



Review

The burden of illness in patients with hereditary angioedema

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ARTICLE INFO

Article history:

Received for publication June 18, 2013.
Received in revised form August 2, 2013.
Accepted for publication August 22, 2013.

ABSTRACT

Objective: Hereditary angioedema (HAE) is a rare genetic disease characterized by long-term recurrent attacks of subcutaneous or submucosal edema in different parts of the body. A comprehensive review of the literature on burden of illness for patients with HAE is presented.

Data Sources: A Boolean search was performed using MEDLINE and EMBASE databases and the Internet.

Study Selection: Articles discussing aspects of the burden of illness in HAE were selected. Topics focused on the course of the disease, nature of attacks, treatment, quality of life, and costs.

Results: Hereditary angioedema is associated with a significant and multifaceted disease burden. Diagnosis is often delayed for years, with patients receiving ineffective treatment and unnecessary medical procedures before diagnosis. HAE attacks are painful, unpredictable, and debilitating and often require emergency medical attention. Attacks can affect a patient's daily activities, including work or schooling. Depression and anxiety are prevalent in patients with HAE. Recent advances in treatment provide patients with effective and well-tolerated prophylactic and on-demand therapeutic options. However, end points specific to HAE that better measure the impact of treatment on disease burden are lacking. Furthermore, there is a notable paucity of literature directed toward physicians who are instrumental in diagnosing and treating patients with HAE (eg, emergency department).

Conclusion: More publications are broadening the understanding of HAE. However, important gaps remain. Effective management of HAE requires a more comprehensive understanding of the disease burden so that disease management can be individualized to meet specific patient needs.

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Introduction

Hereditary angioedema (HAE) is a rare autosomal dominant disease characterized by recurrent attacks of subcutaneous or submucosal edema that can affect the face, respiratory tract, extremities, gastrointestinal (GI) tract, genitalia, or other areas of the body. HAE involves all ethnic groups equally, but its global prevalence is not well defined, with estimates ranging from 1 in 10,000 to 1 in 100,000.^{1–4} There are thought to be approximately 6,000 patients living with HAE in the United States.⁵

Three types of HAE have been defined based on levels and activity of plasma complement-1 esterase inhibitor (C1INH). Type I HAE, the most prevalent form (85%), is characterized by the lack of plasma C1INH.⁶ In type II (15%), C1INH is secreted into the plasma but is nonfunctional. These 2 types are caused by mutations in the *SERPINE1* gene, which codes for C1INH. Although autosomally dominant, de novo mutations are thought to occur in approximately 25% of cases.⁷

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Disclosures: Dr. Banerji has served on the advisory board and received clinical research funding from Dyax, Shire, CSL, and Virpharma.

Disclaimer: All opinions expressed in this manuscript are those of the author.

The third and rarest type, HAE with normal C1INH (previously referred to as type III HAE), remains poorly understood.^{8–11} Although attacks are similar to those of types I and II, it is characterized by normal plasma levels of functional C1INH. Symptoms frequently emerge or are worsened by estrogen therapy, and mutations in factor XII are believed to play a role in 20% to 30% of patients.⁸ Although the incidence does not differ between men and women for types I and II, HAE with normal C1INH predominantly affects women.⁸

Symptoms of types I and II usually present during childhood, with approximately 50% of patients presenting by 10 years of age and nearly all by 20 years of age,^{12–14} but diagnosis is often delayed by approximately 8 years on average.^{2,15,16} Patients with HAE with normal C1INH present at a slightly older age compared with those with types I and II. Attacks in all types of HAE are often unpredictable, painful, and potentially life threatening and significantly affect a patient's quality of life (QOL).^{17–19} Depression and anxiety are prevalent.¹⁹

In the past, treatments for HAE in the United States were lacking or associated with significant side effects. Since 2008, some effective and well-tolerated prophylactic and on-demand treatments have become available in the United States, including plasma-derived C1INH concentrates (Cinryze, ViroPharma Inc, Exton, Pennsylvania; Berinert, CSL Behring LLC, Kankakee, Illinois), a recombinant plasma

