

# Emergency Department Management of Hereditary Angioedema Attacks: Patient Perspectives



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**What is already known about this topic?** Emergency department (ED) care comprises a significant portion of hereditary angioedema (HAE) management. ED management of HAE was hindered by limited treatment options until Food and Drug Administration approval of 4 on-demand HAE therapies starting in 2009.

**What does this article add to our knowledge?** Patient-reported data identified lack of HAE awareness and medication mismanagement as areas for improvement in the ED. Having an established, effective treatment plan appears to improve medical management of HAE in the ED.

**How does this study impact current management guidelines?** Although ED management of HAE attacks has improved since the development of HAE therapies, there is room for improvement with a focus on HAE awareness and administration of effective HAE therapies.

**BACKGROUND:** Emergency department (ED) management of hereditary angioedema (HAE) has been hindered by misdiagnosis and limited treatment options. Food and Drug Administration approval of 4 on-demand HAE therapies starting in 2009 and the publication of ED guidelines for angioedema management in 2014 should facilitate improvement of HAE management in the ED.

**OBJECTIVE:** The objective of this study was to identify patient-reported areas for improvement in ED management of HAE attacks.

**METHODS:** Patients with self-reported HAE with C1 inhibitor deficiency who attended the 2015 HAE Association Patient Summit were asked to complete an anonymous 30-question survey. Questions addressed patient characteristics and HAE management in the ED.

**RESULTS:** Patients indicated that understanding of HAE in the ED needed improvement (99%, 104 of 105 patients).

Recognition of HAE as a diagnosis (48%, 50 of 105 patients), appreciation of HAE as a serious disease (45%, 47 of 105 patients), and medication management (59%, 62 of 105 patients) were identified as areas needing improvement. Among 39 patients who required ED care within the last year, 6 did not receive any HAE-targeted therapy, and treatment with corticosteroids ( $n = 3$ ), epinephrine ( $n = 2$ ), and antihistamines ( $n = 7$ ) was reported. Among 68 patients whose treatment plan was to receive home on-demand therapy, 26 required ED care because of an inability to receive on-demand therapy at home as outlined in their treatment plan. Having a treatment plan was associated with a greater likelihood of receiving HAE therapy in the ED (99% vs 74%,  $P = .002$ ).

**CONCLUSION:** HAE management in the ED can be improved with a focus on recognition of HAE attacks and administration of effective HAE therapies. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:128-34)

**Key words:** Hereditary angioedema; Hereditary angioedema attacks; Treatment plan; Angioedema management; Emergency department; Angioedema guidelines; On-demand treatment; Patient-reported outcomes; Quality of life; Disease burden

Hereditary angioedema with C1 inhibitor deficiency (HAE-C1INH) is an autosomal dominant disease with an estimated prevalence of 1/10,000 to 1/100,000.<sup>1</sup> In HAE-C1INH, mutations in the C1-INH gene, *SERPING1*, lead to deficiency or dysfunction of the C1-INH protein.<sup>1,2</sup> C1-INH protein

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*Abbreviations used*

ED- Emergency department  
FDA- Food and Drug Administration  
HAE- Hereditary angioedema  
HAE-C1INH- HAE with C1 inhibitor deficiency

deficiency or dysfunction leads to activation of the contact system with generation of bradykinin, which triggers increased vascular permeability via bradykinin-2-receptors on endothelial cells. Clinically, this translates into unpredictable, potentially life-threatening, recurrent angioedema of cutaneous (face, genitalia, extremities) and mucosal (abdomen, oropharynx, larynx) tissues that can require emergency care.<sup>2,5</sup> Emergency department (ED) care comprises a significant portion of HAE medical management in the United States, with prior publications reporting conservative estimates of 2282 to 5040 ED visits and 1691 to 3375 hospitalizations annually.<sup>4-6</sup>

HAE is a rare disorder and is often not considered in the differential of patients presenting to the ED with angioedema or recurrent abdominal pain.<sup>7</sup> Until recently, ED management of HAE has been hindered by misdiagnosis and limited treatment options.<sup>8</sup> Effective treatment of HAE attacks has become increasingly possible with the Food and Drug Administration (FDA) approval of 4 on-demand HAE therapies starting in 2009.<sup>9</sup> Despite advances in HAE care, a survey performed at the 2013 HAE Association Patient Summit revealed that 70% of patients with HAE in the United States were not satisfied with their ED care.<sup>8</sup> A recent study from outside the United States suggests that medication mismanagement and inappropriate discharge planning are areas of HAE ED management that need improvement.<sup>10</sup>

In 2014, ED guidelines for angioedema management, including HAE emergency care, were published.<sup>11</sup> These guidelines should facilitate future efforts to improve HAE care in the ED.<sup>11</sup> In addition, other HAE guidelines have addressed the treatment of acute attacks.<sup>1,12,13</sup> As HAE attacks result in significant and multifaceted disease burden, patient perspectives must be considered to ensure that efforts to improve ED HAE care also result in decreased disease burden and improved quality of life.<sup>7</sup> The purpose of our study was to investigate the concordance between ED HAE care and published guidelines, and to identify areas that need further improvement.

