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Challenges in the management of hereditary angioedema in urban and rural settings

Results of a United States survey

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ABSTRACT

Background: Caring for patients with hereditary angioedema (HAE), especially rural patients, has challenges.
Objective: To confirm experiences of allergy and immunology health professionals in diagnosing and treating patients with HAE, including those living in rural settings.
Methods: An online survey of 2996 members of the American College of Allergy, Asthma, and Immunology was conducted in April 13 to May 3, 2022. Eligible participants were association members (physician, fellow, or allied health professional members) currently practicing allergy or immunology, in the United States, seeing or treating at least 1 patient with HAE yearly.
Results: A total of 138 responders saw an average of 9 patients with HAE yearly; 12% of the patients resided in a rural area. They reported that 66% of their patients with HAE had type I, 15% type II, and 19% HAE C1nl-INH. Misdiagnosis was the top diagnostic challenge reported (82%). Inability to afford treatment was the top treatment challenge (76%). Other observations include the sentiment that patients with HAE with government insurance are at a disadvantage because it is not accepted by many specialists who treat HAE (64%) and that better payments for drugs from Medicaid and Medicare (57%) and better payments to providers from Medicaid and Medicare (49%) could better support the treatment of patients in rural settings. Responders expressed a preference for therapies administered at home (72%). Since the coronavirus disease 2019 pandemic, 86% of the respondents used telehealth for appointments occasionally.
Conclusion: Our findings illustrate the challenge of diagnosing HAE, especially HAE C1nl-INH, and the economic challenges of treatment, which can be compounded for those living in rural areas. We provide a call to action for addressing several of these real challenges.

Introduction

Hereditary angioedema (HAE) is a rare disease characterized by sudden cutaneous and submucosal swelling.[1] Swelling occurs most often in the limbs, face, intestinal tract, and airway. Swelling of the airway can be life threatening. HAE is an autosomal-dominant disorder that in most cases is caused by a deficiency of a functional protein called C1 esterase inhibitor (C1-INH). Type I and type II HAE are caused by mutations in the gene *SERPING1* resulting in C1-INH deficiency.[1,2] In type I HAE, mutations in *SERPING1* result in low levels and reduced function of C1-INH. In type II HAE, levels of C1-INH are normal or elevated, but C1-INH has reduced activity. Since 2006, additional gene mutations have been described that result in HAE with normal C1-INH function.[2] Here, we refer to this uncommon type as HAE C1nl-INH (previously called type III).

Allergists and immunologists are specialists who can help diagnose and treat patients with HAE. Treatment of HAE involves both on-demand therapy, which is used to minimize the effects of an HAE attack, and prophylactic treatment, which is used in appropriate patients to reduce the frequency and severity of attacks.[3] On-demand treatment is recommended to treat all attacks, as soon as possible, and is preferably self-administered.[4,5] Short-term prophylaxis may be indicated when patients are exposed to triggers such as invasive dental or medical procedures, surgery, or stressful life events.[5] The decision to initiate long-term prophylaxis in a patient should be individualized, taking into account disease activity, including frequency and severity of HAE attacks; patient's quality of life; availability of health care resources; and failure to achieve adequate control by appropriate on-demand therapy.[4,5]

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Previous surveys have been conducted to physicians and patients to evaluate the medical management of HAE. Riedl et al[6] conducted a 2019 survey of US physicians treating patients with HAE which reported trends in comparison with 2 previous surveys conducted in 2010 and 2013. Respondents to the 2019 survey reported that family history, laboratory testing, and presenting symptoms were the most important factors they considered in making a diagnosis of HAE. Icatibant was reported as the agent most frequently prescribed for acute attacks, and C1 esterase inhibitor (C1-INH) was used most frequently for long-term HAE prophylaxis. In a 2020 survey, Riedl et al[7] compared physician and patient perspectives concerning prophylactic treatments of HAE. That survey also evaluated the prophylactic medications prescribed and evaluated treatment burden more closely. Physicians reported prescribing subcutaneous C1-INH and lanadelumab most frequently for HAE prophylaxis. Concerning treatment burden, physicians and patients agreed that patients find injections or infusions unpleasant and that patients would prefer to administer their treatment when and where they need it. Although these previous surveys asked physicians to rate various factors that influenced their choice of treatment, the surveys did not focus on the challenges faced by physicians in diagnosing and treating HAE. Moreover, since the publication of those surveys, health care worldwide has been affected by the global coronavirus disease 2019 (COVID-19) pandemic. One such impact was the dramatic rise in the use of telehealth.[8]

The challenges of diagnosing and treating HAE are exacerbated in underserved and rural areas. Approximately 24% of patients with HAE reported living in rural areas (population of <20,000) in a 2015 survey.[9] Patients in rural areas may have difficulty finding a specialist in their area who has experience treating HAE. As reported by the Centers for Disease Control and Prevention, rural counties in the United States have fewer specialists, emergency facilities, and transportation options than more urban areas.[10] Furthermore, persons living in rural counties may be more likely to have poorly accepted government-issued health insurance.[11]

To further explore the challenges of managing patients with HAE, particularly those living in rural areas, Riedl et al[12] recently conducted a review of the literature. That literature identified several types of challenges in the care of patients with HAE living in rural areas, which are as follows: (1) barriers to diagnosis, such as misdiagnosis and misinterpretation of laboratory test results; (2) barriers to access specialist care, including the difficulty and cost of travel; (3) challenges of local health care as affected by physician shortages and the time needed for providers to initiate on-demand or prophylactic therapy; (4) challenges in patient education; (5) challenges in maintaining an adequate supply of on-demand and prophylactic medication; (6) barriers to using telemedicine services, such as a lack of internet access or not having a smartphone; and (7) health economic disparities (eg, insufficient patient insurance, insufficient payments to providers).[12]

We sought to update the survey literature on the diagnosis and management of HAE and were specifically interested in learning more about how allergy and immunology health care professionals view the challenges of diagnosing and treating patients with HAE, including patients living in rural settings. Our goal was to conduct a survey of members of the American College of Allergy, Asthma, and Immunology (ACAAI) to determine their experiences in treating patients with HAE.

