

Managed Care Implications of Hereditary Angioedema

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Hereditary angioedema (HAE) is a rare autosomal dominant genetic disorder caused by a deficiency of functional C1 inhibitor that results in recurrent episodes of nonpruritic subcutaneous and submucosal swellings usually localized to the extremities, face, bowels, genitalia, or upper respiratory tract.^{1,2} While individual angioedema attacks follow a fairly predictable clinical course—symptoms gradually worsen over the first 24 hours, then subside—they can be highly unpredictable and may vary considerably in frequency and severity.¹ Abdominal attacks may be accompanied by severe pain, nausea, and vomiting that sometimes necessitates emergent supportive therapy.¹ Laryngeal edema, though relatively rare compared with abdominal and skin swellings, is the most clinically significant manifestation of HAE; death can result from sudden airway obstruction and asphyxiation.³

HAE is a chronic, life-altering disease that can put tremendous emotional and financial strain on patients and caregivers. Individuals with HAE require lifelong therapy and must constantly be vigilant for angioedema attacks, as any attack involving the upper airway is potentially life-threatening. Compared with healthy individuals, people with HAE report significantly poorer outcomes on health-related quality-of-life (HRQL) measurements, increased rates of depression, and reduced productivity in the form of missed time at work and school, with lasting negative impacts on career and educational prospects.⁴

In recent years, several new HAE therapies have been approved by the US Food and Drug Administration (FDA).² These agents, while highly effective, are also quite expensive, which will put additional economic burden on patients, payers, and the healthcare system as a whole. This article reviews the humanistic and economic costs of HAE, including both indirect and direct costs, as well as reimbursement issues and new developments in HAE management (eg, the increasing adoption of home care) that may help improve patient-centered and economic outcomes associated with the disease.

Diagnostic Delays and Misdiagnosis

HAE is a rare disease—prevalence estimates suggest it affects 2000 to 30,000 people in the United States⁵—making it a nonobvious diagnosis. Many physicians, even allergists or immunologists,

Abstract

Hereditary angioedema (HAE) is a genetic syndrome caused by a functional deficit in complement C1 inhibitor that results in recurrent episodes of nonpruritic swelling of the hands, feet, arms, legs, trunk, face, genitalia, bowels, and larynx beginning in childhood or adolescence and continuing throughout the patient's lifetime. Delays in the diagnosis of HAE average several years owing to the rarity of the disorder and the mimicking of clinical symptoms of those of a variety of other diseases. The lives of people with HAE have been transformed in recent years by the approval of several effective new therapies for the treatment and prevention of angioedema attacks. Nonetheless, evidence from surveys shows that many patients still report suboptimal disease control accompanied by significant morbidity, psychological stress, and diminished productivity and quality of life. Further, new HAE agents are costly—the average wholesale price of a single dose of ecallantide (Kalbitor) is \$9540—which will further strain an already stressed healthcare system. This article reviews the economic burdens, both direct and indirect, of HAE, and how changes in treatment practices, such as the wider adoption of home-based therapy, may improve patient outcomes and reduce costs.

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Reports

may not see a case in their entire career. While time to diagnosis for HAE patients has, on average, improved over the past several decades, physician and patient surveys indicate that delayed diagnosis remains a significant problem.^{6,7} Data from a Spanish HAE patient registry from 2003 to 2004 reported an average time to diagnosis of greater than 10 years.⁶ More recently, a 2009 to 2010 Internet-based survey of 172 US physicians—the Surveillance Project on Hereditary Edema—found that while most physicians (about 82%) who treated patients with HAE reported that their patients were diagnosed within 7 years of their first reported symptoms, only 37% said that patients were diagnosed within 1 to 3 years from symptom onset, and nearly 6% said that patients were diagnosed more than 10 years from symptom onset.⁷

In addition to diagnostic delays, HAE is often initially misdiagnosed, resulting in inappropriate treatment, unnecessary or inappropriate medical procedures, and more frequent utilization of costly health resources, such as visits to an emergency department (ED) and referrals to multiple specialists.^{8,9} An online survey of 63 patients with HAE conducted in 2004 found that patients averaged 4.7 ED visits each year, and that nearly 25% received treatment for anaphylaxis in the ED.⁸ Patients surveyed generally reported a high level of dissatisfaction with the management of their illness.⁸