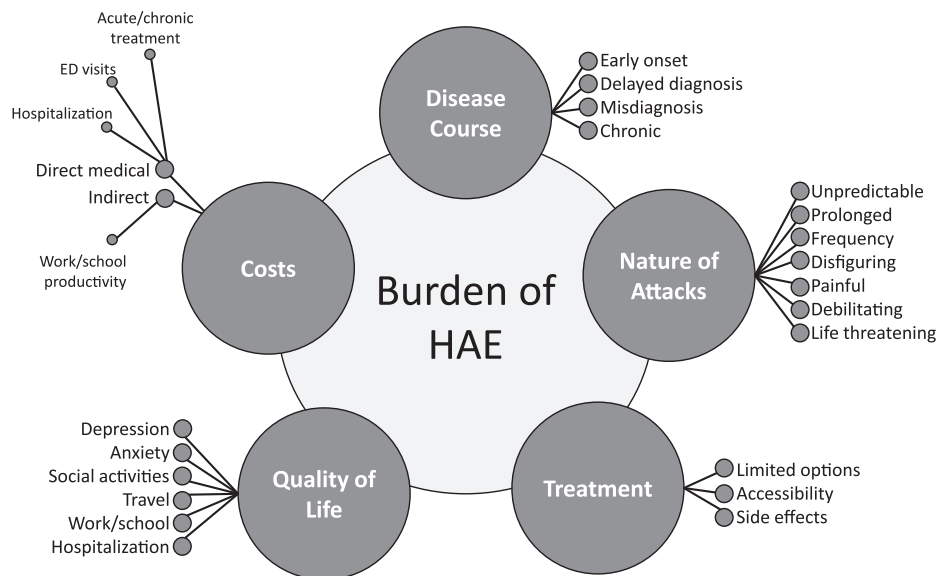


Figure 1. Complex burden of illness in patients with hereditary angioedema (HAE). ED, emergency department.

kallikrein inhibitor, ecallantide (Kalbitor, Dyax Corp, Burlington, Massachusetts), and a small-molecule selective bradykinin B2 receptor antagonist, icatibant (Firazyr, Shire Orphan Technologies, Lexington, Massachusetts). However, these treatments can be expensive, and their availability may be limited at some medical facilities.^{20,21}

Because of the rarity of HAE, it has been difficult to systematically assess its humanistic and economic burden to better understand the challenges facing patients, caregivers, and health care systems, to identify knowledge gaps, and to improve disease management. Recently, some retrospective and prospective studies and patient and physician surveys have begun to establish a portrait of its multifaceted burden of illness (Fig 1). The present report presents a comprehensive review of the burden of illness of HAE with respect to its diagnosis, symptoms, treatment, QOL, and costs.

Literature Search Methods

A Boolean search was constructed to find articles on the burden of HAE listed on MEDLINE and EMBASE. Search terms included HAE (with thesaurus terms) cross-referenced with searches on topics of interest, including patient-reported outcomes, QOL, disability, productivity, depression, questionnaires, surveys, hospitalizations, and economics. Nonhuman and non-English-language publications were excluded, as were conference and meeting abstracts. Relevant publications were selected and supplemental searches of article bibliographies were performed (Table 1).^{2,5,12,15,19,22–27}

Burden of Disease

Diagnosis

Hereditary angioedema is under-recognized and frequently misdiagnosed, resulting in significant morbidity and mortality. Episodes of swelling involving the skin are frequently mistaken as allergic reactions and abdominal attacks as appendicitis or irritable bowel syndrome. Misdiagnosis can lead to unnecessary treatments and surgical procedures (eg, appendectomy) and premature death.^{15,28} Some patients are misdiagnosed with psychosomatic symptoms and referred for psychiatric evaluation.⁴ In a cohort of 728 patients with HAE from a single German center, 70 died of asphyxiation from a laryngeal attack, with 63 of these deaths in

undiagnosed patients (retrospectively assigned based on family history).²⁸

For patients with type I and II HAE and a familial history of HAE, diagnosis is relatively straightforward by testing serum C1INH levels and C1INH function with the chromogenic assay.^{29,30} Diagnosis is more difficult for patients with de novo mutations or for patients who lack a familial history of angioedema.³¹ Testing serum C4 levels is an excellent screening tool for types I and II because it is a relatively uncomplicated and inexpensive assay. Diagnosing HAE with normal C1INH is more complex because C4 levels and C1INH levels and function are normal; thus, diagnosis is based on clinical symptoms, diagnostics findings, family history of angioedema, lack of response to high-dose antihistamines, and genetic testing (eg, factor XII mutations are present in 20% to 30% of cases).⁸

In an international survey of patients with HAE (N = 313), Lunn et al¹⁵ found that only 48% of immediate and 26% of extended family members were tested for HAE, 65% of patients reported having received a misdiagnosis, and 19% in the United States (24% in Europe) underwent unnecessary surgical procedures. Furthermore, 43% of patients reported waiting longer than 1 year after their first attack before seeking medical attention. On average, patients visited approximately 4 physicians over approximately 8 years before receiving an HAE diagnosis.

