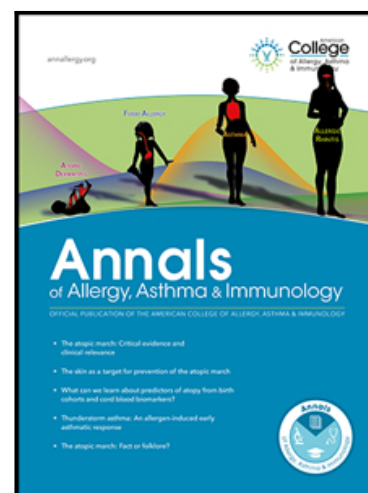


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Title Page**Canadian Physician Survey on the Medical Management of Hereditary Angioedema**

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Abbreviations/Acronyms: Hereditary Angioedema (HAE); C1 esterase inhibitor (C1-INH), long term prophylaxis (LTP); short-term prophylaxis (STP)

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Introduction

Hereditary angioedema (HAE) is a rare and potentially life-threatening condition that affects 1 in every 10,000 to 50,000 persons.^{1,2} This autosomal dominant condition is caused by a deficiency or dysfunction in the C1 esterase inhibitor (C1-INH), and manifests as recurrent, acute attacks of non-pruritic, non-pitting, subcutaneous or submucosal edema. Areas typically affected include the upper airway, face, extremities, genitals and gastrointestinal system.^{3,4,5} Angioedema of the larynx can be life-threatening and severe abdominal pain may result in unnecessary surgical procedures. In addition, the impact of attacks on quality of life for patients are substantial.⁶⁻²⁰

Management of HAE includes the use of short-term prophylaxis and long-term prophylaxis for recurrent attacks.²¹ Treatments have included androgens (such as danazol and oxandrolone), frozen plasma, and tranexamic acid. In the past 7 years, the US Food and Drug Administration (FDA), as well as Health Canada, have approved several novel therapies for the treatment of acute HAE attacks. For example, plasma-derived C1-INH has been approved for acute HAE episodes (Berinert®) and long term prophylaxis (Cinryze®). Icatibant (Firazyr®) has also received Health Canada approval in 2014 for the treatment of acute HAE attacks.

Physician treatment practices were surveyed in the USA and showed a wide variability in the treatment of patients with HAE.²² A follow-up publication was instrumental in understanding how practice patterns changed as newer treatments became available in the USA.²³ Similar surveys have not been conducted on Canadian physicians.

Several national and international guidelines have been published outlining recommendations for the medical management of patients with Hereditary Angioedema (HAE).²⁴⁻²⁷ However, little is known about how Canadian physicians treat patients with HAE, and if they follow guideline recommendations.

Methods

Written consent was obtained from participants. Institutional review board (IRB) approval was obtained.

Population and Setting

We invited Canadian physicians currently providing care to one or more patients with HAE to take part in a web-based survey. Given the relative rarity and complexity of HAE we anticipated that there would be no more than 100 physicians involved in its treatment. We approached relevant clinical organizations [Canadian Hereditary Angioedema Network (CHAEN), Canadian Society of Allergy and Clinical Immunology

(CSACI), and Canadian Hematology Society (CHS)] to help us reach their respective members. The invitation to participate, as well as the survey itself, were provided in both English and French.

Variables

The survey included 33 questions grouped into five sections for ease of completion.

Section 1: Demographics

Variables collected in this section included education, years in practice, setting and area of practice, number of HAE patients under the physicians' care, and source(s) of HAE patient referrals.

Section 2: Clinical Practice

Data collection on patients included diagnostic methods, sites of swelling, impact on their quality of life, and the use of symptom (or attack) diaries.

Section 3: Prophylaxis and Treatment

Treatments being used for both long and short-term prophylaxis were collected along with factors that might impact prescribing decisions.

Section 4: Knowledge and Confidence

Using a 5-point Likert scale (where 1=minimal and 5=expert), data was collected on physician knowledge/skills regarding suspected HAE including identification and

diagnosis, performance of a medical history, and appropriate treatment and management. We also used a Likert scale (1=not confident and 5=extremely confident) to assess physician confidence in prescribing various treatment options for HAE.

