

Economic costs associated with acute attacks and long-term management of hereditary angioedema

David A. Wilson, MA*; Konrad Bork, MD†; Elizabeth P. Shea, PhD‡; Anne M. Rentz, MSPH§; Marc B. Blaustein, MPP‡; and William E. Pullman, MBBS, PhD, FRACP‡

Background: Hereditary angioedema (HAE) is a rare autosomal dominant disorder characterized by recurrent acute attacks of swelling of the larynx, abdomen, and periphery.

Objective: To assess the economic burden associated with acute attacks and long-term management of HAE.

Methods: Burden was assessed via a Web-based survey of HAE patients (≥ 18 years old) that solicited information on attack characterization, short-term treatment, long-term disease management, impact on work, and patient costs. A standardized instrument, the Work Productivity and Activity Impairment questionnaire, was included to assess impact on work productivity. Standard medical costs and US average wage costs were assigned to survey items to assess direct medical and indirect costs, respectively.

Results: Total annual per-patient costs are estimated at \$42,000 for the average HAE patient, with costs totaling \$14,000 for patients with mild attacks, \$27,000 for patients with moderate attacks, and \$96,000 for patients with severe attacks. Hospital costs account for 67% of direct medical costs. Respondents reported high rates of missed work, lost productivity, and lost income, contributing to indirect costs totaling \$16,000 annually for the average patient. Almost all costs increase with disease severity, although the distribution varies with severity: indirect costs account for 75% of costs for patients with mild attacks, whereas emergency department and hospital costs account for 68% of costs for patients with severe attacks.

Conclusions: HAE results in considerable economic burden to patients, payers, and society in terms of direct medical and indirect costs and compounds the substantial humanistic burdens, which will be reported separately.

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Hereditary angioedema (HAE) is a rare, debilitating, and potentially life-threatening autosomal dominant disease (estimated incidence, 1 in 50,000 people^{1,2}). HAE is characterized by acute attacks of pain and edema that may involve nearly every body area.^{1,3,4} With the potential for asphyxiation, laryngeal attacks pose the greatest risk.^{5,6} Abdominal attacks can be especially painful and may mimic acute abdominal emergencies, often resulting in exploratory procedures or unnecessary surgery.^{3,7} Peripheral attacks are disfiguring and debilitating.

HAE attacks can last up to 5 days,¹ are unpredictable, and often occur with no known precipitating factor.⁷ However, attacks can be induced by stress, medical and dental procedures, and hormonal changes.⁸ Untreated patients average 1 to 2 attacks per month.³ The frequent need for medical

intervention can be costly, and interruptions to everyday activities, especially work, can lead to high indirect costs.^{9–11}

As with other diseases characterized by acute attacks, such as asthma, the burden of HAE is not limited to the costs of attacks.¹² The disease requires ongoing, long-term care and often takes a toll on patients' quality of life, education, and career, all of which contribute to the economic burden.

The objective of this study was to assess the economic burden associated with both acute HAE attacks and the long-term management of the disease. This study is 1 component of a larger survey-based study assessing the comprehensive humanistic and economic burden of HAE. The results of the health-related quality-of-life (humanistic) burden will be reported separately.

METHODS

Survey and Recruitment

The survey was conducted from November 2007 to January 2008. The US Hereditary Angioedema Association (HAEA) recruited participants from its database of patients who had contacted the HAEA, identified themselves as HAE patients, and requested information or HAEA membership. Patients were e-mailed an initial invitation and 1 reminder to complete a voluntary, cross-sectional, one-time, Web-based survey. Eligible participants were at least 18 years old (19 years old in Alabama and Nebraska), had a diagnosis of HAE, and were able to participate in a Web-based survey in English. The survey, consent form, and recruitment method were approved

Affiliations: * Massachusetts General Hospital Institute of Health Professions, Boston, Massachusetts; † Johannes Gutenberg University, Mainz, Germany; ‡ Dyax Corp, Cambridge, Massachusetts; and § United BioSource Corporation, Center for Health Outcomes Research, Bethesda, Maryland.

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by the Essex Institutional Review Board Inc (Lebanon, New Jersey). All participants provided electronic informed consent before completing the survey; responses were completely anonymous.

