

Original Article

Development of the Hereditary Angioedema Rapid Triage Tool

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What is already known about this topic? Patients with hereditary angioedema (HAE) experience delays in diagnosis because they exhibit overlapping symptoms that are commonly associated with allergic or gastrointestinal conditions, leading to emergency department (ED) visits.

What does this article add to our knowledge? Currently, there are no tools that can quickly diagnose and appropriately manage patients with undiagnosed HAE who present to the ED.

How does this study impact current management guidelines? We developed a prototype tool that has the potential to facilitate the rapid triage of undiagnosed patients with HAE who present in the ED.

BACKGROUND: Patients with hereditary angioedema (HAE) present to the emergency department (ED), where their symptoms are often incorrectly attributed to common allergic and gastrointestinal conditions, resulting in major delays in diagnosis and treatment.

OBJECTIVE: To develop a rapid triage HAE (Hereditary AngioEdema Rapid Triage [HAE-RT]) tool for ED settings.

METHODS: A mixed-methods approach was used in 3 phases: Phase 1: A literature review on the current management of patients with HAE in the ED. Phase 2: A Delphi study with HAE specialists (N = 9) and Patient Advocacy Group Members (N = 3) to reach consensus on the predictor variables (PVs) to be included in the HAE-RT tool. Phase 3: A retrospective chart review to assess the performance of the PVs for HAE.

RESULTS: The literature review informed the final list of PVs included in the HAE-RT prototype. Nine experts participated in the Delphi study. Of 8 identified HAE-specific PVs, 3 reached consensus: (1) absence of urticaria, (2) recurrent abdominal pain/swelling, and (3) lack of response to allergic-directed therapy. The retrospective study included 107 patients (N = 66 with HAE; N = 41 non-HAE). Patients with HAE were more likely to have a family history of HAE (71%; $P < .0001$), previous recurrent angioedema (96%; $P < .002$), and previous recurrent abdominal pain (77%; $P < .0001$), and only 6% responded to allergy treatments ($P < .0001$). The HAE-RT tool had 98% sensitivity and specificity.

CONCLUSIONS: Expert consensus led to the identification and prioritization of variables that when incorporated into an HAE-

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*Abbreviations used**ED- Emergency department**HAE- Hereditary angioedema**HAE-RT- Hereditary AngioEdema Rapid Triage*

RT tool were associated with a high level of sensitivity and specificity when applied to known patients. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;■:■-■)

Key words: Hereditary angioedema; Delphi study; Retrospective study

BACKGROUND

Hereditary angioedema (HAE) is a rare and serious disease caused by a deficiency or dysfunction of a serum protein C1 inhibitor. This deficiency causes a biochemical imbalance characterized by painful and unpredictable attacks of swelling of the extremities, face, trunk, airways, genitals, and abdomen.¹ Symptoms of HAE can be spontaneous or can result from stressors such as trauma, hormonal changes, and stress. When the body experiences these stressors, it triggers normal swelling, which is controlled by serum protein C1 inhibitor. If this protein is absent or not functioning properly such as in patients with HAE, the swelling becomes abnormal (ie, excessive, recurrent, and painful). Approximately 50% of patients with HAE experience laryngeal edema at least once during their lifetime, and the risk of dying from airway obstruction if left untreated ranges between 14% and 33%.¹ Another challenge is that patients go undiagnosed for an average of 8 years.² It is common for patients to experience major delays in diagnoses because they exhibit overlapping symptoms that are commonly associated with allergic or gastrointestinal conditions. This can result in emergency department (ED) visits as well as inappropriate treatments such as epinephrine or unnecessary surgery due to misdiagnosis of HAE as allergic reactions.²

Misdiagnosis of HAE can also have an economic impact on already burdened health care systems. A study conducted by the US Hereditary Angioedema Association in the period 2007 to 2008 identified that 73% of patients who experienced an HAE attack went to an ED and 59% were subsequently admitted to the hospital, with stays ranging from 0 to 14 days.³ If left untreated, patients may experience multiple attacks and/or life-threatening attacks, thus requiring more frequent medical intervention, resulting in additional cost to the health care system.³ ED visits and hospital stays can account for a significant proportion of all medical costs. On the basis of a study by Wilson et al,³ the average per-patient medical costs total US \$25,884 annually, of which US \$17,335 are accounted for by hospital stays and US \$2,614 is attributed to ED visits during acute HAE attacks. HAE is also associated with high indirect costs such as interruptions to work life. For example, the average cost of missed work due to acute attacks amounts to approximately US \$3402 annually.³ This study also found that the average annual per-patient cost of lost wages for working less than full time was about US \$6512.³

Currently, no tools exist to quickly diagnose and appropriately manage undiagnosed patients with HAEs who present to the ED.

