Original Article

A National Survey of Hereditary Angioedema and Acquired C1 Inhibitor Deficiency in the United Kingdom

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What is already known about this topic? There are limited data on the demographics and the treatments used in hereditary angioedema (HAE) and acquired C1 inhibitor deficiency in the United Kingdom.

What does this article add to our knowledge? This study provides more up-to-date data on demographics, treatments modalities, and services available to patients with HAE and acquired C1 inhibitor deficiency in the United Kingdom.

How does this study impact current management guidelines? This study provides information about how real-world practice compares with published management guidelines and identifies areas where care could be improved.

BACKGROUND: Detailed demographic data on people with hereditary angioedema (HAE) and acquired C1 inhibitor deficiency in the United Kingdom are relatively limited. Better demographic data would be beneficial in planning service provision, identifying areas of improvement, and improving care.

OBJECTIVE: To obtain more accurate data on the demographics of HAE and acquired C1 inhibitor deficiency in

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Abbreviations used
AAE-C1-INH- Acquired angioedema due to C1 inhibitor deficiency
C1-INH- C1-esterase inhibitor
HAE- Hereditary angioedema
HAE-1- Type 1 hereditary angioedema
HAE-2- Type 2 hereditary angioedema
HAE-nC1-INH- Hereditary angioedema with normal C1 inhibitor
LTP- Long-term prophylaxis

the United Kingdom, including treatment modalities and services available to patients.
METHODS: A survey was distributed to all centers in the United Kingdom that look after patients with HAE and acquired C1 inhibitor deficiency to collect these data.
RESULTS: The survey identified 1152 patients with HAE-1/2 (58% female and 92% type 1), 22 patients with HAE with normal C1 inhibitor, and 91 patients with acquired C1 inhibitor deficiency. Data were provided by 37 centers across the United Kingdom. This gives a minimum prevalence of 1:59,000 for HAE-1/2 and 1:734,000 for acquired C1 inhibitor deficiency in the United Kingdom. A total of 45% of patients with HAE were on long-term prophylaxis (LTP) with the most used medication being danazol (55% of all patients on LTP). Eighty-two percent of patients with HAE had a home supply of acute treatment with C1 inhibitor or icatibant. A total of 45% of patients had a supply of icatibant and 56% had a supply of C1 inhibitor at home.
CONCLUSIONS: Data obtained from the survey provide useful information about the demographics and treatment modalities used in HAE and acquired C1 inhibitor deficiency in the United Kingdom. These data are useful for planning service provision and improving services for these patients. **(J Allergy Clin Immunol Pract 2023;■:■-■)**

Key words: *Hereditary angioedema; Acquired C1 inhibitor deficiency; Demographics; Epidemiology; C1 inhibitor; Androgens; Icatibant; Tranexamic acid*

Hereditary angioedema (HAE) is a rare inherited disease characterized by episodic angioedema (without urticaria) affecting the skin and mucous tissues in the abdomen and respiratory tract. The edema in HAE is the result of capillary leakage into the tissues caused by inappropriately elevated bradykinin levels, which promote increased vascular permeability, vasodilatation, and smooth muscle contraction.[1]

Type 1 HAE (HAE-1) is characterized by reduced levels and function of C1-esterase inhibitor (C1-INH) and type 2 HAE (HAE-2) by normal or increased levels but reduced function. C1-INH is an enzyme that plays key inhibitory roles in the complement, contact, and coagulation systems.[1] Within the contact system, C1-INH directly inhibits the activity of plasma kallikrein, thereby regulating the production of bradykinin.

