

Economic Burden Limiting Proper Healthcare Delivery, Management, and Improvement of Patient Outcomes

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The Cost Burden of Hereditary Angioedema

The health burden of hereditary angioedema (HAE) has been well documented with more than 72% of patients reporting that the disease has significantly impacted their quality of life (QOL).¹ In fact, approximately 28% of patients with type I/II HAE reported at least 1 attack a week, with an additional 36% reporting attacks at least once a month, 18% reporting attacks every 2 to 3 months, and 18% experiencing attacks less than every 6 months.¹ These attacks are extremely painful and are also associated with high mortality.¹

However, the impact of both direct and indirect medical costs of HAE can also be substantial and negatively impact patient management and QOL.² A landmark study by Wilson et al was designed to assess the economic burden associated with both acute HAE attack and costs related to long-term disease management (see [Figure 1](#)).³ The study used an Internet-based survey of adult patients with HAE, 18 years or older, conducted from November 2007 to January 2008. Patients were recruited from the US Hereditary Angioedema Association (HAEA) database. These were patients who contacted the HAEA and identified themselves as having HAE or who requested information or membership from the association.

Approximately 2400 patients were recruited and 457 patients met inclusion criteria. Information was requested surrounding characterization of HAE attacks, including severity, affected body areas, and duration. Those studied reported a mean attack rate of 26.9 HAE attacks annually, and 94% surveyed had at least 1 attack in the past year. Patients were also questioned about use of short-term therapy, long-term disease management, and patient costs, including medical resources used and indirect costs associated with travel and childcare. In addition, the standardized Work Productivity and Activity Impairment questionnaire was used to analyze the effect of HAE on individual patient productivity at work.³ Average direct medical costs were \$25,884 per patient annually, with nearly 83% (\$21,339) of the cost attributed to medical treatment for acute attacks. Routine care outside of acute therapy accounted for approximately \$4545 each year. Average annual costs were \$14,379 for mild attacks, \$26,914 for moderate attacks, and \$96,460 for severe attacks.² Visits to the emergency department (ED) accounted for almost 50% of

ABSTRACT

Although several new therapies to both treat acute hereditary angioedema (HAE) attacks and provide prophylaxis for patients with recurrent episodes have been introduced in the past several years, HAE remains a disease with a substantial physical, psychosocial, and economic burden to both affected patients and society in general. Not all treatments work for all patients, and research is ongoing to improve HAE diagnosis and selection of therapy for individual patients to optimize outcomes. But the disease has a significant economic impact with high direct and indirect costs, and high charges related to the new therapies developed for patients to reduce symptoms and attack recurrence. Overall, effective management of HAE is often complicated by clinical and economic barriers to optimal patient outcomes that must be overcome to provide the best care possible and prevent future attacks and complications associated with this rare disease.

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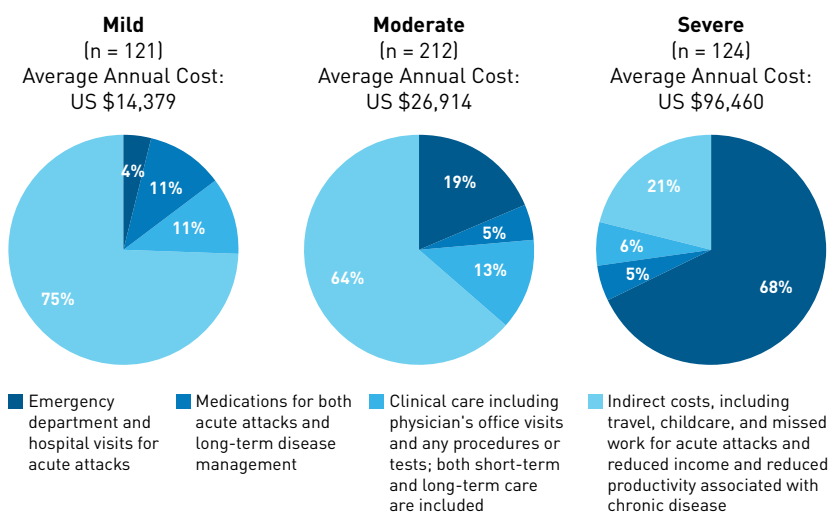
direct costs, and ED/hospital care comprised 68% of the total costs of care for patients with severe HAE attacks versus only 4% of costs for those with mild attacks.²⁻⁴