Symptoms

Hereditary angioedema attacks are usually unpredictable, with varying intervals between attacks.^{32,33} Episodes can be triggered by physical trauma, medical procedures (eg, surgery), infection, emotional stress, and medications (eg, angiotensin-converting enzyme inhibitors and estrogen therapy), but triggers often are not identifiable.^{4,17,34,35} If untreated, patients average approximately 1 attack every 1 to 2 weeks, with episodes lasting 2 to 5 days, but the frequency, duration, and severity are variable.^{3,17,19,22,36} Pregnancy might aggravate or precipitate attacks in some women but alleviate symptoms in others.³⁷ Adults and adolescents generally have more frequent attacks than prepubertal children,³⁸ and women tend to be more symptomatic than men and thus more readily diagnosed, but attack duration is similar between the sexes.^{11,19}

The most common attack sites are the skin and GI tract, but more than half of patients will experience at least 1 laryngeal attack

Table 1Key articles on the burden of illness in patients with HAE^a

Reference	Study summary	Relevance to burden of illness ^b
Bygum, ² 2009	Survey of patients with HAE (N = 82) registered in the national HAE comprehensive care center in Denmark	Diagnosis, symptoms
Zilberberg et al, ⁵ 2011	Retrospective analysis to examine burden, epidemiology, and outcomes of HAE; hospitalizations (n = 10,125) captured in the NIS database (2004–2007)	Hospitalization, economics
Zilberberg et al, ²⁷ 2010	Retrospective analysis of HAE hospitalizations (n = 1,691) and ED visits (n = 2,282) captured in the NIS and NEDS databases	Hospitalization, economics
Bork et al, ¹² 2006	Retrospective analysis of patients with HAE (N = 209) registered at a single center in Germany to assess disease course and frequency of attacks at various skin regions and organs	Symptoms
Bork et al, ²² 2006	Retrospective and prospective analysis to describe disease course of abdominal attacks in a cohort of patients with HAE (n = 153) registered at a single center in Germany	Symptoms
Lumry et al, ¹⁹ 2010	Survey of patients with HAE (n = 457) recruited through the US HAEA to characterize attacks, treatment, side effects, pain, and psychosocial burdens	Symptoms, treatment, QOL
Lunn et al, ¹⁵ 2010	US-based survey of physicians (n = 80) and international survey of patients with HAE (n = 313) to assess diagnosis and screening patterns of patients and family members	Diagnosis
Huang, ²³ 2004	US-based survey of patients with HAE (n = 63) to assess clinical status of patients, including, diagnosis, symptoms, treatment, psychosocial issues, and ED experiences	Diagnosis, symptoms, treatment, QOL, hospitalization
Bygum et al, ²⁴ 2012	Study protocol that describes a European cross-sectional study, HAE Burden of Illness Study–Europe, designed to assess management and impact of HAE on the patient	QOL, treatment, hospitalization, economic burden
Wilson et al, ²⁵ 2010	Web-based survey of patients with HAE (n = 457) recruited through the US HAEA to estimate the economic burden of disease with respect to acute attacks and long-term disease management	QOL, treatment, hospitalization, economic burden
Prior et al, ²⁶ 2012	Study protocol for development and validation of QOL questionnaire specific to patients with HAE	QOL

Abbreviations: ED, emergency department; HAE, hereditary angioedema; HAEA, Hereditary Angioedema Association; NEDS, Nationwide Emergency Department Sample; NIS, Nationwide Inpatient Sample; QOL, quality of life.

^aBased on a literature search of MEDLINE (n = 612) and EMBASE (n = 428) on October 19, 2012, and supplemental searches of article bibliographies and the Internet.

^bGeneral categories for burden of illness include diagnosis, symptoms, QOL, treatment, hospitalization, and economics.