Patients were asked about their most recent attack, including severity, affected body sites, and duration; medical resources used; indirect costs associated with travel and child-care; and amount of missed work. Patients were also asked about average attack severity, medical resources regularly used during the prior 12 months, and average annual attack frequency.

The survey included demographic questions; questions about the impact of HAE on careers and working life; and the Work Productivity and Activity Impairment–General Health (WPAI-GH) questionnaire—a standard 6-question instrument assessing work and activity impairment due to health problems during the previous 7 days.¹³ The WPAI-GH outcomes are expressed as impairment percentages; higher numbers indicate greater impairment and less productivity. The percentage of impairment while working is included in the cost analysis. There is no disease-specific instrument available for HAE; the WPAI-GH responses may also reflect lost productivity due to general or non-HAE-related health issues. To account for this possibility, before assigning costs, the percentages of impairment while working were reduced by 25%, which is just above the greatest variability noted in the measures of impairment while working across 10 conditions and 6 instruments in an extensive WPAI validity and reproducibility study.¹⁴

Assigning Direct Medical Costs

Standard unit costs from 2007^{15–17} were assigned to the medical resources that patients reported using. Annual direct medical costs for treating attacks were calculated from the resources used for patient's most recent attacks, multiplied by the patient's average annual attack frequency, and averaged for the entire population. Patients who received only experimental treatment during the attack were excluded from this cost analysis.

Costs for long-term care were calculated from the resources used outside acute attacks during the prior year and the reported frequency of the resource use. Costs were averaged for the entire survey population.

Assigning Indirect Costs

Indirect costs associated with acute attacks included missed workdays and patient-reported out-of-pocket expenses for travel and childcare. The cost of a missed workday was derived from the 2007 average daily US wage.^{9,18} These costs were multiplied by patient's reported annual attack frequency and averaged for the entire population.

Long-term indirect costs included reduced productivity and reduced income due to an inability to work full-time. The cost of reduced productivity was assessed by multiplying the adjusted WPAI-GH outcome of impairment while working by the average annual wage for all workers. An inability to

work full time was assigned the cost of average 2007 wages: either full-time wages or the difference between full- and part-time wages.^{9,18} These income-related costs were evaluated for working respondents and averaged for the entire survey population.

Analysis by Attack Severity

All cost analyses were stratified by the severity of the patient's most recent attack. Although work-impairment costs, based on a 1-week recall period, and long-term medical costs, based on a 1-year recall period, could be stratified by either most recent attack severity or patient-reported average severity, most recent attack severity is likely more reliable because it is an assessment of a single event.

Patients rated the severity of their attack as follows: mild, "noticeable symptoms but does not impact activities of daily living (eg, hand is swollen but you can still hold a pencil or grip a utensil)"; moderate, "intervention is highly desirable for symptoms; activities of daily living are affected (eg, hands are swollen and you cannot button your shirt, or your feet are swollen and wearing shoes is uncomfortable)"; or severe, "treatment or intervention required; unable to perform activities of daily living (eg, your throat is swollen and you are having difficulty breathing, or your lips are swollen and you cannot eat)."

Statistical Analyses

All available survey data from patients who met the inclusion criteria were used for the analysis; no data were imputed. If patients were missing data for any analysis, they were excluded from that analysis. Descriptive statistics were used to characterize sociodemographic and clinical characteristics and disease experience.

RESULTS

Sociodemographics and HAE Attack Characteristics

Approximately 2,400 HAE patients were invited to participate in the study; 457 (19.0%) responded and met the inclusion criteria. Most were female (75.5%) and white (92.1%). A total of 67.4% were employed full or part time, 7.7% were homemakers, 2.6% were unemployed, and 9.0% were disabled. The highest level of education completed was postgraduate for 19.0%, college for 40.5%, and secondary or high school for 35.0%. The reported median annual income in US dollars was \$40,000 (e-Table 1).

Patients experienced a mean of 26.9 HAE attacks per year; 94% had at least 1 attack in the previous 12 months. More than half reported abdominal symptoms for their most recent attacks (56.5%); 24.5% reported laryngeal symptoms (Table 1).