Thus, developing a reliable point-of-care tool to identify patients with HAE provides an opportunity to address challenges. First, an HAE tool has the potential to reduce health care costs by decreasing the number of ED visits and hospital stays if undiagnosed patients are identified and treated early, thereby reducing the frequency of attacks. Second, the tool may improve the quality of life of patients. With timely diagnosis, patients can self-administer prophylaxis treatment at home and reduce the frequency of attacks, which will decrease the cost of missed work due to acute attacks, and time away from family and social events.

The objective of this study was to develop and validate an easy-to-use tool that emergency physicians and nurses can use to appropriately diagnose people with HAE: the Hereditary AngioEdema-Rapid Triage (HAE-RT) tool.

METHODS

To create the HAE-RT tool prototype, we conducted a multi-phase mixed-methods study involving the identification of variables that predict the diagnosis of HAE (phase 1), to identify which predictor variables should comprise the HAE-RT tool prototype (phase 2), and to pilot test the prototype with a retrospective chart review of HAE cases across 3 allergy clinics (phase 3).

Phase 1: Literature review to identify HAE predictor variables

Search strategy. A literature review was conducted to gain key insights into the management of patients with HAE (diagnosed or undiagnosed) in the ED. A database search for articles (up to February 2017) was conducted using a search strategy (see [Appendix E1](#) in this article's Online Repository at www.jaci-inpractice.org).

Eligibility criteria. We considered for inclusion any experimental (eg, randomized controlled trials, nonrandomized trials, controlled before-after studies, and interrupted time series) and observational studies (eg, prospective or retrospective cohort, cross-sectional, and case-control) that included a strategy for diagnosis, treatment, or management of HAE. We excluded case reports, opinion-based reports, and basic science or animal studies. The population of interest was patients with HAE (diagnosed or undiagnosed) or those presenting with angioedema in the ED or urgent care.

Data abstraction

Using a standardized data extraction form, one reviewer extracted data on study, patient (demographic characteristics, presenting symptoms, treatments received, discharge plans, and if admitted to hospital), and intervention (diagnostic, treatment, or management); a second reviewer checked the first reviewer's extraction, and disagreements were settled through consensus.

Analysis

Data were summarized descriptively using narrative synthesis (ie, qualitative content analysis and descriptive tables to give an overview of the included study characteristics). The literature review was not designed to perform quantitative analysis, meta-analysis, or assessment of risk of bias. Findings were used to inform the development of the Delphi questionnaire of statements used in phase 2.

Outputs

Outputs were a list of variables predicting HAE (symptoms, triggers, and history) in different settings.

Phase 2: A Delphi study to identify the predictor variables to consider for inclusion in the HAE-RT prototype

Study design. We used a modified Delphi approach^{4,5} to establish consensus on the factors that predict HAE from a panel of experts in HAE. A total of 3 rounds of ratings, consisting of a structured online questionnaire (round 1) followed by a facilitated discussion via teleconference (round 2), were held. To validate round 2 findings, we applied the identified predictors in round 2 to HAE case reports identified from the literature ($n = 65$). The final list of predictor variables was pilot tested by extracting data from 65 HAE case reports (for methods, see [Appendix E2](#) in this article's Online Repository at www.jaci-inpractice.org) published between January 2007 and March 2017. We analyzed the data in terms of the performance characteristics of the predictors, and prepared a table showing the frequencies of each predictor variable across the cases. This table was shown to the expert panel who made the decision on which predictor variables should be included in the HAE-RT prototype (round 3).

Population and sampling. We used a purposive sampling strategy to recruit the panel of experts: 7 HAE specialists and 2 national HAE patient advocacy group members.

Delphi questionnaire development. The findings from phase 1 informed the development of the Delphi questionnaire, which consisted of consensus statements about the desired outcome (ie, identification of patients in ED), impact (ie, provide implicit or explicit recommendations), the patient population (ie, HAE diagnosis or not), clinical findings, treatment, and follow-up plans that may be included in the HAE-RT prototype.

