

The burden of hospitalizations and emergency department visits with hereditary angioedema and angioedema in the United States, 2007

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ABSTRACT

Hereditary angioedema (HAE) is a rare inherited disorder of complement factor C1 inhibitor. HAE is frequently confused with angioedema (AE), and little is known about emergency department (ED) or hospital utilization by patients with attacks in the United States. We examined hospitalizations and ED utilization for HAE and AE in two large nationally representative databases. We evaluated annual rate and resource use of HAE (International Classification of Diseases, Version 9, Clinical Modification [ICD-9-CM] code 277.6) and AE (ICD-9-CM code 995.1) hospitalizations within Nationwide Inpatient Sample (NIS), part of the Agency of Healthcare Research and Quality's Healthcare Costs and Utilization Project (AHRQ-HCUP), for 2007. We also used AHRQ-HCUP's 2007 Nationwide Emergency Department Sample (NEDS) to study annual rates of ED visits and subsequent hospitalizations with these conditions. There were 1691 hospitalizations with HAE and 22,572 with AE (4.25 HAE and 57.08 AE cases/100,000 hospitalizations). HAE was the principal diagnosis (PD) in 46.0% and AE in 62.5%. In aggregate, HAE and AE PD hospitalizations accrued 35,000 hospital days and hospital costs of \$63 million. There were 2282 ED visits with HAE and 112,105 ED visits with AE (1.87 HAE and 91.64 AE cases/100,000 ED visits). HAE occurred as a PD in 51.2% and AE occurred as a PD in 80.0%. Forty-five percent of HAE patients and 18.3% of AE patients required hospitalization. HAE and AE ED use and hospitalization burden are substantial. Because diagnostic uncertainty is likely, HAE-related proportion of patients and resource use are probably underestimated. Clinical validation of current case definition would be useful, because administrative data may present an attractive source for investigating these populations.

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Hereditary angioedema (HAE) is an autosomal dominant disease caused by C1 esterase inhibitor (C1-INH) deficiency. C1-INH is a serine protease inhibitor that plays a key regulatory role in the contact and complement systems.¹ HAE was first described by Quincke in 1882; its inheritance nature was evidenced by Osler in 1888 and further defined as autosomal dominant by Crowder and Crowder in 1917.^{2–4} It is characterized by attacks of edema involving the skin, mucous membranes, genitals, gastrointestinal tract, and airway.^{5,6} In the skin, edema usually occurs in the extremities, involves all skin layers, and is nonpitting, nonurticarial, and nonpruritic and may be accompanied by a rash.^{7–10} Three variants of HAE have been described: HAE type 1, with low C1-INH antigenic protein and functional activity (85% of cases); HAE type 2,

with normal or elevated protein level but low C1-INH function (15% of cases); and an additional type of HAE, sometimes called HAE type 3 or estrogen-dependent angioedema, with normal C1-INH protein level and function occurring mainly in women.

The exact prevalence of HAE is unknown but estimates range from 1 in 10,000 to 1 in 150,000 (with most agreeing that 1 in 50,000 is likely closest to the actual prevalence) and no ethnic group differences have been reported.^{7,11,12} Adjusting to the U.S. population, the total burden of HAE may be between 2000 and 30,000 cases.¹³ Its rare nature makes HAE diagnosis challenging. For example, the average lag time between symptom onset and diagnosis has been reported to be over 10 years.¹⁴

Additionally, it may be easily confused with angioedema (AE), in which its prevention and treatment differ from those for HAE. Although it is believed that many cases present to the emergency department (ED) and require subsequent hospitalization, actual data on the frequency and outcomes of ED visits or hospitalizations remain scant. To start to fill this gap, we explored aggregate data on ED and hospital use for HAE and AE within two large nationally representative U.S. databases.

METHODS

We evaluated the annual rate and resource use associated with ED visits and hospitalizations in the United

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Table 1 Hospitalization rates with hereditary angioedema (HAE) and angioedema (AE) by hospital and patient characteristics

	HAE	HAE/100,000 Hospitalizations	AE	AE/100,000 Hospitalizations
All discharges	1691	4.28	22,572	57.08
Sex				
Male	524	3.23	9354	57.63
Female	1167	5.03	13,162	56.73
Missing		NA	*	NA
Payer				
Medicare	319	2.22	10,393	72.27
Medicaid	347	4.53	2268	29.59
Private insurance	774	5.64	7301	53.22
Uninsured	*	NA	1708	73.95
Other	*	NA	833	60.18
Missing	NA	NA	*	NA
Median income zip code				
Low	427	3.71	7830	68.06
Not low	1220	4.52	14,088	52.22
Missing	*	NA	654	61.56
Ownership				
Government	352	6.21	3342	58.98
Private, not for profit	1141	3.99	15,903	55.60
Private, for profit	198	3.75	3327	63.07
Teaching status				
Nonteaching	858	4.14	12,294	59.31
Teaching	833	4.44	10,249	54.63
Missing	NA	NA	*	NA
Location				
Nonmetropolitan	213	4.21	3035	60.09
Metropolitan	1478	4.29	19,508	56.64
Missing			*	NA
Bed size				
Small	219	4.51	2915	60.00
Medium	309	3.24	5896	61.89
Large	1163	4.63	13,731	54.70
Missing	NA	NA	*	NA

*Statistics based on estimates with a relative SE (SE/weighted estimate) >0.30 or with SE = 0 in the nationwide statistics are not reliable. These statistics are suppressed and are designated with an asterisk.