Section 5: Continuing Medical Education

This section asked about physician awareness and use of HAE treatment guidelines, how they learn about new treatment recommendations, and what aspects of HAE they would be interested in learning more about.

Data Collection

The survey was administered electronically using the Research Electronic Data Capture (REDCap™) system. REDCap™ is a secure, web-based application designed to support data capture for research studies.²⁸ The invitation to participate in the survey included a generic link which took participants to the survey where they entered their responses directly into REDCap™ from any computer, tablet, or smartphone. The survey was launched in January 2017 and the invitation to participate was sent by administrators at CHAEN, CSACI, and CHS to their respective memberships via email with a reminder sent approximately 2 weeks later. The survey closed in February 2017 with data collection lasting approximately 1 month.

Analysis

De-identified data was analyzed by a statistician at the Applied Health Research Centre (AHRC) of St. Michael's Hospital in Toronto, Canada. Descriptive statistics were

calculated for each survey question with continuous data examined using means and standard deviations (SD) as well as medians and interquartile ranges (IQR) and categorical variables summarized using frequencies (N) and percent. Descriptive tables report the number of observations available for each variable as well as the number missing.

Results

Demographics.

Thirty-six physicians responded to the survey. However, two respondents were excluded from the final analysis because neither were currently treating any patients with HAE. The analysis included all remaining participant data (n=34). Table 1 outlines the demographic and practice characteristics of the respondents.

All respondents had at least one Type 1 or Type 2 HAE patient in their care and 5 respondents (14.7%) had more than 20 patients. By comparison, 14 respondents (41.2%) did not have Type 3 HAE HAE-nC1INH patients in their care whereas 1 respondent (2.9%) was treating more than 20 patients with Type 3 HAE HAE-nC1INH. Table 2 illustrates the number of HAE patients under the care of physician respondents. Only 16 participants indicated that they were treating HAE patients of any type under the age of 18.

Participants also indicated that they are diagnosing few new patients each year (mean = 1.8 +/- 1.4) and that the main sources of referral for HAE patients are emergency rooms (82.4% of respondents) and family practitioners (76.5%).

Respondents reported that the most common sites of swelling in their patients were facial (73.5%), peripheral (70.6%), and abdominal (58.8%). The sites of swelling felt to have the most impact on patient quality of life were reported as facial (61.8%), abdominal (61.8%), laryngeal (58.8%), and tongue (44.1%).

Regarding diagnostic testing, 91.2% (n=34) of respondents use complement C4 level to diagnose HAE, 88.2% use C1-INH level, 85.3% use C1-INH function, and 64.7% use family history (Figure 1). C3 level and C1q level are used to a lesser extent (both 20.6%). A patient symptom or attack diary is used by 55.9% (n=34) of participants, and of these the majority (68.4%) are using a written diary while 26.3% are using both written diaries and apps. Those not using a patient diary (38.2%) indicated it was because they felt it was not feasible or practical (46.2%), weren't aware they existed (15.4%), didn't find them clinically helpful (15.4%), or 'other' (15.4%).

Prophylaxis.

Participants indicated similar numbers of their current Type 1 and Type 2 HAE patients were on long-term prophylaxis (53.9% +/- 31.8, n=33) as compared to current Type 3 HAE HAE-nC1INH patients (53.4% +/- 38.7, n=19).

For long term prophylaxis (LTP), 93.5% of physicians used C1-INH, 41.9% used Danazol and 19.4% used tranexamic acid. When deciding to prescribe LTP, respondents (n=34) indicated that the following factors were important: frequency of attacks (91.2%), severity of attacks (88.2%), quality of life (67.7%), laryngeal attacks (61.8%), and location of attacks (50.0%) (Figure 1). Other factors mentioned included patient age (2.9%), gender (2.9%), geography (distance to hospital) (2.9%), and patient willingness to go on LTP (2.9%).

Among those who indicated that frequency of attacks was a factor in their decision to prescribe LTP (n=31), 48.4% indicated that attacks once per month would be sufficient to prompt them to prescribe, while 22.6% indicated once per week, and 19.4% indicated greater than once per year but less than once per month (Figure 2). Three (9.7%) chose not to reply. When choosing between C1-INH and danazol for prophylaxis, the most commonly reported considerations (n=34) were side effect profile (85.3%), mode of administration (47.1%), gender (47.1%), IV access (44.1%), and cost (26.5%).