(Table 2).^{13,22,33} The course of an attack generally follows a predictable sequence. Patients may experience prodromal symptoms (eg, erythema marginatum) before its onset.³⁹ Swelling and other symptoms gradually worsen over 12 to 36 hours, intensifying in a relentless manner, sometimes spreading to other sites, and then resolving over 2 to 5 days (Fig 2).^{3,17,22} Pain often accompanies GI attacks,^{22,40,41} as does vomiting, nausea, constipation, and diarrhea, and circulatory collapse, and loss of consciousness occurs infrequently.^{3,22} In a cohort of 153 patients with abdominal attacks, the average pain score associated with abdominal attacks was 8.4 (scale 0–10), with 69% of patients reporting a maximum pain score of 10.²²

Although not as frequent as cutaneous and GI episodes, oropharyngeal and laryngeal attacks are life threatening because of the potential for asphyxiation; thus, patients experiencing an oropharyngeal or laryngeal attack should always seek immediate medical attention even if they self-treat the attack.^{13,23,28,32,42} Rates of mortality by asphyxiation as high as 40% have been reported in some HAE patient cohorts.⁴² In the German cohort study mentioned earlier,²⁸ the average lifespan was 40.8 years (range 18–76) for the 63 patients with undiagnosed HAE who died of a laryngeal attack compared with 72.0 years (range, 25–97) for the 144 patients with undiagnosed HAE who died of other causes.

Lumry et al¹⁹ recently conducted a survey of 457 patients recruited from November 2007 through January 2008 through the US Hereditary Angioedema Association (HAEA). The most common attack sites in this cohort were abdominal (56.5%) and peripheral cutaneous (43.1%). One fourth of patients (24.5%) experienced laryngeal attacks. The number of attacks per year averaged 26.9, with a higher incidence in women than in men (mean 29.8 vs 17.9 per year), although attack duration was similar (mean 60.8 vs 62.6 hours). In terms of severity, 15.5% of patients described attacks as

mild (noticeable symptoms, no impact on activities of daily living), 56.0% as moderate (intervention desirable, activities of daily living were affected), and 28.4% as severe (intervention required, unable to perform activities of daily living).

Quality of Life

As a chronic, debilitating, and disfiguring disease, HAE can affect almost all aspects of a patient's life.^{18,19,24,25,41,43} Attacks affecting the hands and feet can impair a patient's ability to work and perform daily activities (eg, typing on a computer), and because of

Table 2Frequency and prevalence of attacks by site in a survey of 209 patients with hereditary angioedema treated at a single center in Germany¹²

	Frequency of attacks, % ^a	Prevalence of attacks, % ^b
Skin	50	100
Extremities	45.1	98 ^c
Genitals	2.1	65 ^c
Face	1.6	79 ^c
Trunk/neck	0.9	28 ^c
Gastrointestinal	48	97
Larynx	0.9	54
Brain	0.7	8
Uvula	0.6	22
Muscles	0.4	4
Bladder	0.3	5
Tongue	0.3	9
Chest	0.2	5
Kidneys	0.1	4
Joints	0.1	4
Esophagus	0.05	2

^aBased on 131,110 attacks in 209 patients over 5,736 cumulative years.

^bBased on 201 patients with recurrent attacks of the skin.

^cEstimated from relative values (%) provided for all patients in Figure 2A of Bork et al.¹²



Figure 2. Hereditary angioedema attacks can be disfiguring, debilitating, and life threatening. Depicted is a patient experiencing hereditary angioedema attacks. Source: Bygum et al.²⁴

the unpredictability of attacks, many patients refuse to travel and have anxiety. In a survey of 63 patients with HAE,²³ the 3 greatest fears were sudden airway closure (85%), intolerable pain (65%), and transmission of HAE to their children (55%). Facial attacks can be disfiguring, resulting in social stigmatization, isolation, and depression.^{19,25,44,45} It is estimated that patients with HAE lose 20 to 100 days of social activities per year.³⁶ Use of psychotropic medication is prevalent, as is the use of pain relievers and narcotics.^{19,25} Nonetheless, only a limited number of studies have assessed QOL in patients with HAE using standardized measurements,^{14,19,46} and there are currently no validated QOL questionnaires specific to HAE, although these are under development.²⁶