NA = not available/not applicable.

States with HAE or AE within the Nationwide Emergency Department Sample (NEDS) and Nationwide Inpatient Sample (NIS) databases, respectively, both a part of the Agency of Healthcare Research and Quality's Healthcare Costs and Utilization Project (HCUP), for the year 2007. NIS was specifically designed to identify, track, and analyze national trends in healthcare utilization, access, charges, quality, and outcomes.¹⁵ The 2007 NIS contains all discharge data from 1044 hospitals located in 40 states, approximating a 20% stratified sample of U.S. community hospitals.¹⁵ The NEDS was created to enable analyses of ED utilization patterns and support public health profession-

als, administrators, policymakers, and clinicians in their decision making regarding this critical source of care.¹⁶ The NEDS contains almost 26 million records for ED visits for over 950 hospitals and approximates a 20% stratified sample of U.S. hospital-based EDs.¹⁶ Complex survey methods exist to develop national and regional estimates for conditions addressed in both databases.

For the current study, all data were derived in aggregate from the publicly available website HCUPNet.¹⁷ We identified HAE- and AE-related visits and hospitalizations based on the presence of the International Classification of Diseases, Version 9, Clinical Modification (ICD-9-CM) codes

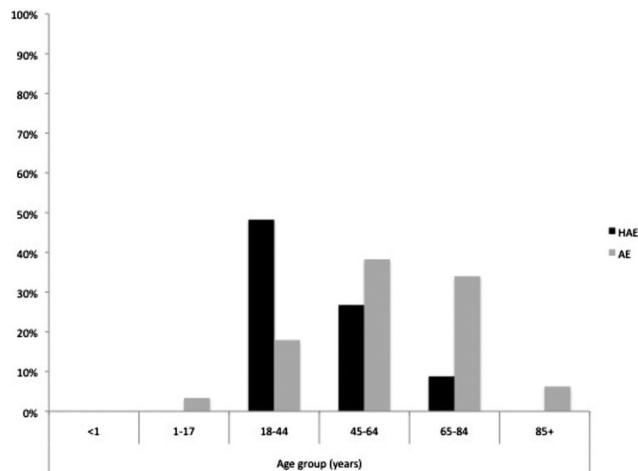


Figure 1. Age distribution of hereditary angioedema (HAE) and angioedema (AE) hospital discharges.

277.6 (other deficiencies of circulating enzymes, HAE) and 995.1 (angioneurotic edema), and standardized them as a proportion of all ED visits and all hospitalizations in NEDS and NIS, respectively. We also examined rates of ED visits and hospitalizations with HAE or AE as the principal diagnosis (PD; “for” rather than simply “with”) as a proportion of the total ED visits and hospitalizations with the corresponding diagnosis. Additionally, we examined the characteristics of HAE and AE ED visits ending in a hospitalization. We describe their demographic and hospital characteristics, as well as outcomes.

RESULTS

Hospitalizations, NIS, 2007

In 2007 there were 1691 hospitalizations with HAE and 22,572 with AE (Table 1). This corresponded to 4.28 HAE cases/100,000 hospitalizations and 57.08 AE cases/100,000 hospitalizations. Although the highest rate of HAE hospitalizations was in the 18- to 44-year-old group, for AE it was among the 45- to 64-year-old patients (Fig. 1). Although women predominated over men in HAE, no sex-based difference in AE hospitalization rates was observed. The South census region had the highest volume of both HAE and AE hospitalizations (Fig. 2).

