



# The multifactorial impact of receiving a hereditary angioedema diagnosis

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## ABSTRACT

Hereditary angioedema (HAE) is a rare, chronic, debilitating genetic disorder characterized by recurrent, unpredictable, and potentially life-threatening episodes of swelling that typically affect the extremities, face, abdomen, genitals, and larynx. The most frequent cause of HAE is a mutation in the *serpin family G member 1* (*SERPING1*) gene, which either leads to deficient plasma levels of the C1-esterase inhibitor (C1-INH) protein (type I HAE-C1-INH) or normal plasma levels of dysfunctional C1-INH protein (type II HAE-C1-INH). Mutations in *SERPING1* are known to be associated with dysregulation of the kallikrein-bradykinin cascade leading to enhancement of bradykinin production and increased vascular permeability. However, some patients present with a third type of HAE (HAE-nI-C1-INH) that is characterized by normal plasma levels and functionality of the C1-INH protein. While mutations in the *factor XII*, *angiopoietin-1*, *plasminogen*, *kininogen-1*, *myoferlin*, and *heparan sulfate-glucosamine 3-O-sulfotransferase-6* genes have been identified in some patients with HAE-nI-C1-INH, genetic cause remains unknown in many cases with further research required to fully elucidate the pathology of disease in these patients. Here we review the challenges that arise on the pathway to a confirmed diagnosis of HAE and explore the multifactorial impact of receiving a HAE diagnosis. We conclude that it is important to continue to raise awareness of HAE because delays to diagnosis have a direct impact upon patient suffering and quality of life. Since many patients will seek help from hospitals during their first swelling attack it is vital that emergency department staff are aware of the different pathological pathways that distinguish HAE from other forms of angioedema to ensure that the most appropriate treatment is administered.

As disease awareness increases, it is hoped that patients will be diagnosed earlier and that pre-authorization and insurance coverage of HAE treatments will become easier to obtain, ultimately reducing the burden of treatment for these patients and their caregivers.

**Keywords:** Hereditary angioedema, Quality of life, Caregiver, Physician, Healthcare resources

## INTRODUCTION

Hereditary angioedema (HAE) is a rare, incurable, chronic, debilitating genetic disorder characterized by recurrent, unpredictable, and

potentially life-threatening episodes of swelling that most commonly affect the extremities, face, abdomen, genitals, and larynx.<sup>1-3</sup> The most frequent cause of HAE is a mutation in the *serpin family G member 1* (*SERPING1*) gene, which

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encodes a regulator of the kallikrein-bradykinin cascade termed C1-esterase inhibitor (C1-INH).<sup>1,3</sup> Mutations in *SERPING1* either result in deficient plasma levels of the C1-INH protein (type I HAE-C1-INH) or normal plasma levels of dysfunctional C1-INH protein (type II HAE-C1-INH), which subsequently leads to unregulated bradykinin production and increased vascular permeability.<sup>1,3</sup> Currently, more than 500 different variants in *SERPING1* have been associated with type I and type II HAE-C1-INH,<sup>4,5</sup> which have a combined estimated global prevalence of 1 in 50,000.<sup>1,3-5</sup> However, some patients present with a third type of HAE (HAE-nl-C1-INH) that is characterized by normal plasma levels and functionality of the C1-INH protein.<sup>3</sup>

Mutations in the *factor XII* (published in 2006), *angiopoietin-1* (published in 2018), *plasminogen* (published in 2018), *kininogen-1* (published in 2019), *myoferlin* (published in 2020), and *heparan sulfate-glucosamine 3-O-sulfotransferase-6* (published in 2021) genes have been identified in some patients with HAE-nl-C1-INH. However, in many cases, the genetic cause is unknown, further contributing to significant challenges to diagnosis.<sup>4,6-12</sup> Early clinical evidence suggests that bradykinin may play an important role in most forms of HAE-nl-C1-INH, similar to its role in HAE-C1-INH, particularly in patients with mutations in the *factor XII* and *plasminogen* genes.<sup>4,13</sup> However, further research is required to more fully characterize the pathology of disease in patients with HAE-nl-C1-INH.<sup>4</sup> Therefore, this review aims to raise awareness of HAE by describing the challenges that arise on the pathway to, and exploring the multifactorial impact of, a confirmed diagnosis of HAE. Patient, caregiver, and physician perspectives have been included where possible and are based largely on the authors' own experiences managing patients with HAE.