Methods

Study Design and Participants

The survey was conducted by The Harris Poll on behalf of the ACAAI. Survey participants were recruited from the association's member mailing list by e-mail (1 initial e-mail and 1 follow-up). A total of 2996 members were contacted and asked to complete a survey online through a link provided in the e-mail. Survey data were collected from April 13 to May 3, 2022.

To be eligible for the survey, participants had to be an ACAAI member (physician, fellow, or allied health professional member) in the United States who was currently practicing allergy or immunology and seeing or treating at least 1 patient with HAE each year. Fellows were physicians certified by the American Board of Allergy and Immunology. Allied health professionals were nurse practitioners or physician assistants. We refer to eligible participants, whether physician, fellow, or allied health professional members, as *respondents* in our discussion of survey results.

The results are based on the voluntary, self-reported information provided by the respondents. The participants were told that the survey would take approximately 10 minutes to complete. They were informed that their responses would remain confidential and that all data would be anonymized and provided to the study authors in an aggregate form. The first 105 qualified respondents were eligible for an incentive worth $50. They were allowed to pick between a variety of gift cards (worth $50) or a donation to The Allergists' Foundation (worth $50).

Survey Instrument

The survey items were generated through collaborative discussion between the study authors and The Harris Poll. After an initial discussion, The Harris Poll created an outline for the survey flow and questions, which was reviewed and approved by the study authors and the ACAAI. The survey was pretested by The Harris Poll internally and by the association using a client-facing link.

The survey included 6 screening questions, 23 base questions all qualified respondents were asked, and 1 additional question with a conditional base. Each respondent saw approximately 37 pages on screen. Respondents could not review their answers once complete. The final survey questions are found in eTable 1 in the online data supplement.

Data Analysis

Deidentified data were compiled using Quantum and were analyzed using basic descriptive statistics. Statistical testing was done by using Student's t test with a 95% confidence level. Survey results were not weighted and are only representative of those who participated in the survey. Two extreme outliers were removed from the mean calculations (responses for these outliers were so extreme that we questioned whether they had accurately completed the survey).

Respondents for this survey were members who agreed to participate. The sampling precision of Harris online polls is measured by using a Bayesian credible interval. For this study, the sample data are accurate to within $\pm$8.2 percentage points using a 95% confidence level. This credible interval is wider among subsets of the surveyed population of interest. All sample surveys and polls, whether or not they use probability sampling, are subject to other multiple sources of error that are most often not possible to quantify or estimate, including, but not limited to coverage error, error associated with nonresponse, error associated with question wording and response options, and post-survey weighting and adjustments.

Survey data are available by reasonable request to the corresponding author.

Results

Survey Respondents

A total of 180 ACAAI members accessed the link to the survey (6% response rate), and 138 both met the criteria for inclusion and successfully completed the survey. Of the 138 respondents included in the analysis, 80 were physician members, 48 were physician fellows, and 10 were allied health professionals (nurse practitioners or physician assistants). The demographic characteristics of the survey respondents are found in Table 1.

Table 1
Demographic Characteristics of the Respondents Who Completed the Survey According to Membership Type

Demographics	Total (N = 138)	Physician member (n = 80)	Fellow[a] (n = 48)	Allied health professional[b] (n = 10)
Sex, n (%)				
Male	74 (54)	40 (50)	33 (69)	1 (10)
Female	62 (45)	39 (49)	14 (29)	9 (90)
Age, y (mean)	48	46	54	40
No. of years in practice (mean)	15	13	21	10
Practice location, n (%)				
Northeast	24 (17)	14 (18)	9 (19)	1 (10)
Midwest	25 (18)	13 (16)	9 (19)	3 (30)
South	51 (37)	26 (33)	19 (40)	6 (60)
West	38 (28)	27 (34)	11 (23)	0
Medical practice, n (%)				
Mostly office or clinic based	133 (96)	77 (96)	46 (96)	10 (100)
Exclusively hospital based or laboratory based	1 (1)	0	1 (2)	0
Equally hospital based and office/clinic based	4 (3)	3 (4)	1 (2)	0

[a]Physicians certified by the American Board of Allergy and Immunology or the American Osteopathic Association.
[b]Nurse practitioner or physician assistant in allergy/immunology.

Patient Profile

Respondents reported seeing a mean number of 9 patients with HAE yearly. Most of the patients with HAE were female (67%) with moderate disease severity (53%). Most patients seen by the respondents were 18 to 64 years of age (79%). Other reported patient demographics are found in Table 2.

Of note, respondents reported that 66% of their patients with HAE had type I HAE. An additional 15% of patients were reported to have type II and 19% to have HAE C1nl-INH.

On average, 12% of the respondents' patients resided in a rural area. Respondents who saw or treated more than 5 patients with HAE each year (n = 43) were more likely than those who saw or treated 1 to 5 patients yearly (n = 95) to have patients with HAE who lived in a rural area (22%, on average, vs 8%, respectively).

Survey Update on the Diagnosis and Treatment of Hereditary Angioedema

Diagnosis

Approximately 55% of the respondents diagnosed more than half of their patients with HAE and 45% diagnosed less than half. The most common sources of referrals were primary care provider of a patient with HAE and patient self-referral, which were reported by 31% of the respondents, on average, for each. On average, nearly one-fifth of the patients were referred by another specialist (18%). Fewer patients with HAE were referred by an emergency department provider (12%), a patient's pediatrician (5%), or a gastrointestinal specialist (2%).

Table 2
Patient Characteristics as Reported by the Survey Respondents

Demographics	% of Patients
Sex	
Female	67
Male	33
Age, y	
<12	3
12-17	10
18-64	79
≥65	8
Disease type	
Type I	66
Type II	15
C1nl-INH	19
Disease severity	
Mild	30
Moderate	53
Severe	17
Patient location	
Suburban	58
Urban	30
Rural	12

Abbreviations: C1nl-INH, HAE with normal C1 esterase inhibitor; HAE, hereditary angioedema.