Hospitalizations with the PD of HAE comprised 46.0% of all HAE hospitalizations, and for AE this proportion was 62.5% (Fig. 3). Hospital outcomes were available for all discharges with the PD of HAE ($n = 778$) or AE ($n = 14,104$). Mean hospital length of stay was longer among HAE than AE discharges (Fig. 4 A). Median hospital length of stay did not differ between HAE and AE (2.0 days). Hospital charges and costs for both HAE and AE hospitalizations were comparable (Fig. 4, B and C). Approximately 90% of all patients admitted for either HAE or AE experienced a routine

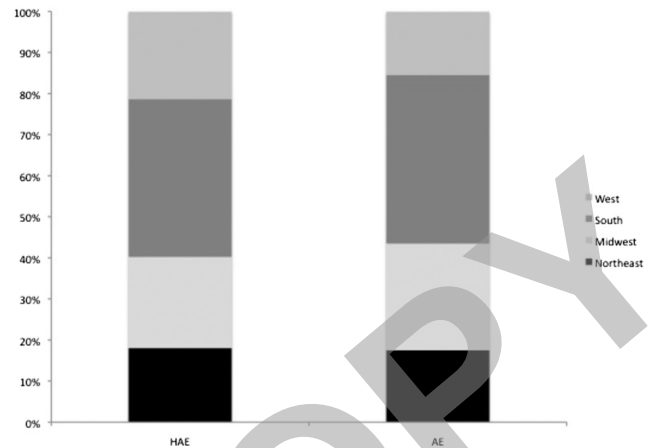


Figure 2. Regional distribution of hereditary angioedema (HAE) and angioedema (AE) hospital discharges.

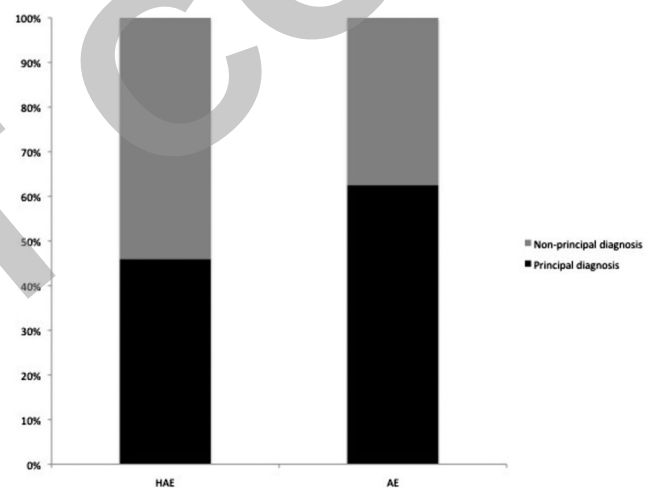


Figure 3. Proportion hospital discharges with the principal diagnoses, hereditary angioedema (HAE), and angioedema (AE).

discharge home (Fig. 4 D). In aggregate, HAE and AE PD hospitalizations were responsible for 35,000 hospital days and hospital costs of nearly \$65 million in the United States in 2007.

ED Visits, NEDS, 2007

In 2007 there were 2282 ED visits with HAE and 112,105 with AE (Table 2). This corresponded to 1.87 HAE cases/100,000 visits and 91.64 AE cases/100,000 visits. Although the highest rate of HAE ED visits was in the 18- to 44-year-old group, for AE it was among the 65- to 84-year-old patients (Fig. 5). The rates for ED visits were directionally higher among women than men in both HAE and AE (Table 2). Similar to hospitalizations, the South census region had the highest volume of both HAE and AE visits (Fig. 6).

Visits with the PD of HAE comprised 51.2% of all HAE ED visits, and for AE this proportion was 80.0% (Fig. 7). Although 45.0% of all HAE visits resulted in