## THE HAE DIAGNOSTIC PATHWAY

### Diagnostic guidelines

The 2021 revision and update to the international World Allergy Organization/European Academy of Allergy and Clinical Immunology (WAO/EAACI) guidelines for the management of HAE indicate that a diagnosis of HAE should be

explored in patients with a history of recurrent skin swelling (particularly in the extremities, face, and genital regions), gastrointestinal attacks (including painful abdominal cramps), or edema of the larynx.<sup>4</sup> These guidelines also state that further suspicion of type I or type II HAE-C1-INH should be elicited when there is a positive family history of the condition, although this may be absent in as many as 25% of patients; symptoms begin in childhood or adolescence; the patient is experiencing unexplained, recurrent abdominal pain; there are swelling episodes in the upper airway; the patient does not respond to conventional treatments for swelling including antihistamines, epinephrine, glucocorticoids and/or omalizumab; specific prodromal symptoms including erythema marginatum, fatigue, malaise, nausea, and irritability appear prior to episodes of swelling; and urticaria or wheals are absent.<sup>4,14,15</sup> It is important to note, however, that not all patients with HAE experience prodromal symptoms and that prodromal symptoms are more common in females and in patients who experience frequent attacks.<sup>14,15</sup> A lack of pruritus can also support a diagnosis of HAE.<sup>16</sup>

When a suspicion of HAE is raised, a combination of biochemical tests to determine plasma levels of both C1-INH protein and complement component 4 (C4) protein as well as C1-INH functionality can aid diagnosis (Table 1).<sup>4,17-20</sup> For type I and type II HAE-C1-INH, these biochemical tests are considered an effective way of confirming diagnosis. Additionally, genetic testing to identify mutations in the *SERPING1* gene can be useful in some scenarios, including in patients with a family history of HAE, and for prenatal diagnosis.<sup>4,21</sup>

In the absence of a confirmatory biomarker or diagnostic test for HAE-nl-C1-INH (Table 1), genetic testing focused initially on detecting mutations in the *factor XII*, *angiopoietin-1*, and *plasminogen* genes can aid diagnosis.<sup>1,21</sup> However, it is important to note that the absence of mutations in these genes does not disprove a diagnosis of HAE, which can be disheartening for the patient. The 2020 United States (US) Hereditary Angioedema Association Medical Advisory Board Guidelines for the management of HAE suggest that apart from C1-INH, C4, and genetic testing, family history and a lack of

Parameter	HAE-C1-INH		HAE-nl-C1-INH
	Type 1	Type 2	
C1-INH function <sup>a</sup>	Lower than normal	Lower than normal	Normal
Serum C1-INH protein level <sup>b</sup>	Lower than normal	Normal or higher than normal	Normal
Serum C4 protein level <sup>c</sup>	Lower than normal	Lower than normal	Normal
Genetics	<ul style="list-style-type: none"> <li>Genetic testing for mutations in the <i>SERPING1</i> gene is useful in some patients, including for prenatal diagnoses, however, biochemical testing of C1-INH is more cost effective and may be sufficient</li> <li>If a patient's laboratory parameters raise suspicion of C1-INH-HAE type I but they have no family history of the condition and symptoms developed after 30 years of age, then acquired angioedema due to C1-INH deficiency is often the most likely diagnosis</li> </ul>		<ul style="list-style-type: none"> <li>If patients have a positive family history of the condition, then genetic testing can be useful for identification of cases of HAE-nl-C1-INH that are caused by known mutations in specific genes (including <i>FXII</i>, <i>ANGPT1</i>, <i>PLG</i>, <i>KNG1</i>, <i>MYOF</i>, and <i>HS3ST6</i>)</li> <li>If patients have no family history and no known mutation that is associated with HAE-nl-C1-INH then other conditions, such as mast cell-mediated angioedema, idiopathic angioedema, and angiotensin converting enzyme inhibitor-induced angioedema, should also be ruled out</li> </ul>