Medical Resource Use for Acute Attacks

Table 1 presents medications and medical resources used during acute attacks. For their most recent attack, 317 patients (69.4%) sought no immediate medical attention, 73 (16.0%) went to an emergency department, and 43 (58.9%) were subsequently admitted to the hospital, staying 0.0 to 14.0 days. Twelve patients (2.6%) underwent intubation for their

Table 1. Hereditary Angioedema (HAE) Attack Characteristics and Treatments Received During Acute Attack

Characteristics and treatments	No. (%) of HAE patients (N = 457) ^a
No. of attacks per year, mean (SD)	26.9 (43.1)
Duration of a typical HAE attack, mean (range), h	61.3 (1.0–360)
Median length of time since most recent attack, d	12.0
Severity of most recent attack	
Mild	121 (26.5)
Moderate	212 (46.4)
Severe	124 (27.1)
Body sites affected during most recent attack ^b	
Internal head or neck (laryngeal)	112 (24.5)
Stomach or gastrointestinal (abdominal)	258 (56.5)
Genitals or buttocks (peripheral)	73 (16.0)
External head or neck (peripheral)	70 (15.3)
Cutaneous (peripheral)	197 (43.1)
Treatment facility visited during most recent attack ^c	
Physician's office or clinic only	29 (6.3)
Hospital emergency department only	57 (12.5)
Both physician's office or clinic and hospital emergency department	16 (3.5)
None	317 (69.4)
Treatment received	
Experimental treatment	47 (10.3)
Intubation	12 (2.6)
Magnetic resonance imaging	10 (2.2)
Ultrasonography	9 (2.0)
X-ray examination	22 (4.8)
Endoscopy	4 (0.9)
Abdominal surgery	1 (0.2)
Blood work	46 (10.1)
Other	32 (7.0)
Medications received	
Amino caproic acid (AMICAR)	8 (1.8)
Androgen therapy (steroid)	166 (36.3)
Antihistamines	90 (19.7)
Antinausea or antiemetic medication	67 (14.7)
C1 esterase inhibitors	26 (5.7)
Corticosteroids	27 (5.9)
Epinephrine or adrenaline	29 (6.3)
Histamine ₂ blocker	15 (3.3)
Fresh frozen plasma	17 (3.7)
Intravenous fluid (unspecified)	36 (7.9)
Pain relievers or narcotics	144 (31.5)
Tranexamic acid (Cyklokapron)	2 (0.4)
Other	51 (11.2)
None	76 (16.6)

^a Data are presented as number (percentage) of patients unless otherwise indicated.

^b Patients could experience symptoms at more than 1 body site.

^c Patients visiting treatment facilities for their most recent attack include patients who received nonexperimental treatments (whether or not they also received experimental treatment). Thirty-eight patients (8.3%) received only experimental treatment for their most recent attack.

most recent attack. Forty-seven patients (10.3%) received experimental treatment for their most recent attack, 9 of whom received additional nonexperimental treatments. The 38 patients who received only experimental treatment are not included in the acute attack costs.

Medical Resource Use for Long-term Care

For long-term management of HAE, approximately half (50.8%) of the patients reported that they typically see allergists/immunologists for medical treatment. Approximately a quarter (26.3%) typically see a general family practitioner, internist, or primary care physician, whereas 10.5% see an emergency medical physician (e-Table 2). Most respondents (68.3%) reported taking medications on a regular basis during the prior year (Table 2).

Direct Medical Costs

The average direct per-patient medical costs total \$25,884 annually, with medical treatment of acute attacks (\$21,339) accounting for 82.4% (Table 3). Long-term costs—routine care outside acute attacks—account for \$4,545 annually. The largest component (67.0%) of all direct medical costs is hospital stays for acute attacks, followed by emergency department visits during acute attacks (10.1%) and routine care visits (9.8%).

Indirect Costs

Table 4 presents indirect costs. Survey respondents reported that HAE significantly affected work. A total of 50.6% of patients who identified themselves as employed full or part time missed at least 1 day of work due to their most recent attack (Table 5). For employed HAE patients, the average cost of lost wages for missed work due to a single attack totals approximately \$525. When annualized by mean attack frequency and calculated for the entire survey population (ie, not just workers), the average cost of missed work due to acute attacks amounts to approximately \$3,402 annually.