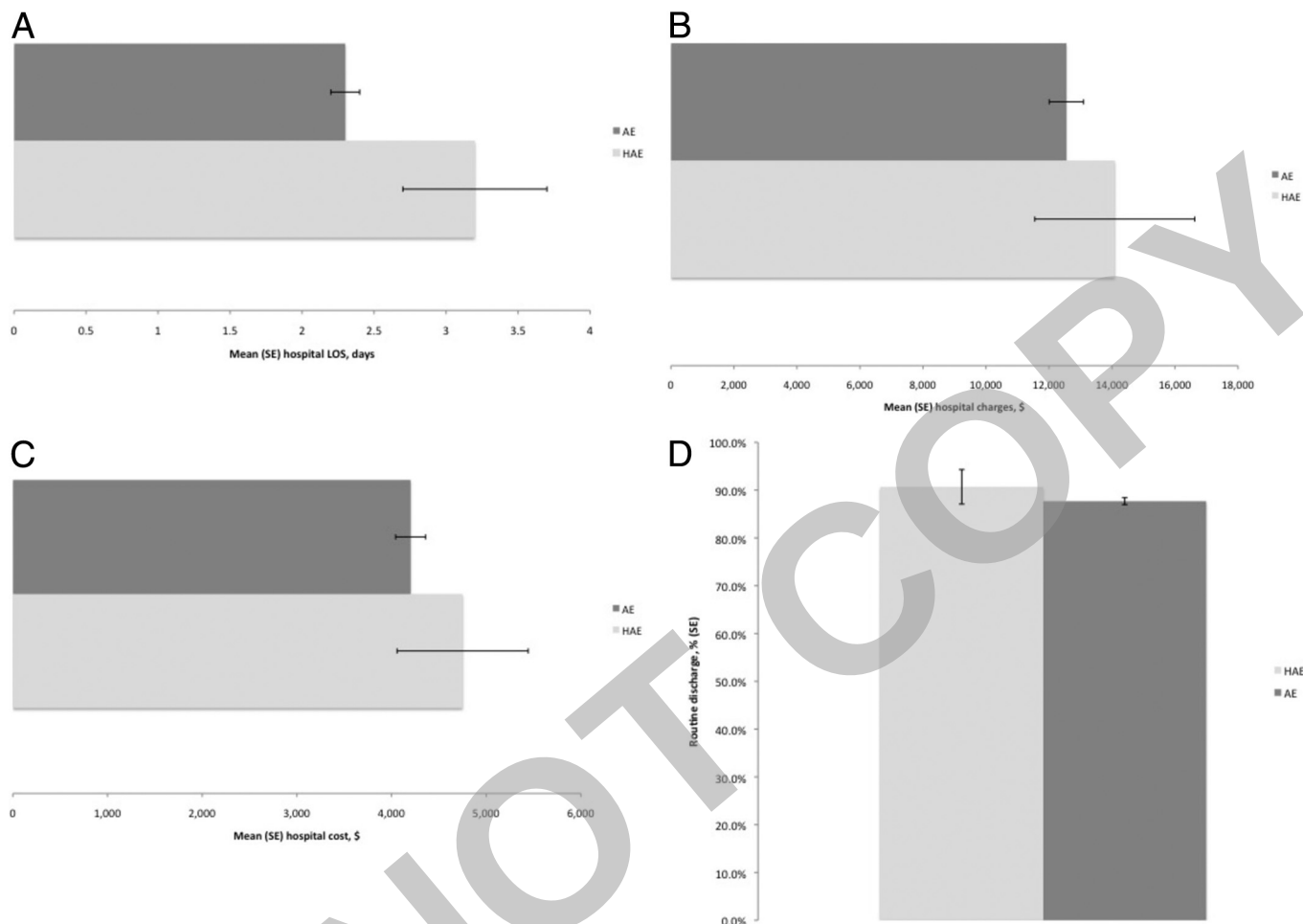


Figure 4. Outcomes of hospitalizations for principal diagnoses hereditary angioedema (HAE) and angioedema (AE). (A) Hospital length of stay (LOS); (B) hospital charges; (C) hospital costs; (D) routine discharge home.

hospitalization, only 18% of all AE visits had the same outcome (Fig. 8). Among ED visits with HAE and AE as PDs, the corresponding proportions were 44.4 and 15.1% (data not shown).

ED outcomes were available for all visits with the PD of HAE ($n = 1169$) or AE ($n = 89,676$; Table 3). Hospitalization rates were higher for HAE (44.5%) than for AE (15.1%). Among the 55.5% ($n = 649$) HAE visits resulting in discharge from the ED, 615 (94.8%) were discharged home routinely. For the remaining 5.2% the specific discharge destination was not available because of small numbers. Among the 84.9% ($n = 76,148$) AE visits resulting in discharge from the ED, the vast majority ($n = 72,654$, 95.4%) were discharged home routinely. Of the remaining 1576 visits not discharged routinely with a known destination, 566 went to another short-term hospital, 559 went to a skilled nursing facility and 461 signed out against medical advice (Fig. 9 A). Discharge destination for those hospitalized for AE was 87.1% routine, 0.6% another long-term hospital, 5.1% skilled nursing facility, 4.7% home healthcare, and 2.0% against medical advice (Fig. 9 B).

DISCUSSION

We have shown that ED and hospital utilization, as well as the attendant healthcare costs for both HAE and AE in the United States are substantial. In 2007 HAE and AE together played a role in nearly 115,000 ED visits and nearly 23,000 hospitalizations. Assuming that all of the ED and hospital utilization among discharges with HAE or AE as the PD is attributable to these conditions, the attendant aggregate burden is not trivial, adding up to 35,000 hospital days and \$65 million. Additionally, although the majority of both HAE and AE ED visits resulted in a routine discharge home, a substantial number of discharged patients required further management at another short-term hospital or a skilled nursing facility, thus adding further to the total resource utilization.