## METHODS

### Subjects

We recruited potential patients with HAE from across the United States in attendance at the 2015 HAE Association Patient Summit (October 9-11, Denver, Colo). Patients self-reported HAE-C1INH and were asked to complete an anonymous 30-question survey (available in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). The purpose of data collection was explained to patients by investigators. Parents recorded responses for patients 0 to 15 years of age. An Investigational Review Board waiver was granted because the data were deidentified.

### Survey

The survey was developed by IMO and collaborating HAE experts (AB, MAR, SCC, PB) to characterize HAE management in the ED. The survey was created through a review of prior survey data, obtaining consensus among the authors, and a review of ED

guidelines for angioedema management. Questions were categorized into several broad areas. All patients were instructed to complete the first 8 questions in the questionnaire addressing baseline patient characteristics (demographics, HAE type, emergency treatment plan).

Patients with at least one ED visit were instructed to complete questions 9 through 30. Questions 9 through 16 addressed general ED care issues (understanding of HAE in the ED and comparing ED HAE care and understanding before and after 2009) that were reported for this ED group. Questions 18 to 30 asked patients about their experiences during their most recent ED visit.

Patients who had at least one ED visit for HAE treatment during their lifetime were identified based on their answers to question 3 (answers a, b, c, and d). This group is referred to as the "ED group" throughout the article.

Question 3: How many times have you been to the emergency department (ED) for treatment of HAE?

- a. Once
- b. 1 to 10 times
- c. 10 to 25 times
- d. More than 25 times
- e. I have never gone to an ED for HAE treatment

Patients who reported that their last ED visit for HAE occurred during or after 2009 were identified based on their answers to question 17 (answers a, b, and c). These patients are referred to as the "2009+ group."

Patients who reported that their last ED visit for HAE was within the last year, or after October 2014 as the survey was deployed in October 2015, were also identified based on their answers to question 17 (answer a). These patients are subsequently referred to as the "2014+ group."

Question 17: How long ago was your most recent visit to the ED?

- a. Within the past year
- b. Within the last 1-2 years
- c. Greater than 2 years
- d. Before 2009
- e. I do not remember

The 2009+ group and the 2014+ group were created so that the data reported would accurately reflect changing practices of ED HAE care, as 2009 was when the first FDA-approved HAE medications became available and April 2014 was when the ED angioedema guidelines were published.<sup>11</sup>

The total number of patients who answered each question is shown in [Table E1](#) (available in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). The numbers of patients who answered each question among the ED group, the 2009+ group, and the 2014+ group are also shown in [Table E1](#).

### Statistical Analysis

Statistical analyses were performed using Stata/IC 14.0 (Stata-Corp, College Station, Tex). Fisher's exact test or  $\chi^2$  test was used as appropriate for comparisons of proportions between 2 groups. All *P*-values were 2-tailed, with *P* < .05 considered statistically significant. Missing answers for questions were excluded from analysis.

## RESULTS

### Patient demographics

Patients with HAE-C1INH who completed the survey (*n* = 118) were representative of all age groups (0-15, 16-25,

26-45, 46-65, >65 years of age) (Figure 1, A). Most patients were 46 to 65 years old (42%) and 26 to 45 years old (29%). The majority of patients (91%, 107 of 118 patients) reported at least one ED visit for HAE treatment during their lifetime. All patients who reported their distance from the nearest ED lived within 100 miles from the nearest ED ( $n = 117$ ) (Figure 1, B).

There were 107 patients who reported at least one ED visit for HAE treatment during their lifetime (ED group). There were 87 patients who reported that their last ED visit for HAE occurred during or after 2009 (2009+ group), and 39 patients who reported that their last ED visit for HAE was within the last year (2014+ group).

### Emergency treatment plans

Answers regarding emergency treatment plans are reported for all 118 patients because this was felt to be a necessary part of managing a patient with HAE independent of having an ED visit. Patients were asked in question 5 how they would decide which ED to go to if necessary. Patients were allowed to choose more than one answer. Patients answered that they would present to the nearest ED (55%, 65 of 118 patients), the ED at the hospital where their regular HAE doctor works (31%, 36 of 118 patients), follow doctor recommendation (6%, 7 of 118 patients), present where there was patient familiarity with the ED care provided (4%, 5 of 118 patients), follow HAE Association recommendation (3%, 4 of 118 patients), present where there was known availability of HAE-approved therapy at the ED (3%, 4 of 118 patients), or present to the ED that accepted the patient's health care insurance plan (1%, 1 of 118 patients).