Analysis. We determined *a priori* that to include as a predictor item, the panel would need to reach consensus on that item (ie, at least 80% agreement) or a median score of item ratings of 5 or more out of 7 on a 7-point Likert scale (1 = not at all agree; 7 = very much agree). All items that did not reach consensus were considered for reassessment in round 2 (teleconference), and any items that remained unresolved after round 2 were reassessed in the final round 3 (teleconference). The decision to include items was iterative and based on the consistency between quantitative ratings and supporting qualitative data from teleconference discussions.

Analysis. Quantitative data were analyzed using descriptive statistics to assess central tendency (means, median, and their SDs). We also calculated the level of dispersion using the interquartile range, which provides an assessment of the extent of agreement between participants. Facilitated discussions from teleconferences were audiotaped and transcribed verbatim and analyzed using content analysis. This involved one reviewer reading and coding the data and identifying themes and a second reviewer checking the coding and discussing any disagreements in interpretation with the primary reviewer. Findings from quantitative and qualitative data were triangulated and informed the final list of predictor variables to be included in the HAE-RT prototype.

Outputs. Output was patient type for the HAE-RT prototype (ie, undiagnosed HAE presenting with recurrent angioedema).

Phase 3: Pilot validation of the HAE-RT prototype

To assess the predictive performance of the variables included in the HAE-RT tool prototype, we conducted a retrospective chart review and applied the HAE-RT tool for each identified case.

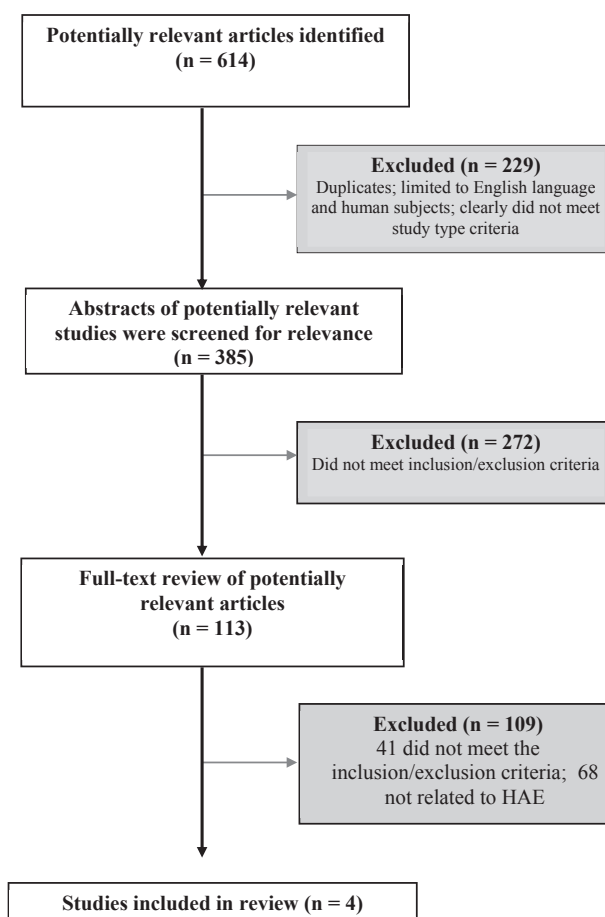


FIGURE 1. Study identification flowchart.

Sampling and eligibility criteria. We used a convenient sampling strategy to identify patients (any age and sex) presenting with angioedema (with and without HAE) at 3 allergy specialty clinics in Canada (Hamilton, Vancouver, Toronto) between January 2012 and January 2017.

Validation process. Data on patient characteristics were abstracted by 1 reviewer from charts and consult notes using a standardized form (sex, age, family history, current medications, symptoms, treatments, laboratory tests, and diagnosis if available). Data were classified according to patients who had an HAE diagnosis versus those who did not. These were then mapped to the final list of HAE predictors (identified from phase 2) in preparation for performing the analytics to assess the performance of the HAE-RT prototype (see [Appendix E2](#) in this article's Online Repository at www.jaci-inpractice.org).