Twenty-seven respondents (79.4%) indicated that they prescribe short-term prophylaxis (STP) for their HAE patients while 5 (14.7%) indicated that they do not, and 2 (5.9%) chose not to reply. Among those using STP in their patients (n=27), the agents being used included C1-INH (76.5%), danazol (11.8%), and tranexamic acid (2.9%). Notably this question was meant to allow respondents to 'check all that apply'. However, due to a programming error the survey was initially launched such that this question only

allowed for one response and was only subsequently changed to allow for multiple responses. As a result, of the 27 participants indicating use of STP in their patients, 15 could select only one response while 12 were able to check all applicable responses.

Acute attacks.

With regard to acute attacks (Figure 3), the most commonly used agents for treating acute attacks in HAE patients are C1-INH (88.2%), Icatibant (79.4%), IV Hydration (35.3%), and IV analgesics (32.4%). Six respondents indicated that they only use a single treatment modality for acute attacks with two using icatibant and four using C1-INH.

Knowledge and confidence.

Using a 5-point Likert scale ranging from 1 (minimal) to 5 (expert), respondents were asked to rate their knowledge and skills across 5 domains. In the following 4 domains, all 34 respondents rated themselves as either above average or expert:

- Performing a medical history in a patient suspected of having HAE
- What laboratory investigations to order to diagnose HAE
- Determining choice of treatment for HAE
- Managing symptoms of HAE

In the 5th domain (differentiating HAE from other conditions), two respondents (5.9%) rated their knowledge and skills as average while the remainder rated themselves as either above average (38.2%) or expert (55.9%).

Using a 5-point Likert scale ranging from 1 (not confident) to 5 (extremely confident), respondents were asked to rate their confidence with prescribing specific therapies. Overall, participants indicated the most confidence in prescribing C1-INH, regardless of indication, with 94% (n=34) indicating they were confident, very confident, or extremely confident. Confidence levels for prescribing icatibant were similar with 91.2% indicating they were confident, very confident, or extremely confident. For danazol, 79.5% were confident, very confident, or extremely confident while 17.6% were not confident or somewhat confident. Lastly for tranexamic acid, 61.7% of respondents indicated they were confident, very confident, or extremely confident while 32.4% indicated they were either not confident or somewhat confident.

All respondents (100%, n=34) indicated that they were aware of guidelines for the management of HAE and almost all (97.1%) were aware of the existence of Canadian guidelines. Most (94.1%) used guidelines in their own HAE management although one respondent did not (2.9%). Guidelines were the most frequently reported means by which participants became aware of new HAE treatment recommendations (85.3%). Other common responses were continuing medical education (79.4%), discussion with colleague(s) (76.5%), pharmaceutical reps (50.0%), patients (14.7%), and journals/current literature (11.8%). Ninety-one percent of respondents rely on multiple sources.

Continuing medical education.

There were several areas of HAE that respondents indicated an interest in learning more about, with the most frequent response being HAE in pregnancy (61.8%) followed by pediatric HAE (44.1%), prophylactic treatment (41.2%), acute treatment (35.3%), diagnosis (32.4%), complications and quality of life (both at 29.4%), basic science of HAE (23.5%), and 'other' (5.9%) (Figure 5).

Three respondents (8.8%) chose not to reply.

Discussion

This is the first study to examine the treatment and management of HAE patients by Canadian physicians. The findings from this survey provide a baseline understanding of Canadian physician practices, that can be used as a basis for comparison with future studies particularly as new therapies are introduced to the Canadian market.