Treatment Selection

Most respondents reported that their patients' disease was managed using prophylaxis (eg, berotralstat [Orladeyo], C1 esterase inhibitor [Cinryze, Haegarda], lanadelumab [Takhzyro]) and on-demand treatment as needed (eg, C1 esterase inhibitor [Berinert, Ruconest], ecallantide [Kalbitor], icatibant [Firazyr]; 60%, on average). Approximately one-third of patients (34%, on average) were treated with acute on-demand treatment only (eg, C1 esterase inhibitor [Berinert, Ruconest], ecallantide [Kalbitor], icatibant [Firazyr]). Few respondents indicated that the disease of their patients with HAE was managed through use of androgens as prophylaxis treatment (4%, on average) or plasma as acute on-demand treatment (2%, on average).

The frequency of HAE attacks (90%) and the severity of these attacks (88%) were among the top concerns taken into consideration by the respondents when selecting a treatment for a patient with HAE (Fig 1). Two-thirds of respondents reported that a patient's preference(s) (67%) and the impact of HAE on a patient's daily life (67%) are taken into consideration when selecting a treatment. In addition, 41% of the respondents reported that they considered the distance a patient must travel to an emergency department if they were experiencing a life-threatening attack.

The top 3 treatment goals in prescribing medication for patients with HAE were to improve patients' overall quality of life (68%), reduce the severity of attacks (51%), and reduce the frequency of attacks (49%). Approximately one-third of the respondents also felt that achieving attack-free status in prolonged periods of time (33%) and reducing the number or eliminating the times a patient visits the emergency department (33%) are top treatment goals. The full results for this question are reported in the online data supplement.

Topics Discussed During a Patient Visit

Symptoms of HAE and when to seek emergency medical attention were discussed at approximately half or more patient visits by 91% of the respondents (Fig 2). Costs associated with care were discussed at half or more visits by 62% of the respondents. Other topics discussed are found in Figure 2.

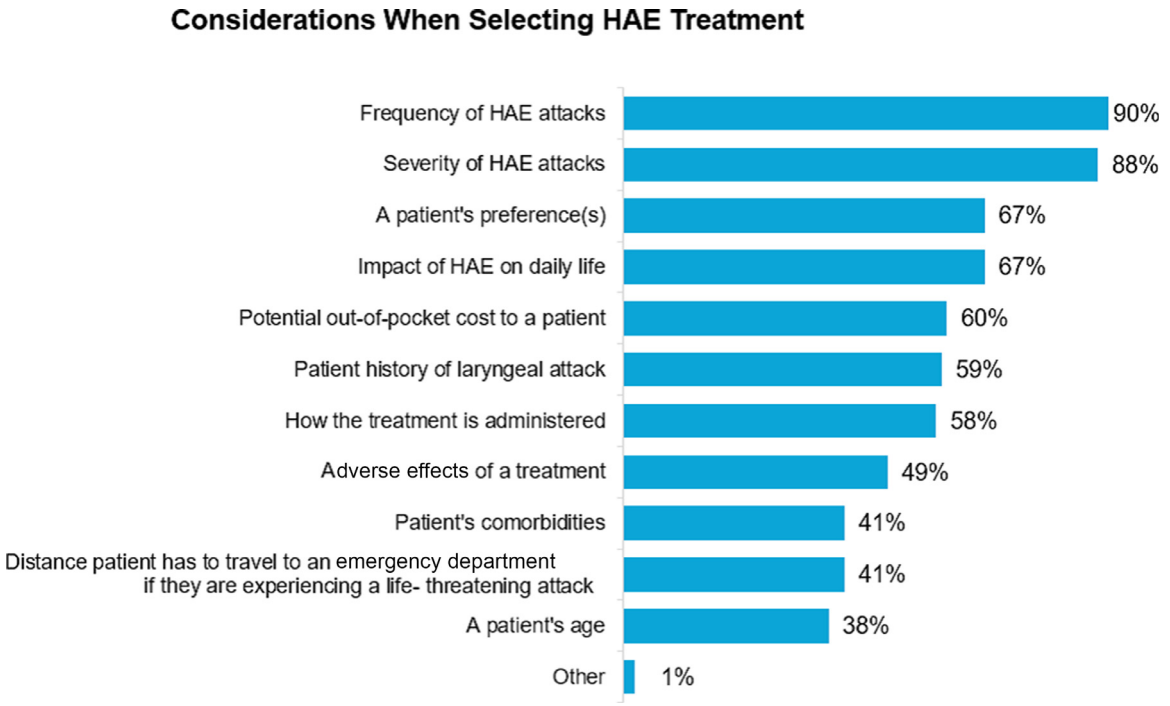

Figure 1. Considerations when selecting a treatment for hereditary angioedema. HAE, hereditary angioedema.

In the subanalysis according to number of patients treated, respondents who saw or treated more than 5 patients with HAE yearly (n = 43) were more likely than those who saw or treated 1 to 5 patients (n = 95) to discuss how to administer treatment at home during approximately half or more of patient visits (88% vs 62%).

Reported Challenges in the Diagnosis and Treatment of Hereditary Angioedema

Challenges to Diagnosis

Nearly all respondents (98%) agreed that there are challenges to diagnosing a patient with HAE. Because it is rare, HAE is often not recognized. As illustrated in Figure 3, among the top challenges in diagnosis reported were symptoms often being misdiagnosed as other conditions (82%). The majority 66% also reported that a lack of common indicators of HAE (eg, a family history of HAE) in every patient is a challenge in diagnosing HAE. A further challenge is that health care providers may lack familiarity with the disease (reported by 64% of the respondents). In addition, patients may lack understanding of HAE symptoms (reported by 41% of the respondents) and may lack awareness of the need for diagnosis (45%).

Approximately half of the respondents (51%) reported misinterpretation of test results as a barrier to properly diagnosing a patient, and 3 in 10 respondents (30%) reported problems with the laboratory, such as a laboratory producing unreliable results or samples being mishandled, leading to false results.