As measured by the WPAI-GH, among working respondents, the mean impairment while working was 33.5%. Adjusted to account for HAE-specific impairment and distributed over the survey population, the average cost of

Table 2. Medications Taken During the Last 12 Months for Long-term Management of Hereditary Angioedema (HAE)

Medications	No. (%) of HAE patients (N = 457)
Any medication on a regular basis	312 (68.3)
Amino caproic acid (AMICAR)	10 (2.2)
Androgen therapy (steroids)	226 (49.5)
Antinausea or antiemetic medication	61 (13.3)
C1 esterase inhibitors	65 (14.2)
Fresh frozen plasma	16 (3.5)
Intravenous fluid (unspecified)	32 (7.0)
Pain relievers or narcotics	106 (23.2)
Tranexamic acid (Cyklokapron)	2 (0.4)
Other	48 (10.5)

impairment while working amounts to \$5,750 per patient per year.

In addition to the costs for missed work and impairment while working associated with acute attacks, there is a long-term cost associated with being unable to maintain full-time employment. A total of 75 patients (16.4%) were unable to work full time as a direct result of HAE (23 were working part time and 52 were unemployed, homemakers, or disabled). The annual per-patient cost of lost wages for working less than full time is \$39,683 for these 75 patients. Averaged for the entire survey population, the cost is \$6,512.

Relatively small proportions of all indirect costs were associated with travel and childcare during acute attacks. The largest proportion (40.4%) of indirect costs for the average HAE patient is the cost of being unable to work full time; 35.7% is the cost of reduced productivity while working.

Table 3. Annual Direct Medical Costs

Medical resource	No. of patients ^a	Mean per-patient cost, \$ ^b	Total direct costs, % ^c
Total direct medical costs		25,884	
Direct medical costs of acute attacks (n = 419) ^d			
Total	298	21,339	82.4
Emergency department visit	73	2,603	10.1
Clinic or physician's office treatment	29	189	0.7
Hospital stay	43	17,335	67.0
Treatment costs ^e	59	978	3.8
Medication costs	284	235	0.9
Direct medical costs for chronic disease management (treatment outside acute attacks) (n = 457) ^f			
Total	329	4,545	17.6
Routine visit costs	230	2,532	9.8
Medication costs	282	2,013	7.8

^a Number of patients reporting use of the listed resource.

^b Total annual cost of the resource listed in US dollars.

^c Percentage of the total direct medical costs. Percentages do not add up to 100 because of rounding.

^d Analysis excludes patients who received only experimental treatment during most recent attack. A total of 47 patients received experimental treatment, 9 of whom received additional treatment.

^e Treatment costs include costs for procedures or tests, including intubation, magnetic resonance imaging, ultrasonography, x-ray examination, endoscopy, blood work, and abdominal surgery.

^f Analysis based on the entire survey population, including those who received only experimental treatment during most recent attack.

Table 4. Annual Indirect Costs

Source of indirect cost	No. of patients ^a	Mean per-patient cost, \$ ^b	Total indirect costs, % ^c
Total indirect costs		16,108	
Indirect costs associated with acute attacks (n = 419) ^d			
Travel costs ^e	42	372	2.3
Childcare costs	15	71	0.4
Cost of missed work	162	3,402	21.1
Indirect costs associated with chronic disease (n = 457) ^f			
Reduced productivity while working	285 ^g	5,750	35.7
Reduced income because working less than full time	75	6,512	40.4

^a Number of patients reporting use of the listed resource, unless otherwise noted.

^b Total annual cost listed in US dollars.

^c Percentage of the total indirect costs. Percentages do not add up to 100 because of rounding.

^d Analysis excludes patients who received only experimental treatment during most recent attack.

^e Travel costs include out-of-pocket expenses, such as bus fare, taxi, parking, and hotel.

^f Analysis based on the entire survey population, including those who received only experimental treatment during most recent attack.

^g Number of patients who responded to the productivity while working question on the Work Productivity and Activity Impairment questionnaire (only includes patients who worked during the week before the survey).

Effect of Attack Severity on Costs

Total annual costs increased from \$14,379 for mild attacks to \$26,914 for moderate and \$96,460 for severe attacks. The cost increases are driven primarily by emergency department and hospital costs. For moderate attacks, emergency department and hospital costs total \$5,041 annually—almost 10 times the costs for mild attacks; for severe attacks they total \$65,482—more than 100 times that for mild attacks (e-Table 3).