HAE-1/2 are caused by autosomal dominant mutations in the *SERPING1* gene. However, although approximately 75% of HAE cases are inherited, the remaining 25% are thought to result from *de novo* mutations. Among the total population with HAE, it has been estimated that approximately 80% to 85% are patients with HAE-1, with the remaining 15% to 20% being HAE-2.[2]

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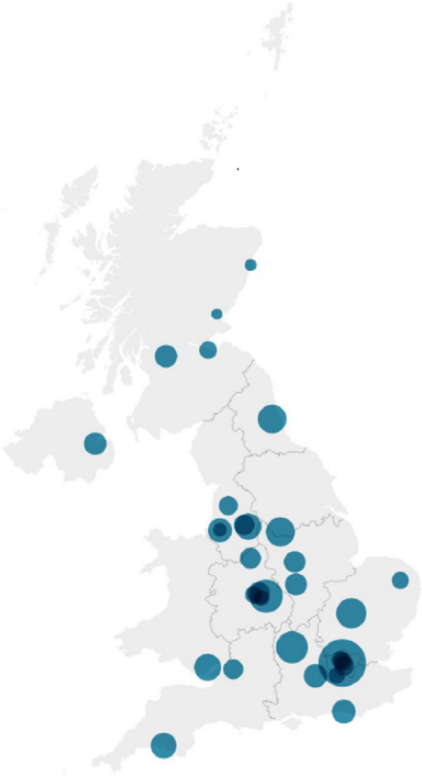

FIGURE 1. Map showing responses from treatment centers. The locations of the responding centers are shown with circles proportional to the number of patients in the data set. Created in DataWrapper (www.datawrapper.de).

HAE with normal C1-INH (HAE-nC1-INH; previously classified as HAE type 3), in which patients have symptoms of HAE but normal C1-INH levels and function, has also been described. HAE with normal C1-INH is rarer than HAE-1/2. HAE-nC1-INH is now understood to be a cluster of conditions caused by multiple gene mutations, some of which are related to mutations in factor XII,[3] angiopoietin-1,[4] plasminogen,[5] and kininogen genes.[6] However, a significant proportion of cases of HAE with normal C1-INH do not have an identified genetic mutation.

Acquired angioedema due to C1-INH deficiency (AAE-C1-INH) causes symptoms similar to those of HAE. AAE is caused by either increased consumption or increased inactivation of C1-INH.[7] AAE-C1-INH is most often associated with B-cell lymphoproliferative disorders and more rarely with autoimmune disease.[8]

HAE prevalence has traditionally been quoted at 1:50,000[1] although there is limited confirmatory evidence for this figure.[9] A systematic analysis of published data from 6 European countries (Spain, Norway, Denmark, Sweden, Italy, and Greece) gave an estimated HAE prevalence of 1:67,000. AAE-C1-INH is believed to occur at a prevalence of 1:100,000-150,000.[8]

Treatment for HAE and AAE-C1-INH can be divided into on-demand and prophylactic treatment. Options for on-demand treatment of attacks include C1-INH (plasma-derived and recombinant), icatibant (a bradykinin B2 receptor antagonist), and ecallantide (a kallikrein inhibitor, available in the United States but not in Europe).[10] Options for prophylactic treatment include oral therapies such as attenuated androgens (eg, danazol and oxandrolone) and antifibrinolytics (eg, tranexamic acid), and replacement intravenous C1-INH.[10] More recently, lanadelumab (a monoclonal antibody against kallikrein) and subcutaneous C1-INH (both licensed in the United States and in Europe) have been shown to be highly effective for prophylaxis in HAE.[11,12] However, at present, subcutaneous C1 inhibitor is unavailable for routine use in the United Kingdom. An oral kallikrein inhibitor, berotralstat, has also received marketing authorization[13] in the United States and Europe. In addition, there are various other oral and injectable therapies that are in clinical trials for use in HAE.[14]

The last published data in the United Kingdom looking at epidemiology and service provision in HAE are from 2013 and 2014.[15,16]

As there are limited recent data on the demographics of and services for HAE and with the development of new treatments, the UK HAE network undertook a survey in February 2019 to determine current demographics of patients with HAE and AAE-C1-INH in the United Kingdom and to assess services available in HAE centers. This was done with the aim of getting more accurate figures on the numbers of patients with HAE and AAE-C1-INH, the current treatments being used and the services available to patients. At the time of the survey, the available medications in the United Kingdom for on-demand treatment included plasma-derived C1-inhibitor (Berinert, Cinryze), recombinant C1-inhibitor (Ruconest), and icatibant. The available treatments for long-term prophylaxis (LTP) included the aforementioned C1-inhibitor products, androgens (danazol, oxandrolone) and tranexamic acid. LTP with C1-inhibitor was restricted to patients having 2 or more clinically significant attacks per week despite oral prophylaxis, or if they were intolerant or unable to have oral therapy. Lanadelumab and berotralstat were not available at the time of the survey, although they were subsequently approved for use.