In terms of indirect costs, 50% of participants reported missing at least 1 day of work due to their most recent attack with an average number of 3.3 missed days. The average cost of lost wages for work absence for a single HAE attack was estimated at \$525.² Assessed by main frequency across the entire survey population, including those nonworkers, the average cost of missed work related to acute HAE attacks was estimated at \$3402 per year.³ The long-term cost associated with being unable to continue full-time employment (working less than full time) was \$39,693 (total of 75 patients), at an average of \$6512 across the total survey population.³ A later review of this study in 2018 determined that if inflation were taken into account, today's average annual cost per patient with HAE would be approximately \$65,000 in 2017 dollars.⁴

ED care and hospitalization comprise the leading direct cost burdens for patients with HAE. A study by Zilberberg et al examined the epidemiology and outcomes of hospital ED visits for patients with HAE. During the period from 2006 to 2007, there were 5040 HAE-related visits, of which 53.7% (2705) documented HAE as the primary diagnosis (HAE-PD). A total of 2059 visits (40.9%) resulted in the patient being hospitalized. The mean cost of each ED visit was estimated at \$1479, with a total cost of \$3,727,080 overall for emergency care during the study period.^{4,5}

Another study headed by Zilberberg was designed to assess the burden, epidemiology, and outcomes of hospitalizations of patients with HAE. This analysis covered the epidemiology, use of resources, and discharge destinations of hospitalizations for HAE through the Agency for Healthcare Research and Quality Healthcare Costs and Utilization Project, which took place from 2004 through 2007. During this time, there were a total of 10,125 hospitalizations with HAE, of which 3216 hospitalizations (31.8%) documented HAE-PD. Of total patients included, approximately 66% were female and 60% were white. The most common comorbidity seen was hypertension, affecting 26.9% of all patients with HAE, and 28.0% with documented HAE-PD with a mortality of 1.4% for the HAE cohort and 0.3% for those with HAE-PD. Mean hospital length of stay was 3.7 days for those with HAE-PD (range of 3.0 to 4.4 days) compared with a mean of 5.0 days (range of 4.6 to 5.4 days) for those in the HAE group. Results demonstrated mean costs of \$4760 (range of \$3612 to \$5907) for those in the HAE-PD group versus \$8383 (range of \$7432 to \$9334) in the HAE cohort. More than 80% of patients in both study

FIGURE 1. Costs by Hereditary Angioedema Attack Severity³



Adapted from Wilson DA, et al. *Ann Allergy Asthma Immunol.* 2010;104(4):314-320.

groups were discharged routinely to their homes; however, 15.9% of those with HAE versus 4.9% with HAE-PD required discharge to either home-based healthcare or needed transfer to either another short-term hospital or a skilled nursing facility for follow-up care. HAE hospitalization volume is substantial. The investigators also noted that because diagnostic uncertainty with HAE is common, the actual related resource use and cost presented in these data may be underestimated.⁶

Another study by Lumry et al, assessing the burden of HAE on health-related QOL, including patient productivity, found that mean overall work impairment, calculated as a combination of missed workdays in the previous week and overall reduced productivity, totaled 33.6%. Workers lost a mean 3.3 working days related to their most recent HAE attack, and students lost a mean 1.9 days of school. Nearly 70% of patients stated that HAE was a barrier to them performing certain jobs and approximately 58% believed that HAE had negatively impacted their career advancement.⁷