**Table 1.** Typical laboratory profile of patients with HAE and recommended diagnostic tests based on the 2021 international WAO/EAACI guidelines for HAE management<sup>4</sup> *ANGPT1*, angiopoietin-1; *HAE-C1-INH*, hereditary angioedema due to C1-inhibitor deficiency or dysfunction; *C1-INH*, C1-esterase inhibitor; *HAE*, hereditary angioedema; *HAE-nl-C1-INH*, hereditary angioedema with normal C1-inhibitor levels; *HS3ST6*, heparan sulfate-glucosamine 3-O-sulfotransferase; *KNG1*, kininogen; *MYOF*, myoferlin; *PLG*, plasminogen. <sup>a</sup>Normal C1-INH function in adults is considered to be >67%.<sup>51</sup> <sup>b</sup>The normal range for C1-INH in adults is 16–33 mg/dL.<sup>22</sup> <sup>c</sup>The normal range for C4 complement in adults is 10 or 14 mg/dL to 40 or 44 mg/dL.<sup>51</sup> Note that C4 can be normal or low normal in between attacks.

efficacy of high-dose antihistamine therapy can also support the diagnosis of HAE-nl-C1-INH.<sup>1</sup>

### Diagnostic challenges

Patients without a confirmed HAE diagnosis are more likely to present at emergency care departments versus other clinical settings when they experience their first attack.<sup>22</sup> It is, therefore, critical that emergency department staff have an awareness of HAE symptomology, and the ability to recognize how it differs

from histaminergic angioedema to ensure optimization of patient treatment outcomes.<sup>22,23</sup> However, while emergency department physicians may receive didactic training on angioedema as part of the emergency medicine curriculum, not all of them will see real life cases of HAE during their residency.

Distinguishing between HAE and histaminergic angioedema in the emergency department can be challenging due to a lack of point-of-care and

laboratory-based tests in this environment that could guide physicians towards the most appropriate immediate treatment and patient referral pathway.<sup>23</sup> Measurement of C4 and tryptase levels could help physicians distinguish between HAE and anaphylaxis because C4 levels are typically low during an active HAE attack, and tryptase may be elevated in some cases of anaphylaxis but not during an acute HAE episode. Measurements of serum C2 can also be helpful for making the diagnosis of HAE because the levels of C2 can be low during an acute attack.<sup>24,25</sup> However, these tests are often not available in the emergency room setting,<sup>22,26</sup> and as such patients are not usually diagnosed in this setting but rather by a specialist upon referral.

Diagnosis of HAE can also be delayed because patients often present with various nonspecific signs and symptoms, which can lead to multiple misdiagnoses and, in some cases, to unnecessary surgical procedures.<sup>27,28</sup> In the international, prospective, observational Icatibant Outcome Survey (IOS) study, 185 of the 418 patients (44.3%) with confirmed type I or type II HAE-C1-INH who had provided data by January 2016 had received one or more prior misdiagnoses.<sup>29</sup> The most common misdiagnoses identified in the IOS study included allergic angioedema (103/185 [55.7%]) and appendicitis (50/185 [27.0%]). Furthermore, it is widely reported in the literature that many patients with HAE often experience unexplained recurrent abdominal pain as one of their first symptoms.<sup>28-31</sup>

In the literature, the median time from onset of symptoms to a confirmed diagnosis of HAE has been reported as 1.4-8.5 years.<sup>3,27,32</sup> However, diagnostic delays for some patients can exceed 13-20 years.<sup>29,33-36</sup> In the IOS study, misdiagnosis of non-allergic angioedema and biliary disorder resulted in the longest mean time from presentation of symptoms to a confirmed diagnosis of HAE-C1-INH.<sup>29</sup>