Analysis. We used the following analytics techniques to estimate the performance of the HAE-RT prototype: (1) to test the association between predictor variables and HAE diagnosis (via χ^2 tests); (2) to test the extent of an interaction between predictor variables and HAE diagnosis (loglinear analysis); and (3) to test the test characteristics (ie, sensitivity/specificity) of the HAE-RT tool prototype (logistic binary regression analysis). All data analyses were performed using SPSS version 24 (IBM Corporation, Armonk, NY).

TABLE I. Characteristics of included studies

Author, year, country	Study design	Setting	Population	Objective	Outcome
Otani et al, ⁶ 2017, United States	Cross-sectional survey	2015 HAE Association Patient Summit	Adult patients with HAE (N = 118)	To investigate the concordance between ED HAE care and published guidelines, and to identify areas that need further improvement	Patient characteristics Emergency treatment plan Perception of ED HAE care
Ucar et al, ⁷ 2016, United States	Qualitative interviews	Allergy and Immunology Clinic	Adult patients with HAE (N = 34)	To evaluate the difficulties encountered in the ED by patients with HAE	Clinical features ED admissions Frequency of attacks Treatments provided Procedures done Referral patterns
Ohsawa et al, ⁸ 2014, Japan	Retrospective chart review (2010-2013)	Outpatient clinic Juntendo University Hospital	Adult patients with angioedema (N = 72)	To identify characteristics that can differentiate HAE from other types of angioedema	Patient characteristics Medical history Laboratory data
Ishoo et al, ⁹ 1999, United States	Retrospective chart review (1985-1999)	Boston Medical Center	Adult patients with angioedema (N = 80)	To determine criteria for the identification of patients at risk from progressive airway compromise	Identification of patients at risk from progressive airway compromise Demographic, etiologic, and therapeutic information Anatomic site of edema and symptoms on presentation Triage patterns into the appropriate treatment setting—outpatient, ward, or intensive care unit

RESULTS

Phase 1: Literature review

Of 614 potentially relevant articles identified in the literature review, 4 articles met our inclusion criteria and provided key insights into the management of patients with HAE (diagnosed or undiagnosed) in the ED. [Figure 1](#) shows the flow of article selection. Studies were retrospective chart reviews (n = 2), a cross-sectional survey (n = 1), and a qualitative study (n = 1). [Table I](#) presents the study characteristics. Most of the studies included patients who presented to the hospital or allergy clinic

(n = 3); 1 study was conducted in the community setting (n = 1). Patients who presented in the ED had either HAE^{6,7} (n = 152) or angioedema^{8,9} (n = 152).

Qualitative analysis of included studies revealed 4 major themes addressing characteristics of HAE management in the ED setting (see [Table E1](#) in this article's Online Repository at www.jaci-inpractice.org): (1) reason for ED visit, (2) whether admitted to hospital, (3) the treatments they received, and (4) the discharge plans. Of patients with HAE, reasons for presenting to the ED were peripheral angioedema (58%),⁷ laryngeal attacks

TABLE II. Summary of consensus-based statements

Statement	Agreement (%)	Range (1-7), median ≥ 5	Interquartile range	Consensus: Y/N
HAE-RT will use clinical findings to triage patients presenting to the ED with angioedema to:				
Identify patients at risk for HAE	78	6.0	2	Y
Identify patients who would potentially benefit from HAE treatment	89	7.0	2	Y
Identify patients who would potentially benefit from referrals to HAE specialists	89	7.0	3	Y
Identify patients who do not require hospitalization	56	5.0	2	N
In the ED setting, the HAE-RT tool will be used as:				
An assistive tool, providing probabilities with implicit recommendations	78	5.0	2	N
A directive tool, providing explicit recommendations	78	6.0	2	Y
In the ED setting, the HAE-RT tool will be applied to:				
All patients presenting to the ED with angioedema	89	7.0	1	Y
All patients diagnosed with HAE	67	6.0	3	N
Clinical findings: Assess the probability or likelihood of each clinical finding to predict the likelihood of HAE				
Acute angioedema	11	4.0	1	N
Absence of urticaria	78	6.0	2	Y
Site of angioedema	55	5.0	2	N
Prodromal symptoms	33	4.0	3	N
Speed of onset of symptoms	67	5.0	1	N
Triggers (sex)	89	5.0	1	Y
Risk factors (family history of HAE; recurrent episodes of angioedema/abdominal pain)	78	6.0	2	Y
If HAE is suspected, emergency personnel should:				
Administer first-line therapies (plasma-derived C1-INH; icatibant)	89	7.0	1	Y
If first-line not available: fresh-frozen plasma	89	6.0	2	Y
If HAE is suspected, at discharge, emergency personnel should:				
Refer for prompt evaluation by immunologist	100	7.0	0	Y
Order laboratory tests (complement proteins C4 and C2 are consumed during an acute attack)	89	6.0	2	Y

C1-INH, Serum protein C1 inhibitor; N, no; Y, yes.