Our numbers for AE are consistent with another recent study that examined AE hospitalizations in the United States.¹⁸ Lin and Shah looked at the trajectory of discharge volumes for AE as the PD between 1998 and 2005 in the NIS. For year 2005, they reported the

Table 2 Emergency department (ED) visit rates with hereditary angioedema (HAE) and angioedema (AE) by hospital and patient characteristics

	HAE	HAE/100,000 ED Visits	AE	AE/100,000 ED Visits
Sex	2282	1.87	112,105	91.64
Male	890	1.59	48,807	87.41
Female	1392	2.09	63,292	95.23
Payer				
Medicare	429	1.80	30,918	129.50
Medicaid	556	2.08	13,730	51.31
Private insurance	969	2.30	48,101	113.97
Uninsured	275	1.20	14,774	64.51
Other	*	NA	4048	68.37
Missing	*	NA	534	79.73
Median income zipcode				
Low	640	1.57	36,946	90.92
Not low	1582	2.01	72,381	92.00
Missing	*	NA	2777	91.90
Patient residence				
Large central metro	491	1.58	27,016	87.23
Large fringe metro (suburbs)	579	2.13	25,084	92.31
Medium and small metro	736	1.91	35,866	93.19
Metropolitan and noncore (rural)	471	1.89	23,652	94.87
Missing	*	NA	487	63.53
Owner				
Government	393	1.80	19,290	88.18
Private, not for profit	1580	1.88	75,199	89.36
Private, for profit	309	1.90	17,616	108.06
Teaching status				
Nonteaching	1468	1.93	72,756	95.60
Teaching	814	1.76	39,349	85.12
Location				
Nonmetropolitan	364	1.57	22,547	96.99
Metropolitan	1918	1.94	89,558	90.39
Trauma center designation				
Trauma center	1680	2.01	79,373	95.03
Not a trauma center	602	1.55	32,732	84.34

*Statistics based on estimates with a relative SE (SE/weighted estimate) >0.30 or with SE = 0 in the nationwide statistics are not reliable. These statistics are suppressed and are designated with an asterisk.

NA = not available or not applicable.

number of AE discharges to be 11,925 cases, for a population prevalence of 4.0/100,000. Our estimate of 14,104 PD of AE discharges in 2007 is not inconsistent with their finding of a steady rise in AE prevalence over time.¹⁸ There is, however, an apparent small discrepancy in the costs between Lin and our studies. Although we did not explicitly report this number, the aggregate charges for PD AE discharges in 2007 was \$177,085,865, and the costs were \$59,271,344.¹⁷ Although it is likely that Lin's estimate of ~\$123 million for year 2005 for the PD AE discharges represents charges rather than costs, we chose to report the cost

estimate rather than charges, because costs are usually more representative of the actual expenditures and are also more generalizable across institutions.

For the last several decades, the U.S. national health-care expenditures have been escalating at a staggering rate, far outpacing the rate of inflation, topping the total of \$2.1 trillion and representing 16% of the gross domestic product.¹⁹ For this reason policy makers and payers are focusing much greater attention on the economic aspects of healthcare delivery. Within this context, just as more hospitals are reporting negative operating margins, both EDs and hospital wards are

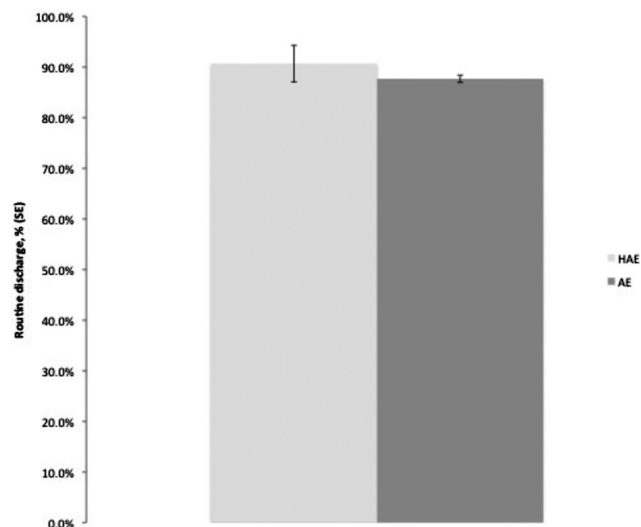


Figure 5. Age distribution of hereditary angioedema (HAE) and angioedema (AE) emergency department (ED) visits.

seeing a consistent rise in admissions.²⁰ For EDs, specifically, as the actual number of operating departments has gone down, patient visits have increased by 30% from 10 years ago, topping 120 million in 2008, and forcing a large proportion of EDs to confront capacity issues.²⁰

The tension between containing rapidly escalating healthcare costs and the need to provide adequate patient care has engendered a close examination of how healthcare is delivered in the United States. One obvious strategy for reducing the need for expensive emergent management and hospitalizations is prevention. This is highly relevant to HAE, where multiple therapeutic modalities aimed at prevention are on the market. To estimate their value, we need to understand not only their effectiveness at abrogating disease exacerbations, but, indeed, their