It is hoped that these data will provide useful information for understanding the current state of services in the United Kingdom, service planning and commissioning, and ultimately, improving patient care for these rare diseases.

METHODS

This survey was undertaken by the UK HAE network, a group of physicians, nurses, and patient organization representatives that was established in 2018 to improve the treatment of patients with HAE in the United Kingdom. The survey was developed by the UK HAE network committee to collect center-level data at a specific point in time on HAE and AAE-C1-INH patient numbers, data on available therapies (emergency treatment and LTP), policies on treatment, service provision, and patient care. Data on patient numbers were broken down by whether patients were adult (aged >18 years), adolescent (aged 12-18 years), or pediatric (<12 years) and whether male or female.

The survey was distributed electronically in the form of a Microsoft Excel spreadsheet to all UK centers treating patients with HAE and AAE-C1-INH via regional representatives on the UK HAE network committee.

TABLE I. UK centers that provided data for the survey

Aberdeen Royal Infirmary, Aberdeen, Scotland
Addenbrooke's Hospital, Cambridge, England
Alder Hey Children's Hospital, Liverpool, England
Birmingham Heartlands Hospital, Birmingham, England
Bristol Children's Hospital, Bristol, England
City Hospital, Birmingham, England
Derriford Hospital, Plymouth, England
Frimley Park Hospital, Frimley, England
Great Ormond Street Hospital, England
John Radcliffe Hospital, Oxford, England
King's College Hospital, London, England
Leicester Royal Infirmary, Leicester, England
Manchester Royal Infirmary, Manchester, England
Queen Elizabeth University Hospital, Glasgow, Scotland
Ninewells Hospital, Dundee, Scotland
Norfolk and Norwich University Hospital, Norwich, England
Northern General Hospital, Sheffield, England
Nottingham University Hospitals NHS Trust, Nottingham, England
Royal Free Hospital, London, England
Royal Hospital for Sick Children, Glasgow, Scotland
Royal Hospital for Children and Young People, Edinburgh
Royal Infirmary of Edinburgh, Edinburgh, Scotland
Royal Liverpool and Broadgreen Hospital, Liverpool, England
Royal London Hospital, London, England
Royal Manchester Children's Hospital, Manchester, England
Royal Preston Hospital, Preston, England
Royal Stoke University Hospital, Stoke, England
Royal Surrey County Hospital, Guildford, England
Royal Sussex County Hospital, Brighton, England
Royal Victoria Infirmary, Newcastle, England
Russells Hall Hospital, Dudley, England
Salford Royal Hospital, Salford, England
Sheffield Children's Hospital, Sheffield, England
St Helier Hospital, London, England
The Royal Hospitals, Belfast, Northern Ireland
University Hospital Birmingham, Birmingham, England
University Hospital of Wales, Cardiff, Wales

RESULTS

Patient demographics

Patient data were supplied by 37 centers across the United Kingdom (Figure 1 and Table I), of which 89% (n = 33) provided data from a formal patient database. A total of 30% (n = 11) reported that some of their patients experienced shared care with another center.

A total of 1174 patients with HAE were identified as being managed within the centers that responded, comprising 1056 patients with HAE-1, 96 patients with HAE-2, and 22 patients with HAE-nC1-INH, defined by having a recognized gene mutation or family history (Table II).

In addition, 91 patients with AAE-C1-INH were identified (Table II).

Fifteen centers provided data on patients who were no longer engaging with the service—in total, 77 patients with HAE were lost to all medical follow-up. Of these, 40 (52%) were male, 37 (48%) female, and the majority aged >18 years (n = 69; 90%), with the remainder being adolescents (n = 6; 8%) or pediatric patients (n = 2; 3%). A much smaller proportion of patients with AAE-C1-INH were lost to medical follow-up (n = 3; 4%). These patients were not included in the data analysis.