The distribution of costs differs substantially by most recent attack severity. Costs by expense type, with short-term and long-term costs combined, are depicted in Figure 1. For patients with mild attacks, the indirect costs are the largest component of the total costs (74.5%), and emergency department and hospital stays (4.0%) are the smallest. For patients with moderate attacks, the indirect costs are also the largest component (63.5%) and medications (4.6%) the smallest. For patients with severe attacks, the largest cost component is emergency department and hospital stays (67.9%), followed by indirect costs (20.8%), clinical care (6.4%), and medications (4.9%).

Table 5. Missed Days Due to Most Recent Hereditary Angioedema Attack

	No. of patients ^a	Patients reporting missed days, No. (%)	No. of workdays missed	
			Mean (SD)	Range
Overall	308	156 (50.6)	3.3 (14.4)	0.5–180.0
Mild attack	91	18 (19.8)	2.2 (3.3)	1.0–15.0
Moderate attack	139	77 (55.4)	1.8 (1.0)	0.5–5.0
Severe attack	78	61 (78.2)	5.5 (22.9)	1.0–180.0

^a Number of respondents who identified themselves primarily as full- or part-time workers.

DISCUSSION

This study provides the first comprehensive examination of the economic burden of HAE; the burden is assessed in terms of direct medical costs, borne by patients and payers, and indirect costs, borne by patients and society. HAE patients experience multiple burdens due to the unpredictable but recurring, debilitating, and potentially life-threatening attacks of edema.^{7,9,19} This study shows the substantial economic costs associated with both acute attacks and the ongoing chronic nature of the disease. Although the distribution of costs varies considerably with changes in acute attack severity, almost all costs increase with disease severity.

Given the dearth of standardized measures and instruments, there is great variation in cost studies. Two studies involving direct and indirect costs provide benchmarks for the comprehensive economic burden of a chronic disease. A comprehensive study of asthma reported total per-patient costs in 1998 dollars of \$4,912 annually (approximately \$6,200 in 2007 dollars); for severe asthma, these costs total \$12,813 annually (approximately \$16,300 in 2007 dollars).¹² A US prevalence-based economic study of diabetes in 2007

reported a total estimated cost of \$174 billion, including \$58 billion in reduced productivity, with an average per-patient medical cost of \$6,649 per year.²⁰

Although no economic burden-of-illness studies for orphan diseases appear to be published, a review of the clinical and cost effectiveness of enzyme replacement therapy (Ceredase) for Gaucher disease type 1 (prevalence of 1 per 40,000 to 1 per 60,000) reported an annual cost of £85,501 (approximately \$168,000 in 2007 US dollars) for treatment.²¹

Combining indirect and direct costs, the total annual cost for an average HAE patient is approximately \$42,000. Costs increase considerably with increasing attack severity; the annual cost of \$96,000 for patients with severe attacks more than triples the costs for patients with moderate attacks, which are in turn almost twice as much as for those with mild attacks.

The largest cost component, accounting for approximately 48% of total costs for the average HAE patient, is that of emergency department visits and hospital stays for treating acute attacks. Although hospital costs are relatively low for treating mild attacks, they increase with increasing attack