In the United States, a similar survey of US physicians conducted between October 2009 and February 2010²² with a follow-up survey conducted between March and June 2013. Comparison between these two studies showed a shift in practice, namely the use of danazol for LTP had decreased from 55.8% to 23.4% while the use of C1-INH had increased from 20.4% to 56.7% and become the most frequently prescribed product for this purpose.²³ This considerable change in practice was attributed to adherence to updated guidelines. In Canada, recently updated guidelines were published which enabled a similar initial approach to determine the treatment patterns of physicians treating HAE across Canada.²⁷

The timing of the current survey (early 2017) already allows for some important observations regarding the uptake of certain disease-specific therapies that have become available in Canada relatively recently. Specifically, C1-INH products have been licensed by Health Canada for use in HAE since 2010, and icatibant has been approved for use in acute HAE attacks since July 2014. Our findings indicate that C1-INH is the most frequently prescribed product for LTP, STP, or acute attacks and, in the case of acute attacks, icatibant is a close second. Also, physicians more frequently indicated a high degree of confidence in prescribing C1-INH for either prophylaxis or acute attacks and icatibant for acute attacks than they did with other medication (i.e., danazol or tranexamic acid).

In the United States, where the first C1-INH product was approved by the FDA in 2008, a similar survey of US physicians conducted between October 2009 and February 2010 did not find the same degree of adoption of recently approved therapies.²² However, a follow-up survey between March and June 2013 showed a shift in practice, namely the use of danazol for LTP had decreased from 55.8% to 23.4% while the use of C1-INH had increased from 20.4% to 56.7% and become the most frequently prescribed product for this purpose.²³ What was an initial lag in adoption in the US changed relatively quickly likely as physicians became more knowledgeable and experienced with this new product. The current situation in Canada where C1-INH is already the most frequently prescribed may reflect either quicker adoption or differences in the US and Canadian healthcare and remuneration systems.

The adoption of icatibant as a treatment for acute HAE attacks has been relatively rapid amongst Canadian physicians. Approved by Health Canada for treatment of acute attacks in July 2014, 1.5 years later it is used by 79.4% of respondents (second only to C1-INH) for the treatment of acute attacks.

We hypothesize that the publication of Canadian-specific HAE guidelines in October 2014 may have influenced physician prescribing practices and approaches to HAE management.²⁴ Our findings indicate that all but one of the survey respondents (97.1%) was aware of the Canadian HAE guidelines and that most (94.1%) used guidelines in their management. Furthermore, 85.3% of respondents indicated that they used guidelines to become aware of newer treatment options and recommendations. The Canadian guidelines recommend either C1-INH or icatibant for acute attacks which is reflected by the frequency with which these products are prescribed (88.2% and 79.4% respectively). Danazol and tranexamic acid are not recommended for acute attacks, but 5.9% of respondents indicated that they used danazol or tranexamic acid for this purpose. This underscores the need for more education and, 35.3% of respondents indicated that they would like to learn more about acute treatment.

There are some limitations to this survey study. Since it is not known how many or which Canadian physicians are currently treating patients with HAE, we attempted to contact them through the clinical organizations to which they were likely to belong. However, we acknowledge that we may have failed to reach all some of the

respondents and that even among those that we did reach, some may have chosen not to participate in this voluntary survey. 952 surveys were sent out to members of the organizations mentioned above, however it is important to note that a large portion of the survey recipients do not treat HAE and therefore would not have responded. In addition, two other organizations to which we reached out to did not respond or declined to distribute our survey. Our response rate (3.6%) was similar to those of the US survey (3.1%).²² The majority of our respondents were allergists and immunologists (82.4%). However, in the US the second most common specialty among respondents was dermatology. We had no respondents from dermatology suggesting that we may have missed a potentially important physician group.

The survey was made available in both English and French, the two official languages of Canada. There was only one respondent to the French version which means that our sample was not as geographically representative it could have been. Quebec is the second-most populous province in Canada and most residents are francophone. That said, many Quebecois clinicians are in fact bilingual and it is feasible that some of them may have completed the English version of the survey. We cannot know for certain as we did not specifically ask about province in which the respondent practiced medicine.

Another limitation of this survey was regarding the question about agents used for short-term prophylaxis (question #23). The frequency of use of some of these agents may have been underestimated due to an oversight in the original survey design which only

allowed for one response to be selected rather than allowing participants to check all that applied. This was remedied when the survey was already partially completed.