TABLE III. Delphi round 2 pilot test of predicted outcomes for HAE using published case reports of diagnosed HAE

Total published case reports (N = 65)	n	%	Missing data (n)
Recurrent angioedema (Y)	63	96.9	1
Angioedema (Y)	62	95.3	0
Absence of urticaria (Y)	58	89.2	3
Sex (F)	45	69.2	0
Past recurrent abdominal pain/swelling (Y)	39	60	11
Family history of HAE (Y)	27	41.5	6
Response to therapy for angioedema (N)	22	33.8	21

F, Female; N, no; Y, yes.

(33%),⁶ and abdominal pain (24%).⁷ In one study, 35% of patients reported having difficulty with home treatment.⁶ A survey of 118 patients with HAE reported that all experienced at least 1 ED visit in their lifetime, where 22% were not given HAE treatment, 50% did not receive a prescription for home on-demand HAE therapy, and only 31% were referred for follow-up with an allergist.⁶ In the qualitative study, interviews with 34 patients showed that 38% were admitted to hospital once per month, 88% were not given HAE treatment, and 53% were referred for follow-up with an allergist.⁷

Of the 2 retrospective chart review studies of patients who presented to the ED with angioedema (n = 152),^{8,9} 15% were diagnosed with HAE (n = 23). Of 85% who did not have HAE, 33% cases of angioedema were drug-induced (from angiotensin-converting enzyme inhibitors, antibiotics), 22% were mast cell-mediated, 12% had food allergy, and 18% had other triggers (ie, multiple agents, idiopathic). Of those diagnosed with HAE (n = 23), 65% experienced peripheral angioedema (in the extremities), 61% had abdominal pain, 30% had laryngeal swellings, 20% had genital angioedema, and 83% had a family history of HAE.

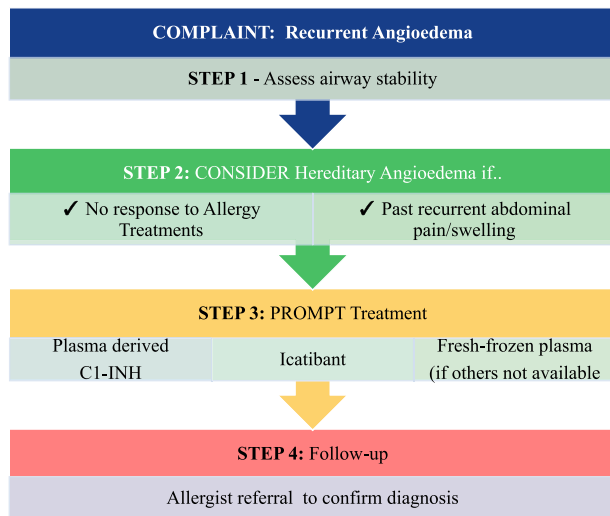


FIGURE 2. HAE-RT prototype.

Phase 2: Delphi study

Of the 12 experts invited, 9 (75%) participated in the Delphi study. The expert panel reached consensus on 7 HAE-specific predictor variables to be included in the HAE-RT prototype: sex, family history, angioedema, recurrent angioedema, absence of urticaria, recurrent abdominal pain/swelling, and response to allergic therapy. In addition, the panel indicated that the HAE-RT tool can be used to direct management in the ED setting and be applied to all patients presenting with angioedema (Table II).

The pilot validation of the 7 HAE predictor variables against the 65 identified case reports is presented in Table III. On reviewing this table, the expert panel reached consensus on the following 3 of 7 HAE predictor variables, which were then included in the HAE-RT prototype for undiagnosed patients presenting to the ED with recurrent angioedema: (1) angioedema with absence of urticaria, (2) recurrent abdominal pain/swelling, and (3) lack of response to allergy-directed therapy (Figure 2).