HAE Therapy: The Cost Factor

The development of new, disease-specific therapies to treat HAE has revolutionized patient management; however, the costs of these treatments are high.⁸ The development of new drugs for treatment of HAE was made possible by the orphan drug policies now available in the United States and the European Union. Under the US Orphan Drug Act, a drug is given orphan designation if the disease it treats affects fewer than 200,000 persons or if there is not a reasonable expectation of profitability for the agent.^{8,9} Some incentives provided for manufacturers of orphan drugs include tax credits toward research costs, clinical research grants, and a 7-year

exclusivity toward marketing approved orphan agents.⁸ While the cost per patient to treat an orphan disease is often substantial, the perception that overall costs to treat rare disease in general has an unreasonable impact on total drug expenditures and healthcare costs is erroneous. Data from both the United States and the European Union have demonstrated a minimal impact related to orphan drug costs and shown them to be in line with the 8% to 10% disease prevalence in these populations studied. In fact, in 2014, total expenditures for pharmaceutical agents in the United States comprised only 9.8% of the \$3.0 trillion in total healthcare costs. Expenses for orphan drugs for rare disease indications were estimated at approximately \$33.5 billion, which were less than 10% of total pharmaceutical expenditures and only 1% of the total healthcare expenses.^{8,10,11}

However, it remains that the costs for newer agents to treat HAE are substantial. For example, an analysis by Tilles et al showed that the cost of 1 form of C1 esterase inhibitor (C1-INH) approved for HAE prophylaxis and used at appropriate intervals was estimated at \$487,000 per patient in 2012. It must be noted that third-party insurers/payers often counteract these costs with shifts to coinsurance models. In the case of some agents, even a 10% coinsurance requirement for patients with HAE could cost as high as a \$50,000 annual out-of-pocket expense for a drug such as this one. However, that scenario has been countered and avoided by assistance programs funded by the pharmaceutical companies that manufacture drugs for HAE.¹² Current average wholesale prices for treatments for acute HAE attacks can range from \$5000 to \$10,000 per each attack. The costs are generally higher in the United States because national health systems outside of this country are usually able to obtain these vital drugs at a lower cost.⁸

An analysis in 2015 determined that the drug costs for HAE had tripled in a 2-year period. Patients were found to be accruing specialty drug treatment costs of more than \$300,000 per year. Among commercially insured members of health plans analyzed, 212 members used an HAE drug, leading to higher than \$69 million in HAE drug costs that averaged \$325,675 in costs per member. Just 23 people among 12.5 million commercially insured members incurred more than \$1.0 million in costs for HAE drugs. A total of 66% of HAE drug costs (\$45,385,602) were paid via the medical benefit, with 34% (\$23,656,387) paid through the pharmacy benefit. Per-member per-month (PMPM) cost of HAE drugs increased a total of 191% from \$0.11 in the first quarter of 2012 to \$0.32 PMPM in just the first 3 months of 2014 alone. These increased costs were partially driven by a notable increase in the number of members using these agents. As an example, in the first quarter of 2012, 45 members received an HAE drug, which later increased to 118 members in the first quarter of 2014, an increase of 162%. Considering these costs, healthcare professionals (HCPs) and case managers must assist patients with HAE in navigating their medical and pharmacy benefits, and help

them to better understand their individual HAE drug utilization to enhance optimal disease management and outcomes.¹³

Another analysis released by a pharmacy benefits management group in April 2018 demonstrated that the cost of some drugs used to treat HAE comprised more than 97% of the total costs of care. In this study, the investigators assessed pharmacy and data claims for 15 million commercially insured members. Data demonstrated that 226 members had at least 1 claim for an HAE during the first 6 months of 2016. These members were then followed for 12 months following their first HAE drug claim to determine their drug use patterns, hospital and ED visits, and total care costs. The average 12-month total cost of care amounted to \$409,925. The HAE drug costs totaled \$395,507 (97%), with all other medical and pharmacy costs totaling \$14,418 (3%) of total healthcare costs. Among the members studied, 49% met criteria for total enrollment, and 43% of these 111 members submitted claims for 2 or more drugs for HAE. Approximately 9% had more than \$1.0 million in HAE drug expenditures, with this small group of patients accounting for 20% of the \$43.9 million overall HAE drug expenses in the group's commercial book of business. Fifty percent of HAE drug expenditures were billed through the pharmacy benefit with the other half billed through the medical benefit. One of the investigators noted that with drug costs driving such a high percentage of HAE treatment expenses, medical costs cannot realistically be lowered through use of HAE drugs. Instead, diligent case management following each patient's first use of HAE treatments must be utilized to ensure appropriate drug use and best realize cost savings regardless of whether the drug is billed to the medical or pharmacy benefit.^{14,15}