In another online patient survey—the International Survey of Patient Experience of Hereditary Angioedema—313 patients with HAE or their guardians were asked about their experiences regarding diagnosis and disease management in the healthcare systems of their respective countries: United States (n = 125), Germany (n = 64), United Kingdom (n = 52), France (n = 50), and the Netherlands (n = 22).⁹ Respondents reported visiting an average of 4.4 physicians before receiving a diagnosis of HAE (average time to diagnosis = 8.3 years).⁹ In the process, 65% of patients were initially misdiagnosed, most commonly with allergy/allergic reaction (38%) or appendicitis (17%).⁹

Notably, 19% of American respondents and 24% of European respondents underwent an inappropriate surgical procedure, such as an appendectomy, related to their misdiagnosis.⁹ Unnecessary abdominal procedures, including appendectomy, colonoscopies, and cholecystectomy, have been reported elsewhere in previously undiagnosed patients with HAE experiencing severe abdominal pain as their initial or primary presenting symptom.¹⁰ Undoubtedly, inappropriate medical procedures, particularly abdominal surgery, are associated with substantial morbidity, risk of complications, and utilization of expensive healthcare resources.

Burden of Illness

As with other serious, chronic illnesses, the total disease burden of HAE includes indirect economic costs (lost productivity and earnings, lack of career advancement, missed educational opportunities), direct economic costs (acute and long-term medical care), and humanistic costs (impaired quality of life, emotional distress, depression, isolation), which also contribute to the total economic burden of illness.⁴ Because HAE is a rare condition with long delays in diagnosis and disparate treatment settings, the total burden of illness has been difficult to quantify.

From November 2007 to January 2008, investigators in conjunction with the US Hereditary Angioedema Association (HAEA) conducted an Internet-based survey of 457 patients with HAE to assess the humanistic and economic burdens of the disease.⁴ Patients were recruited through the HAEA patient database. The group's findings were published separately in 2010 in 2 different medical journals.^{4,11} It should be noted that the survey was conducted before the FDA approvals of nanofiltered C1 esterase inhibitor (Cinryze) for routine HAE prophylaxis, and Berinert, ecallantide (Kalbitor), and icatibant (Firazyr) for the treatment of acute angioedema attacks.⁷ The introduction of these effective but highly expensive agents into the HAE treatment arsenal has undoubtedly impacted both the patient-centered and economic sides of the condition, so the results of the HAEA survey should be interpreted with this in mind.

Of the 457 survey respondents, 92.1% were white and 75.5% were female.⁴ The average age at diagnosis was 22 years (range, 1-72 years); the average number of attacks per year was 26.9, with the majority of patients (94%) experiencing at least 1 attack within the previous 12 months.⁴ Respondents rated their attacks as mild (noticeable symptoms, but does not interfere with tasks of daily living); moderate (intervention is highly desirable for symptoms; interferes with tasks of daily living); or severe (treatment or intervention required; unable to perform tasks of daily living—eg, throat swelling that interferes with breathing).⁴ Slightly less than half (46.4%) rated their most recent attack as moderate in severity, while 26.5% rated their most recent attack as mild, and 27.1% as severe.^{4,11}

Health-Related Quality of Life. The burden of HAE related to HRQL outcomes was assessed using 3 standardized instruments: the 12-Item Short Form, the Hamilton Depression Inventory-Short Form (HDI-SF), and the Work Productivity and Activity Impairment-General Health (WPAI-GH) questionnaire.⁴ Results showed that patients

with HAE scored significantly lower on both physical and mental HRQL measurements compared with normal populations.⁴ Overall, respondents were significantly more likely to exhibit depressive symptoms than the general population: 42.5% of patients with HAE reported at least mild symptoms of depression; more severe HAE attacks correlated with increased depressive symptomatology.⁴ Nearly twice as many survey respondents reported taking psychotropic or antidepressant medication than the general population (19.5% vs 11.1%).⁴

Chronic use of androgen therapy for HAE prophylaxis was associated with significant side effects that further diminished HRQL in study patients.⁴ More than half of patients taking androgens reported weight gain (70.8%) and mood changes (59.7%), while nearly half reported agitation and sleeplessness/insomnia (45.6% for both).⁴ Compared with patients not taking androgens, androgen-receiving HAE patients scored significantly higher on the HDI-SF (8.7 vs 7.4; $P < .001$).⁴