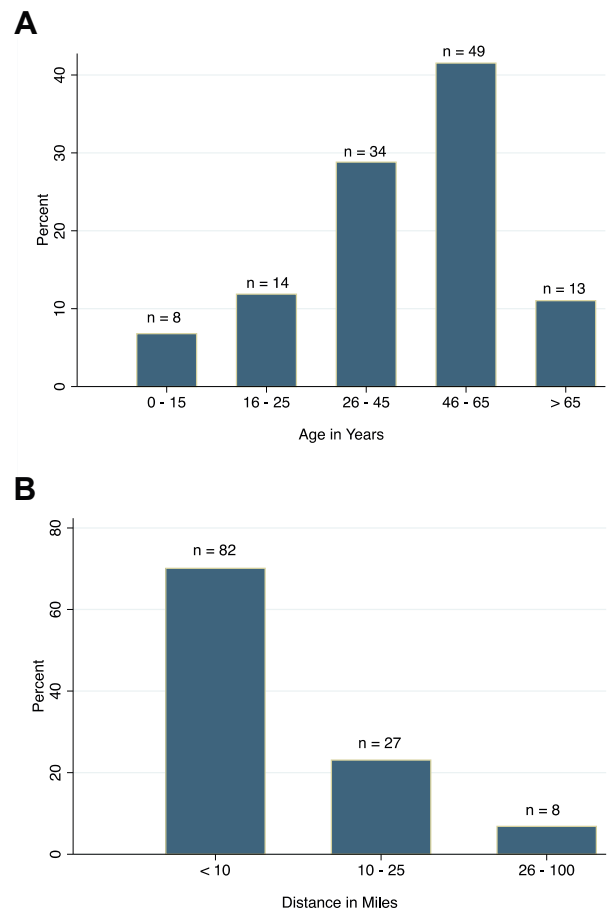
Most patients (92%, 108 of 118 patients) answered that their doctor had provided a plan for how to treat their HAE attacks in question 7. Only 50% (53 of 106 patients who answered question 11) reported having a written emergency plan they could bring to the ED during an HAE attack.

Question 8 asked patients to identify if and how they received on-demand therapy. Answers provided by 117 patients are shown in Table I. Among patients who had at least one treatment plan for HAE attacks, most had a plan to receive on-demand therapy at home (89%, 95 of 107 patients). The most common method for home administration was self-administration ( $n = 79$ ), followed by administration by a friend or family member ( $n = 10$ ) and administration by home infusion nursing services ( $n = 10$ ).

### Patient perception regarding understanding of HAE in the ED

There were 107 patients who reported requiring at least one ED visit for HAE treatment during their lifetime (ED group). Answers for questions assessing patient perception regarding understanding of HAE in the ED are reported for patients in the ED group ( $n = 107$ ). A high percentage of patients reported that ED understanding of HAE was poor or that only a few ED doctors had good understanding of HAE (88%, 93 of 106 patients who answered question 9).

To identify perceived improvements in ED care after the FDA approval of on-demand HAE therapies starting in 2009, patients were asked to compare their ED care before and after 2009 in question 15. Of the 104 patients who answered question 15, 20 patients answered that they could not compare ED care before and after 2009 because they did not have ED visits during both time frames. Of the remaining 84 patients, more than half (65%, 55 of 84 patients) reported that their HAE care in the ED was



**FIGURE 1. A**, Distribution of patient ages. The Y-axis represents percent of patients who answered 0-15 years, 16-25 years, 26-45 years, 46-65 years, or >65 years, for the question: "How old are you currently?" The number of patients in each group is above each bar. **B**, Distance from nearest emergency department (ED). The Y-axis represents percent of patients who answered <10 miles, 10-25 miles, or 26-100 miles, for the question: "How far are you from the nearest ED?" The number of patients in each group is above each bar.

improved. However, 29 patients (35%, 29 of 84 patients) reported that their HAE care in the ED was worse (2%, 2 of 84 patients) or unchanged (32%, 27 of 84 patients).

To identify perceived improvements in ED care after the publication of guidelines for ED management of angioedema, patients were asked to compare their ED care before and after 2014 in question 14. Of the 104 patients who answered question 14, 40 patients (38%) answered that they could not compare ED care before and after 2014 because they did not have ED visits in both time frames. More than half of the remaining patients (61%, 39 of 64 patients) reported that their HAE care in the ED was improved, whereas 25 patients (39%, 25 of 64 patients) reported that their HAE care in the ED was worse (3%, 2 of 64 patients) or unchanged (36%, 23 of 64 patients).

Patients were asked what areas of HAE knowledge could be improved in the ED in question 12. Patients were allowed to choose more than one area for improvement in the ED. Nearly all patients in the ED group reported that ED understanding of

**TABLE I.** Treatment plans for acute HAE attacks

Treatment plan	n (%)
One plan	102 (87)
Home	90 (77)
Self	75 (64)
F	7 (6)
RN	8 (7)
Medical Facility	6 (5)
ED	6 (5)
Two plans	5 (4)
Self or F	3 (3)
Self or RN	1 (1)
ED or RN	1 (1)
No plan	10 (9)
Total	117

ED, Emergency department; HAE, hereditary angioedema.

Patients were asked to answer: “Which of the following best describes your typical plan for use of on-demand (‘rescue’) therapy when you have an HAE attack?” Patients were allowed to choose more than one answer. Of 118 patients who started the survey, 117 answered this question. Answer choices are displayed as number (%). Of the 10 patients who had no plan, 5 answered that they had no typical approach to have their on-demand therapy administered and 5 answered that they did not have access to on-demand therapy.

Self = “I self-administer on-demand treatment at home”; F = “A family member or friend administers my on-demand HAE treatment at home”; RN = “I call a visiting nurse to administer my on-demand medication at home”; Medical Facility = “I go to a medical facility such as a doctor’s office or infusion center to have the treatment”; ED = “I go to the ED to receive my on-demand HAE treatment.”

