	18.77%	312	9.73%
No	8195	80.94%	2892	90.15%
Missing	30	0.30%	5	0.16%
Weekend admission				
Yes	2153	21.26%	2375	74.03%
No	7972	78.74%	833	25.97%
Treated in a teaching hospital				
Nonteaching	4773	47.14%	1619	50.47%
Teaching	5352	52.86%	1589	49.53%
Missing/unknown	0	0.00%	0	0.00%
Geographic region				
Northeast	1982	19.58%	518	16.15%
Midwest	2384	23.55%	600	18.70%
South	3725	36.79%	1384	43.14%
West	2034	20.09%	707	22.04%

Table 1 Continued

	HAE All (<i>n</i> = 10,125)		HAE-PD (<i>n</i> = 3216)	
	<i>n</i>	%	<i>n</i>	%
Missing/unknown	0	0.00%	0	0.00%
Urbanicity				
Rural	1416	13.99%	486	15.15%
Urban	8709	86.01%	2731	85.13%
Missing	0	0.00%	0	0.00%

CI = confidence interval; ER = emergency room; HMO = Health Maintenance Organization; PD = principal diagnosis.

specifically designed to identify, track, and analyze national trends in health care use, access, charges, quality, and outcomes.⁷ The 2007 NIS contains all discharge data from 1044 hospitals located in 40 states, approximating a 20% stratified sample of U.S. community hospitals.⁷ Stratum-specific sample weights, based on multilevel survey design, are applied to each discharge in the sample frame to develop national and regional population estimates for conditions addressed in the database.

We identified HAE-related visits and hospitalizations based on the presence of the International Classification of Diseases, Version 9, clinical modification (ICD-9-CM) code 277.6 (other deficiencies of circulating enzymes, HAE). We examined demographic, clinical, and hospital characteristics of the individual discharges, as well as their hospital outcomes, including hospital length of stay (LOS), hospital charges and costs, and the associated discharge destinations. We performed the same computation for the subgroup of HAE discharges carrying HAE-PD.

Because the intent of the study was to provide descriptive epidemiology for HAE hospitalizations in the United States, no formal hypothesis testing was undertaken. All calculations were done in Stata/SE Version 10.1 (Stata Corp., College Station, TX).

RESULTS

In the 4 years included in the analysis, there were 10,125 hospitalizations with HAE, of which 3216 (31.8%) had HAE as the PDs (Table 1). The mean age for all HAE discharges was 42.3 (95% confidence interval [CI], 40.7–44.0) years, with 74.0% of the population falling into the age range between 18 and 64 years. Two-thirds of HAE hospitalizations were among women, and 60% among white populations. Although >80% of all admissions were not classified as elective, only 53% came *via* the Emergency Department.

There were 3216 hospitalizations for HAE-PD (Table 1). Although their age distribution generally mirrored that of the entire HAE cohort, their mean age was directionally lower, 37.8 (95% CI, 35.4–40.2) years. In this group, 73.9% were women, and similar to the total

cohort, 52.3% were white. The HAE-PD group was slightly more likely to have Medicaid as the payer than the overall HAE cohort (25.8% HAE-PD versus 20.4% all HAE).

Hypertension was the most common comorbidity, present in 2728 (26.9%) of all HAE discharges and in 898 (28.0%) of HAE-PD discharges (Fig. 1, A and B). Among the 6909 HAE admissions with HAE as a secondary diagnosis, the most frequent PD was that of chronic obstructive pulmonary disease with exacerbation, listed in 418 (4.1%) of the cases, and 5 of the top 10 PDs were referent to the respiratory system, accounting for 12.4% of these hospitalizations (Table 2). The most common procedure during the hospitalization for the entire HAE cohort was a transfusion of serum components, occurring in 567 (5.6%) of all HAE hospitalizations (Table 2). The vast majority of these events (90.8%) occurred in the HAE-PD admissions, for which it was also the most common procedure, occurring in 515 hospitalizations (16.1%; Table 3).