A patient's ability to afford proper diagnosis and care may be an additional hindrance to diagnosis. Some respondents indicated that a

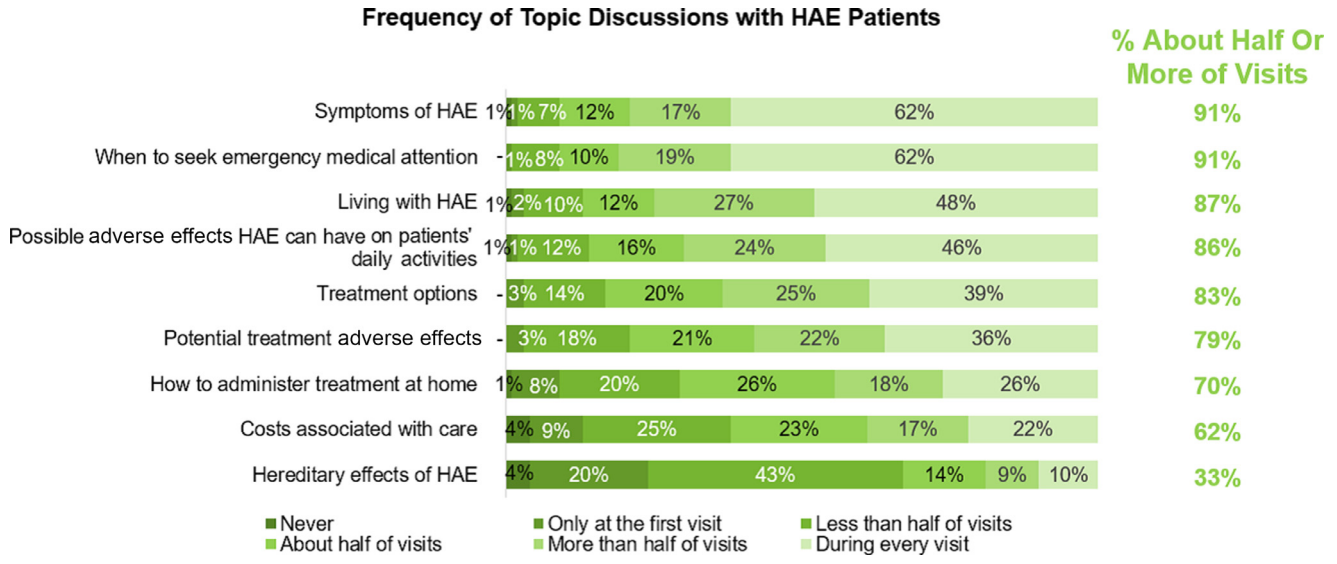

Figure 2. Frequency of topic discussions in patients with HAE. HAE, hereditary angioedema.

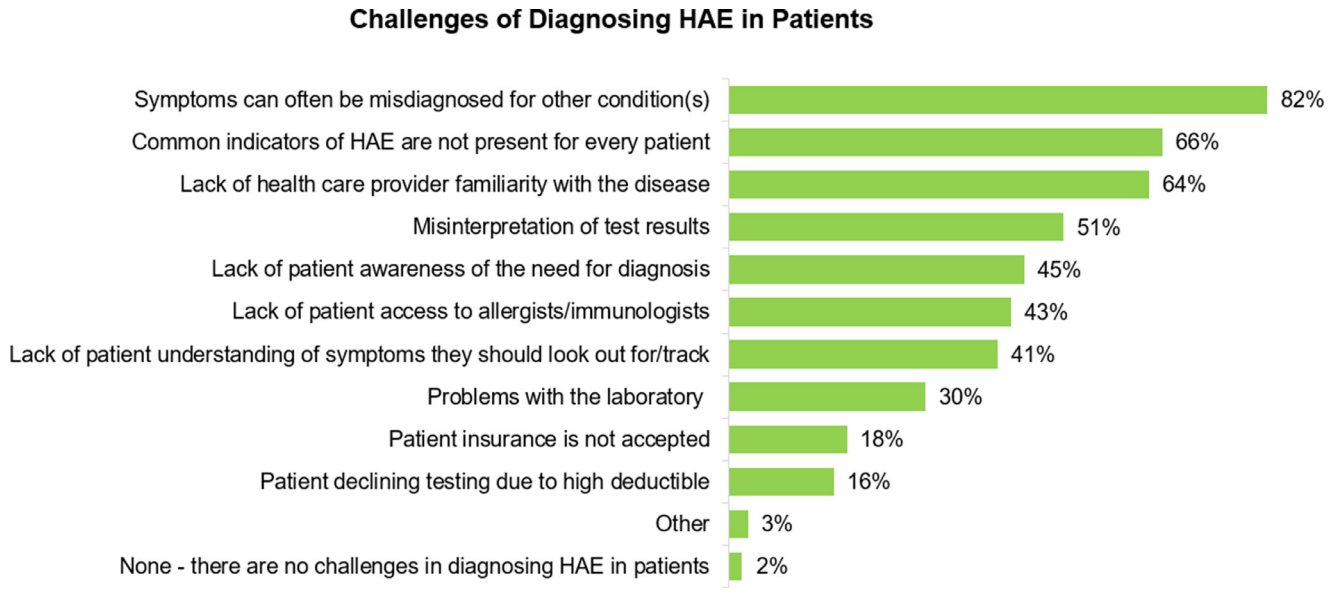

Figure 3. Challenges of diagnosing hereditary angioedema. HAE, hereditary angioedema.

patient's insurance not being accepted (18%) and patients declining testing because of high deductibles (16%) are among the challenges to diagnosis.

Lack of patient access to allergists or immunologists was reported as a challenge by 43% of the respondents. Slightly more than 2 in 5 respondents (42%) agreed with the statement, "There aren't enough specialists who can treat HAE in my area." Respondents who saw or treated more than 5 patients with HAE each year (n = 43) were more likely to say there were not enough specialists in their area (56% vs 36% of those who saw or treated 1 to 5 patients yearly [n = 95]). Respondents with patients with HAE residing in a rural area (n = 55) were more likely than those with patients in a suburban area (n = 117) to strongly agree that there are not enough specialists who treat HAE in their area (24% vs 15%, respectively).