Phase 3: Retrospective chart review

The retrospective chart review included 107 patients (65% women; mean age, 42.1 ± 19.7 years). There were 66 patients with HAE and 41 patients without HAE. Compared with patients without HAE, 71% of individuals with HAE were more likely to have a family history of HAE (2% non-HAE; $P < .0001$), 96% had previous recurrent angioedema (75% non-HAE; $P < .002$), 71% did not present with hives (73% non-HAE; $P < .827$), 77% had previous recurrent abdominal pain (0% non-HAE; $P < .0001$), and 94% did not respond positively to allergy treatments (2% non-HAE; $P < .0001$) (Table IV).

Association between X variables and HAE outcome. Our χ^2 test results revealed a strong association among all the predictor variables, except for the absence of urticaria (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). As a result, we removed this predictor from any subsequent analyses.

Extent of the interaction between X variables and HAE outcome. Our analysis revealed 2 statistical outputs including the K-way and higher order effects (see Table E3 in this article's Online Repository at www.jaci-inpractice.org) and

partial associations (see Table E4 in this article's Online Repository at www.jaci-inpractice.org) that confirmed significant interactions between the predictor variables (previous recurrent abdominal pain and lack of response to allergy treatments) and HAE diagnosis ($P = .002$).

Sensitivity/specificity of the HAE-RT tool. The sensitivity and specificity of the HAE-RT tool prototype was 98% (Table V).

DISCUSSION

Our study identified predictor variables gathered from our literature review that were refined through a Delphi study and pilot tested on 65 case reports that informed the HAE-RT prototype. A validation procedure through chart review also revealed that the HAE-RT tool has high sensitivity for identifying and high specificity for ruling out undiagnosed patients who are at risk for HAE (ie, patients who present in the ED with recurrent angioedema who do not respond to allergic therapy and have a history of recurrent abdominal pain).

A tool such as the HAE-RT prototype has the potential to have significant impact. First, the prototype can identify a large proportion of undiagnosed patients with HAE and therefore has the potential to reduce health care costs. Studies have reported that HAE affects approximately 1 in every 30,000 to 80,000 individuals and estimates 8,000 individuals in the United States, 15,000 in Europe, and 200,000 worldwide.¹⁰ According to Statistics Canada, the estimated Canadian population in 2016 was about 35 million people and would translate to 5515 affected Canadians with HAE for an estimated incidence of 20 to 50 patients with HAE per million population,^{11,12} a much larger number than the currently known number of patients with HAE treated in Canada (about 300-500 people).¹³ Therefore, the HAE-RT tool has the potential to identify a large number of undiagnosed individuals in the ED, which in turn can have a significant impact on reducing health care costs and improving the quality of life. For example, 5000 undiagnosed patients at the estimated direct per-patient medical costs of US \$25,884 (on the basis of US Hereditary Angioedema Association 2007-2008 data)³ would translate to US \$129.4 million direct health care costs annually, of which 67% are related to hospital stays and 10% are due to ED visits. Diagnosed patients can receive treatment that they can self-administer at home for acute HAE attacks, thus reducing future costly ED visits and hospital stays, and more importantly reducing the significant morbidity and mortality seen in undiagnosed patients.

Second, the unpredictability of the onset, severity, and frequency of HAE attacks can significantly affect the ability of an individual to maintain a good quality of life because undiagnosed patients often receive invasive unnecessary procedures when they present to the ED.^{6,7,14} A 2008 report from the US Hereditary Angioedema Association indicates that patients experienced a mean of 26.9 HAE attacks per year.³ A significant number of these patients (~ 3 of 4)³ present to the ED, and many emergency physicians have encountered challenges with recognizing HAE. Traditionally, emergency physicians manage each visit as discrete clinical events and rarely provide continuous care; therefore, tracking undiagnosed patients who present repeatedly with angioedema in the ED is a challenge. Furthermore, there are no standardized directives in the ED to assist with the differentiation of HAE from other allergic or gastrointestinal

TABLE IV. Retrospective chart review patient characteristics

Total patient charts (N = 107)	HAE (n = 66)	Non-HAE (n = 41)	P value χ^2
Recurrent angioedema (Y)	63 (96)	31 (76)	.002
Absence of urticaria (Y)	47 (71)	30 (73)	.826
Past recurrent abdominal pain/swelling (Y)	51 (77)	0 (0)	.0001
No response to allergy therapy (Y)	62 (94)	1 (2)	.0001
Family history of HAE (Y)	47 (71)	1 (2)	.0001

Y, Yes.