Among all HAE hospitalizations, 145 (1.4%) resulted in death, while the proportion for this outcome was directionally lower in the HAE-PD group (*n* = 9, 0.3%; Table 4). Similarly, mean hospital LOS (3.7 and 95% CI, 3.0–4.4 days, versus 5.0 and 95% CI, 4.6–5.4 days), charges (\$13,185 and 95% CI, \$10,566–15,804, versus \$22,728 and 95% CI, \$20,368–25,088), and costs (\$4760 and 95% CI, \$3612–5907, versus \$8383 and 95% CI, \$7432–9334) were all directionally lower in the HAE-PD group than in the overall HAE cohort. Although >80% in each group were discharged home routinely, a substantial number (*n* = 1612, 15.9% for all HAE, and *n* = 156, 4.9% for HAE-PD) required either home health care or a transfer to another short-term hospital or a skilled nursing facility (Fig. 2).

DISCUSSION

In the current study we have documented the descriptive epidemiology of hospitalizations with HAE in the United States between the years 2004 and 2007. We identified >10,000 discharges carrying HAE as at least one of their diagnoses, with >30% being hospitalized specifically for HAE as the reason for admission. Al-

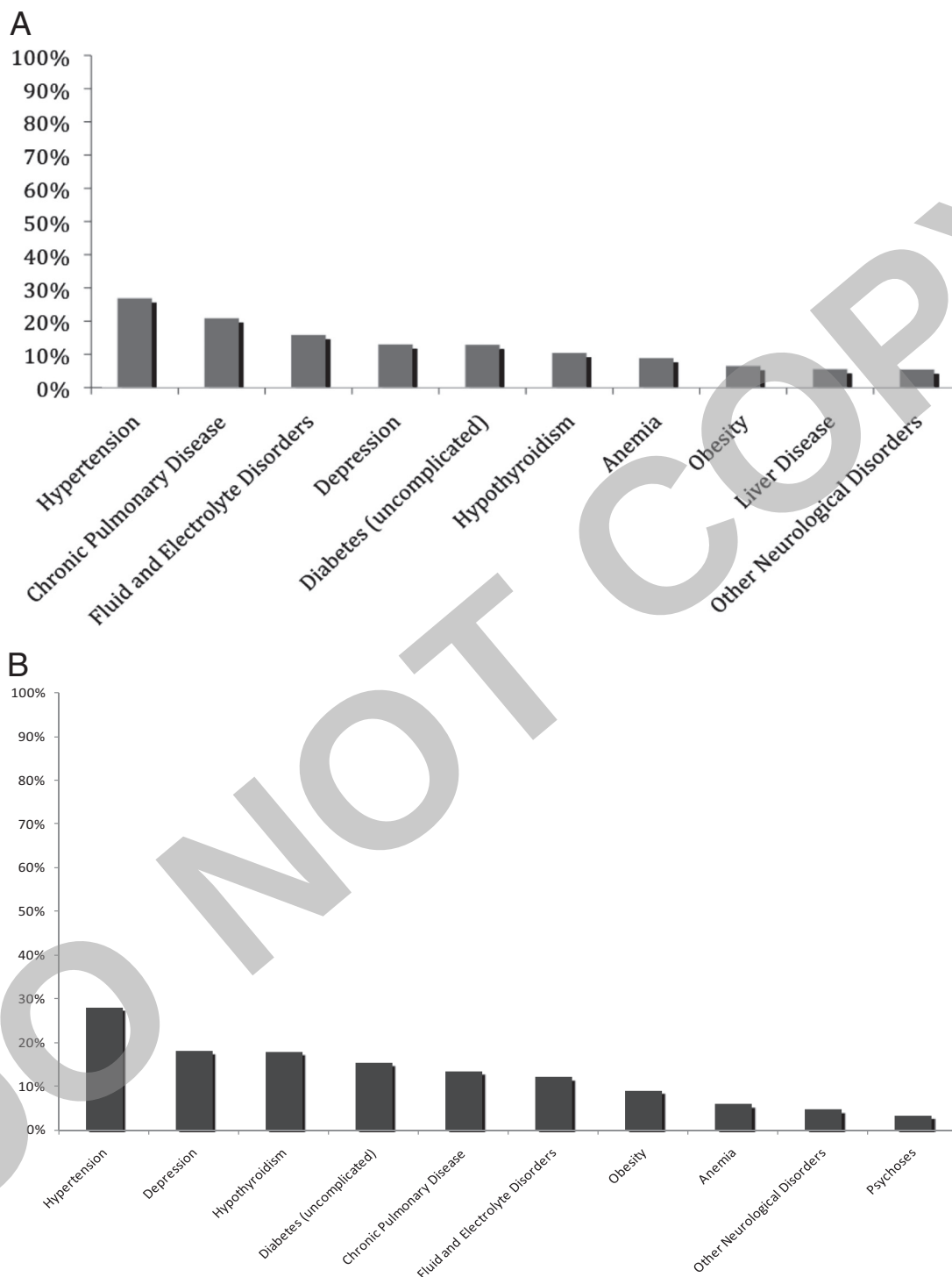


Figure 1. (A) Top 10 comorbidities among all hereditary angioedema (HAE) discharges. (B) Top 10 comorbidities among HAE principal diagnoses (PDs).