However, despite drug costs, appropriate and timely treatment of HAE decreases ED visits, hospitalizations, lost productivity (work/school), and prevents mortality, lowering the overall costs of HAE to the healthcare system.^{7,8} Innovative treatment paradigms may further lower the cost, especially the encouragement and education of patients to self-manage their disease. As an example, 1 study in the United States demonstrated a \$650,000 savings when 249 HAE attacks over 5 months were treated at home by an infusion nurse compared with ED or in-hospital therapy.⁸

As noted earlier, it must be kept in mind that expenditures to treat orphan diseases, such as HAE, remain proportionately lower than the actual incidence of these diseases.⁸ As the number of newly approved therapies to treat HAE increases, it is likely that the cost of therapy will decrease.⁴ It must also be remembered that the costs of not treating HAE appropriately are also quite high. These include not just the direct cost of providing medical care for the patient but the indirect costs on patients, families, and caregivers.⁸ Orphan drugs, such as those to treat HAE, often represent a sole hope for patients and their families.¹⁶ Judicious choices in HAE therapy, usage of evolving treatment pathways, and better availability and access to new treatments will continue to improve QOL for patients with HAE, and coverage for these agents by payers and healthcare

systems must continue to end barriers to access and use.⁴ There is truly an ethical imperative to address and provide better access to orphan drugs for these patients. The development and marketing of safe, effective treatments remains a crucial imperative to optimally address the healthcare needs of patients with rare diseases.¹⁶

The Importance of Patient-Reported Outcomes in HAE Management

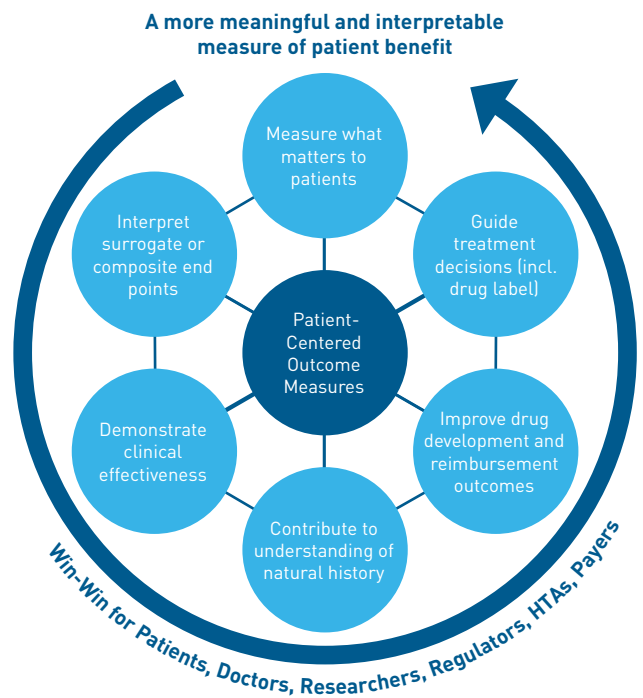
The goal for best practices in management of HAE is to improve patient outcomes and overall QOL. A patient-reported outcome (PRO) is now the favored terminology for a data element directly reported by either the patient or patient surrogate about their healthcare preferences and experiences. This may include data surrounding their symptoms, functional status, or QOL in general.^{17,18} Multiple organizations have produced guidance assistance for developing and assessing PROs, including the FDA.^{18,19} The FDA formally defines a PRO as “any report of the status of a patient’s health condition that comes directly from the patient, without interpretation of the patient’s response by a clinician or anyone else.”^{19,20}

Because rare diseases have a low prevalence in the general population, PROs can be vital in addressing the potential benefits for treatments of these conditions. Surrogate outcomes, such as laboratory or physiologic measures, may not reflect therapy benefits personally valued by patients. While these measures may have demonstrated therapeutic benefit, the patient may not actually feel better or experience improved survival.²⁰ In addition, PROs may be responsive to more discreet therapy effects in smaller studies.^{20,21} Appropriately chosen PROs could potentially determine smaller improvements in patient physical and emotional function.²⁰