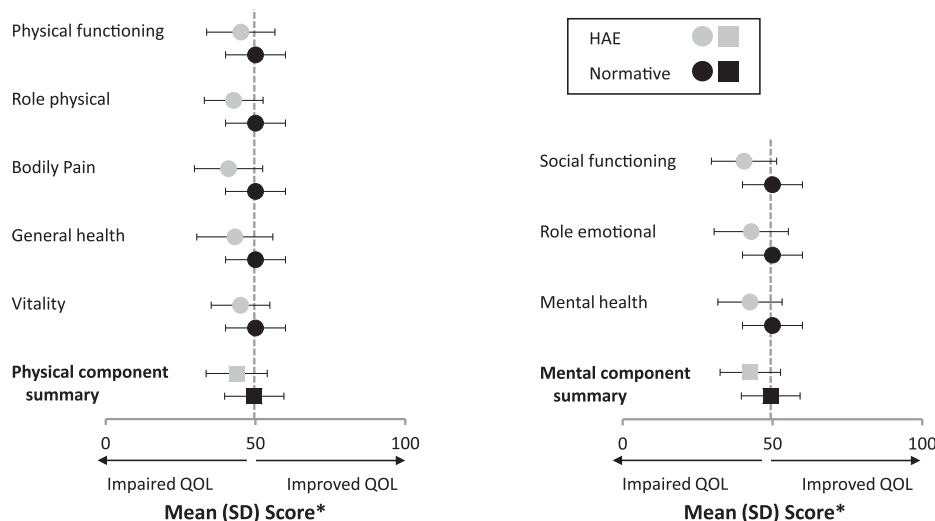
In the HAEA survey, patients consistently reported poorer health-related QOL measurements compared with a healthy control population.¹⁹ The Short-Form 12 Physical Component Summary score was lower in patients with HAE compared with a control population (mean 43.7 vs 49.6, $P < .001$), as was the Mental Component Summary score (mean 42.6 vs 49.4, $P < .001$; Fig 3). Depression was more evident in the HAE population than in the control group based on the Hamilton Depression Inventory short form (mean 8.1 vs 3.1, $P < .001$). Depression increased based on attack severity, with mean scores of 5.6 for mild attacks, 7.8 for moderate attacks, and 10.1 for severe attacks. Overall, 42.5% of patients with HAE in the survey exhibited at least mild symptoms of depression. Work impairment was reported by 34% of adult patients, with a loss of 3.3 days of work for their last attack, and

57.5% reported that HAE affected career advancement. Younger patients reported missing an average of 1.9 school days for their last attack, and 48.4% believed HAE hindered educational attainment. The impact of HAE on QOL parameters is comparable to that of other chronic diseases associated with morbidity and mortality, such as severe asthma and Crohn disease (Fig 4).¹⁹

The most common treatments reported by participants in the HAEA survey included androgen therapy (36.3%), pain relievers or narcotics (31.5%), and psychotropic or antidepressant agents (19.5%).²⁵ Participants taking androgens reported a significantly greater burden of treatment-related side effects than patients not receiving androgens ($P < .001$), a higher Hamilton Depression Inventory short form score (mean 8.7 vs 7.4, $P < .001$), and a higher score on the Work Productivity and Activity Impairment–General Health questionnaire (mean 35.4 vs 32.7, $P = .003$).¹⁹ Notably, the survey was conducted before the introduction of plasma-derived C1INH, ecallantide, and icatibant to the United States.

Treatment

Historically, acute treatment of HAE in the United States involved supportive care with narcotic analgesics, antiemetics, and fluid replacement.¹⁷ Corticosteroids, antihistamines, and epinephrine are ineffective for HAE, but are frequently administered nonetheless.²⁵ Fresh frozen plasma has been used for acute attacks and short-term prophylaxis, with some success, but there is concern



*HAE vs normative $P < .001$ for all subscales and overall physical and mental summary components

Figure 3. Hereditary angioedema (HAE) has a significant impact on the physical and psychosocial well-being of patients. Health-related Quality of Life 12-Item Short Form scores in patients with hereditary angioedema participating in a survey by the US Hereditary Angioedema Association compared with a normative population.¹⁹ QOL, quality of life.