Indirect Costs. A substantial proportion of patients with HAE report that their condition is detrimental to their work productivity, career advancement, and educational achievement. The studies examining the impact of HAE on work productivity generally evaluated missed work days due to HAE attacks (ie, missed work days/HAE attack). Half of all respondents to the HAEA survey reported missing at least 1 day of work due to their most recent HAE attack (average number of missed workdays = 3.3; range, 0.5-180).¹¹ As measured by the WPAI-GH, mean overall work impairment—a weighed combination of missed workdays (in the previous 7 days) and reduced productivity—was 33.6%.⁴ More than two-thirds (69.1%) said that having HAE prevented them from taking certain jobs, and 57.5% said the condition inhibited their career advancement.⁴ In terms of impact on productivity, HAE was similar to severe asthma and slightly less than Crohn's disease.⁴

The indirect economic costs of HAE were calculated using 2007 US wage data.¹¹ Based on average attack frequency (26.9/year) and average wages lost per attack (\$525 among employed patients), the average annual cost for missing work due to attacks was calculated at approximately \$3402, while the average annual cost of working while impaired was calculated to be \$5750 per patient.¹¹ Seventy-five patients (16.4%) were able to work only part time or not at all due to HAE, which was calculated to cost these patients \$39,683 in lost wages per year (compared with an average per patient cost of \$6512 among the overall survey population).¹¹ Although the study did not analyze costs associated with improper medical procedures or medications,

annual per patient costs for treating subclinical depression were reported to be \$2780, and \$8630 for treating depressive disorder.¹¹

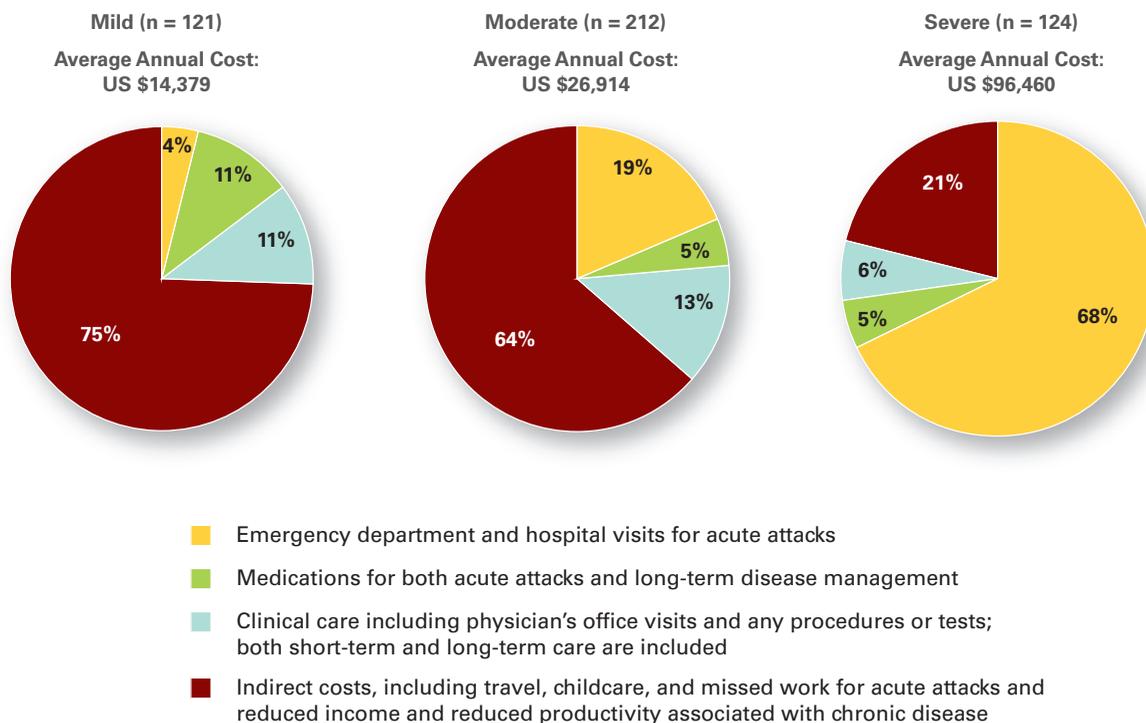
Direct Costs. Direct medical costs attributable to HAE were based on healthcare resources utilized during a patient's most recent attack (using 2007 standard unit costs) multiplied by the patient's average annual attack frequency, and averaged for the entire survey population.¹¹ Long-term medical costs were calculated from resources used outside of acute attacks for the prior year.¹¹ Average direct medical costs were \$25,884 per patient annually, of which \$21,339 (82.4%) was the cost of medical treatment for acute attacks.¹¹ Routine care outside of the acute treatment setting accounted for \$4545 annually.¹¹