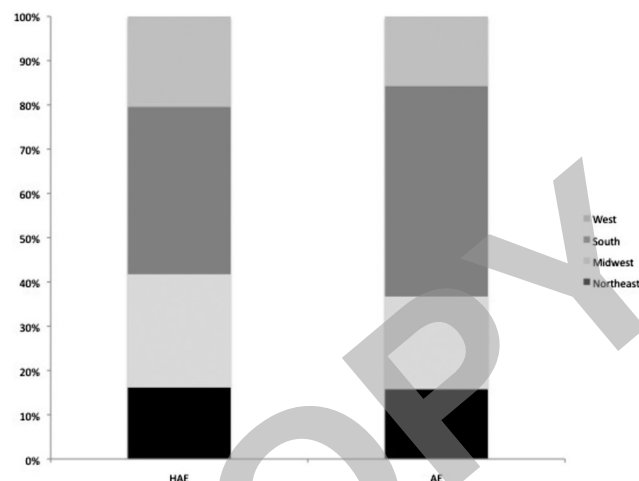


Figure 6. Regional distribution of hereditary angioedema (HAE) and angioedema (AE) emergency department (ED) visits.

cost-effectiveness in reducing the patients' exposure to the healthcare system, and, specifically, ED visits and hospitalizations. To this end, our study is the first to estimate the utilization burden against which novel therapies should be measured.

To the best of our knowledge, only one other recent study has addressed costs associated with HAE in the United States.²¹ In a survey design, Wilson and co-workers estimated total annual costs in 2007 U.S. dollars to range from \$14,000 for a mild case to over \$96,000 for a severe case of HAE. Although these were aggregate costs including the indirect component, the study provided an estimate of ED and hospitalization cost components as well, reporting them to be 4% of the total cost for a patient with mild disease and 68% for one with severe disease.²¹ Our estimate for the cost

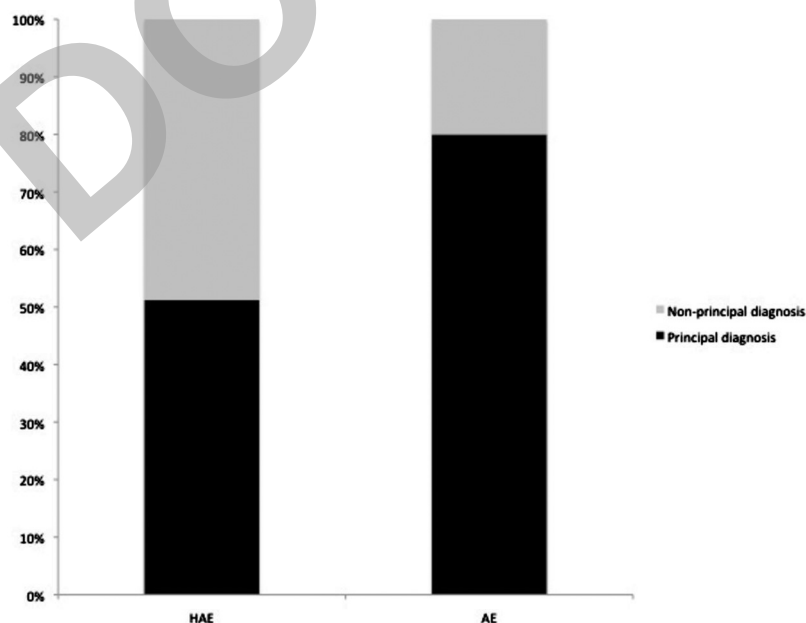


Figure 7. Proportion of principal diagnosis, hereditary angioedema (HAE) and angioedema (AE) emergency department (ED) visits.

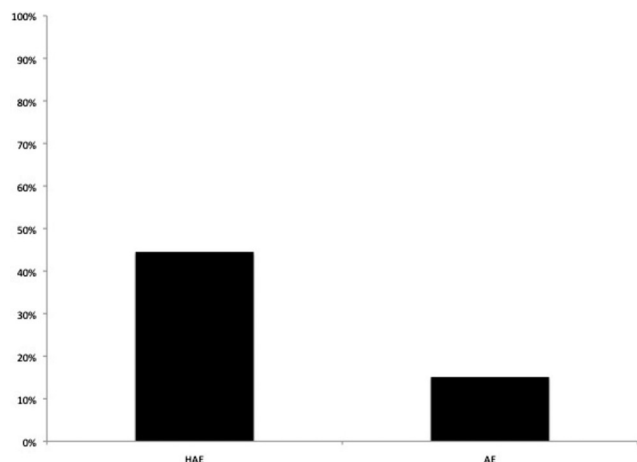


Figure 8. Proportion of any hereditary angioedema (HAE) and angioedema (AE) emergency department (ED) visits resulting in hospitalization.

of a hospitalization of ~\$4000 falls within this range. It differs from Wilson’s because the latter focused on the total per-patient annual hospitalization costs, while we report the mean cost of a single hospitalization for HAE, not taking into account repeat hospitalization(s) within the calendar year for the same patient.

