

Descriptive epidemiology of hereditary angioedema emergency department visits in the United States, 2006–2007

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ABSTRACT

Hereditary angioedema (HAE) is a rare inherited disorder of complement factor C1 inhibitor. In 2007 there were over 2000 HAE-related emergency department (ED) visits, nearly one-half of which culminated in a hospitalization. This study examines epidemiology and outcomes of hospital ED visits among HAE patients. We evaluated epidemiology, resource use, and discharge destinations of HAE (International Classification of Diseases, Version 9, clinical modification [ICD-9-CM] code 277.6) ED visits within the Nationwide Emergency Department Sample, part of Agency for Healthcare Research and Quality Healthcare Costs and Utilization Project, in 2006 and 2007. In 2006–2007, there were 5040 ED visits with HAE, of which 2705 (53.7%) had HAE as the principal diagnosis (HAE-PD). The mean age for all HAE visits was 38.2 years, and women accounted for 56.5% of all HAE visits. When HAE was not the primary reason for the visit, abdominal pain was the most prevalent (10%) presenting diagnosis. Two thousand fifty-nine (40.9%) resulted in a hospitalization. Although of all HAE ED visits that did not require a hospitalization, the vast majority was discharged routinely home, further care either at a skilled nursing facility or at home was required after 45 (0.9%) of all the HAE visits and 10 (0.4%) of the HAE-PD visits. Mean HAE ED visits costs were \$1479 (95% confidence interval, \$1028–1929). HAE ED visit volume is substantial. Although likely representing a fraction of the entire HAE population, prevention and acute treatment strategies aimed at those at risk for frequent exacerbations and disproportionate resource use need to be examined.

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Hereditary angioedema (HAE) is a rare inherited deficiency or dysfunction of the complement factor C1 inhibitor. It generally manifests in the second or third decade of life as recurrent episodes of mucosal angioedema, affecting the skin and gastrointestinal and respiratory tracts.¹ Although the prevalence of HAE is low at 1 case per 50,000 population, ranging from 1 per 10,000 to 1 per 150,000 population,^{2,3} its associated mortality without treatment approaches 30% and results predominantly from laryngeal edema and asphyxiation.¹

Among the ~6000 patients with HAE in the United States, nearly one-half suffers a monthly exacerbation, and another 40% have 6–11 attacks annually.⁴ A recent study reported HAE emergency department (ED) use based on the aggregate data from the Agency for

Healthcare Research and Quality's Nationwide Emergency Department Sample (NEDS).⁵ It showed that in 2007 there were >2000 HAE-related ED visits, nearly one-half of which culminated in a hospitalization.⁵

Although the high price of U.S. health care has dominated our national health care debate, a more hidden crisis is looming with respect to hospital capacity. With the hospital costs responsible for roughly one-third of the total national health expenditures,⁶ the drive to contain these costs has had some unintended consequences; in the face of a consistent rise in ED visits and admissions, hospitals are reporting negative operating margins.⁷ The end result of these imbalances for EDs specifically is that as the actual number of operating departments has gone down, visit numbers have increased by 30% from 10 years ago, topping 120 million in 2008, thus forcing a large proportion of EDs to confront capacity issues.⁷ Indeed, nearly one in four EDs reports having to spend time on ambulance diversion, with the most frequent reasons being lack of staffed intensive care unit beds (42%) and ED overcrowding (27%).

Optimizing outpatient care to avoid emergent situations requiring ED evaluations may be an attractive target for improving quality and cost containment efforts in health care. Because the HAE population is small, to the best of our knowledge, there are no studies examining in detail ED use and outcomes in this population. To fill this gap, we conducted a retrospec-

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tive descriptive cohort study of individual hospitalization data available from the NEDS of all HAE-related ED visits in the United States between the years 2006 through 2007.

METHODS

We evaluated the volume, characteristics, and resource use associated with ED visits in the United States with HAE within the NEDS database, combining data for the years 2006 through 2007. The NEDS was created to enable analyses of ED use patterns and support public health professionals, administrators, policymakers, and clinicians in their decision making regarding this critical source of care.⁸ The NEDS contains almost 26 million records for ED visits for >950 hospitals and approximates a 20% stratified sample of U.S. hospital-based EDs.⁸ Complex survey methods exist to develop national and regional estimates for conditions addressed in the database.

We identified HAE-related ED visits 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 visits, as well as their ED outcomes, including charges and the associated discharge destinations. We performed the same computation for the subgroup of HAE discharges carrying HAE as the principal diagnosis (HAE-PD). All aggregate numbers represent national estimates derived using the weighting coefficients in the database as applied to the 20% sample represented in the data.