Not surprisingly, more severe HAE attacks were associated with higher total costs. As shown in the [Figure](#), average annual total costs were \$14,379 for mild attacks, \$26,914 for moderate attacks, and \$96,460 for severe attacks.¹¹ ED visits and hospital stays for acute attacks accounted for almost half of all direct costs. For patients with severe attacks, ED visits and hospital stays comprised 68% of their total cost of care, compared with only 4% of total costs for patients with mild attacks.¹¹

It is important to note that these cost analyses were conducted prior to the FDA approvals of Cinryze (October 2008),¹² Berinert (October 2009),¹³ ecallantide (December 2009),¹⁴ and icatibant (August 2011).¹⁵ The reported 2010 average wholesale price (AWP) of a 1-month supply of Cinryze (16 vials) was \$39,000.¹⁶ One year of prophylaxis with Cinryze would therefore cost \$468,000 before any payment assistance. In the acute-treatment setting, a single 30-mg dose of ecallantide (Kalbitor) is \$9540 (up to 2 doses may be required to treat a single attack).¹⁶ The AWP of Berinert is \$2070 per 500-unit vial (\$6210 per attack in a 75-kg adult).¹⁶

In a separate study conducted in 2007, researchers at the University of Massachusetts, Amherst, analyzed data on hospitalizations and ED visits for both HAE and angioedema using 2 national databases—the Nationwide Inpatient Sample and the Nationwide Emergency Department Sample, both part of the Agency of Healthcare Research and Quality's Healthcare Costs and Utilization Project.¹⁷ There were 2282 ED visits and 1691 hospitalizations associated with HAE during the survey period. More people who went to the ED with an HAE attack were admitted to the hospital (45%) compared with those who had other forms of angioedema (18.3%). In total, there were 35,000 hospitalizations costing \$63 million for HAE and angioedema.¹⁷ Because of diagnostic uncertainties, the HAE proportion of hospitalization and ED resource use was probably underestimated.¹⁷

■ **Figure.** Resource Utilization by Most Recent HAE Attack Severity¹¹



Average annual costs were calculated in US dollars. The percentages of total costs for emergency department 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. HAE indicates hereditary angioedema.

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Improving Economic Outcomes in HAE

As mentioned, the new HAE treatments are expensive—annual per patient medication costs can easily exceed \$200,000, and many patients likely cannot afford the copayments, even if they have insurance.¹⁶ Each of the manufacturers of these new agents has implemented copayment assistance programs for patients who qualify. In addition, other organizations, such as the HAEA, have patient advocates who can help individuals with HAE navigate the insurance claims and reimbursement processes. There are also indications that changes in treatment practices, such as home-based self-administration of HAE therapy, are beginning to have an impact on patient outcomes and costs associated with HAE management.

Home-Based Management. Home-based management of HAE is becoming an increasingly important component of HAE patient care and has the potential to reduce costs associated with HAE therapy. Reports show that access to self-administered or assisted infusion of plasma-derived C1 inhibitor (C1INH) reduces the frequency and severity of

attacks, improves quality of life, reduces sick time, is well tolerated, and is popular with patients.¹⁸ Two recent studies provide further evidence that home-based administration of HAE therapies improves quality of care and reduces treatment delays and costs associated with visits to the ED.^{19,20}

In the first study, researchers evaluated the effectiveness of a training program for self-administration of Cinryze for routine HAE prophylaxis. They compared site-of-care data from patients with HAE treated in 2010, shortly after the FDA approval of Cinryze, against data collected in 2012 after patients underwent a training and support program for self-administration of C1INH conducted by skilled infusion nurses.¹⁹ Prior to the training, 47.1% of patients received C1INH therapy at home, 23.3% at an infusion center, and 27.5% at a physician's office.¹⁹ Post training, 75.8% of patients were treated at home (of whom 57.9% self-administered), while 16.1% were treated at an infusion center, and 8.1% at a physician's office.¹⁹