The rate at which patients are accurately diagnosed with HAE is known to vary between countries.<sup>36</sup> Geographical differences in diagnosis rate may be related to variability in the availability and the quality of laboratory tests used to determine C4 and C1-INH level, and C1-INH function.<sup>4</sup> This can lead to physicians in some countries having

to adapt their diagnostic approach for HAE.<sup>4</sup> An example of such an adaptation includes testing for C4 level during an active swelling attack to improve sensitivity of the C4 test.<sup>4</sup> Disease awareness level in a particular country can also impact the rate at which HAE is accurately diagnosed.<sup>36</sup> A recent study indicated that the average delay between the development of symptoms and diagnosis of HAE was particularly long in Greece (17 years), Japan (16 years), and Denmark (16 years) compared with other countries such as Spain (13 years), the United Kingdom (10 years), the United States (8 years) and South Korea (8 years).<sup>35,37-41</sup> This could be related to a lower level of disease awareness in the former countries or to lower rates of genetic testing of HAE patients and their relatives.

Delays in diagnosis can cause significant anxiety for both patients and their relatives.<sup>42,43</sup> In part, this is because HAE attacks affecting the larynx can be life-threatening putting patients at risk of asphyxiation if untreated.<sup>3,44</sup> Family members of patients with HAE often report needing a confirmed diagnosis to be able to adequately cope with the disease and offer sufficient support.<sup>45</sup> Many family members and caregivers note that the unpredictability of HAE swelling crises keeps them on high alert all of the time, which can be physically and mentally exhausting.<sup>45</sup>

### Diagnostic considerations in pediatric patients

Symptoms of type I and type II HAE-C1-INH often first appear in childhood, however, most cases are not recognized by pediatricians.<sup>46</sup> In the literature, the average age at which a patient experiences their first symptomatic HAE-C1-INH attack is reported as ten years with initial disease presentation often characterized by recurrent abdominal pain due to swelling of the walls of the intestine.<sup>46-50</sup> However, differential diagnoses are broad for abdominal pain because it occurs so frequently in the general pediatric population.<sup>47</sup> Therefore, raising awareness of HAE in pediatricians is crucial to improving the average time that it takes from a patient experiencing their first symptoms of disease to receiving a confirmed diagnosis. In contrast, the occurrence of HAE-nI-C1-INH is very rare in pediatric

patients, with symptoms usually appearing late in adolescence or in early adulthood.<sup>1,47,51</sup>

Prenatal genetic diagnoses can be considered where there is a family history of HAE-C1-INH with a known disease-causing mutation in the *SERP-ING1* gene.<sup>47</sup> Testing level and functionality of the C1-INH protein can be useful in children less than one year old who have a family history of HAE-C1-INH, but it is recommended that all tests be repeated when the child exceeds one year of age to obtain a more reliable, confirmatory diagnosis.<sup>47</sup> Levels of the C4 protein are not reliable for diagnosing children less than one year old because C4 levels can also be low in non-HAE-C1-INH patients. If the familial gene is known, genetic testing can also help with diagnosis of children in this age group.

## PSYCHOLOGICAL, PHYSICAL, AND FINANCIAL BURDENS OF RECEIVING A HAE DIAGNOSIS

### Psychological and physical burdens

Key burdens that are associated with a diagnosis of HAE include sleep disturbances and other psychiatric symptoms, feeling isolated, fear of the next attack and hospitalizations, responsibility for disease education and lifestyle modifications to avoid triggers, frustration over inconsistency in emergency department care, and guilt due to activity limitations impacting social events as well as work or education.<sup>43,52-54</sup> Therefore, the quality of life of patients with HAE is negatively impacted.

Fear, depression, and anxiety are common in patients with HAE because of the unpredictable nature of attacks and the risk of suffering severe or life-threatening attacks. In a recent survey study, 222/445 (49.9%) US-based patients with type I or type II HAE-C1-INH were showing signs of anxiety, and 107/445 (24.0%) patients had symptoms consistent with depression highlighting the burden of disease associated with receiving a confirmed diagnosis of HAE.<sup>32</sup> Furthermore, in a prospective study of 95 Danish patients with HAE, 83% of patients who answered felt that their disease had some level of psychological impact on their life and 61% reported anxiety about the inherent risk of suffocation from HAE.<sup>55</sup> Fear of

future attacks is also known to limit a patient's ability to socialize and/or travel.<sup>56</sup>