Among those patients with HAE who were identified as being treated within the centers, 165 patients had no other affected family members, indicating that the majority of patients identified by centers were in families where 1 or more members had HAE. This makes up 14% of the total HAE-1/2 cohort.

On-demand treatment

A total of 82% of patients with HAE identified by the survey were provided with a home supply of acute treatment (either C1-INH or icatibant), and 61% could self-administer their own acute treatment (Table III). In the AAE-C1-INH population, 75% were provided with a home supply of acute treatment and 52% could self-administer their treatment (Table III). Among both male and female patients with HAE, adults were more likely to have a home supply of treatment compared with adolescents and pediatric patients (Table IV).

When prescribing C1-INH for acute treatment, the majority of those centers that provided information stated that they always used the licensed dose (n = 24; 67%), and the remainder (n = 12; 33%) stated that they sometimes used the licensed dose.

Emergency acute treatment provided to patients was largely icatibant (n = 565; 45%) and C1-INH (n = 713; 56%), with a minority provided with anabolic steroids (n = 52; 4%) and tranexamic acid (n = 73; 6%).

Centers were also asked about their unit policy regarding the minimum number of doses of acute treatment provided to individual patients. In those centers that provided data, the mean number of doses provided was between 1 and 2 (n = 1.4), and the most common (mode) number of doses was 2, provided by 16 centers. However, this was complicated by the fact that the number of doses was dependent on the acute treatment supplied, with some centers providing 1 dose of C1-INH but 2 doses of icatibant.

Long-term prophylaxis

A total of 45% of the population with HAE were treated with LTP (Table V). Of these, the majority were treated with androgens (55%) or tranexamic acid (18%) as monotherapies, with the remainder being treated with C1-INH or combination therapy (Table VI).

Adults were more likely to be on LTP compared with adolescents, who were more likely to be on LTP compared with children under 12 years (Table V).

A total of 40% of patients with AAE-C1-INH were treated with LTP (Table V), with all patients being treated with either androgens (47%) or tranexamic acid (47%) as monotherapies or in combination (6%) (Table VI).

Service provision and organization

Among responding centers, all reported that their patients were managed by specialists trained in clinical immunology, either pediatric or adult, with an average staff of 2.4 consultants per center and a mode of 2 or 3, out of a total number of 90. The average number of specialist nurses involved in HAE patient care was 2.4 with a mode of 2 per unit.

When asked about their unit policy of allowing the prescription of specific treatments for HAE, the majority of centers were able to prescribe all products available (Table VII), with older products being more uniformly available for prescription, with the exception of androgens in a pediatric setting.

Each unit assessed also provided a summary of the availability of a range of services for patients with HAE relating to training

TABLE II. Total identified UK hereditary angioedema (HAE) and acquired angioedema due to C1 inhibitor deficiency (AAE-C1-INH)

	Male		Female			Percentage of HAE type
	n	%	n	%	Total	
HAE-1						
Adult (>18 y)	356	79	507	85	863	82
Adolescent (12-18 y)	41	9	42	6	83	8
Pediatric (<12 y)	52	12	58	9	110	10
Total HAE-1	449		607		1056	
Percentage of patients with HAE-1	43		57			
HAE-2						
Adult (>18 y)	29	73	43	77	72	75
Adolescent (12-18 y)	6	15	8	14	14	15
Pediatric (<12 y)	5	12	5	9	10	10
Total HAE-2	40		56		96	
Percentage of patients with HAE-2	42		58			
Total HAE-1/2	489		663		1152	
Percentage of patients with HAE-1/2	42		58			
HAE-1/2 in each age bracket						
Adult (>18 y)	385	80	550	84	935	81
Adolescent (12-18 y)	47	9	50	7	97	9
Pediatric (<12 y)	57	11	63	9	120	10
*HAE nC1-INH**	8		14		22	
Percentage of HAE nC1-INH	36		64			
Total HAE-1/2 and HAE nC1-INH	497		677		1174	
No. of patients with AAE-C1-INH†	38		53		91	
Percentage of AAE-C1-INH	42		58			
Total HAE and AAE-C1-INH	535		730		1265	

Of 37 responding centers, 23 (62%) stated that these were accurate figures. Two centers stated that their figures were estimates, and the remaining centers did not state whether the figures were accurate or estimates.
*Defined by gene mutation or family history.
†All adult.