Health-related QOL (HRQOL) is a global goal for all patients throughout life, and HCPs must determine if HRQOL is being optimized among patients with a rare disease to the extent achievable. While generic measures have been previously used to assess both the impact of the disease itself and disease-targeted treatments in orphan diseases, more disease-specific PROs and HRQOL measures are being introduced as efficacy end points for clinical trials of new therapies and long-term surveillance registries for both treated and untreated patient populations.²⁰ As shown in **Figure 2**, PROs (also referred to as patient-centered outcome measures [PCOMs]) convey value across all stakeholders involved in the healthcare of patients with rare diseases, conferring better ability to translate care and/or observed treatment effect into a more straightforward interpretable measure of patient benefit.²²

Currently, optimal and “fit-for-purpose” PROs/PCOMs do not exist for most rare diseases. However, if they are adequately developed, they have a desirable potential to “speak” to patients and better address their principal complaints. PROs offer better ability to obtain a more meaningful and interpretable measure of patient function and the possibility to reduce uncertainty over the effectiveness of

FIGURE 2. Patient-Centered Outcome Measures²²



PCOMs bring value across all healthcare stakeholders. Evaluating value from the perspective of the patient can bring substantial benefit for all healthcare stakeholders. Because they are grounded in what matters most to patients, PCOMs help translate care and/or observed treatment effect into an “interpretable” measure of patient benefit. By doing so, PCOMs bring value to all healthcare stakeholders involved. PCOMs may be used for several purposes, such as: efficacy end points in clinical trials, outcomes measures in registries, guides to treatment choices for daily care, or tools to monitor care delivery. HTAs indicates health technology assessments; PCOMs, patient-centered outcome measures.

treatments for rare diseases. They may be incorporated into both clinical trials and clinical practice, including disease registries, as noted previously, to enhance comprehension of the natural course of disease and to better guide treatment selection. Methods used for PRO/PCOM investigation include but are not limited to²²:

- In-depth pretrial concept elicitation patient interviews to better explore the disease experience (eg, most significant symptoms, disease impact on daily life)
- Interviews in a clinical trial setting (eg, study exit interviews, subject experience interviews) that may better delineate patient-defined improvement and benefits of therapy
- Focus groups for patient interaction and comparison of individual experiences
- Internet and social media platforms
- Direct patient observation/patient “shadowing” for first-hand experience of what it means for a patient to have a rare disease
- Audio/written patient diaries for recording of patient experiences

TABLE. Characteristics and Availability of Relevant PROMs for Disease Activity and QOL Impairment in HAE²⁶

	HAE-AS	AAS	HAE-QOL	AE-QOL
Number of items (questions)	12 (once)	1-6 (everyday)	25 (once)	17 (once)
Recall period	6 months	1 day	6 months	4 weeks
Applicable in HAE 1/2	+	+	+	+
Applicable in other forms of recurrent angioedema	-	+	-	+
Assessment	Retrospective	Prospective	Retrospective	Retrospective
High level of patient compliance required	-	+	-	-
Clinical important difference published	-	+	-	+
Cost-free use in routine patient management and investigator-initiated clinical research	+	+	+	+
Different language versions available ^a	American-English, Spanish	American-English, Azeri, Canadian-English, Canadian-French, Danish, Dutch, French, German, Greek, Hebrew, Hungarian, Italian, Japanese, Macedonian, Mexican-Spanish, Polish, Portuguese, Romanian, Russian, Slovakian, Spanish, Swedish, Turkish	Argentinien-Spanish, Austrian-German, Brazilian-Portuguese, Canadian-English, Canadian-French, Danish, French, German, Greek, Hebrew, Hungarian, Italian, Macedonian, Mandarin-Chinese, Polish, Romanian, Spanish, US-English, UK-English	American-English, Azeri, Canadian-English, Canadian-French, Danish, Dutch, French, German, Greek, Hebrew, Hungarian, Italian, Japanese, Jordan-Arabic, Macedonian, Mexican-Spanish, Polish, Portuguese, Puerto Rican-Spanish, Romanian, Russian, Slovakian, Spanish, Swedish, Turkish

AAS indicates angioedema activity score; AE-QOL, angioedema quality of life questionnaire; HAE, hereditary angioedema; HAE-AS, hereditary angioedema activity score; HAE-QOL, hereditary angioedema quality of life questionnaire. PROMs, patient-reported outcome measures; QOL, quality of life.