 χ^2 : degrees of freedom = 1; computed for a 2 × 2 table.

Values are n (%).

conditions. All these challenges in the ED can result in patients receiving inappropriate treatment, lack of referral to an HAE specialist, and poor management. This can result in patient fear and reluctance to seek help from health care professionals. The HAE-RT tool has the potential to facilitate the diagnosis of HAE in the ED, up until now a significant gap in managing these patients.

Strengths and limitations

We performed a comprehensive and rigorous mixed-methods study to identify the factors that better predict HAE. To our knowledge, we are the first to investigate the potential use of a tool to support the identification of HAE in the ED setting. Previous studies have described the development of questionnaires that address patient perspectives of HAE attacks (triggers, warning signs, symptoms, attack characteristics, and treatments)¹⁵ and health-related quality of life in patients with HAE: health-related quality of life questionnaire for hereditary angioedema¹⁶ and the Angioedema Quality of Life Questionnaire.¹⁷ One US study analyzed an insurance claims database to identify a subset of features (diagnostic, procedural, therapeutic, and health care provider characteristics) that most clearly defined the characteristics of a patient with HAE.¹⁸

Our study has some limitations. First, our analysis may have overestimated the magnitude of the association between the variables. There were other unknown variables (eg, additional symptoms such as nausea, age of onset of symptoms, triggers such as menstrual cycle, and site of angioedema) that were not included, which may have affected the final model. Moreover, the reported frequency of urticaria in patients with HAE (29%) was high. Lesions might have been misinterpreted as urticaria when instead they were erythema marginatum, thus leading to urticaria not being a discriminating factor to rule out HAE in our model. In addition, different ethnic groups may have different clinical manifestations of HAE, for example, less gastrointestinal involvement.¹⁹⁻²¹ Second, a different panel may have come to different conclusions. However, we involved most of the HAE specialists from Canada, so this threat is minimal. Third, in phase 1, we did not perform a systematic review, which may have missed some relevant articles to inform the list of predictor variables. However, there is a paucity of evidence in literature about HAE (our search identified only 641 potentially relevant articles, of which only 4 were relevant), so the likelihood of missing an article was small. Fourth, we used chart review to identify HAE cases to validate the performance of the HAE-RT prototype. However, this was a pilot study, so our design was relevant for this objective. Future work needs to involve real

TABLE V. Classification table

Predicted	Observed – Actual	
	HAE	No HAE
Positive	True positives N = 65	False positives N = 1
Negative	False negatives N = 1	True negatives N = 40

Sensitivity = 98.4%; specificity = 97.6%.

patients in real time presenting to the ED to validate the tool. Thus, it is recommended that the next step should be to observe the effect of the HAE-RT tool on patient care in the ED before it is deployed as a point-of-care tool. Finally, future work should also include a health economic analysis to test the potential economic impact of the HAE-RT prototype on the health system and services.

CONCLUSIONS

Only a small proportion of research outputs is translated into practice and policy to influence patient care. Implementing best evidence into practice will contribute to a more efficient strategy that will enable appropriate diagnosis and care of patients presenting to the ED with symptoms of angioedema. The development of the HAE-RT tool involved all end user groups, and we hope to improve the quality and applicability of the tool with further testing with patients with HAE and/or their informal caregiver.

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ONLINE REPOSITORY

Appendix E1. Literature review database search strategy

Databases accessed: Embase 1974 to November 16, 2016; AMED (Allied and Complementary Medicine) 1985 to October 2016; Global Health 1973 to 2016 week 44; Health and Psychosocial Instruments 1985 to October 2016; Ovid Healthstar 1966 to October 2016; OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, and Ovid MEDLINE(R) 1946 to present; PsycINFO 1806 to November week 1, 2016; McMaster University Full Text Journals@Ovid; Journal Abstracts and Tables of Contents.

Search strategy: (Decision Support Systems or Reminder Systems or Electronic Health Records or Self Administration or Point-of-Care Systems or Algorithms or Triage).af. *AND'd with*

(Angioedema or Hereditary angioedema or Angioedema classification or Angioedema complications or Angioedema diagnosis or Angioedema therapy or C1-INH deficiency or Complement C1 Inactivator Proteins deficiency or Complement C4 metabolism or C1-INH).af.