TABLE III. HAE and AAE-C1-INH—home supply and self-administration of acute treatment

	Male	Female	Total
HAE-1/2 patients			
Total number of HAE patients	489	663	1152
Number provided with a home supply of acute treatment*	403	541	944
Proportion provided with a home supply of acute treatment* (%)	82	82	82
Patients who can self-administer acute treatment*, n (%)			703 (61)
AAE-C1-INH patients			
Total number of AAE-C1-INH patients	38	53	91
Number provided with a home supply of acute treatment*	30	38	68
Proportion provided with a home supply of acute treatment* (%)	79	72	75
Patients who can self-administer acute treatment*, n (%)			47 (52)

AAE-C1-INH; Acquired angioedema due to C1 inhibitor deficiency; *HAE*, hereditary angioedema.
*C1-INH or icatibant.

for self-administration and availability of home delivery for C1-inhibitor and icatibant (Table VIII). Overall, outsourcing of training for self-administration of either icatibant or C1-INH was less common than delivering the training in-house. Between 60% and 70% of centers offered home delivery of either icatibant or C1-INH.

DISCUSSION

The most important learning points from this survey are around the prevalence data of HAE and AAE-C1-INH and data about access and usage of acute and prophylactic therapies in the United Kingdom. Data from this survey provide an estimated prevalence figure very close to the often-quoted prevalence of 1:50,000. This gives an idea of the likelihood of how many undiscovered cases of HAE there are and has implications for where efforts to improve care would be best focused. Data about the usage of acute therapies indicate that a significant percentage of patients with HAE and AAE-C1-INH (39% and 48%, respectively) are not able to self-administer acute therapy, and this warrants further exploration. Data about the use of LTP provide a useful baseline before the availability of more modern, targeted agents becoming available in the United Kingdom, and is useful as a comparison for any future surveys.

This study follows on from previous studies performed by Jolles et al and Read et al in 2013 and 2014, respectively.[15,16] To our knowledge, it is the largest study to date in the United Kingdom with data on 1152 patients with HAE-1/2 (of whom 217 were under the age of 18) and 91 patients with AAE-C1-INH deficiency from 37 centers from all the nations within the United Kingdom. The study by Jolles et al[15] identified 376 patients with HAE, and more recent data from the UK immunodeficiency registry showed that only 514 patients with HAE (for a minimum prevalence of 0.73/100,000) were registered.[17] Read et al[16] reported data on 111 pediatric patients with HAE from 16 of 28 centers that were contacted.

Because of the way services for people with HAE are commissioned in the United Kingdom, it is possible to identify all specialist centers that treat HAE for circulation of the survey. The survey captures data from 90% of centers in the United Kingdom, with only 4 centers not participating.

Patient demographics

Using a mid-year 2019 UK population estimate of 67 million,[18] the minimum prevalence of HAE-1/2 is 1:59,000. The true prevalence will be higher than this as not all centers submitted data for the survey. This prevalence is higher than the aggregate prevalence calculated by Aygören-Pürsün et al.[9] If there were a proportionate number of patients in the centers that did not submit data, the prevalence would be 1:52,000. In addition, there appears to be a not insignificant number of patients who are not currently engaging with a specialist HAE center and are lost to medical follow-up.

AAE-C1-INH is much rarer with a minimum prevalence of 1:734,000, and HAE-nC1-INH (defined by either the presence of a family history of angioedema or identification of a mutation in one of the genes recognized to cause HAE-nC1-INH) is extremely rare in the United Kingdom with a minimum prevalence of 1:3,000,000.