The results showed some physicians used C3 and C1q in the diagnosis of HAE. These tests are not widely accepted to be useful in the diagnosis however they are helpful to rule out other causes of angioedema that may be on the differential when evaluating someone for possible HAE.

Our results showed genetic testing is rarely used. Likely this is because of the unavailability of genetic testing in Canada. In addition, other diagnostic tests which are widely available are sufficient in the diagnosis of HAE.

The sites of swelling felt to have the most impact on patient quality of life were reported as facial (61.8%), abdominal (61.8%), laryngeal (58.8%), and tongue (44.1%). In contrast a study found that impact on time prevented from daily activity did not vary significantly across attack location, extremity, genitals or buttocks were just as impactful as other locations.²⁹

Results of this survey provide the first characterization of HAE medical management by Canadian physicians. We learned that most physicians were using guidelines to guide their practices. The uptake of newer therapies to treat HAE is also high. Future work is needed to address how many physicians look after these patients in Canada and what is their geographic location. Also, a patient registry would help identify how many

patients with HAE are currently in Canada. Treatment of HAE patients during pregnancy is another area that need to be further studied. In the future, we would like to conduct a survey of Canadian HAE patients and the current survey will therefore allow for an interesting comparison of physician versus patient-reported management practices and clinical priorities in the Canadian context. It will be important to periodically conduct follow-up surveys with Canadian physicians to better understand how their clinical decision making evolves over time and how, or to what extent, their prescribing practices are impacted by the introduction of novel HAE therapies.

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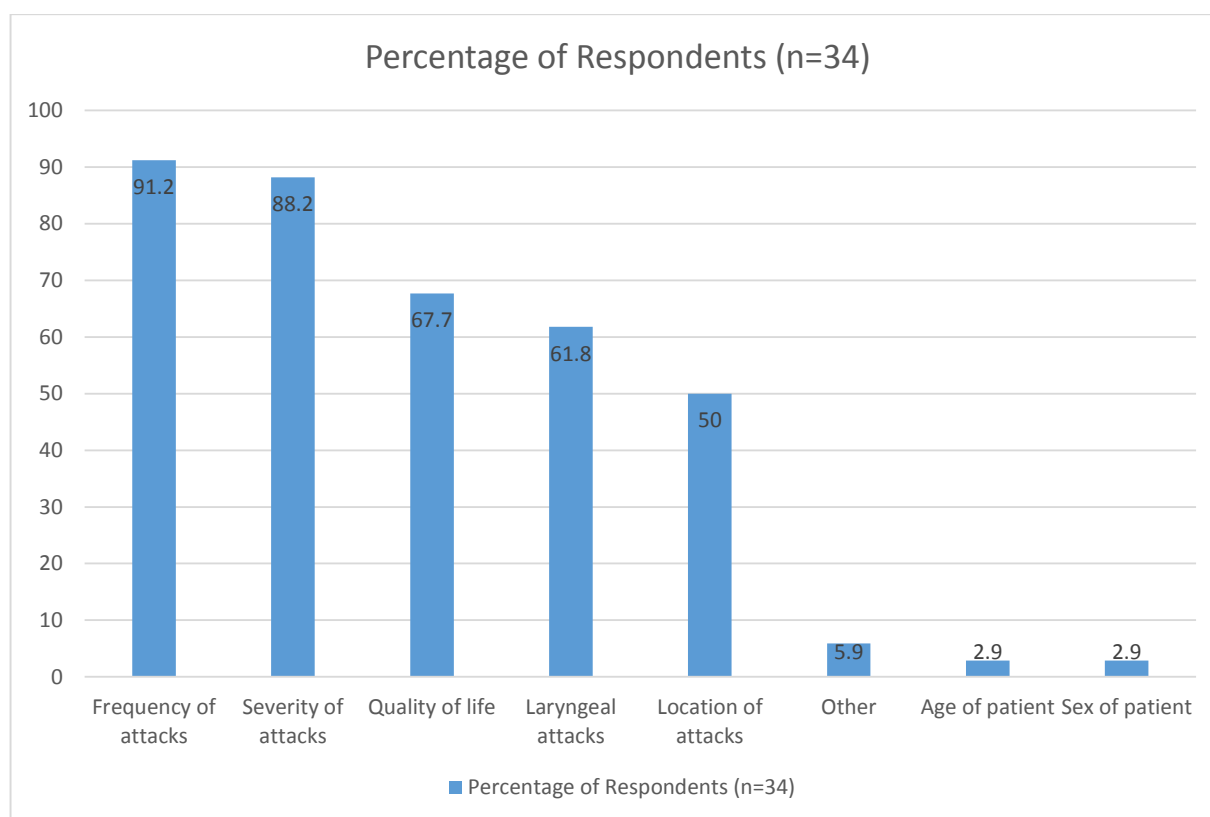