Absence from work or school, reduced productivity at work in the time between attacks, and delays to professional and education advancement have also been reported in the literature for both patients with HAE and their caregivers.<sup>43,57,58</sup> According to the US-based survey study, HAE attacks exclusively affecting the face were generally associated with higher absenteeism (26.5%), presenteeism (44.0%), and work productivity loss (48.2%) than attacks affecting other areas of the body.<sup>32</sup> In addition, a cross-sectional web-based survey study of 457 patients with HAE found that productivity was impaired in all categories of the Work Productivity and Activity Impairment-General Health questionnaire, including 34% overall work impairment.<sup>59</sup>

HAE also affects quality of life because it interferes with patients' personal lives. For example, in the cross-sectional web-based survey study of 457 patients with HAE, 59% of respondents reported missing  $\geq 1$  day of leisure activity because of their most recent HAE attack.<sup>59</sup> Moreover, because patients feel that they need to avoid suspected attack triggers, they often find themselves modifying their lifestyle.<sup>4</sup>

### Financial burden

The costs associated with HAE can lead to a substantial economic burden for patients living with the disease.<sup>58</sup> Direct costs include the cost of medical care, including medication, medical visits, supportive care, and travel. For example, as genetic testing for HAE is often not routinely conducted and may not always be available to a patient's primary care physician,<sup>36,60</sup> patients often search and pay for genetic tests themselves. Some patients may also decline any additional genetic testing if no mutations are identified in their *SERPING1* gene for financial reasons, which can create difficulties in obtaining future insurance coverage for any long-term treatments.<sup>61</sup>

In addition to direct medical costs, loss of productivity and absenteeism from work and/or school are associated with indirect costs for the patient.<sup>62</sup> For example, in a cross-sectional web-based survey study of 457 patients with HAE from



2007 to 2008, it was reported that the average lost income for missed work due to an HAE attack was approximately \$525.<sup>63</sup> When considering the mean attack frequency for the entire survey population, this equates to about \$3400 per year.

### Pediatric caregiver burden

If prenatal genetic testing is performed and confirms HAE, parents can face a significant burden. The decision around whether to proceed with the pregnancy should be made by evaluating the potential benefits and risks. Some pediatricians and clinicians are likely to be uncomfortable discussing this issue with parents because of their own lack of direct experience with patients who are diagnosed with HAE. Although the course of disease is variable and there are poor correlations between genetic defect and severity, advances in treatment options have improved the quality of life of patients with HAE.<sup>47</sup>

Parents can experience significant levels of anxiety waiting for their child's first HAE attack. Moreover, depending in which country the patient lives, this anxiety can be further exacerbated by the knowledge that there are a very limited number of approved acute treatments for patients under the age of 2 years and approved prophylactic treatments for patients under the age of 12 years.<sup>46,47</sup> A list of first-line on-demand and prophylactic therapies approved by the US Food and Drug Administration (FDA) and their respective indications are detailed in [Table 2](#). Additional parental concerns include difficulty in obtaining long-term treatment funding, lack of awareness of HAE in schools, and possible issues when traveling overseas.<sup>64</sup>

Parents with HAE can also become caregivers to any of their children who receive a positive diagnosis, further increasing the emotional, physical, and financial burdens of disease.<sup>45</sup> In support of this, 77% of the 30 caregivers included in a recent survey study reported having a diagnosis of HAE themselves.<sup>73</sup> The most frequently reported roles of the caregivers participating in this study in the management of patients with HAE included making treatment decisions (70%), traveling to and from appointments (70%), communicating with doctors (63%), preparing medication (60%), helping to administer

medication (53%), and scheduling appointments (53%). In some cases, management of HAE also involved helping the patient with everyday household (47%) and daily living (13%) tasks.<sup>73</sup>

### Pediatric considerations

Children who are diagnosed with HAE are concerned about the immediate impact the disease will have on their health and life, including the need to go to the hospital and the fact that attacks may prevent them from going out.<sup>64</sup> Children with HAE may also suffer from impaired emotional competence or alexithymia, which can lead to additional stress.<sup>74</sup>