HAE needed improvement (99%, 104 of 105 patients who answered the question), and 100% of patients in the 2009+ group reported that ED understanding of HAE needed improvement (Table II). The percentages of patients identifying recognition of HAE as a diagnosis, appreciation of HAE as a serious disease with impact on quality of life, and medication management as an area that needed to be improved were similar between the ED group and the 2009+ group. In the 2009+ group, 19 patients reported not receiving any HAE-targeted therapy, and treatment with corticosteroids (n = 9), epinephrine (n = 9), and antihistamines (n = 21) was reported.

Taken together, analysis of these data suggests that although patients perceive improvements in the ED, they also agree that understanding of HAE in the ED needs further improvement.

### Patient perception regarding the most recent ED visit

There were 87 patients who reported that their most recent ED visit for HAE occurred during or after 2009 (2009+ group). Answers for questions assessing patient experience before and during their most recent ED visit are reported for the 2009+ group (n = 87), as 2009 was when the first FDA approved HAE medications became available.

Of 83 patients who answered question 19 asking what the main reason for their most recent ED visit was, 37% (31 of 83 patients) reported that they presented to the ED because of an inability to receive home on-demand therapy (answer choices B, C, D; Table III). Of note, 38% (26 of 68 patients) of patients who reported that they had treatment plans involving home administration of on-demand therapy answered that inability to receive home on-demand therapy was the main reason for their most recent ED

**TABLE II.** Patient perceptions of ED HAE care

Area(s) of HAE knowledge in the ED needing improvement	ED group	2009+ group
	(n = 105) n (%)	(n = 87) n (%)
A: HAE itself (diagnosis)	50 (48)	44 (51)
B: Understanding about effective medications	62 (59)	51 (59)
C: Appreciation of serious nature of HAE attacks	47 (45)	40 (46)
D: Nothing, current knowledge of HAE in ED is sufficient	1 (1)	0 (0)

ED, Emergency department; HAE, hereditary angioedema.

Patients in the ED group (n = 107) and the 2009+ group (n = 87) were asked to answer question 12: “In general, what area(s) of HAE knowledge in the ED could be most improved?” The total number of patients who answered the question in each group is shown as “n = number.” Patients were allowed to choose more than one answer. Answer choices are displayed as number (%).

visit. The serious implication of these data is that plans to receive home on-demand therapy are not consistently successful.

More than half of the patients (63%, 52 of 83 patients who answered question 22) were seen within 1 hour of arrival to the ED. However, among 35 patients with throat swelling, 11 (31%) reported waiting more than 1 hour before being evaluated by a physician.

Most patients recalled receiving effective, on-demand HAE therapy (78%, 68 of 87 patients). More than half of the patients who received HAE therapy received it after the first hour (59%, 34 of 58 patients). Patients who had on-demand therapy at home and patients who had a treatment plan for their HAE attacks were more likely to report having received HAE therapy in the ED (Table IV). More patients whose last ED visit was within the last 2 years reported that they were treated with HAE medication compared with those patients whose last ED visit was more than 2 years ago.

### Patient-reported characteristics affecting HAE ED outcomes

Patient-reported characteristics were investigated as possible factors associated with important HAE ED outcomes. Patient-reported characteristics that were independent of the development of HAE medications and the publication of angioedema guidelines were investigated in the ED group (n = 107). Patient-reported characteristics related to treatment with HAE medication were investigated in the 2009+ group (n = 87).

Twenty-two patients in the ED group (22%, 22 of 101 patients who answered question 26) reported being admitted during their most recent visit to the ED. Patients who presented to the ED within 4 hours after symptom onset were less likely to be admitted or observed in the ED for  $\geq 4$  hours before discharge, and patients who were evaluated by a physician within 1 hour after ED arrival were also less likely to be observed in the ED for  $\geq 4$  hours before discharge (Table V). A significantly greater proportion of patients who received IV fluids or opiates were admitted or observed in the ED for  $\geq 4$  hours before discharge.

A recommendation or plan to follow up with an allergist was made for more than half of the patients and on discharge from the hospital or the ED in the ED group (69%, 68 of 99 patients who answered question 29). Patients who presented with throat or abdominal swelling were more likely to follow up with an allergist at the time of discharge (Table VIA).

**TABLE III.** Reasons for the most recent ED visit among patients with and without home on-demand therapy in the 2009+ group

	A	B	C	D	E	F	G	BLANK	Total answered
All 2009+	11 (13)	21 (25)	6 (7)	4 (5)	11 (13)	20 (24)	10 (12)	4 (5)	83
Planned	6 (9)	16 (24)	6 (9)	4 (6)	11 (16)	16 (24)	9 (13)	3 (4)	68

ED, Emergency department, HAE, hereditary angioedema.

Patients were asked: "What was your main reason for your last ED visit for HAE?" Answer choices are displayed as number (%) for patients who answered that receiving on-demand therapy at home was part of their treatment plan in question 8 (Planned). Percentages are calculated with the denominator set as the number of patients who answered the pertinent question(s).

Answer Choices:

- A. The ED is where I was instructed to go for on-demand ("rescue") treatment as part of my established HAE treatment plan.
- B. I did not have any effective on-demand ("rescue") therapy available at home.
- C. I had on-demand ("rescue") treatment but did not feel comfortable self-administering it.
- D. The person who administers my on-demand ("rescue") treatment (visiting nurse, family member, or friend) could not be reached or was not available.
- E. My symptoms did not get better or returned even though I used my on-demand ("rescue") treatment at home.
- F. I had symptoms that made me worried: airway angioedema (throat swelling), head or neck swelling.
- G. None of the above, but I felt safest going to the ED.