^aAdditional language versions of the HAE-AS and HAE-QOL (check www.idipaz.es for updates) and the AAS and AE-QOL (check www.moxie-gmbh.de for updates) are in preparation.

Methods used for PROs in individual instances will also depend on some degree of constraint. However, use of more sources improves the chance to increase the depth and breadth of information available to make qualitative comparisons across groups of patients. This may assist in creation of conceptual models combining patient-based evidence to delineate the relationship between core signs/symptoms, concerns that matter to most patients with the rare disease, and the hypothesized treatment benefit.²²

Two validated PROs are available to assess patients with HAE. These include the angioedema activity score (AAS) and the hereditary angioedema activity score (HAE-AS).²³⁻²⁵ The AAS is a symptom-specific PRO measure targeted at the assessment of angioedema activity. This method is validated for all angioedema types, including HAE. AAS is designed as a diary where patients document the presence or absence of angioedema over the past 24-hour period. If angioedema is present, patients answer 5 additional questions based on a 0- to 3-point scoring system. Minimum and maximum daily score can range from 0 to 15 points total. Cumulative data over 4 weeks (termed AAS28) are then used to present an analysis of disease activity.^{23,25} The AAS has very good internal consistency,

good validity and test-retest reliability, and is sensitive to changes in the activity of angioedema over time. The minimal important difference is 8 points for a 7-day cumulative AAS run (AAS7).²⁵ In contrast, the HAE-AS is a specific method to detect disease activity in C1-INH-HAE.^{24,25} HAE-AS documents retrospective disease activity over the previous 6-month period. It consists of 12 items that demonstrate a sole dimension/line. A raw score ranges from 0 to 29, which is then adapted to a linear measure with a 0-to-30 score that exhibits good internal consistency. Overall, the AAS and HAE-AS exhibit some similarities and some differences.²⁵

In addition to the AAS and HAE-AS, 2 QOL measures have been developed. The AE-QOL is a symptom-specific questionnaire for adult patients with angioedema that assesses HRQOL. It contains 17 items addressing 4 functions^{25,26}:

- Functioning
- Fatigue/mood
- Fears/shame
- Food

The AE-QOL covers a recall period of 4 weeks. A higher AE-QOL score indicates a lower HRQOL.^{26,27} The HAE-QOL is a questionnaire

for adult patients with C1-INH-HAE. This survey comprises 25 items grouped into 7 HRQOL domains^{25,27}:

- Treatment difficulties
- Physical functioning and health
- Disease-related stigma
- Emotional role and social functioning
- Concern about offspring
- Perceived control over illness
- Mental health

This survey covers a 6-month recall period.^{25,27} This questionnaire has been used in clinical practice, notably in a study that determined that home-based therapy for HAE was associated with better compliance compared with inpatient-based treatment, and that the choice to adopt at-home management was correlated with higher HAE attack frequency.^{25,28} As shown in the **Table**, these various questionnaires/methods not only exhibit some differences but also some similarities, and are available in different languages.²⁵

While a validated tool for disease control is not yet available, one is under investigation. It is also important to note that these tools are intended for adult patients and have yet to be validated for the pediatric population with AE/HAE. In addition, while developed in line with FDA and other requirements, such tools have yet to receive formal approval from these governing bodies. That said, they remain promising options in determining important patient values and factors affecting treatment of rare diseases, such as HAE, with more PROs in the pipeline for the future.²⁵

Conclusions

Although prompt and effective diagnosis and treatment of HAE are paramount to successful patient outcomes, the economics and costs of HAE and its therapy must also be addressed and managed by healthcare systems treating patients with this disorder. Costs of effective therapies must be balanced against the substantial costs of the disease, both in terms of direct medical costs and the impact of HAE on patient functioning and productivity. It is critical to consider PROs in all steps of HAE management and use validated questionnaires to assess patient preferences and status. This truly individualizes HAE management for every patient and potentially provides meaningful and interpretable measures of patient function and an assessment of the effectiveness of treatments and overall management. ■

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