## TREATMENT CHALLENGES

Prior to the approval of efficacious on-demand and prophylactic options specific to HAE, symptomatic relief often involved hydration, administration of fresh frozen plasma, and/or the prescription of narcotics to help with pain management.<sup>75,76</sup> When only supportive care was available emergency department visits were high.<sup>62</sup> Since then, improved access to HAE-specific therapies (on-demand and prophylactic; [Table 2](#)) and the possibility to self-administer at home have reduced the need for emergency department care.<sup>77</sup> Even with access to current treatment options, however, some patients with HAE will still need to attend the emergency department. For example, patients suffering from facial attacks that extend to the larynx will require emergency department visits, often for intubation or tracheotomy to prevent asphyxiation.<sup>76</sup> Patients also visit the emergency department for support with pain management, especially during an acute abdominal swelling attack.<sup>76</sup> Due to almost all attacks being accompanied by pain, patients with HAE can therefore be perceived and labeled as narcotic-seekers.<sup>78</sup>

In the United States, it is estimated that up to half of patients diagnosed with HAE require emergency department management at some point.<sup>23,26,79</sup> A survey study conducted in Japan also indicated that, while the number of days a patient spent hospitalized per year significantly decreased following diagnosis of HAE, 19/46 patients (41.3%) still needed to be hospitalized for one or more days as part of their care after

Treatment	Indication
<b>On-demand</b>	
Ecallantide <sup>65</sup>	Treatment of acute attacks in patients $\geq 12$ years
Icatibant <sup>66</sup>	Treatment of acute attacks in adults $\geq 18$ years
Plasma-derived C1-INH <sup>67</sup>	Treatment of acute abdominal, facial, or laryngeal attacks in adult and pediatric patients
Recombinant C1-INH <sup>68</sup>	Treatment of acute attacks in adult and adolescent patients
<b>Prophylactic</b>	
Berotrastat <sup>69</sup>	Prophylaxis to prevent attacks in adults and pediatric patients $\geq 12$ years
Lanadelumab <sup>70</sup>	Prophylaxis to prevent attacks in adult and pediatric patients $\geq 2$ years
Plasma-derived C1-INH (IV) <sup>71</sup>	Routine prophylaxis against attacks in adults, adolescents, and pediatric patients $\geq 6$ years
Plasma-derived C1-INH (SC) <sup>72</sup>	Routine prophylaxis to prevent attacks in patients $\geq 6$ years

**Table 2.** Approved first-line treatments for HAE<sup>4</sup> C1-INH, C1-esterase inhibitor; HAE, hereditary angioedema; IV, intravenous; SC, subcutaneous.

receiving the confirmed diagnosis.<sup>36</sup> Furthermore, an international survey of 242 patients from France, the United Kingdom, Spain, Canada, Australia, Switzerland, Germany, and Austria indicated that, over the course of the year prior to study initiation, 37.6%, 19.4%, and 18.2% of patients reported  $\geq 1$  HAE-related visit to the emergency department, hospitalization, or urgent care visit, respectively.<sup>54</sup>

Treatment in the emergency department can still be required for acute or severe HAE attacks, even when a patient is receiving long-term prophylaxis, placing a significant financial burden on patients and their families compared to treatment at home.<sup>47,80</sup> Analysis of the 2015–2016 Nationwide Emergency Department Sample in the United States indicated that the mean total annual emergency department cost of care for patients with HAE was \$32,939,152 with a mean cost per visit of \$3,598.<sup>81</sup> A recent modeling study indicated that the cost and efficacy of on-demand HAE treatment per attack can vary by therapeutic agent with annual health plan expenditure estimated to be \$6.94 million for recombinant C1-INH, \$7.90 million for plasma-derived C1-

INH, \$7.97 million for icatibant, and \$11.3 million for ecallantide.<sup>82</sup>

The current standard of care approach to HAE treatment is aimed at reducing both the frequency and the severity of attacks, however, it is recommended that patient-specific factors that influence the burden of their disease and the burden of treatment should also be considered when assessing disease control and attempting to normalize a patient's life.<sup>52,83</sup> While it is recommended that a detailed management plan be developed for all patients following a HAE diagnosis, putting a treatment plan in place can be challenging. In many cases, implementation of the management plan will involve coordination of care with an emergency department that is geographically close to the patient but may not necessarily be close to the practice of the physician who is responsible for initiating creation of the plan. Adequate coordination of care can thus result in the requirement for multiple phone calls between the patient's physician, the hospital pharmacist, and the emergency department medical director as well as preparation of a written care plan.