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

RESULTS

In the 2 years included in the analysis, there were 5040 ED visits with HAE, of which 2705 (53.7%) had HAE-PD (Table 1). The mean age for all HAE visits was 38.2 (95% confidence interval [CI], 36.3–40.1) years, with 78.4% of the population falling into the age range between 18 and 64 years. Women accounted for 56.5%, and nearly one-half were in the Southern census region, and 27.8% of all HAE ED visits occurred on a weekend. Only one-third of all patients were seen in a metropolitan teaching hospital, and the remainder visited an ED in either a metropolitan nonteaching or a nonmetropolitan hospital.

There were 2705 visits for HAE-PD (Table 1). Their age distribution was generally similar to that of the entire HAE cohort and 54.4% were women. The HAE-PD group was slightly less likely to have Medi-

care or Medicaid as the payer than the overall HAE cohort (33.3% HAE-PD versus 38.1% all HAE). Among the remaining HAE ED visits that did not have HAE as the primary reason for the visit, the most common presenting diagnoses were referable to abdominal pain, accounting for 10% of all visits ($n = 488$).

Of all of the HAE ED visits, 2059 (40.9%) resulted in a hospitalization, with a similar proportion of HAE-PD visits necessitating admission ($n = 1037$ [38.3%]; Table 1). Among those admitted there was a higher proportion of women, Medicaid coverage was more prevalent, and patients were more likely to live in large or medium metropolitan locales and be treated in a large metropolitan teaching hospital than among their respective source groups overall (Table 1). Regionally, although a plurality of ED visits were observed in the Midwest, it was the Southern region that led in the proportion of all admissions from the ED.

ED outcomes are examined in Fig. 1, A (all HAE) and B (HAE-PD). Of all HAE ED visits that did not require a hospitalization, the vast majority was discharged routinely home. Although there were no deaths among those presenting to the ED with HAE as the PD, three patients (0.1%) in the entire HAE cohort died during the ED visit. Further care either at a skilled nursing facility or at home was required after 45 (0.9%) of all the HAE visits and 10 (0.4%) of the HAE-PD visits.

Mean ED visits costs were \$1479 (95% CI, \$1028–1929) among all HAE and \$1465 (95% CI, \$856–2076) among those with HAE-PD. Extrapolating these numbers to the entire HAE cohort visiting an ED in the United States results in annual aggregated ED visit cost for patients with HAE of \$3,727,080 (95% CI, \$2,590,560–4,861,080), of which at least \$1,981,413 (95% CI, \$1,157,740–2,807,790) is attributable to HAE itself.

DISCUSSION

In the current study we have documented the descriptive epidemiology of ED visits with HAE in the United States in the years 2006 and 2007. We identified over 5000 visits carrying HAE as at least one of their diagnoses, with >50% presenting specifically for HAE as the reason, and another 10% for complaints referable to abdominal pain. Of all HAE visits, 41% resulted in a hospitalization. If one assumes that the entire process of the ED visit is directly attributable to HAE among patients with HAE-PD, the total aggregate annual charges for the entire HAE-PD population presenting to the ED in the United States amount to ~\$2 million. These estimates constitute the absolute minimum for ED resource use by the HAE population overall, because they do not include any proportion of the charges among HAE visits with a secondary diagnosis of HAE, which may nevertheless be attributable to HAE. Additionally, these estimates do not include ei-