Similar to our finding of a 45% hospitalization rate from the ED, Wilson *et al.* reported that of the 16% of the survey responders who sought attention at an ED during an exacerbation, 59% were hospitalized.²¹ By focusing on the ED and hospitalization components of healthcare utilization in the setting of HAE we build on these data to establish further granularity in understanding the contribution of HAE to this high cost service. A unique contribution of our study is that it is based on highly generalizable data derived from a

representative survey of the U.S. facilities designed for the purpose of understanding healthcare costs and utilization. Finally, acknowledging the likely diagnostic confusion between HAE and AE, we also report our estimates for the AE population. Although it is highly probable that at least some of the utilization and cost estimates calculated for the AE population represent HAE, it is not possible to estimate this proportion.

Our study has a number of limitations. First, we relied on administrative coding to identify cases of HAE and AE. This may have resulted in misclassification of the diagnoses. Conversely, given the challenges of recognizing these diseases, our data likely underestimate the full burden of hospitalizations with them. For example, there are a number of other potential ICD-9-CM codes that may be used with symptoms of AE and HAE: laryngeal edema, abdominal pain, edema, urticaria, localized swelling of skin, *etc.* Because our aim was to present conservative estimates of these conditions, we chose not to introduce further uncertainty by including the corresponding codes. However, one needs to recognize this limitation of administrative data sets and the consequent potential to misclassify a substantial number of cases based on coding heterogeneity.

Second, because the HCUP data are reported as individual discharges and not patients, it is impossible to differentiate initial visit or hospitalization from repeat ones. However, this does not reduce the validity of the estimate of total resource utilization 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, HAE and AE ED and hospital utilization in the United States is substantial. Because diag-

Table 3 Discharge outcomes of emergency department (ED) visits for hereditary angioedema (HAE) and angioedema (AE) as principal diagnoses

	HAE		AE	
	All ED Visits (n = 1,169)	Hospitalized from ED (n = 519)	All ED Trauma Center designation (n = 89,676)	Hospitalized from ED (n = 13,528)
Hospitalized	519 (44.5%)	NA	13,528 (15.1%)	NA
Routine discharge	650 (55.5%)	NA	72,654 (81.0%)	11,778 (87.1%)
Died during ED visit	*	*	*	*
Died during hospitalization	*	*	*	*
Another short-term hospital	*	*	566 (0.6%)	77 (0.6%)
SNF/NH	*	*	559 (0.6%)	695 (5.1%)
Home health care	*	*	*	634 (4.7%)
AMA	*	*	461 (0.5%)	275 (2.0%)
Missing	*	*	*	*

*Statistics based on estimates with a relative SE (SE/weighted estimate) >0.30 or with SE = 0 in the nationwide statistics (NIS and NEDS) are not reliable. These statistics are suppressed and are designated with an asterisk.
 NA = not available or not applicable; SNF/NH = skilled nursing facility/nursing home, AMA = against medical advice.