**TABLE IV.** Characteristics associated with differences in HAE therapy administration in the emergency department

	HAE therapy administered		
	Yes (n = 68)	No (n = 19)	P-value
On-demand available at home	63 (93)	14 (74)	.02
Had treatment plan	67 (99)	14 (74)	.002
Last ED visit <2 y ago	51 (75)	8 (42)	.01

ED, Emergency department; HAE, hereditary angioedema.

Analyses performed in the 2009+ group because effective HAE therapies were only approved starting in 2009. Data presented as n (%).

In the 2009+ group, having a prescription for home on-demand HAE therapy at the time of discharge (seen in 60%, 51 of 85 patients who answered question 30) was associated with having a treatment plan, having a written ED plan, and receiving HAE therapy in the ED (Table VIB).

### HAE-specific issues addressed in ED angioedema guidelines

There were 39 patients who reported that their last ED visit for HAE was within the last year (2014+ group). ED guidelines for angioedema recommend that patients with a prior diagnosis of HAE receive targeted HAE treatment.<sup>11</sup> Of 39 patients in the 2014+ group, 6 (15%) reported that they did not receive any HAE treatment. Treatment with inappropriate medications for HAE care was reported: corticosteroids (n = 3), epinephrine (n = 2), and antihistamines (n = 7). The ED guidelines also stress the importance of patients having a prescription for home on-demand HAE therapy at the time of discharge. In the 2014+ group, only half of the patients (51%, 20 of 39 patients) had a prescription for home on-demand HAE therapy at the time of discharge. The proportion of patients who had a prescription for home on-demand HAE therapy at the time of discharge was not significantly different between 2009 and 2014 and 2014 onward.

## DISCUSSION

Recent studies have identified the need to improve ED care of HAE.<sup>8,10</sup> However, there are limited data regarding the current state of ED care of HAE attacks. This survey provides information regarding emergency care of HAE attacks from the perspective of patients with HAE-C1INH in the United

States. To our knowledge, this is the first time a large US population of patients with HAE-C1INH has been surveyed regarding their experience with emergency care of HAE attacks.

Survey results indicate that improvements have been made in ED care since the FDA approval of on-demand HAE therapies and the publication of guidelines for ED management of angioedema. For instance, patients were more likely to report that they had received HAE therapies during the last 2 years compared with  $\geq 2$  to <5 years ago. Despite these advances, one-third of patients (35%, 29 of 84 patients) reported that their ED care was unchanged or worse since 2009, despite the FDA approval of on-demand HAE therapies, suggesting that additional education of HAE in the ED is necessary.

Recently, a study from Turkey identified medication mismanagement, lack of awareness of HAE, and delays in triage times as difficulties encountered by patients with HAE in the ED.<sup>10</sup> Our study found that the same areas need improvement in the United States. Medication mismanagement and lack of recognition of HAE were areas identified by patients as needing improvement. Triage times were reportedly greater than 1 hour for 31% of patients who presented with throat swelling in 2009 or after. Recognition and management of HAE should improve in the future because guidelines for ED management of angioedema were recently published.<sup>11</sup> Encouragingly, 61% of patients have already perceived improvement in HAE care in the last year since the publication of these guidelines. Continued education regarding the following specific points in the guidelines will likely continue to improve HAE care.

ED guidelines for angioedema acknowledge the difficulty, if not impossibility, of establishing the etiology of angioedema in the ED, which can be categorized broadly as (1) anaphylaxis, (2) histaminergic angioedema without anaphylaxis (including both allergic and idiopathic angioedema), and (3) nonhistaminergic angioedema (including both HAE and ACE inhibitor-induced angioedema). As histamine-mediated angioedema is the most common etiology, epinephrine is recommended as the first-line treatment of angioedema of unclear cause, and its use should be encouraged in the ED.<sup>11</sup> However, for patients such as those in our study, who present with a definitive diagnosis of HAE (and frequently an HAE action plan), guidelines recommend the use of HAE-targeted acute therapies.<sup>11</sup> As patients in our study reported not receiving effective HAE therapies, even in 2014 or

**TABLE V.** Characteristics associated with differences in admission and length of emergency department observation before discharge

	Admitted*			Length of ED observation before discharge†		
	Yes (n = 21)	No (n = 73)	P-value	<4 h (n = 23)	≥4 h (n = 58)	P-value
<4 h between symptom onset and ED arrival	9 (43) n = 22	53 (73) n = 76	.01	20 (87) n = 25	36 (62) n = 58	.03
<1 h between ED arrival and assessment	15 (68) n = 22	47 (62) n = 75	.59	20 (80) n = 24	31 (53) n = 58	.02
IV fluids administered	18 (82) n = 20	42 (56) n = 74	.04	8 (33) n = 25	37 (64) (n = 56)	.01
Opiates administered	12 (60)	23 (31)	.02	2 (8)	24 (43)	.002

ED, Emergency department; HAE, hereditary angioedema; IV, intravenous.  
Data presented as n (%).