Figure 1. Factors influencing when to prescribe long term prophylaxis.

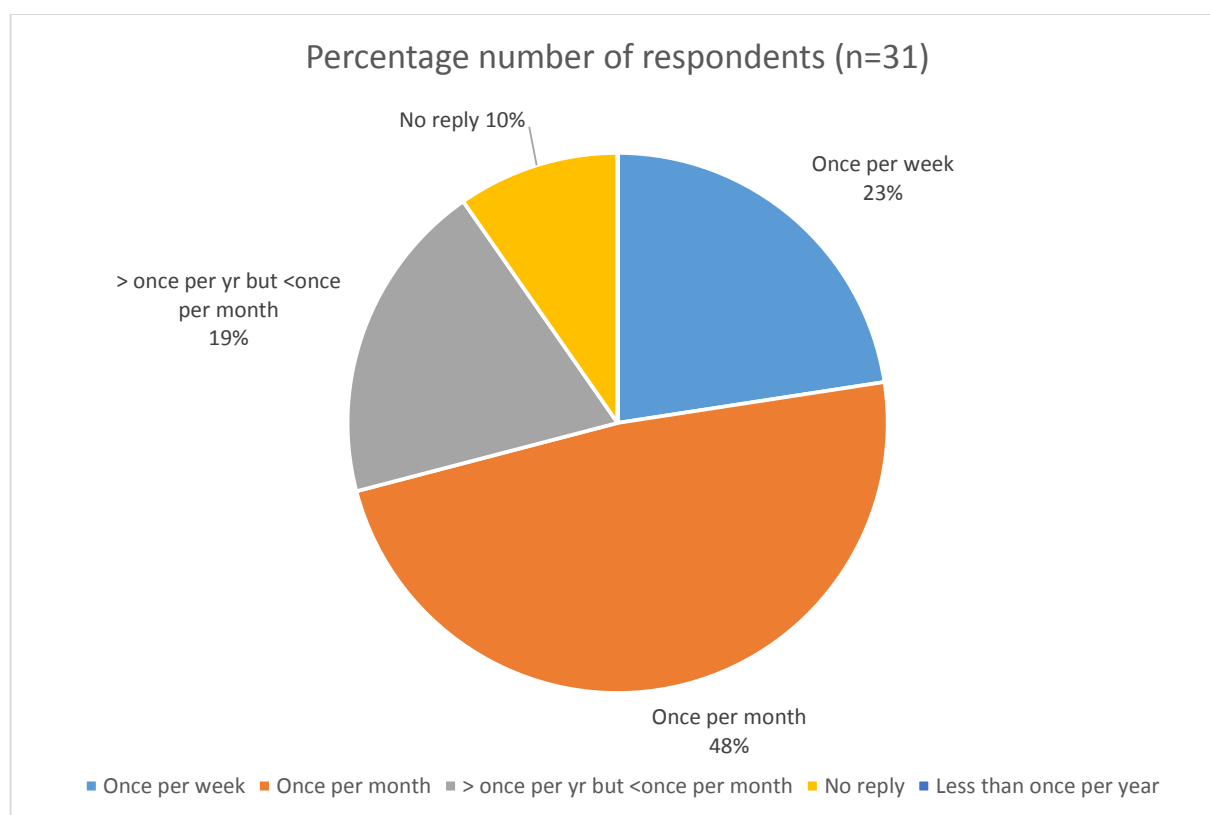


Figure 2. Frequency of attacks at which respondents would start Long Term Prophylaxis (LTP).