though the population is relatively young, there is a substantial prevalence of comorbidities, especially such common ones as hypertension and chronic lung disease. If one assumes that the entire process of hospitalization is directly attributable to HAE among patients with HAE-PD, the total hospital charges for the entire HAE-PD cohort amount to >\$42 million, spread

over the 4 years of analysis, corresponding to nearly 12,000 hospital days. These estimates constitute the absolute minimum for hospital resource use by the HAE population overall, because they do not include any proportion of the hospital charges among HAE admissions with a secondary diagnosis of HAE, that may nevertheless be attributable to HAE. Addi-

Table 2 Top 10 principal diagnoses, other than hereditary angioedema, and primary procedures among all hereditary angioedema discharges

Rank	ICD-9-CM code	Description	n	Percent
Diagnoses				
1	491.21	Obstructive chronic bronchitis with acute exacerbation	418	4.13
2	486	Pneumonia, organism unspecified	361	3.57
3	518.81	Acute respiratory failure	260	2.57
4	577.0	Acute pancreatitis	159	1.57
5	571.5	Cirrhosis of the liver without mention of alcohol	144	1.42
6	492.8	Other emphysema	119	1.18
7	493.22	Chronic obstructive asthma with acute exacerbation	95	0.94
8	558.9	Other and unspecified noninfection gastroenteritis and colitis	90	0.89
9	584.9	Unspecified acute renal failure	85	0.84
10	995.1	Angioneurotic edema	75	0.74
Procedures				
1	99.07	Transfusion of other serum	567	5.60
2	96.71	Continuous mechanical ventilation, <96 consecutive hr	273	2.70
3	38.93	Venous catheterization not elsewhere classified	236	2.33
4	74.1	Low cervical cesarean section	208	2.05
5	45.16	EGD with closed biopsy	127	1.25
6	54.91	Percutaneous abdominal drainage	97	0.96
7	39.95	Hemodialysis	90	0.89
8	99.04	Transfusion of packed cells	89	0.88
9	96.04	Insertion of endotracheal tube	86	0.85
10	96.72	Continuous mechanical ventilation > 96 consecutive hr	85	0.84

EGD = Esophagogastroduodenoscopy; ICD-9-CM = International Classification of Disease, Version 9, clinical modification.

Table 3 Top 10 primary procedures among hereditary angioedema principle diagnoses discharges

Rank	ICD-9-CM code	Description	n	Percent
1	99.07	Transfusion of other serum	515	16.05
2	38.93	Venous catheterization not elsewhere classified	101	3.15
3	31.42	Laryngoscopy and other tracheoscopy	67	2.09
4	96.71	Continuous mechanical ventilation <96 consecutive hr	60	1.87
5	96.04	Insertion of endotracheal tube	43	1.34
6	31.1	Temporary tracheostomy	41	1.28
7	99.04	Transfusion of packed cells	34	1.06
8	99.23	Injection of steroid	31	0.97
9	45.13	Other endoscopy of small intestine	24	0.75
10	45.16	EGD with/closed biopsy	23	0.72

EGD = Esophagogastroduodenoscopy; ICD-9-CM = International Classification of Disease, version 9, clinical modification.

tionally, these estimates do not include either the direct costs of postdischarge care either at another facility or at home or any indirect costs associated with the hospitalization.