Overall, the percentage of patients who self-administered C1INH increased from 20% in 2010 to 44% post training

in 2012.¹⁹ Of 234 patients enrolled in the program, 55% were successfully self-trained, and 13% were in the process of learning how to self-administer C1INH.¹⁹ Patients required an average of 5 visits to be successfully trained.¹⁹ Notably, twice as many untrained patients (10%) discontinued C1INH therapy as trained patients (5%), suggesting that self-administration training and support programs for HAE may improve adherence among patients receiving routine prophylaxis C1INH therapy.¹⁹

The second study, conducted by a national US pharmacy chain, included 50 patients with HAE who received the plasma kallikrein inhibitor ecallantide administered in the home by trained infusion nurses for the treatment of acute attacks.²⁰ In total, 249 ecallantide doses were administered during a 5-month period, from October 2011 to February 2012.²⁰ The study found that 65% of patients were treated within 1 hour, 92% within 2 hours, and 100% within 4 hours.²⁰ By comparison, the median length of stay in the ED in 2008 was 2.6 hours, and 65% of patients spent more than 2 hours, much of it waiting to be seen by a physician.²⁰ According to the analysis, insurance plans saved \$648,147 with home infusion of ecallantide based on the average cost of an ED visit (\$2603) versus \$150 for a home-infusion nurse visit.²⁰ The cost of ecallantide was not included in the analysis. Several countries outside the United States have implemented home-based HAE management programs following a comprehensive-care model similar to that used for people with hemophilia.^{18,21} In 2010, an international consensus document on HAE home therapy was published based on a moderated discussion involving an interdisciplinary panel of physician experts at the 6th C1 Inhibitor Deficiency Workshop held in Budapest, Hungary, in May 2009.¹⁸ The panel concluded that virtually all patients with HAE could benefit from self-administration of Cinryze.¹⁸ A summary of the recommendations is as follows:

- **Inclusion criteria:** All patients with HAE should be considered for home-based management with C1INH; extremes of age or lack of an infusion partner are not necessarily contraindications.
- **Attack therapy:** Acute attacks of HAE should be treated as early as possible. Individualized “on-demand” therapy during the initial or prodromal stages of an attack can greatly mitigate the severity of symptoms. The C1INH dose should be individualized for best response.
- **Prophylaxis:** Short-term prophylaxis with C1INH is recommended for high-risk events; long-term prevention may be needed in patients with frequent attacks.
- **Site of attack:** Attacks affecting any anatomical site may be treated at home. Patients with laryngeal attacks

should go to the hospital as quickly after self-treatment as possible.

- **Counseling/consent:** The physician and patient should take individual and joint responsibility for the safe and appropriate use of home therapy.
- **Training:** Patients should be trained for self-management at an experienced facility; refresher training should be planned at least every 12 months.
- **Therapies:** Plasma-derived C1INH for HAE prophylaxis and acute therapy is well established. Ecallantide is not recommended for self-administration at home due to the risk for anaphylaxis.

Conclusion

HAE is a debilitating illness that requires lifelong management. Novel therapies for HAE are transforming the prevention and treatment of angioedema attacks—in many cases offering patients a degree of symptom control, quality of life, and personal and economic independence that was previously unattainable. This improvement in treatment efficacy comes at a very high cost. The potential exists for allowing the most severely afflicted patients with HAE access to prophylactic therapy, which will hopefully reduce the number of attacks, as well as the severity of those attacks. Prophylactic therapy may also offer these patients the ability to return to work or school. Careful definition of which patients would qualify for prophylaxis might provide a reasonable return on investment. Wider adoption of home and self-administration of HAE therapies may provide further patient-centered and cost benefits. Reduction in ED visits and hospitalizations would yield the largest economic benefit for payers. Clearly, there is a need for additional cost-effectiveness research in this area. There is also an educational need here. Accurate diagnoses, with guideline-driven treatments delivered in a timely fashion, will result in lower total medical expenses. Reducing the time to accurate diagnosis will also improve patient satisfaction. In light of the high costs of HAE agents, close cooperation between drug manufacturers, payers, pharmacies, and physicians is required to ensure that patients have access to these important new treatments.

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