\*Analyses performed for all patients who answered the question: “Were you discharged home or admitted to the hospital after your last ED visit?”

†Analyses performed for patients who were discharged home and answered the question: “If you were discharged from the ED, how many hours were you in the ED before discharge?”

after, this is an area that needs improvement. The possible causes of lack of or delay in treatment with effective HAE therapy include lack of awareness of HAE as a diagnosis, lack of awareness of guidelines for treatment of HAE attacks, and inability to access effective HAE therapies. Education regarding HAE and angioedema guidelines may address the first 2 issues. The last issue is multifaceted and highlights the importance of developing more effective communication between allergist/immunologists and emergency physicians.

Current guidelines recommend that HAE physicians work with patients to create an emergency action plan as part of ongoing care and prescribe specific therapy for home administration or to take them to an ED for administration during an emergency.<sup>11,13</sup> Once the patient arrives at the ED in an emergency situation, it is recommended that the ED should accommodate administration of HAE therapies.<sup>11</sup> The guidelines also recommend that at the time of discharge ED physicians ensure that patients can access at least one modality to treat the next HAE attack.<sup>11</sup> Our data support the effectiveness of these guidelines. Having a treatment plan or a written HAE ED plan provided by an allergist and/or immunologist was associated with more patients receiving appropriate HAE therapy and having a prescription for HAE therapy on discharge. There is room for improvement in this area as 8% of patients did not have a treatment plan and 47% of patients did not have a written HAE ED plan. Furthermore, many patients reported that they required ED care because of an inability to access or receive their home on-demand therapy, consistent with data from a prior study showing most patients present to the ED because on-demand therapy is not available.<sup>14</sup> A total of 40% of patients did not have a prescription or access to effective HAE therapy and 32% were not recommended to follow up with an allergist where they could get a prescription. Improved discharge planning and instructions could possibly decrease repeated admissions or presentations to the ED.

The finding that shorter ED triage times were associated with shorter ED observation lengths before discharge has potentially significant economic impact. Increases in total annual HAE costs are primarily due to ED and hospital costs, with ED and hospital costs accounting for 68% of the total annual \$96,000 per-patient cost for patients with severe attacks.<sup>15</sup> Currently, there is no specific recommendation for ED triage times of HAE in the

**TABLE VI.** Characteristics associated with differences in discharge planning

A. Follow-up with allergy specialist on discharge			
	Yes (n = 60)	No (n = 26)	P-value
Throat swelling	31 (52)	3 (12)	.001
Abdominal swelling	25 (42)	18 (69)	.02
B. On-demand HAE therapy prescribed on discharge*			
	Yes (n = 51)	No (n = 34)	P-value
Had treatment plan	51 (100)	29 (85)	.01
Had written ED plan	32 (63) n = 51	13 (38) n = 34	.03
HAE therapy administered in ED	45 (88)	23 (68)	.02

ED, Emergency department; HAE, hereditary angioedema; IV, intravenous.  
Data presented as n (%).

\*Analyses performed in the 2009+ group, as effective HAE therapies were only approved starting in 2009.

guidelines. Future studies are needed to investigate the effect of ED triage time on HAE ED outcomes.

Finally, this study supports guideline recommendations that allergists ensure that patients themselves are educated about when it is appropriate to seek emergency care and are comfortable with their emergency treatment plans.<sup>11,13</sup> The majority of patients (62%, 63 of 102 patients) did not consult any physician (including physicians managing their HAE) or the HAE Association when making the decision to seek emergency care. Therefore, allergists should discuss beforehand in detail with patients the necessity of seeking medical attention if their symptoms persist or worsen despite therapy or if they have upper airway swelling.<sup>11</sup> It is important for patients who require emergency care to present as soon as possible to the ED, as patients who reported presenting earlier to the ED were less likely to require admission to the hospital or observation in the ED for 4 or more hours before discharge.

Our study has limitations associated with survey-based data. Perceptions and reported treatment outcomes are based on subject recall and opinion and must be interpreted as such and quantitative studies investigating the current state of HAE management in the ED are needed. There is population bias due to the self-reported nature of HAE by all patients. However, this was likely

minimized by limiting the analysis to patients who reported a definitive diagnosis with low C1INH level or function, as only patients with conclusive labs were likely to have received this diagnosis. Despite this limitation, patient-reported data can still help us identify which aspects of ED HAE care impact the patient experience and help physicians focus efforts to improve those aspects that will also lead to improved quality of life.

In summary, using patient-reported data, we found that while ED management of HAE attacks has improved since the development of HAE therapies, there is room for improvement with a focus on HAE awareness and administration of effective HAE therapies. Rapid triage of patients with HAE, shorter time to treatment, and early presentation to the ED appear to improve patient outcomes by shortening ED observation times and decreasing likelihood of admission. Having a treatment plan provided by an allergist and/or immunologist was associated with a higher likelihood of receiving HAE therapy in the ED or having a prescription for HAE therapy on discharge, and inability to access home on-demand therapy was a top reason for presenting to the ED. These data highlight the importance of the HAE care provided by both allergist/immunologists and emergency physicians.