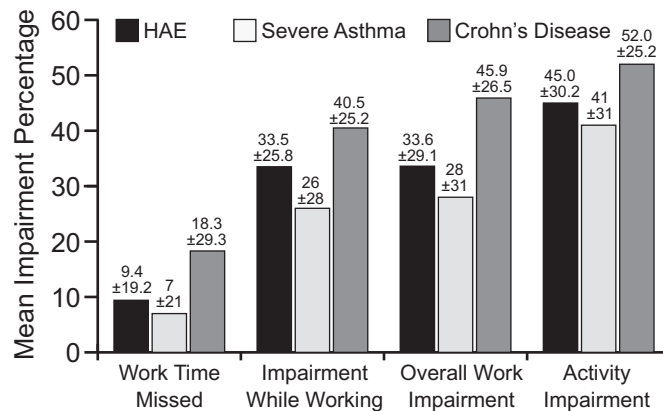


Figure 4. Hereditary angioedema (HAE) has a negative impact on the productivity of patients comparable to other chronic diseases associated with morbidity and mortality. Outcomes from the Work Productivity and Activity in Impairment–General Health questionnaire in patients participating in the Hereditary Angioedema Association survey compared with patients with severe asthma and with Crohn disease. Reproduced with permission from Lumry et al.¹⁹ <http://www.oceansidepubl.com/aap/>. No further reproduction permitted. For additional reproductions, visit www.rockwaterinc.com.

that angioedema could worsen because of the presence of contact-system proteins, which could increase bradykinin production.^{17,47,48} Ecallantide became available in the United States in 2009 and icatibant in 2011. Studies have shown the benefits and tolerability of ecallantide^{49–51} and icatibant^{52–54} as on-demand treatments to decrease the duration and severity of HAE attacks. Adverse events associated with ecallantide treatment include headache, diarrhea, pyrexia, nasal congestion, and an infrequent (3.9%) but serious risk of anaphylaxis.^{49–51} The most notable side effect with icatibant is injection site reactions.^{52–54}

In the past, attenuated androgen therapy (eg, danazol) was the only long-term prophylactic treatment available in the United States. Although androgens are effective for short- and long-term prophylaxis, administered orally, and inexpensive,^{43,55} these agents may be contraindicated for children and pregnant women and are associated with significant side effects, including weight gain, virilization, menstrual irregularities, headache, depression, hypertension, and liver adenomas.^{17,43,55,56}

Plasma-derived C1INH concentrates are very effective for acute and prophylactic treatment of HAE and have a better safety profile than androgens. The most common side effects reported with C1INH concentrates include pruritus, rash, headache, light headedness, and fever.^{45,57–61} C1INH concentrate has been available in some European countries since 1979 but was not approved in the United States until 2008 for prophylactic therapy for one product (Cinryze) and in 2009 for acute treatment for a second product (Berinert).

There have been no head-to-head trials comparing plasma-derived C1INH, ecallantide, and icatibant, and none of these treatments are approved by the Food and Drug Administration for use in children, although studies have been initiated (ClinicalTrials.gov, NCT01095510, NCT01832896, and NCT01386658). C1INH concentrates are administered intravenously, and ecallantide and icatibant are administered by subcutaneous injection. Plasma-derived C1INH and icatibant can be self-administered after proper training. Ecallantide must be administered by a health care professional who is trained to manage the risk of anaphylaxis.

The ability to self-administer these products can be of significant benefit. Early intervention during an attack can improve symptom outcomes by decreasing attack duration and severity (Fig 5)^{18,22,38,60,62–67} and may decrease dosing needs.⁶⁸ Self-administration provides patients greater autonomy, less disruption of daily activities, and may decrease the economic burden of HAE, particularly for patients who are not near health care facilities.^{38,63,64} Moreover, hospital pharmacies do not always stock these products.^{20,69}

Several factors should be considered with self-administration, including the patient's preference, route of administration, ability to identify onset of attacks, frequency of laryngeal attacks, and medical insurance coverage.³⁸ These treatments can be expensive, but this must be weighed against their potential impact on the direct costs and burden of other medical interventions, such as emergency department (ED) visits and hospitalizations, indirect costs such as loss of work productivity, and QOL.

Hospitalization

Patients with HAE will frequently require hospitalization,^{5,23,27} and there is a high rate of ED visits,²³ particularly for those who are undiagnosed or experiencing severe attacks.⁴⁰ Unfortunately, in the early-onset stage of the disease, ED visits can be accompanied by misdiagnoses and ineffective treatments. In a survey by Huang,²³ patients with HAE reported an average of 4.7 ED visits per year, with many misdiagnosed and treated for allergic reactions, including anaphylaxis (20.6%). More than 40% of patients in this survey reported having no trust in ED physicians.²³

A large cohort study by Zilberberg et al²⁷ examined hospitalization and ED usage by patients with HAE in the United States using 2 large nationally representative databases. In 2007, there were 2,282 ED visits and 1,691 hospitalizations for patients with HAE. Close to half of patients with HAE (45%) who visited the ED required