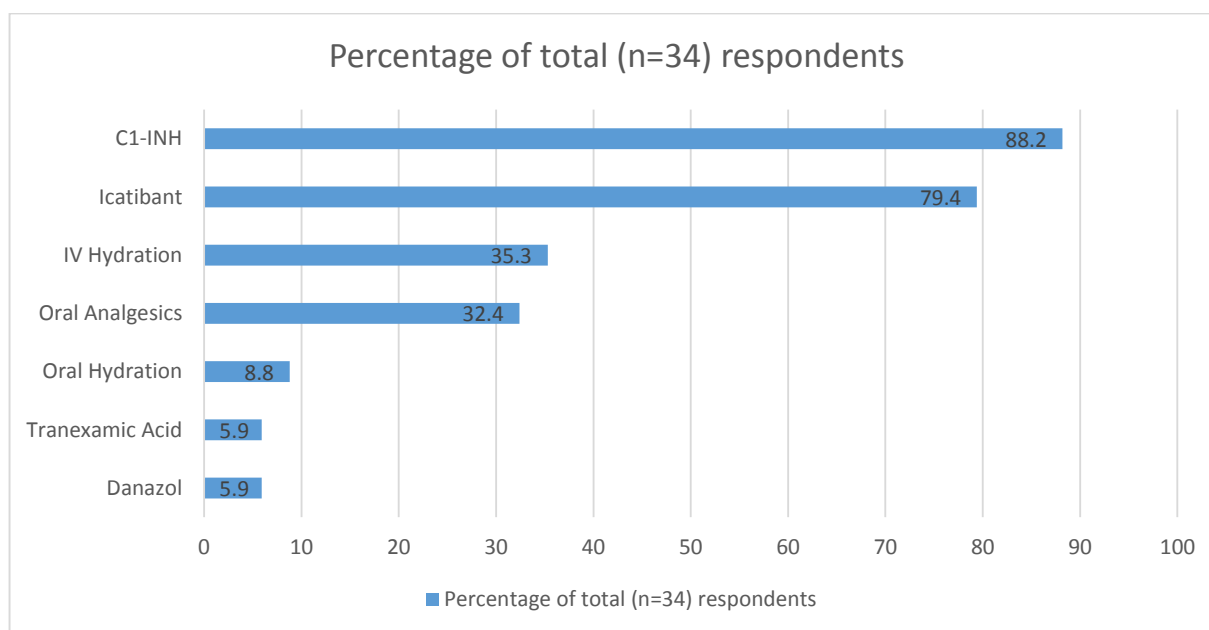


Figure 3. Treatment for acute attacks.

Table 1. Demographic and practice characteristics of respondents.

	Frequency (No.) Total: 34	Percent (%)
Degree		
MD	32	94.1%
MD and PhD	2	5.9%
Specialty (Respondents checked all that applied)		
Internal Medicine	6	17.7
Pediatrics	3	8.8
Allergy	28	82.4
Immunology	2	5.9
Dermatology	0	0
Hematology	5	14.7
Family Medicine	0	0
Affiliation		
Academic only	17	50
Non-academic only	5	14.7
Both academic and non-academic	11	32.4
Do not wish to reply	1	2.9
Practice Location		
Community	7	20.6
Hospital	17	50
Both community and hospital	9	26.5
Do not wish to reply	1	2.9

Table 2. Number of respondents currently treating patients with HAE, by patient volume and HAE type.

Number of Type 1 and Type 2 HAE patients under care	Number of Type 3 HAE patients under care						Total
	0 patients	1-5 patients	5-10 patients	10-20 patients	>20 patients	Do not wish to reply	
1-5 patients	11 (32%)	2 (6%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	14 (41%)
5-10 patients	1 (3%)	6 (18%)	2 (6%)	0 (0%)	1 (3%)	0 (0%)	10 (29%)
10-20 patients	1 (3%)	2 (6%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	4 (12%)
>20 patients	1 (3%)	1 (3%)	1 (3%)	2 (6%)	0 (0%)	0 (0%)	5 (15%)
Do not wish to reply	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)	1 (3%)
Total	14 (41%)	11 (32%)	5 (15%)	2 (6%)	1 (3%)	1 (3%)	34 (100%)