In addition, prescribing HAE medication represents a significant, non-compensated burden for physicians, particularly where prior authorizations are needed. Prior authorizations are part of a cost-control process that requires healthcare professionals in some countries to obtain advanced approval from healthcare plans before a prescription medication qualifies for payment and can be administered to the patient. Obtaining prior authorization of a medication used to treat any condition that requires it can be difficult and time consuming. While not specific to patients with HAE, findings from the 2021 American Medical Association (AMA) prior authorization survey of more than 1000 physicians indicated that practices complete an average of 41 prior authorizations per physician per week; physicians and their staff spend at least 13 hours per week completing prior authorizations; 40% of physicians have staff who work exclusively on prior authorizations; and 88% of physicians described the burdens associated with prior authorizations as high or extremely high.<sup>84</sup>

In addition to the burden placed on physicians, many patients, including those diagnosed with HAE, experience further distress at the prior authorization stage, particularly if they are unaware of the challenges physicians face when trying to get specific treatment options in place for them. Overall, 93% of the physicians participating in the 2021 AMA prior authorization survey indicated that they felt the prior authorization process delayed their patients from accessing the necessary care for their condition with 24% indicating that they felt the requirement for prior authorization had led to a patient's hospitalization.<sup>84</sup>

It is often more challenging to put a treatment plan in place for patients with suspected HAE-nl-C1-INH than it is for patients with type I or type II HAE-C1-INH due to the lack of a confirmatory biomarker or diagnostic test to fully verify the diagnosis.<sup>61,85</sup> Moreover, many physicians never come across a patient with HAE-nl-C1-INH or only end up diagnosing and treating a few. Physicians of patients with suspected HAE-nl-C1-INH may initiate a trial course, or use a sample of, HAE-specific therapies as part of the diagnostic process. If a response is observed to this treatment then the prescriber and the patient may be better able to navigate the prior authorization process

and obtain insurance coverage for long-term prophylaxis, although the success rate of obtaining funding for cases like this is currently unclear.<sup>85</sup>

HAE attacks in pediatric patients will often not begin for several years after the plan is made, therefore, the treatments that were recommended at the time of conception might not be the best immediate option for the patient during their first attack. Furthermore, some patients may not have a plan in place at the time of their first attack, and many HAE medications are not consistently kept on formulary across all emergency departments.<sup>86</sup> This provides a significant challenge with regards to the management of pediatric patients with HAE because treatment of acute swelling attacks in this population will typically require intravenous infusion of C1-INH products that are not readily available in most clinical practices.<sup>47,86</sup>

Although a range of first-line on-demand and long-term prophylactic treatments are available for HAE (Table 2), many patients still face significant financial, physical, and emotional burdens with a reduced quality of life.<sup>1,32,87,88</sup> Most of these first-line therapies are injectable treatments, which can be difficult for patients, particularly needle phobic individuals, who may suffer from significant psychological distress because of self-injection.<sup>61,87,89,90</sup>

In a survey of 75 patients with type I or type II HAE, 44% indicated that receiving HAE treatment had impaired their everyday work and activities "by at least a little bit". This included 78% of the patients who had received intravenous prophylaxis and 39% of the patients who had received subcutaneous prophylaxis.<sup>90</sup> Overall, 23% of patients, including 33% of those receiving intravenous prophylaxis and 23% of those receiving subcutaneous prophylaxis, reported having to schedule personal and professional obligations around the administration schedule of their medications.<sup>90</sup> Furthermore, 19% of patients reported skipping their medication on occasion because their injections or infusions were inconvenient.<sup>90</sup> A significant proportion of patients also reported feeling nervous (47%), overwhelmed (33%), stressed (31%), or intimidated (26%) when faced with starting a new prophylactic medication.<sup>90</sup>