C1-INH, Serum protein C1 inhibitor.

Appendix E2. Pilot validation of predicted outcomes for HAE using case reports of diagnosed HAE methodology

Literature search (January 2007-March 2017)

Inclusion criteria: Case reports, English language, human subjects, full-text available

Yield: 189 cases; 124 excluded (angiotensin-converting enzyme, acquired angioedema, surgical, dental cases, case studies/educational)

Included 65 cases for analysis

TABLE E1. Data abstraction

Study	Reason for presenting in ED	ED visits/admissions	Treatments received	Discharge plans
Otani et al, ^{E1} 2017, United States,	33% had laryngeal attacks	All had least 1 ED visit in their lifetime	22% were not given HAE treatment	50% did not receive prescription for home on-demand therapy
Patients with HAE who had at least 1 ED visit (survey) (N = 107)	35% had inability to receive home treatment		10% received corticosteroids	31% were not referred to allergist
			10% received epinephrine	
			25% received antihistamines	
Ucar et al, ^{E2} 2016, United States	58.8% had peripheral angioedema	38.2% were admitted to ED once per month	88.2% were not given HAE treatment	52.9% were not referred to allergist
	23.5% had abdominal pain		67.6% received corticosteroids and/or antihistamines	
Patients with HAE (qualitative) (N = 34)			8.8% received analgesic drugs	
			2.9% received fresh-frozen plasma	
Ohsawa et al, ^{E3} 2014, Japan	23 patients with HAE	In patients with HAE,	In patients with HAE,	In patients with HAE,
Adults with angioedema (retrospective chart review; 2010-2013) (N = 72)	33 mast cell-mediated	61% abdominal	95.6% C4 below normal	82.6% had a family history of HAE (P < .0001)
	5 drug-induced angioedema	65% extremities	100% C1-INH <50%	Age of onset was 19.5 ± 8.0 y (P < .0001)
	11 idiopathic	20% genitals		
		30% laryngeal		
Ishoo et al, ^{E4} 1999, United States	39% from angiotensin-converting enzyme inhibitors	31% had facial rash, facial edema, lip edema	C1-esterase inhibitor (C1-INH), C2, or C4 levels were reported	Data not available
Adults with angioedema (retrospective chart review; 1985-1999) (N = 80)	19% from food	32% had tongue edema	No cases of HAE	
	11% from antibiotics	31% had laryngeal edema		
	9% from multiple agents	5% had soft-palate edema		
	33% had no etiologic agent			
	1% had T-cell lymphoma			

C1-INH, Serum protein C1 inhibitor.

TABLE E2. Test for association between X variables and HAE outcome (χ^2 tests; df = 1)

HAE	Tx Res		Re Angio		No hives		Abdominal pain	
	No	Yes	No	Yes	No	Yes	No	Yes
No	1	40	10	31	11	30	41	0
Yes	62	4	3	63	19	47	15	51
	χ^2*	Significance	χ^2*	Significance	χ^2*	Significance	χ^2*	Significance
	87.5	.000	9.3	.002	4.4	.827	60.5	.000

Angio, Angioedema; Re, recurrent; Res, response; Tx, treatment.

*df = 1; computed only for a 2 × 2 table.

TABLE E3. K-way and higher order effects

Effects	K	df	Likelihood ratio		Pearson		No. of iterations
			χ^2	Significance	χ^2	Significance	
K-way and higher order effects*	1	7	192.246	0.000	200.364	0.000	0
	2	4	182.725	0.000	209.203	0.000	2
	3	1	.004	0.948	.004	0.948	2
K-way effects†	1	3	9.521	0.023	−8.838	1.000	0
	2	3	182.721	0.000	209.198	0.000	0
	3	1	.004	0.948	.004	0.948	0

df used for these tests have *not* been adjusted for structural or sampling zeros. Tests using these df may be conservative.

*Tests that K-way and higher order effects are 0.

†Tests that K-way effects are 0.

TABLE E4. Partial associations

Effects	Estimate	SE	Z	Significance
HAE × Recurrent abdominal pain × No treatment response to allergic therapy	−.367	.299	−1.226	.220
HAE × Recurrent abdominal pain	.943	.299	3.152	.002
HAE × No treatment response to allergic therapy	−1.024	.299	−3.422	.001

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