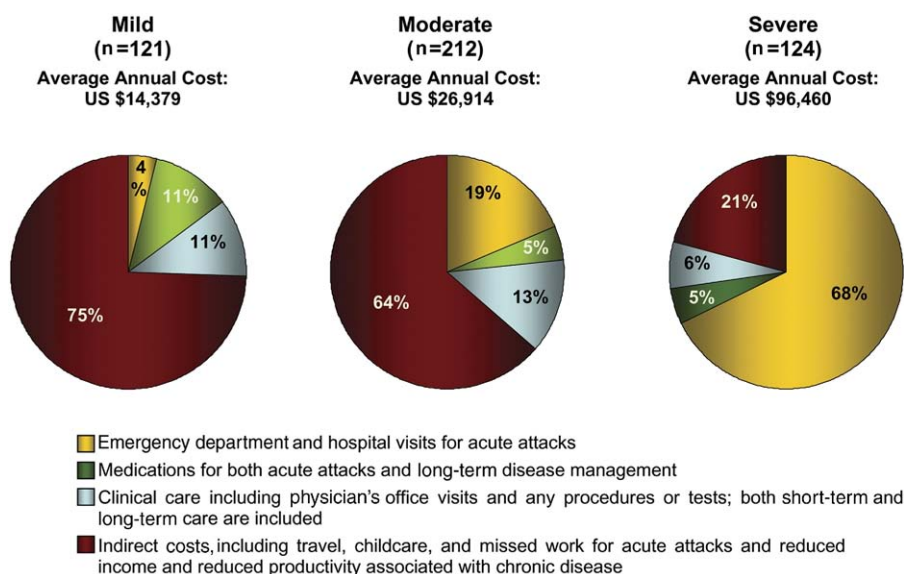


Figure 1. Resource use by most recent hereditary angioedema attack severity. Mean annual costs were calculated in US dollars. The percentage of total costs for emergency department visits and hospital stays, medications, clinical care, and indirect costs are depicted for mild, moderate, and severe attacks. Percentages do not add up to 100% due to rounding.

severity. For severe attacks, emergency department visits and hospital stays account for 68% of all costs.

The medical resources that patients in this study reported using may not fully reflect the actual need for treatment for acute attacks. Although most respondents reported that their most recent attack was moderate or severe, 69% did not seek immediate medical assistance for the most recent attack. This is likely explained by the frequent misdiagnosis and limited treatment options for acute attacks.

Compounding the direct medical costs associated with HAE, patients reported significant decreases in productivity, lost work days, and, in many cases, an inability to work full-time. The costs associated with these reductions in work and productivity are substantial and increase with disease severity.

Patient income and education data have not been previously published within the HAE literature. In this study, the reported income and education levels are higher than national norms.^{18,22} It is unlikely that these higher levels are representative of the overall HAE patient population because the Web-based survey may be biased in terms of income and education. Participants likely had sufficient health care access to have a diagnosis for this rare disease, were knowledgeable enough about HAE to contact the HAEA, and had sufficient Internet access and familiarity to respond to the survey. As determined by the survey, the patients in this study, despite their education and income levels, still bear substantial opportunity costs of hindered progress in school and career. The higher-than-average income levels did not inflate costs in this study because national norms were used for all wage-based cost analyses.

This study was a one-time cross-sectional survey designed to provide the first comprehensive account of the economic burden of HAE. The economic costs are based on patient-reported information related to acute attacks, disease characteristics, and resource use; the reliability of the data is dependent on patient recall. Whereas the recall periods for acute attack data varied from patient to patient, depending on time since most recent attack (median, 12.0 days), the recall periods for other measures ranged from a week to a year, depending on the instruments and specific questions.

All costs were stratified by the patient's most recent attack severity. Overall, the severity of patients' most recent attack was similar to the mean attack severity (27.1% vs 28.4% reported severe attacks). However, more patients reported mild severity (26.5%) for their most recent attack compared with for their average attack (15.5%), indicating that the choice to analyze by recent attack severity was the more conservative approach for examining the increase in cost with increase in severity.

Several other elements contribute to the variability in the cost estimates. Work impairment due to HAE was assessed with a general health instrument; however, the analysis of cost of work impairment accounted for the possibility of comorbidities and general health conditions.

Costs of improper procedures and medications were not included but could also alter the total costs associated with HAE. Patients' open responses indicated that improper treatments are not uncommon. Given the challenge of diagnosing HAE, reflected in the range of time between first symptom and confirmed diagnosis (as determined by this survey: up to 53 years; median, 4.0 years), HAE patients are particularly prone to improper or unnecessary treatments.

The cost of C1 esterase inhibitor replacement therapy could also alter the total costs for short-term and long-term care; this survey was conducted before the approval of C1 esterase inhibitor therapy in the United States.

The cost of managing depression is not reflected in this study and could represent an increase in actual direct medical costs for long-term management. As determined by this survey, 42.5% of HAE patients reported a Hamilton Depression Inventory–Short Form score greater than 8.5, indicative of at least mild depressive symptoms; a total of 19.5% of the HAE patients reported that they were taking psychotropic or antidepressant medication. Reported annual per-patient costs for treating depression in the United States range from \$2,471 for subclinical depression to \$7,659 for depressive disorder, in 2003 dollars (\$2,780 to \$8,630 in 2007 dollars).²³ Other comorbid conditions, which may affect resource use and work impairment, were not directly assessed in the study.

Finally, some humanistic burdens are not easily monetized but have a tangible financial impact. The financial consequences attributable to the impact on regular activities, such as work around the house, shopping, exercising, and studying, were not included in the calculations of economic burden of HAE. In addition, indirect costs related to nonpaid caregivers (eg, family members) were not assessed in this survey. As such, the indirect costs may be underestimated.