Challenges to Treatment

A patient's financial abilities may play a role in their HAE treatment. Approximately three-quarters of the respondents (76%) said that a patient's inability to afford treatment, such as insurance coverage and out-of-pocket costs, are among the challenges of treating HAE (Fig 4). Insurance coverage may also play a large role in patient access to care. Nearly two-thirds of the respondents (64%) agreed with the statement that patients with HAE with government insurance coverage are at a disadvantage because it is frequently not accepted by specialists who treat HAE, and nearly one-quarter strongly agreed with this statement (24%).

More than 2 in 5 respondents reported a patient's inability to physically access treatment as a barrier to care. Other challenges of treatment are found in Figure 4.

Challenges of Treating Patients in Rural Areas

Barriers to care are amplified in rural areas. Informed by the previous literature review, we were interested in learning more about the challenges of treating patients who live in rural areas. For example, nearly 3 in 5 (59%) respondents agreed with the statement "Some of my HAE patients have to travel a great distance to see me/their health care provider." An average of 23% of the respondents' patients must travel for an hour or more to get to their practice. Respondents with

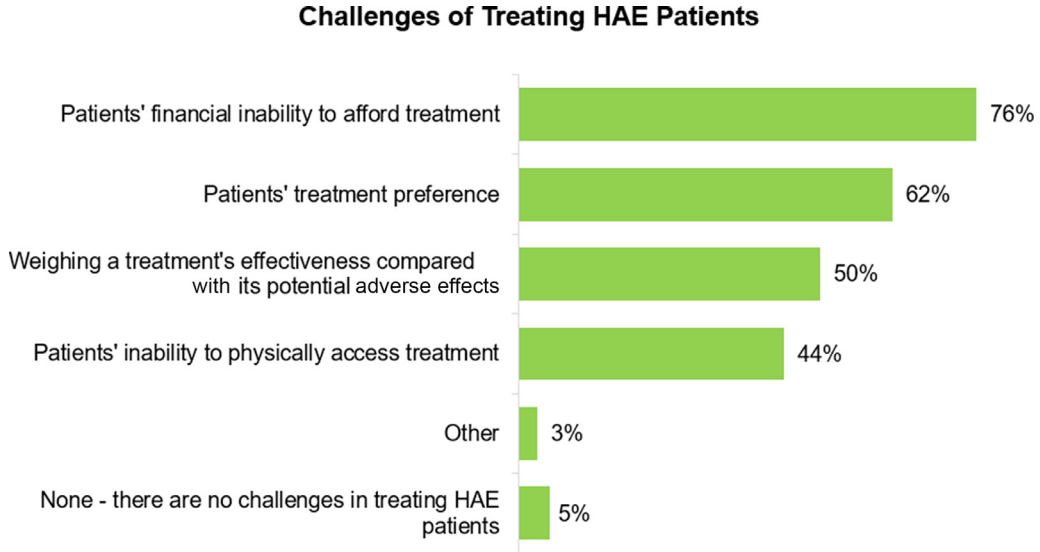

Figure 4. Challenges of treating hereditary angioedema. HAE, hereditary angioedema.

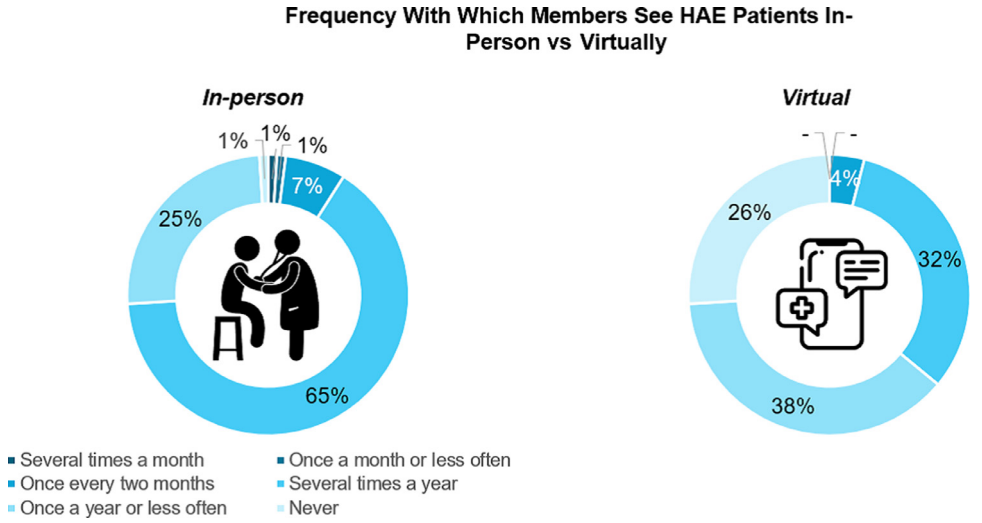

Figure 5. Frequency of visits and whether in person or virtual. HAE, hereditary angioedema.

patients with HAE in rural areas (n = 55) were more likely to note the hindrance of travel. They were more likely than respondents with patients in an urban (n = 76) or suburban (n = 117) area to report that half or more of their patients must travel an hour or more to get to their practice (42% vs 30% and 23%, respectively) and that some of their patients with HAE had to travel "a great distance" to see them or their health care provider (84% vs 67% and 58%, respectively).One survey question addressed how to better support the treatment of patients in rural settings. The most frequently selected option (chosen by 72% of the respondents) was the availability of treatments that could be administered at home. The respondents also indicated that better partnering between community providers and allergists/immunologists (63%) and the availability of peer-to-peer consultations (30%) could better support this group of patients. Some respondents (22%) indicated that live or virtual events about HAE may be useful. Direct support to patients including education/support groups (chosen by 50%) or services that can drive patients to and from appointments with their health care provider(s) (chosen by 28%) may also help support those in rural settings.