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1. How old are you currently?
  - a. 0-15 years
  - b. 16-25 years
  - c. 26-45 years
  - d. 46-65 years
  - e. >65 years
2. What type of HAE do you have?
  - a. Type 1 HAE
  - b. Type 2 HAE
  - c. HAE with normal C1INH (Type 3)
  - d. Other or I don't know
- b. I go to a medical facility such as a doctor's office or infusion center to have the treatment
- c. I self-administer on-demand ("rescue") treatment at home
- d. A family member or friend administers my on-demand ("rescue") HAE treatment at home
- e. I call a visiting nurse to administer my on-demand ("rescue") medication at home
- f. I don't have access to any of these therapies
- g. I don't have a typical approach

### General Emergency Treatment Plan Information

3. How many times have you been to the emergency department (ED) for treatment of HAE?
  - f. Once
  - g. 1 to 10 times
  - h. 10 to 25 times
  - i. More than 25 times
  - j. I have never gone to an ED for HAE treatment
4. How far are you from the nearest ED?
  - a. <10 miles
  - b. 10 to 25 miles
  - c. 26 to 100 miles
  - d. >100 miles
5. How would you decide which ED to go to?
  - a. I would always go to the hospital where the doctor who treats my HAE works
  - b. I would go to the nearest ED when I was having an HAE attack
  - c. I would call the doctor who treats my HAE and ask where to go
  - d. I would call the Hereditary Angioedema Association (HAEA) and ask for advice
  - e. Other \_\_\_\_\_
6. Do you have an effective on-demand (rescue) therapy available to you at home for HAE? On-demand (rescue) therapies include Firazyr (Icatibant), Berinert or Cinryze (C1 inhibitor), Kalbitor (Ecallantide), and Ruconest (rC1 inhibitor).
  - a. Yes
  - b. No
7. Has the doctor who treats your HAE provided you with a plan for how to treat your HAE attacks?
  - a. Yes
  - b. No
  - c. I don't know
  - d. I don't have a doctor who treats my HAE
8. Which of the following best describes your typical plan for use of on-demand ("rescue") therapy when you have an HAE attack?
  - a. I go to the ED to receive my on-demand ("rescue") HAE treatment
9. How would you rate the level of HAE knowledge/understanding among the ED doctors you have interacted with?
  - a. Most ED doctors have a good understanding
  - b. About half of the ED doctors have a good understanding
  - c. Only a few ED doctors have a good understanding
  - d. There is a very poor understanding of HAE in the ED
10. When I tell ED physicians that I have HAE and what my acute attacks should be treated with, they:
  - a. Understand that I have HAE and administer an effective on-demand ("rescue") treatment
  - b. Call the doctor who treats my HAE, the HAEA, or an HAE specialist and follow their recommendations
  - c. Call the doctor who treats my HAE, the HAEA, or an HAE specialist but still first treat with ineffective therapy (epinephrine, antihistamines, steroids) before following their recommendations
  - d. Do not listen to me or seek additional information and treat me with ineffective therapy (epinephrine, antihistamines, steroids)
11. Do you have a written emergency plan to show the doctor in case you need to go to the ED for an attack of HAE?
  - a. Yes
  - b. No
12. In general, what area(s) of HAE knowledge in the ED could be most improved?
  - a. HAE itself (diagnosis, what it is)
  - b. Understanding about what medications are effective to treat HAE attacks
  - c. Appreciation of the serious nature of HAE attacks and its impact on quality of life
  - d. Nothing, the current knowledge about HAE in the ED is sufficient
13. Are the ED doctors you have seen in the last year aware of ED treatment guidelines for hereditary angioedema?
  - a. Yes

**If you answered "I have never gone to an ED for HAE treatment" for question 3, you are done with the survey.**

**If you have gone to the ED for HAE treatment, please continue with the additional questions to evaluate the patient experience with treatment at an ED.**

### Understanding of HAE in the Emergency Department (ED)

### Changes in ED HAE care and understanding



- b. No
  - c. I don't know
  - d. Not applicable, I have not been to the ED for treatment of HAE in the past year
14. Has your HAE care in the ED improved in the past year compared with prior years?
- a. Worse
  - b. The same
  - c. A little better
  - d. Moderately better
  - e. Much better
  - f. Not applicable, I either didn't visit the ED for angioedema last year or before last year, so I can't compare.
15. Has your HAE care in the ED improved during the past 5 years as more effective HAE treatment options have become available?
- a. Worse
  - b. The same
  - c. A little better
  - d. Moderately better
  - e. Much better
  - f. Not applicable, I either didn't visit the ED for angioedema before 2009 or after 2009, so I can't compare.
16. How many times have you received FFP (fresh frozen plasma) for treatment of HAE in the ED?
- a. Never
  - b. Less than 5 times
  - c. 5 to 10 times
  - d. More than 10 times
  - e. I do not remember