Table 1 Hereditary angioedema (HAE) emergency department visit characteristics

	HAE (<i>n</i> = 5040)		HAE-PD (<i>n</i> = 2705)		HAE admitted (<i>n</i> = 2059)		HAE-PD admitted (<i>n</i> = 1037)	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
HAE-PD	2705	53.67	NA	NA	1037	50.36	NA	NA
Age group (yr)								
<1	69	1.37	0	0.00	40	1.94	0	0.00
1–17	526	10.44	221	8.17	228	11.07	107	10.32
18–44	3094	61.39	1933	71.46	1053	51.14	703	67.79
45–64	850	16.87	353	13.05	418	20.30	145	13.98
65–84	404	8.02	190	7.02	246	11.95	72	6.94
85+	97	1.92	9	0.33	74	3.59	9	0.87
Mean (95% CI) age for patients >1 yr	38.2 (36.3, 40.1)		36.9 (34.5, 39.4)		40.6 (37.9, 43.3)		35.3 (32.4, 38.2)	
Gender								
Female	2845	56.45	1471	54.38	1294	62.85	666	64.22
Primary payor								
Medicare	996	19.76	463	17.12	497	24.14	176	16.97
Medicaid	925	18.35	437	16.16	484	23.51	267	25.75
Private including HMO	2483	49.27	1461	54.01	785	38.13	435	41.95
Self-pay	487	9.66	268	9.91	218	10.59	120	11.57
No charge	23	0.46	15	0.55	18	0.87	13	1.25
Other	106	2.10	50	1.85	57	2.77	27	2.60
Missing/unknown	20	0.40	10	0.37	0	0.00	0	0.00
Weekend admission	1401	27.80	738	27.28	583	28.31	292	28.16
Intention of self-harm	20	0.40	0	0.00	14	0.68	0	0.00
Location of the patient's residence								
Large metropolitan	987	19.58	512	18.93	515	25.01	226	21.79
Large fringe metropolitan	1123	22.28	629	23.25	548	26.61	316	30.47
Medium metropolitan	978	19.40	493	18.23	427	20.74	221	21.31
Small metropolitan	386	7.66	226	8.35	227	11.02	126	12.15
Micropolitan	589	11.69	242	8.95	220	10.68	77	7.43
Not metropolitan or micropolitan	971	19.27	598	22.11	116	5.63	65	6.27
Missing	5	0.10	5	0.18	5	0.24	5	0.48
Treated in a teaching hospital								
Metro nonteaching	1817	36.05	1026	37.93	779	37.83	409	39.44
Metro teaching	1849	36.69	960	35.49	1019	49.49	532	51.30
Nonmetropolitan	1374	27.26	719	26.58	261	12.68	96	9.26
Region								
Northeast	880	17.46	434	16.04	417	20.25	205	19.77
Midwest	1936	38.41	1113	41.15	545	26.47	263	25.36
South	1362	27.02	674	24.92	661	32.10	315	30.38
West	862	17.10	484	17.89	497	24.14	253	24.40

CI = confidence interval; PD = principal diagnosis.

ther the direct costs of postdischarge care at another facility or at home or any indirect costs associated with the visit.

Although ostensibly small, the total expenditure on the HAE ED visits still requires attention. According to the Centers for Disease Control and Prevention, the

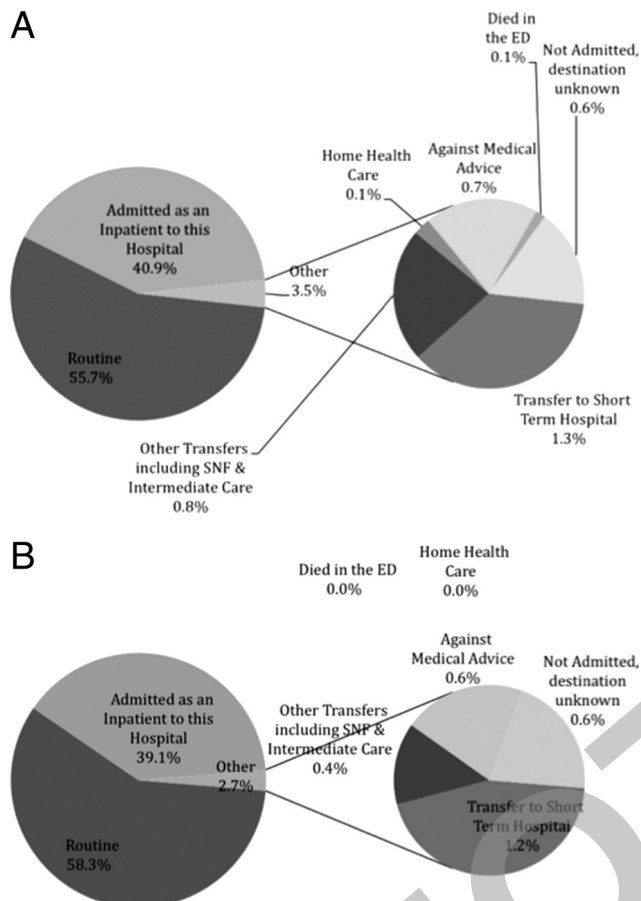


Figure 1. (A) Discharge destination among all hereditary angioedema (HAE) emergency department (ED) visits. (B) Discharge destination among HAE-PD ED visits. PD, principal diagnosis; SNF, skilled nursing facility.