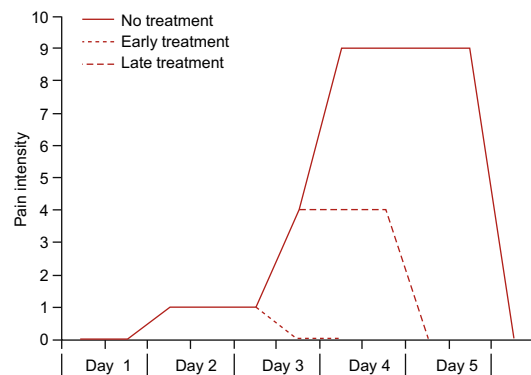


Figure 5. Early intervention may further decrease the duration and severity of hereditary angioedema attacks. Impact of early versus late treatment on symptom duration and severity in patients with hereditary angioedema.^{22,60,66} Reprinted from Longhurst H, Cicardi M. Hereditary angio-oedema. *Lancet*. 2012;379:474–481, with permission from Elsevier.¹⁸

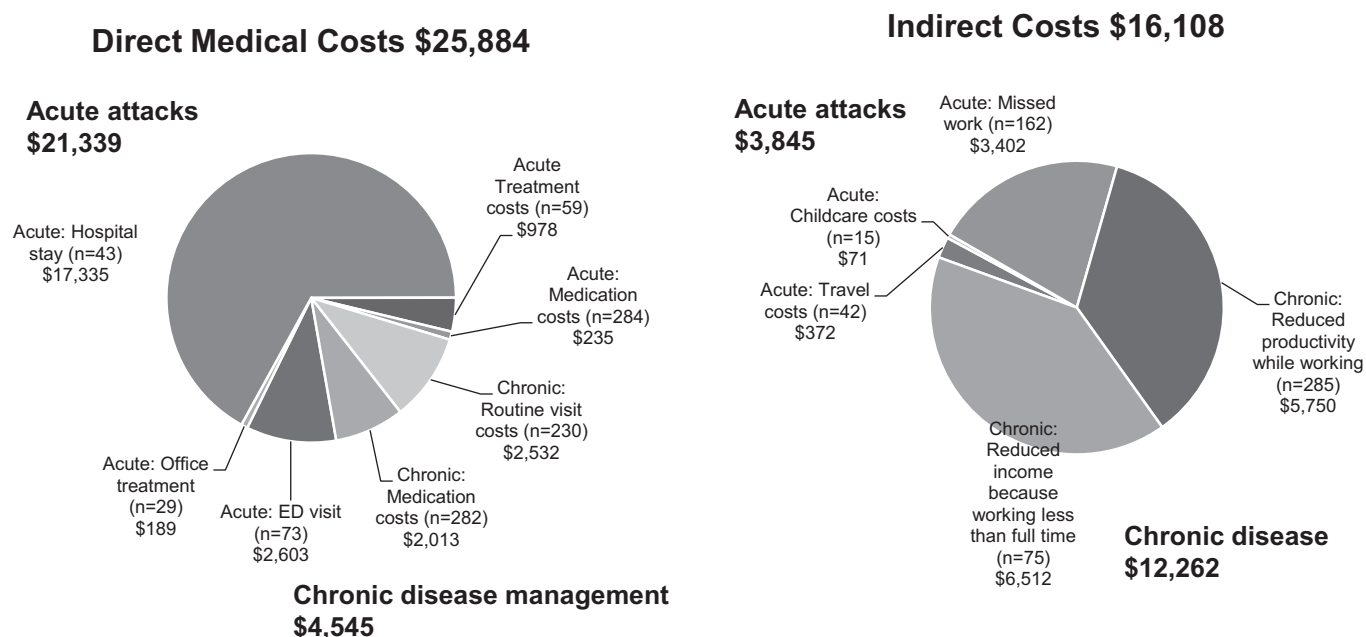


Figure 6. Patients with hereditary angioedema face significant direct medical and indirect costs associated with acute treatment of attacks and long-term disease management. Estimated direct and indirect costs of acute attacks and long-term management of hereditary angioedema in patients participating in a survey by the US Hereditary Angioedema Association.²⁵

hospitalization for a median of 2 days.²⁷ As a comparison, the rate of hospitalization was 18% in a cohort of patients with angioedema. In a second study by Zilberberg et al,⁵ there were 10,125 hospitalizations for patients with HAE from 2004 through 2007, with HAE as the primary diagnosis in 3,216. More than half the patients (53%) came through the ED. Notably, 15.9% of these cases required additional home health care or stays at a short-term hospital or nursing facility after hospital discharge.