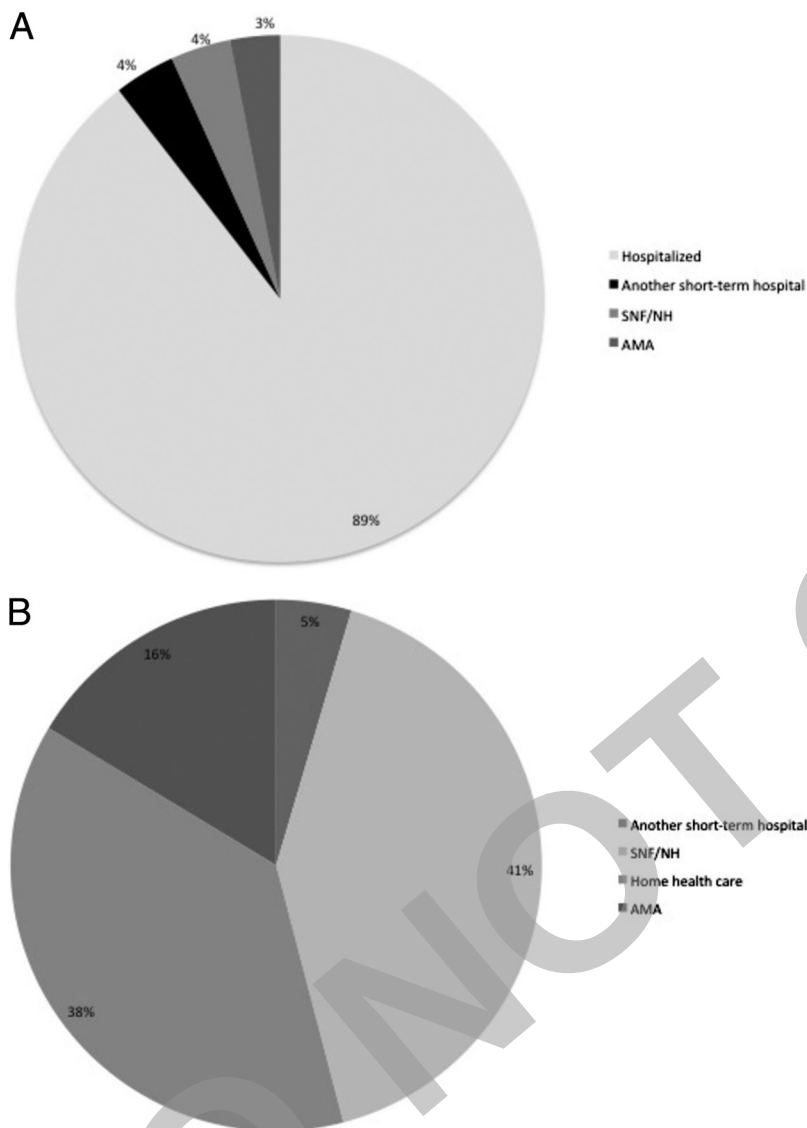


Figure 9. Discharge destination. (A) Angioedema (AE) principal diagnosis emergency department (ED) visits not discharged routinely from the ED. (B) AE principal diagnosis ED visits resulting in hospitalization not discharged routinely from the hospital. HAE, hereditary angioedema; SNF, skilled nursing facility; NH, nursing home; AMA, against medical advice.

nostic uncertainty is likely to be present, the proportion of patients and resource utilization due to HAE is probably an underestimate. Clinical validation of the current case identification method would be useful, because administrative data may present an attractive source for investigating these populations.

REFERENCES

1. Donaldson VH, and Evans RR. A biochemical abnormality in hereditary angioneurotic edema: Absence of serum inhibitor of C1-esterase. *Am J Med* 35:37–44, 1963.
2. Quincke H. Concerning the acute localized oedema of the skin. *Monatsh Prakt Dermatol* 1:129–131, 1882.
3. Osler W. Hereditary angio-neurotic oedema. *Am J Med Sci* 95:362–367, 1888.
4. Crowder JR, and Crowder TR. Five generations of angioneurotic edema. *Arch Intern Med* 20:840–852, 1917.
5. Eck SL, Morse JH, Janssen DA, et al. Angioedema presenting as chronic gastrointestinal symptoms. *Am J Gastroenterol* 88:436–439, 1993.
6. Bork K, and Barnstedt ES. Treatment of 193 episodes of laryngeal edema with C1 inhibitor concentrate in patients with hereditary angioedema. *Arch Intern Med* 161:714–718, 2001.
7. Nzeako UC, Frigas E, and Treamine WJ. Hereditary Angioedema: A broad review for clinicians. *Arch Intern Med* 161: 2417–2429, 2001.
8. Christiansen SC, and Zuraw BL. Update on therapeutic developments for hereditary angioedema. *Allergy Asthma Proc* 30: 500–505, 2009.
9. Zuraw BL. Hereditary angioedema. *N Engl J Med* 359:1027–1036, 2008.
10. 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.
11. Cicardi M, and Agostoni A. Hereditary angioedema (editorial). *N Engl J Med* 334:1666–1667, 1996.
12. Talavera A, Larraona JL, Ramos JL, et al. Hereditary angioedema: An infrequent cause of abdominal pain with ascites. *Am J Gastroenterol* 90:471–474, 1995.
13. Zuraw BL. Hereditary angioedema: A current state-of-the-art review IV: Short- and long-term treatment of hereditary angio-

- edema: Out with the old and in with the new? *Ann Allergy Asthma Immunol* 100:S13–S18, 2008.
14. 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* 94:498–503, 2005.
 15. Agency for Healthcare Research and Quality. Overview of the national inpatient sample. Available online at www.hcup-us.ahrq.gov/nisoverview.jsp; last accessed February 12, 2010.
 16. Agency for Healthcare Research and Quality. Overview of the national emergency department sample. Available online at www.hcup-us.ahrq.gov/nedsoverview.jsp; last accessed February 12, 2010.
 17. Agency for Healthcare Research and Quality. HCUPNet. Available online at www.hcupnet.ahrq.gov/; last accessed February 12, 2010.
 18. Lin RY, and Shah SN. Increasing hospitalizations due to angioedema in the United States. *Ann Allergy Asthma Immunol* 101:185–192, 2008.
 19. Organization for Economic Cooperation and Development. Healthcare statistics for 2008. Available online at www.oecd.org/statsportal/; last accessed September 9, 2010.
 20. American Hospital association Chartbook 2010. Trends affecting hospitals and healthcare systems. Available online at www.aha.org/; last accessed June 30, 2010.
 21. 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. □

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