Concerning payment, the respondents indicated that better payments for drugs from Medicaid and Medicare (57%) and better payments to providers from Medicaid and Medicare (49%) could help to support patients in rural areas. Some (24%) indicated that a payment system that pays both primary care practitioners and specialists a monthly fee to provide preventative care may support rural patients.

More than 9 in 10 respondents (93%) agreed that patients with HAE who live in rural communities should always have access to prophylaxis treatment owing to their distance to rural hospitals. Nearly 7 in 10 (69%) strongly agreed with that statement.

Nearly half (45%) thought that changing federal telehealth rules to allow more people to use telehealth services without onerous requirements could help patients who live in rural areas.

Use of Telehealth Services

Nearly three-quarters (74%, n = 102) of the respondents reported that they typically see their patients with HAE in person several times a year or more often (ie, "several times a month" [1%], "once a month or less often" [1%], "once every two months" [7%], and "several times a year" [65%]) (Fig 5). One-quarter of the respondents (25%, n = 35) reported seeing their patients with HAE in person "once a year or less often." Concerning virtual visits, slightly less than three-quarters of the respondents (74%, n = 102) said that they ever see patients this way, of which 36% (n = 50) said that they see patients with HAE several times a year or more often (ie, "once every 2 months" [4%] and "several times a year" [32%] virtually) (Fig 5).

More than 9 in 10 respondents (93%) provide telehealth services to patients within the same state their practice is located, and more than 4 in 5 (82%) do not provide telehealth services to any patients outside the state in which their practice is located. However, this may have only been a recent occurrence during the COVID-19 pandemic, because 4 in 5 respondents (80%) said they had never used telehealth for appointments with their patients with HAE previously. Since the pandemic began, most of the respondents (86%, n = 119) have been using telehealth for appointments at least occasionally, and nearly one-fifth (17%, n = 24) have been doing so "most" or "all" of the time.

Discussion

We were interested in performing an updated survey of allergy and immunology health professionals and learning more about the challenges of diagnosing and treating patients with HAE, including those living in rural areas. The health professionals who responded to the present survey reported treating a mean number of 9 patients with HAE yearly. In a 2019 survey, most physicians reported treating 1 to 5 (70%) or 6 to 10 (19%) patients in the previous year,[6] and in a 2020 survey, 63 of 109 respondents (58%) reported treating 6 or more patients with HAE per year.[7]

We noted a difference from previous surveys in the reported type of HAE being treated. Historically, the prevalence of the 2 types has been described as approximately 85% type I and approximately 15% type II.[13] Our survey responders reported that 19% of their patients had HAE C1nl-INH, representing a much higher proportion than has been suggested historically. By comparison, in a 2019 survey of physicians treating patients with HAE, most physicians reported having no patients (38%) or 1 to 5 patients (52%) with HAE C1nl-INH.[6]

Challenges in Diagnosing and Treating Hereditary Angioedema

Our finding of such a high proportion of patients with HAE C1nl-INH illustrates one of the challenges of diagnosing HAE, especially HAE C1nl-INH. Currently, most patients with HAE C1nl-INH are diagnosed clinically. In our survey, 82% of the respondents reported misdiagnosis of symptoms as a challenge in diagnosing HAE. Although genetic testing is available, it does not test all known variants. A negative genetic test result does not rule out HAE C1nl-INH.

From our data, we are unable to verify the diagnostic journey of these patients.

Other challenges inherent to the treatment of HAE are economic ones. In our survey, 62% of the respondents discussed the cost of care with their patients at half or more visits. In the survey by Riedl et al,[6] approximately 44% of the respondents reported cost or insurance coverage as important nonefficacy factors when considering long-term prophylaxis (a significant increase from the 24% of respondents in 2010). HAE can be time consuming to assess and treat, and this time is inadequately reimbursed despite diagnostic coding rules. Approximately three-quarters of our respondents said that a patient's inability to afford treatment is a challenge of treating HAE, and nearly two-thirds agreed that patients with government insurance coverage are at a disadvantage because it is frequently not accepted by specialists who treat HAE.

In our survey, 12% of the respondents' patients resided in a rural area. Riedl et al[12] previously identified challenges experienced by patients with HAE in rural areas. Among these were that patients could rarely access specialist care without traveling to a secondary or tertiary medical center in an urban area and the difficulty and cost of such travel. In our survey, respondents with patients with HAE in rural areas (n = 55) were more likely to note the hindrance of travel and to report that half or more of their patients had to travel an hour or more to get to their practice. The 2020 update of the US Hereditary Angioedema Association Medical Advisory Board Guidelines for the Management of Hereditary Angioedema includes a strong recommendation that "Patients must have ready access to effective on-demand medication to administer at the onset of an HAE attack."[5] Barriers to access offer many opportunities for advocacy from organized medicine and patient groups.

A Call to Action

Through this survey, we have highlighted real challenges to the diagnosis and management of patients with HAE which can be compounded for those living in rural areas. Fortunately, we see several steps forward.

Our survey identified a lack of access to accurate testing as a barrier to diagnosis, both misinterpretation of test results (51%) and reported problems with the laboratory leading to false results (30%). Hopefully, more rapid and accurate testing will be universally available.

Telehealth has emerged as a vital tool for connecting patients and physicians through the COVID-19 pandemic. Most of our respondents (86%) have been using telehealth appointments at least occasionally since the pandemic, and nearly half thought that changing telehealth rules to allow more people to use these services could better support the care of patients living in rural areas. We are pleased with ongoing efforts to expand this service and encourage our organizations and the Congress to permanently expand this service.

We recognize that managing patients with rare diseases takes considerable time. Our respondents indicated that better payments to providers from Medicaid and Medicare (49%) could help to support patients in rural areas. As such, we strongly advocate for equity in payments for doctor and hospital services for people with Medicare and Medicaid who live in rural areas. One such action would be for the Congress to re-evaluate the geographic price cost index that restricts payments to providers in rural areas. New payment guidelines allow payment based on time; this should make caring for patients with HAE more tenable. Unfortunately, many private insurance companies are refusing to pay the prolonged services code, 99417. Providers and insurance companies should be educated about the proper use of these codes.[14]

Finally, awareness and education remain a great need for all rare diseases. Of our respondents, 50% agreed that patient education and support groups could better support the treatment of patients in rural settings. We applaud our fellow providers for their efforts to educate patients with HAE and their families. We are also grateful to have the US Hereditary Angioedema Association as a partner and invite all to review their available resources.