Many patients with HAE describe feeling tethered to their medication and reliant on others to help administer them.<sup>43</sup> A recent survey of 75 patients with HAE-C1-INH indicated that, while the majority of patients agreed with the necessity of taking long-term preventative medications, 57% regarded prophylactic treatment as burdensome.<sup>87</sup> Of the 48/75 patients in this survey who were taking long-term prophylactic treatment, 98% indicated that, while they were happy with their current medication, they would prefer an oral treatment if one was available.<sup>87</sup> Notably, 85% of these patients indicated that they would be willing to switch from their current therapy to an oral medication if one became available.<sup>87</sup> Furthermore, findings from this survey indicate that efficacy is not necessarily the most important factor in treatment selection for some patients, highlighting the importance of adopting a shared-decision making approach between the treating physician and the patient with regards to management of their HAE following diagnosis.<sup>87,89</sup>

Consideration of patient treatment preferences, and the development of non-steroidal oral options such as berotralstat, which has been approved as a first line once-daily plasma kallikrein inhibitor for long-term prevention of HAE attacks in patients aged 12 years and over, are critical for improving future care of patients with this disease.<sup>4,69,87,91</sup> However, patient accessibility to modern treatments differs widely between countries<sup>36</sup> and findings from a recent survey of 177 US-based HAE physicians indicated that cost and ability to obtain insurance coverage is still one of the strongest non-efficacy based factors that determines which treatments they are able to offer to patients.<sup>85</sup>

## CONCLUSIONS

It is well documented in the literature that HAE places a significant burden on patients, caregivers, and physicians. Therefore, it is important to continue to raise awareness of HAE and the symptoms associated with this condition because delays to diagnosis have a direct impact upon patient suffering and quality of life. Many patients will seek help from hospitals during their first swelling attack, therefore, it is paramount that emergency department staff are aware of the

different pathological pathways that distinguish HAE from other forms of angioedema to ensure that the most appropriate treatment is administered.

While more studies are required to fully assess the impact of receiving a HAE diagnosis on the relationship between a patient and their physician, it is advisable for physicians to work towards adopting a shared decision-making approach when discussing potential HAE therapeutics with patients to ensure that the burdens associated with diagnosis and treatment are adequately addressed. As disease awareness increases, it is hoped that patients will be diagnosed earlier and that both prior authorization of medications and insurance coverage of treatment costs will become easier to obtain, ultimately reducing the burden of treatment for these patients and their caregivers.

## Abbreviations

AMA: American Medical Association; ANGPT1: angiotensinogen 1; C1-INH: C1-esterase inhibitor; C4: complement component 4; COVID-19: Coronavirus-19; EAACI: European Academy of Allergy and Clinical Immunology; HAE: hereditary angioedema; HAE-C1-INH: hereditary angioedema due to C1-inhibitor deficiency or dysfunction; HAE-nl-C1-INH: hereditary angioedema with normal C1-inhibitor levels; HS3ST6: heparan sulfate-glucosamine 3-O-sulfotransferase; IOS: Icatibant Outcome Survey; KNG1: kininogen; MYOF: myoferlin; PLG: plasminogen; QoL: quality of life; SERPING1: Serpin family G member 1; US: United States; WAO: World Allergy Organization

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JR reports receiving fees for serving as a consultant at advisory boards for CSL Behring, Octapharma USA, Inc., Pharming Healthcare, Inc., and Takeda California, Inc. JR is also a principal investigator for clinical trials sponsored by Ionis Pharmaceuticals and Kalvista Pharmaceuticals. MCG has received speaker bureau fees from BioCryst Pharmaceuticals, Inc., and Takeda. MOC reports receiving fees for serving as a consultant and a speaker for BioCryst Pharmaceuticals, Inc., CSL Behring, Kalvista Pharmaceuticals, and Pharming Technologies BV, and has received research funding from Takeda.

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