**Please Think About Your Most Recent ED Visit**

17. How long ago was your most recent visit to the ED?
- a. Within the past year
  - b. Within the last 1-2 years
  - c. Greater than 2 years
  - d. Before 2009
  - e. I do not remember
18. Where did you have swelling?
- a. Face
  - b. Peripheral (hand, arm, foot, leg)
  - c. Throat
  - d. Abdomen
  - e. More than one location (please pick all locations that are correct)
  - f. Other: \_\_\_\_\_
19. What was your main reason for your last ED visit for HAE?
- a. The ED is where I was instructed to go for on-demand ("rescue") treatment as part of my established HAE treatment plan
  - b. I did not have any effective on-demand ("rescue") therapy available at home
  - c. I had on-demand ("rescue") treatment but did not feel comfortable self-administering it
  - d. The person who administers my on-demand ("rescue") treatment (visiting nurse, family member, or friend) could not be reached or was not available
  - e. My symptoms did not get better or returned even though I used my on-demand ("rescue") treatment at home
- f. I had symptoms that made me worried: airway angioedema (throat swelling), head or neck swelling
  - g. None of the above, but I felt safest going to the ED
20. Did speaking to a health care provider (doctor or nurse) or someone from the HAEA influence your decision to go to the ED?
- a. Yes, my HAE doctor advised me to go to the ED
  - b. Yes, a health care provider other than my HAE doctor advised me to go to the ED
  - c. Yes, someone at the HAEA advised me to go to the ED
  - d. Not applicable, I didn't speak to any health care provider or the HAEA
21. How soon after symptoms started did you arrive at the ED?
- a. <2 hours
  - b. 2-4 hours
  - c. 4-8 hours
  - d. 8-24 hours
  - e. >24 hours
  - f. I do not remember
22. How long did you have to wait in ED before a physician saw you?
- a. <1 hour
  - b. 1-2 hours
  - c. 2-4 hours
  - d. 4-6 hours
  - e. >6 hours
  - f. I do not remember
23. How many doses of HAE on-demand "rescue" HAE treatment [Firazyr (Icatibant), Berinert or Cinryze (C1 inhibitor), Kalbitor (Ecallantide), Ruconest (rC1 inhibitor)] did you receive?
- a. 0
  - b. 1
  - c. 2
  - d. 3
  - e. >3
  - f. I do not remember
24. How much time passed between when you arrived in the ED and when you received the first dose of an effective HAE treatment?
- a. <1 hour
  - b. 1-2 hours
  - c. 2-4 hours
  - d. 4-6 hours
  - e. >6 hours
  - f. I do not remember
  - g. Not applicable, I have never received one of these treatments
25. Were you treated with any of the following therapies at the time of your last ED visit?
1. Corticosteroids?
    - a. Yes
    - b. No
    - c. I do not remember
  2. Epinephrine
    - a. Yes
    - b. No
    - c. I do not remember
  3. Anti-histamines (examples: Benadryl, etc.)
    - a. Yes
    - b. No

- c. I do not remember
- 4. Intravenous fluids
  - a. Yes
  - b. No
  - c. I do not remember
- 5. Opiates for pain control (examples: morphine, dilaudid, etc.)
  - a. Yes
  - b. No
  - c. I do not remember
- 6. FFP (fresh frozen plasma)
  - a. Yes
  - b. No
  - c. I do not remember
- 26. Were you discharged home or admitted to the hospital after your last ED visit?
  - a. I was discharged home from the ED
  - b. I was admitted to overnight observation unit (<24-hour stay)
  - c. I was admitted to a regular patient floor
  - d. I was admitted to intensive care unit
  - e. I do not remember
- 27. Was intubation or tracheostomy necessary for airway angioedema at your last ED visit?
  - a. Yes
  - b. No
  - c. I do not remember
- 28. If you were discharged from the ED, how many hours were you in the ED before discharge?
  - a. <4 hours
  - b. 4-12 hours
  - c. 12-24 hours
  - d. >24 hours
  - e. I do not remember
- 29. Before you went home after your last ED visit, were you advised to make a follow-up appointment with a doctor who could help treat your HAE?
  - a. Yes
  - b. No
  - c. No, but I already had a follow-up visit scheduled with my HAE doctor
  - d. I do not remember
- 30. Before you went home after your last ED visit, were you prescribed an effective on-demand "rescue" therapy [Firazyr (Icatibant), Berinert or Cinryze (C1 inhibitor), Kalbitor (Ecallantide), Ruconest (rC1 inhibitor)] to treat your HAE?
  - a. Yes
  - b. No
  - c. No, but I already had a prescription for one of these medications
  - d. I do not remember

**TABLE E1.** Numbers of patients who answered each question

Question	Total	2009+	2014+
1	118	87	39
2	118	87	39
3	118	87	39
4	117	87	39
5	118	87	39
6	118	87	39
7	118	87	39
8	117	87	39
9	106	86	38
10	97	79	35
11	106	87	39
12	105	87	39
13	103	86	39
14	104	87	39
15	104	87	39
16	103	86	38
17	101	87	39
18	103	77	34
19	101	83	38
20	102	83	38
21	97	79	36
22	101	83	38
23	99	80	37
24	95	77	35
25 (1)	96	80	34
25 (2)	99	80	36
25 (3)	95	79	34
25 (4)	100	82	38
25 (5)	97	80	36
25 (6)	97	80	35
26	101	84	38
27	103	85	38
28	87	72	34
29	99	83	39
30	103	85	39

The total numbers of patients who answered each question in the survey are displayed under "Total." The numbers of patients in the 2009+ and 2014+ groups (based on their answers to question 17, see the Methods section) are also displayed under "2009+" and "2014+," respectively. Not all of the patients answered question 17, which is why the sums of the 2009+ and 2014+ subgroups are less than the total.