number of ED visits nationally continues to grow.⁹ Between 1997 and 2007 the annual number of ED visits increased by 23%, and there has been a steady annual 11% growth in ED visits.⁹ This increase is occurring in the face of decreasing numbers of EDs in operation, leading to capacity issues necessitating temporary closures to new patients and ambulance diversions.⁷ Therefore, any possible target for reducing this volume needs to be identified. To this end, we have quantified one such potential target population represented by patients with HAE. Of even greater concern is the fact that 40% of all patients with HAE presenting for an emergent evaluation in the ED end up being hospitalized, contributing to the over a \$10 million aggregate bill associated with annual hospitalizations for HAE.¹⁰ Although probably impossible to eliminate altogether, our data highlight the need to investigate whether at least some of these visits and hospitalizations may be avoidable with aggressive attention to prevention or acute treatment of HAE attacks.

Some have argued that diverting nonurgent care from the EDs to outpatient offices would not be a great

revenue saver. Indeed, Williams quantified the marginal costs of ED care for nonurgent visits to be \$24 on average.¹¹ Based on this, he stated that "The potential savings from a diversion of non-urgent visits to private physicians' offices may therefore be much less than is widely believed." In response to this assertion, Baier rightly maintained that any unnecessary level of care, no matter how inexpensive, should be avoided.¹² Additionally, improving access to primary care rather than relying on the ED to provide care on an as-needed basis may result in preventing not only nonurgent but also those truly urgent and emergent visits.¹² Such reasoning seems well suited to the HAE population, where meticulous follow-up with the specialty outpatient team may reduce the need to expose the patient to the necessity of emergent treatment and hospitalization.

There is general dearth of information on health care use by the HAE population, and specifically data on ED use is scant. Wilson *et al.* surveyed 457 patients with HAE.¹³ Notably, the response rate to the survey was only 20%, exposing the study to a potential for selection bias. Nevertheless, the investigators described in detail important parameters of health care use as reported by the responders. These investigators reported that on average each HAE patient is subject to 27 acute attacks per year, of which 57% are abdominal. This is of interest, because in our study, although not seen specifically for HAE as the primary diagnosis, 10% of the patients not identified as being seen for an HAE attack were evaluated for abdominal pain. This raises the issue of misclassification of the primary diagnosis because of unfamiliarity of the ED staff with the condition and its manifestations and may suggest that targeted educational efforts may streamline the care of HAE patients in the emergency setting. Our data may be used to help target these educational efforts, given that large metropolitan teaching and nonteaching institutions are seeing the bulk of HAE cases.

Wilson's study further suggests that nearly 13% of all HAE attacks get evaluated in the ED, and mean per patient direct annual ED costs are \$2603 in \$US 2007.¹³ This number differs slightly from our ~\$1500 charges per visit. The reason for this discrepancy lies in the fact that Wilson and colleagues evaluated per patient annual costs, including all visits to the ED for each patient. In contrast, our data address the costs of a single visit and thus underestimate aggregate per patient annual ED costs among those patients with multiple ED visits per annum. Furthermore, examining the data on visits alone may mute the interpatient variability in ED use and thus costs. For example, a patient who presents to the ED with an attack only once per year indeed incurs \$1500 in charges. However, if in a patient with 27 or more acute annual attacks even one-half are

evaluated in the ED, this individual alone may incur an annual ED charge of \$21,000.¹³ It is indeed these patients with frequent exacerbations resulting in disproportionately heavy ED use that may define the target population for intensive prevention and acute treatment efforts. Because the time frame for both Wilson's and our studies predates the introduction to market of the new generation of agents aimed at HAE prophylaxis and acute treatment, the data likely reflect the previously reported high reliance on ED services by the treating physicians.¹⁴

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. Most likely, given the difficulties of recognizing this disease, our data likely underestimate the attendant full burden of ED visits with HAE. Because the Healthcare Costs and Utilization Project data are reported as individual visits and not patients, it is impossible to differentiate an initial visit 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 seen in the EDs across the United States with HAE. Although one-half come in with an exacerbation of HAE, an additional 10% present for abdominal pain, which may, nevertheless, represent an HAE exacerbation. Although this condition is rare, at least some of the visits may be preventable with systematic preventive or acute treatment measures in place, thus unburdening both the patients and their families and the EDs that frequently operate over capacity. At the same time, this study, together with our recent analysis of HAE hospitalization outcomes,¹⁰ provides a benchmark for examining costs and effectiveness of various prevention and treatment strategies against the potential ED and hospital costs incurred by this population. In the era of optimizing quality in health care, our study presents potential targets for studying how to increase efficiency of care delivery to this complex population.

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