In addition to starting to understand the hospital resource use burden among patients admitted with HAE, our study is useful in pointing to several potential targets for preventive interventions. Not only does the daunting volume of cases admitted specifically for

HAE management suggest the need to examine the ability of HAE preventive therapies to diminish this burden in a cost-effective way, but also identifying other top reasons for hospitalization may argue for increased efforts at outpatient control. We found that the top three reasons for hospitalization among patients with HAE, other than HAE itself, were chronic obstructive pulmonary disease exacerbations, pneumonia, and respiratory failure. This suggests that pay-

Table 4 Outcomes of hereditary angioedema (HAE) hospitalizations

	HAE All	HAE-PD
Hospital length of stay, days		
Mean (95% CI)	5.0 (4.6, 5.4)	3.7 (3.0, 4.4)
Median (IQR)	3 (2, 6)	2 (1, 5)
Hospital charges, \$		
Mean (95% CI)	\$22,728 (\$20,368; \$25,088)	\$13,185 (\$10,566; \$15,804)
Median (IQR)	\$11,800 (\$6445; \$23,168)	\$8,345 (\$4668; \$13,879)
Hospital costs, \$		
Mean (95% CI)	\$8383 (\$7432, \$9334)	\$4760 (\$3612, \$5907)
Median (IQR)	\$4573 (\$2494, \$8965)	\$2,957 (\$1789, \$5430)
Hospital mortality, n (%)	145 (1.43)	9 (0.28)

PD = principal diagnosis; CI = confidence interval; IQR = interquartile range.

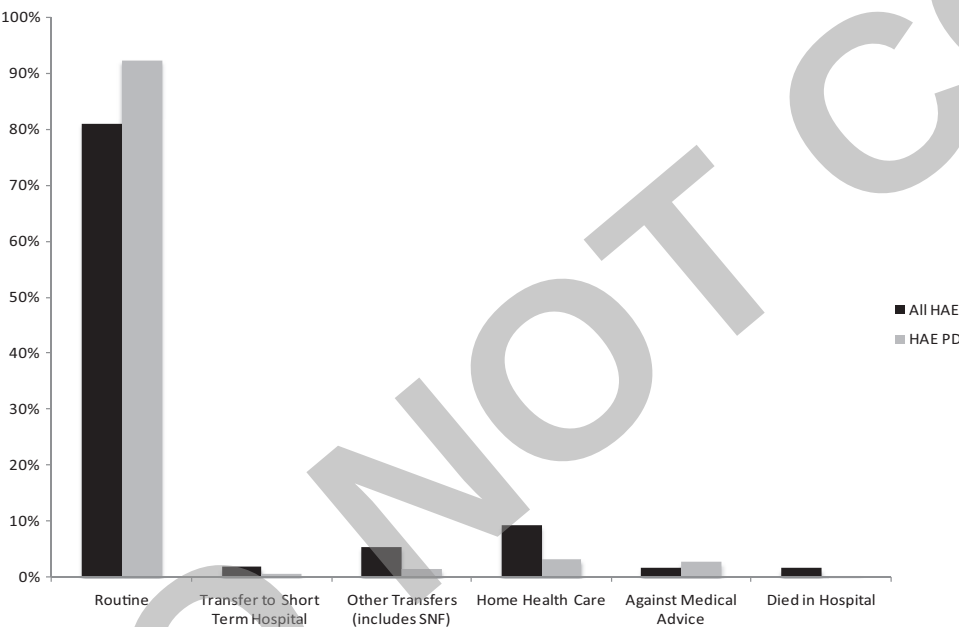


Figure 2. Discharge destination for all hereditary angioedema (HAE) and HAE principal diagnoses (PDs).

ing more routine attention to preventing these conditions may reduce the need for such acute hospitalizations, thereby unburdening not only the patients and their families, but also the entire health care system. Furthermore, the fact that 5 of the top 10 PDs among HAE hospitalizations (other than HAE itself) are referent to the respiratory system may help clinicians prioritize their own limited resources toward maximizing preventive strategies for respiratory disorders overall in this population. Alternatively, given the combined imprecision of HAE diagnosis and hospital record coding, it is possible that these high prevalence respiratory conditions represent hospital-based clinicians' confusion about the diagnosis and presentation of HAE exacerbations, thereby providing a meaningful opportunity for educational efforts in this area.

There is a distinct dearth of studies describing the epidemiology and outcomes of HAE hospitalizations. Recently, our group reported the epidemiology and

outcomes of HAE and AE hospitalizations in the United States in 2007, based on the NIS aggregate data.⁵ In this study we found the mean hospital LOS (SE) for HAE-PD to be 3.2 (0.5) days and the corresponding mean hospital costs of \$4759 (\$692). Our current analysis of 4 years worth of data in this population has resulted in similar findings. Wilson and coworkers performed a survey study of patients with HAE.⁸ It is noteworthy that the response rate to the survey was only 20%, thus exposing the study to a potential for selection bias. Nevertheless, the investigators described in detail important parameters of health care use as reported by 457 responders. To confirm the external validity of our results, their findings are worth highlighting in the context of our study.