Economic Burden

The direct medical and indirect costs of HAE are significant.^{5,25} As part of the HAEA survey, Wilson et al²⁵ conducted an analysis to estimate the economic costs associated with acute attacks and long-term management, but it should be recognized that this study reflects costs before the introduction of “newer” treatments for HAE. The average annual cost per patient was \$42,000. Hospitalizations accounted for 67% of direct medical costs, whereas long-term disease management (routine visits and medications) accounted for 18% (Fig 6). There also were significant indirect costs (eg, travel, missed work) of more than \$16,000. The cost of missed work, lost productivity, and lost income averaged about \$12,300 per year. As the severity of attacks increased, so did overall annual costs, which averaged \$14,379 for mild attacks, \$26,914 for moderate attacks, and \$96,460 for severe attacks. The greatest cost for severe attacks was hospitalization and ED visits (68%), whereas indirect costs were the most significant costs for moderate (64%) and mild (75%) attacks.

Although “newer” treatments for HAE are expensive, these must be considered in the context of overall direct medical and indirect costs.^{21,56} Effective use of these novel agents, particularly as home therapy or self-administration, could provide more cost-effective ways to manage HAE.

Changing the Landscape of HAE

Unfortunately, as a rare disease, it has been difficult to systematically characterize the burden of illness associated with HAE.

Nonetheless, some studies are establishing a landscape. The burden of illness is multifaceted and complex, but the tools specific to HAE to more fully understand its impact on patients, caregivers, and health care systems have not been developed. More epidemiologic data are needed to better understand the scale of the burden and how it might vary across subgroups. Observational studies, surveys, and patient registries should prove useful in characterizing prognostic factors and predictors of attacks, providing “real-world” data of what is working, what is not, and what can be improved.^{24,26,70} Several patient registries for HAE will be initiated in the United States, including those for patients receiving icatibant (NCT01034969) and C1INH concentrates (NCT01108848 and NCT01397864) and another by the HAEA. These registries will be particularly important for HAE with normal C1INH because of the difficulty in recruiting these patients for controlled trials.

There is a clear need to raise awareness of HAE to the broader medical community other than allergists and immunologists to overcome the barriers to early diagnosis. Physician education likely will need to target primary care and family physicians, gastroenterologists, dermatologists, and, importantly, ED physicians. Development and dissemination of up-to-date treatment guidelines are needed for ED physicians who are frequently treating patients with HAE before diagnosis or at the onset of disease. Guidelines from the American Academy of Emergency Medicine for the management of patients presenting with angioedema were last updated in 2006. In the literature search conducted for this review, only 12 of 1,040 (1.2%) articles were published in emergency medicine journals.

The introduction of several novel treatments, including C1INH concentrates, ecallantide, and icatibant, is a significant advance for patients with HAE. Although the efficacy and safety of these treatments have been shown in controlled clinical trials, it is important to understand their effectiveness in the clinical setting and their impact on disease burden. Patients could work with their physicians and specialty pharmacists to optimize home therapy and self-administration, developing individualized strategies to recognize patterns of prodromal symptoms and when additional dosing is needed to control an attack.

Conclusions

Hereditary angioedema is a disease with a great burden of illness that can significantly affect all aspects of a patient's life. As clinical and observational data of this rare disease continue to increase, there is a better understanding of its burden, the knowledge gaps, and potential steps to improve the lives of patients. Barriers to early diagnosis and intervention clearly need to be addressed in the short term. The introduction of novel treatments is a significant advancement, but without a more complete understanding of the disease burden, the use of these treatments cannot be optimized. Physicians need to consider a comprehensive assessment of the patient, individualized treatment, and steps to address all aspects of disease burden—the characteristics of attacks, the impact on a patient's work and social life, depression and anxiety, family support, and economic costs. Because of its rarity, the study of HAE must be broadened outside the controlled-trial setting, with patient registries, surveys, and other observational studies. Although significant progress in HAE has been achieved, there is much work ahead.

Acknowledgments

Medical writing and editing services were provided by Michael Raffin from PHOCUS (North Wales, PA) and were supported by Shire (Eysins, Switzerland).

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