In conclusion, given that HAE is a rare disease, at the population level, the costs of this disease are relatively small. However, at the patient level, HAE confers a significant cost to the health care system and a substantial economic burden to HAE patients and families. Acute HAE attacks result in substantial direct medical costs and significant indirect costs associated with missed work and lowered productivity. Furthermore, the unpredictability of acute attacks results in a significant long-term burden in the form of increased depression, reduced income potential, and missed opportunities. There is a great unmet need for alternative therapies to manage acute HAE attacks to reduce the overall burden of this disease.

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SUPPLEMENTARY DATA

Additional photos and tables accompany the on-line version of this article (available at <http://www.annallergy.org>).

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Requests for reprints should be addressed to:
David A. Wilson, MA
MGH Institute of Health Professions
36 First Ave
Charlestown, MA 02129
E-mail: dwilson@mghihp.edu

e-Table 1. Sociodemographics of the Patients With Hereditary Angioedema (HAE)

Sociodemographics	No. (%) of HAE patients (N = 457) ^a
Age, mean (SD), y	41.4 (13.3)
Sex	
Female	345 (75.5)
Male	112 (24.5)
Ethnicity	
Hispanic or Latino	29 (6.3)
White	421 (92.1)
Black or African American	11 (2.4)
Asian	8 (1.8)
Other	17 (3.7)
Employment	
Employed, full time	255 (55.8)
Employed, part time	53 (11.6)
Homemaker	35 (7.7)
Student	27 (5.9)
Unemployed	12 (2.6)
Retired	27 (5.9)
Disabled	41 (9.0)
Other	7 (1.5)
Income (median; mean), \$ ^b	40,000; 50,350
Education	
Elementary or primary school	4 (0.9)
Secondary or high school	160 (35.0)
College degree	185 (40.5)
Postgraduate degree	87 (19.0)
Other	21 (4.6)

^a Data are presented as number (percentage) of patients unless otherwise indicated.

^b Annual income in US dollars. Number of respondents to this question was 341.

e-Table 2. Type of Medical Professional Typically Seen for Long-term Care of Hereditary Angioedema (HAE)

Medical professional	No. (%) of HAE patients (N = 457)
General family practitioner, internal medicine physician, or primary care physician	120 (26.3)
Pediatrician (general, nonspecialist)	4 (0.9)
Allergist/immunologist	232 (50.8)
Emergency medical physician	48 (10.5)
Ear, nose, and throat specialist	2 (0.4)
Gastroenterologist	6 (1.3)
Hematologist	5 (1.1)
Dermatologist	2 (0.4)
Obstetrician/gynecologist	4 (0.9)
Other	17 (3.7)
Not sure	18 (3.9)

e-Table 3. Costs by Hereditary Angioedema Attack Severity^a

Costs	Overall population	Severity of most recent attack		
		Mild	Moderate	Severe
Total costs	41,992	14,379	26,914	96,460
Direct medical costs for acute attacks				
No. of patients ^b	419	118	189	112
Clinical care ^c	1,166	427	469	3,220
Emergency department visits and hospital stays	19,938	570	5,041	65,482
Medications	235	44	254	404
Direct medical costs for long-term care				
No. of patients	457	121	212	124
Routine visits	2,532	1,133	3,069	2,981
Medications	2,013	1,487	980	4,292
Indirect costs associated with acute attacks				
No. of patients ^b	419	118	189	112
Childcare and travel ^d	444	19	97	1,549
Missed work	3,402	940	3,987	5,109
Indirect costs associated with chronic disease				
No. of patients	457	121	212	124
Reduced income and reduced productivity ^e	12,263	9,759	13,018	13,424

^a Data are presented as costs in US dollars, except for number of patients.

^b Analysis excludes patients who received only experimental treatment during most recent attack.

^c Clinical care for acute attacks includes clinic or physician's office visit and treatment, including procedures or tests (ie, intubation, magnetic resonance imaging, ultrasonography, x-ray examination, endoscopy, blood work, and abdominal surgery).

^d Patient-reported out-of-pocket costs for childcare and travel, including bus fare, taxi, parking, and hotel.

^e Combined costs of reduced income because working less than full time and reduced productivity while working.