Limitations

Our study has several limitations. The sample size of health professionals meeting the study criteria who completed the survey was less than 100 for some analyses. However, the response rate in this survey (6%), which included physicians, fellows, and allied health professionals, was slightly higher than that to previous surveys among US physicians who treated patients with HAE of 3% (in 2019), 3.8% (2013), and 3.1% (2010).[6] We were interested in learning about the challenges of diagnosing and treating patients with HAE living in rural areas, but only 12% of the respondents' patients lived in rural areas. However, 59% of the respondents said that some of their patients travel a great distance to see them or other health care providers. Our survey results indicate that there are many challenges in the delivery of care to patients with HAE but especially in underserved and rural areas.

Other limitations include the likelihood of respondents estimating their answers to some questions. Thus, our findings should be interpreted as being based on provider recall or opinion, creating a gestalt of the current issues with caring for patients with HAE. Other sources of error may include coverage error, error associated with nonresponse, and error associated with the wording of the questions and response options.

In conclusion, our survey results highlight the real and ongoing challenges with diagnosing and treating patients with HAE. Misdiagnosis of symptoms, access to a specialist, and affording medications remain high-priority concerns among those surveyed, and these obstacles are heightened for patients living in rural areas. HAE is rare, but collectively, rare diseases affect many patients. Thus, despite the limitations of a survey design, the insights gained from the challenges of treating patients with HAE, especially those living in rural areas, and the opportunities for advocacy also extend to other patient groups.

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Supplementary Data

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Supplementary Data

eResults

Treatment Goals

In response to the question, "Which of the following are among your top treatment goals when prescribing medication for your HAE patients?" the full responses were as follows: improve patients' overall quality of life (68%); reduce the severity of attacks (51%); reduce the frequency of attacks (49%); achieve attack-free status in prolonged periods of time (33%); reduce the number, or stop altogether, the times a patient visits the emergency department (33%); decrease mortality (31%); reduce or eliminate the number of times a patient is hospitalized (22%); and prevent complications from surgery (7%).

Discussions With Patients

Most respondents (90%) recommended family testing to their patients with HAE, and slightly more than 4 in 5 respondents (81%) felt that their patients with HAE understood the impact of the disease for those who hope to have biological children.

eTable 1
HAE Survey Questionnaire

Survey Base: All Respondents
Q: Please indicate your membership type.
1. Fellow
2. Physician Member
3. Allied Health Professional - Nurse Practitioner/Physician Assistant
4. Allied Health Professional - Registered Nurse/Licensed Practical Nurse
5. Allied Health Professional - Office Manager/Administrator
6. Not sure

Q: Are you…?
1. Male
2. Female
3. Other
4. Decline to answer

Q: In what year were you born?
Q: How many years have you been practicing allergy/immunology?
- [I am not currently practicing in the area of allergy/immunology]
- [I am retired]

Q: In what state or territory is your practice located? If you practice in more than one state/territory, please select the state/territory where you consider your primary practice to be located.
Q: Approximately how many patients do you see/treat each year who have each of the following conditions?
1. Atopic dermatitis
2. Food related allergies
3. Drug related allergies
4. Hereditary angioedema (HAE)
5. Asthma

Survey Base: Qualified Respondents
Q: What proportion of your HAE patients live in the following area(s)? If you are not sure, please provide your best estimate.
1. Urban
2. Suburban
3. Rural

Q: What proportion of your HAE patients fall into each of the following categories? If you are not sure or you do not see any patients who identify as one of the following, please enter 0%.
1. Male
2. Female
3. Other
- [Decline to answer]

Q: What proportion of your HAE patients fall into each of the following age categories? If you are not sure please provide your best estimate.
1. Less than 12 years old
2. 12-17 years old
3. 18-64 years old
4. 65 years and older

*Q: What proportion of your HAE patients were **diagnosed** with HAE by you?*
*Q: What proportion of your HAE patients were **referred** to you by each of the following types of health care providers?*
1. Patient's primary care provider
2. Patient's pediatrician
3. Emergency department provider
4. Gastrointestinal specialist
5. Another specialist
6. Patient referred themselves

Q: Which of the following are among the challenges of diagnosing HAE in patients? Please select all that apply.
1. Symptoms can often be misdiagnosed for other condition(s)
2. Lack of patient awareness of the need for diagnosis
3. Lack of patient understanding of symptoms they should look out for/track
4. Lack of health care provider (eg, primary care, emergency department provider) familiarity with the disease
5. Misinterpretation of test results (eg, C1 esterase inhibitor and C4 may be at normal levels which is often the case for C1nl-INH or low normal between attacks)
6. Common indicators of HAE are not present for every patient (eg, no family history of HAE)
7. Problems with the laboratory (eg, produces unreliable results, samples are handled poorly leading to false results)
8. Patient insurance is not accepted
9. Patient declining testing due to high deductible

(*continued*)

10. Lack of patient access to allergists/immunologists
- [Other]
- [None – there are no challenges in diagnosing HAE in patients]

Q: What proportion of your HAE patients fall into each of the following categories of disease severity?

1 Mild
2 Moderate
3 Severe
- [Not at all sure]

Q: What proportion of your HAE patients are type 1, type 2, or C1nl-INH?

1. Type 1
2. Type 2
3. C1nl-INH
- [Not at all sure]

Q: As far as you know, what proportion of your HAE patients have to travel for one (1) hour or more to get to your practice?

- [Not at all sure]

Q: What proportion of your HAE patients' disease are managed using each of the following methods?