We reported both costs and charges for the cohort because it is unclear which represents the more accurate estimate of the actual expenditure in this relatively young group of patients. A simple modeling exercise

may provide some clues. Because by some estimates 90% of all HAE patients suffer between 6 and 12 acute attacks per year,⁴ and if for every 10 exacerbations 1 requires hospitalization,⁸ it is the average per hospitalization charge of \$13,000 as computed by us that fits in well with the observations by Wilson *et al.*⁸ At the same time, in the HAE population, where only ~45% of the hospitalizations are covered by Medicare or Medicaid, it is difficult to know whether it is costs or charges that reflect the actual expenditures more closely. This is true because hospital costs are representative of reimbursements provided by Medicare and Medicaid and are on average only ~40% of the charges, while private insurance contracts frequently externalize at least some of these institutional losses, thus allowing the reimbursements to reflect the charges more closely, the mix of payers appears important to take into account when reporting the associated costs.^{9,10} Thus, it is likely that the actual estimate for an admission cost is somewhere between the calculated costs of \$4760 and charges of \$13,185, or about \$9000. This figure approximates the total annual hospitalization cost of \$17,000 reported by Wilson *et al.*,⁸ if indeed each HAE patient suffers one to two hospitalizations annually.

Our study is subject to a number of limitations. We relied on administrative coding to identify cases of HAE. This may have resulted in misclassification of the diagnoses. Conversely, given the challenges of recognizing this disease, our data likely underestimate the attendant full burden of hospitalizations. Because the Healthcare Cost and Utilization Project data are reported as individual discharges and not patients, it is impossible to differentiate an initial hospitalization from repeat ones. However, this does not reduce the validity of the estimate of total resource use in aggregate. The main strengths of the data are its size, which allows analysis for rare diseases such as HAE, and their broad generalizability to all of U.S. institutions.

In summary, we have described in detail the characteristics and outcomes of a large cohort of patients admitted to the hospital with HAE. Fully, one-third

come in with an exacerbation of HAE, while an additional 12% present for other respiratory ailments. Although this condition is rare, these patients represent a substantial volume of admissions and incur a large number of hospital days and attendant costs. In this era of cost containment in health care, our study provides potential targets for studying how to increase quality and efficiency of care delivery to this complex population.

REFERENCES

1. Bork K, Meng G, Staubach P, and Hardt J. Hereditary angioedema: New findings concerning symptoms, affected organs, and course. *Am J Med* 119:267–274, 2006.
2. Roche O, Blanch A, Caballero T, et al. Hereditary angioedema due to C1 inhibitor deficiency: Patient registry and approach to the prevalence in Spain. *Ann Allergy Asthma Immunol* 94:498, 2005.
3. Bowen T, Cicardi M, Farkas H, et al. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. *Allergy Asthma Clin Immunol* 28:24, 2010.
4. Agostoni A, Aygoren-Purson E, Binkley KE, et al. Hereditary and acquired angioedema: Problems and progress: Proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. *J Allergy Clin Immunol* 114(suppl):S51–S131, 2004.
5. Zilberberg MD, Jacobsen T, and Tillotson G. The burden of hospitalizations and emergency department (ED) visits with hereditary angioedema (HAE) and angioneurotic edema (AE) in the United States, 2007. *Allergy Asthma Proc* 31:511–519, 2010.
6. Hartman M, Martin A, Nuccio O, and Catlin A. National Health Expenditure Accounts Team. *Health Aff (Millwood)* 29:147–155, 2010.
7. Agency for Healthcare Research and Quality. Overview of the National Inpatient Sample. Available online at www.hcup-us.ahrq.gov/nisoverview.jsp; accessed February 12, 2010.
8. Wilson DA, Bork K, Shea EP, et al. Economic costs associated with acute attacks and long-term management of hereditary angioedema. *Ann Allergy Asthma Immunol* 104:314–320, 2010.
9. Price KF. Pricing Medicare's diagnosis-related groups: Charges versus estimated costs. *Health care financing review*, fall 1989. Available online at www.findarticles.com/p/articles/mi_m0795/is_n1_v11/ai_9338473; accessed September 18, 2009.
10. American Hospital Association Chartbook 2010. Trends affecting hospitals and healthcare systems. Available online at www.aha.org; accessed June 30, 2010. □

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.