1. Acute on-demand treatment only (eg, C1INH/Berinert/Ruconest, ecallantide/Kalbitor, Icatibant/Firazyr)
2. Plasma as acute on-demand treatment
3. Prophylaxis and on-demand treatment as needed (eg, berotralstat/Orladeyo, C1INH/Cinryze/Haegarda, lanadelumab/Takhzyro)
4. Androgens as prophylaxis treatment
- [Not at all sure]

Q: Which of the following are among your top treatment goals when prescribing medication for your HAE patients? Please select up to 3 responses.

1. Achieve attack-free status over prolonged periods of time
2. Improve patients' overall quality of life
3. Reduce the frequency of patients' attacks
4. Reduce the severity of patients' attacks
5. Reduce the number of, or stop altogether, times patients visit the emergency department
6. Reduce the number of, or stop altogether, times patients are hospitalized
7. Decrease mortality
8. Prevent complications from surgery
- [Other]
- [None – I have no top treatment goals when prescribing medication for my HAE patients]

Q: Which of the following do you take into consideration when selecting a treatment for your HAE patients? Please select all that apply.

1. A patient's age
2. Side effects of a treatment
3. A patient's preference(s)
4. Patient's comorbidities
5. Potential out-of-pocket cost to a patient
6. How the treatment is administered
7. Distance patient has to travel to an emergency room if they are experiencing a life-threatening attack
8. Frequency of HAE attacks
9. Severity of HAE attacks
10. Impact of HAE on daily life
11. Patient history of laryngeal attack
- [Other]

Q: Which of the following are among the challenges of treating HAE patients? Please select all that apply.

1. Patients' financial inability to afford treatment (eg, insurance coverage, out-of-pocket costs)
2. Patients' inability to physically access treatment (eg, unable to drive to health care provider's office/hospital/pharmacy)
3. Weighing a treatment's effectiveness compared to its potential side effects
4. Patients' treatment preference (eg, injectable vs oral therapy)
- [Other]
- [None – there are no challenges in treating HAE patients]

Q: Which of the following could help support treating HAE in patients in rural settings in particular? Please select all that apply.

1. Availability of treatments that can be administered at home
2. Service(s) that can drive patients to and from appointments with their health care provider(s)
3. Education/support groups for patients
4. Changing federal telehealth rules to allow more people to use telehealth services without the current onerous requirements
5. Better payments to doctors from Medicaid and Medicare
6. Better payments for drugs from Medicaid and Medicare
7. Payment system that pays both PCPs and specialists a monthly fee to provide preventive care
8. Better partnering between community providers and allergists/immunologists
9. Availability of peer-to-peer consultation
10. Live/virtual events about HAE (eg, Grand Rounds)
- [Other]
- [None – there is nothing that could help support treating HAE in patients in rural settings]

Q: How often do you typically see your HAE patients each year in each of the following ways?

- In person
- Virtually

1. Several times a month
2. Once a month or less often
3. Once every 2 months
4. Several times a year
5. Once a year or less often
6. Never

Q: Do you provide telehealth services to any patients in each of the following areas? If you practice in more than one location, please think of the practice where you spend most of your time.

- Within the same state in which your practice is located
- Outside the state in which your practice is located

1. Yes
2. No

(*continued*)

Q: How often, if at all, did you use telehealth for appointments with your HAE patients prior to the COVID-19 pandemic?

1. Never
2. Occasionally
3. About half of the time
4. Most of the time
5. All of the time

Q: How often, if at all, do you use telehealth for appointments with your HAE patients since the COVID-19 pandemic began?

1. Never
2. Occasionally
3. About half of the time
4. Most of the time
5. All of the time

Q: How often, if at all, do you typically discuss each of the following topics with your HAE patients?

- Treatment options
- Potential treatment side effects
- Symptoms of HAE
- When to seek emergency medical attention
- How to administer treatment at home
- Hereditary effects of HAE (eg, those wanting to have biological children could pass the disease down to them, potential need to have their children or other family members tested)
- Living with HAE
- Possible effects HAE can have on patients' daily activities
- Costs associated with care

1. Only at the first visit
2. Less than half of visits
3. About half of visits
4. More than half of visits
5. During every visit
6. Never

Q: How much do you agree or disagree with each of the following statements?

- I recommend family testing to my HAE patients.
- Some of my HAE patients have to travel a great distance to see me/their health care provider.
- There aren't enough specialists who can treat HAE in my area.
- HAE severely impacts patients' quality of life.
- HAE patients who live in rural communities should always have access to prophylaxis treatment due to their distance to rural hospitals.
- HAE patients with government insurance coverage are at a disadvantage since it is not accepted by specialists who treat HAE.

1. Strongly disagree
2. Somewhat disagree
3. Somewhat agree
4. Strongly agree

Q: How well do you think your HAE patients understand each of the following aspects of HAE?

- The treatment options that are available.
- For those who hope to have biological children, the impact that their disease can have on their children.
- There is no cure for the disease.

1. Not at all well
2. Not very well
3. Somewhat well
4. Very well

Q: Which of the following best describes your medical practice?

1. Mostly office- or clinic-based
2. Mostly hospital- or lab-based
3. Exclusively hospital- or lab-based
4. Equally hospital based and office/clinic based

- [Other]

Q: Which best describes your current employer or practice type? If you practice in more than one location, please select all that apply.

1. Solo practice
2. Single specialty group practice
3. Multispecialty group practice
4. Non-profit community health center
5. Academic, research/teaching/not teaching
6. Non-government hospital or clinic
7. Government hospital or clinic
8. Industry (eg, pharmaceutical company)
9. Integrated health system (IHS)
10. Health maintenance organization (HMO)/managed care organization (MCO)
11. Private equity firm

- [Other]

Survey Base: Have HAE Patients Who Were Referred to Them by Another HCP

Q: How often, if at all, do you typically communicate with each of the following health care provider(s) who referred your HAE patients to you?

- Patient's primary care provider
- Patient's pediatrician
- Emergency department provider
- Gastrointestinal specialist
- Another specialist

1. Only at the time of initial referral
2. As needed since my initial visit with a newly referred patient
3. Regularly since taking on the new patient
4. Never