The proportion of people with HAE-2 (8%) is lower than the typically quoted figure of 15%[1] but similar to the figure by Jolles et al.[15]

TABLE IV. Patients with HAE-1/2 in each age bracket provided with a home supply of treatment

	Male			Female			Total	
	n	Percentage of male age bracket	Percentage of male home supply	n	Percentage of female age bracket	Percentage of female home supply	n	Percentage of age bracket
Adult (>18 y)	331	86	82	476	87	88	807	86
Adolescent (12-18 y)	39	83	10	30	60	6	69	71
Pediatric (<12 y)	33	58	8	35	56	6	68	57
Total with home supply of treatment	403	82		541	82		944	82

HAE, hereditary angioedema.

TABLE V. Provision of long-term prophylaxis (LTP) in HAE and AAE-C1-INH

	Male			Female			Total	
	n	Percentage of total male	Percentage of male LTP	n	Percentage of total female	Percentage of female LTP	n	Percentage of total in age brackets
HAE								
Adult (>18 y)	217	56	96	277	50	93	494	53
Adolescent (12-18 y)	7	15	3	16	32	5	23	24
Pediatric (<12 y)	2	4	1	5	8	2	7	6
Totals	226	49		298	48		524	45
AAE-C1-INH								
Total population*	16	42		20	38		36	40

AAE-C1-INH, Acquired angioedema due to C1 inhibitor deficiency; *HAE*, hereditary angioedema.
*All adult.

Similar to previous studies, there were a higher number of females recorded with HAE (58%). The proportion of people with AAE-C1-INH who were female was similar (58%).

In comparison with the quoted figure of 25% of people with HAE-1/2 who are thought to have *de novo* mutations, 14% of individuals in this study did not have any affected family members. It is possible that this figure is an overestimate as these individuals may not have been aware of a family history.

On-demand treatment

The majority of patients kept some form of injectable acute on-demand treatment (either C1-INH or icatibant or both) at home. However, adults and adolescents were a lot more likely to keep a supply of on-demand treatment at home compared with children under the age of 12. Of the available on-demand treatments, icatibant, Cinryze, and Ruconest are all licensed from the age of 2 years and Berinert is licensed for all ages. It is likely that younger children had fewer or no HAE attacks, resulting in a lower proportion of them being provided with a home supply of treatment. However, the majority of children were still provided with a home supply of treatment, and this is an area of variation in practice to further investigate.

In addition, of the patients with on-demand treatment at home, a significant proportion were not able to self-administer this.

However, compared with the survey by Jolles et al,[15] more people with HAE (82%) now have a home supply of on-demand treatment (62% in the paper by Jolles et al[15]), although a similar proportion are likely to need to attend A&E for on-demand treatment (30% in the paper by Jolles et al[15]).

Both United Kingdom and international published guidelines recommend that patients keep on-demand medication with them,[10,19] and it would be helpful to explore further whether there are patients who prefer not to keep a supply of on-demand medication or whether there are other reasons for this. It would also be useful to explore further why there a significant number of people with their own supply of on-demand medication are not able to self-administer this, particularly as this has implications for usage of emergency department services and added requirement to attend hospital for treatment. The figure that only 61% of patients with HAE are able to self-administer on-demand treatment appears to be relatively low, and it is important to look into this as HAE is a condition with acute attacks that can be life threatening.

In addition, although no longer recommended in published guidelines,[10,19] both androgens and tranexamic acid are still used for on-demand treatment, and this practice should be reviewed as there is scant evidence to justify this.

Long-term prophylaxis

The use of LTP is much higher in adults with HAE compared with children, suggesting that attack frequency increases as people with HAE get older. At the time of the survey, the only licensed LTP agent was Cinryze from the age of 6 years. Berinert, Ruconest, androgens, and tranexamic acid were used off-license for LTP as well. After the survey, lanadelumab and berotralstat have been licensed from the age of 12 years.

About half of the patients taking LTP were on androgens, either on their own or in combination with other medication in a small proportion. Although thought to be of limited efficacy in HAE, almost a fifth of patients with HAE taking LTP were using tranexamic acid on its own. Working on the basis that patients who found this completely ineffective would stop taking it, this would suggest that at least a significant minority may gain some benefit from tranexamic acid. The proportion of patients with AAE-C1-INH on tranexamic acid LTP was almost half.

Although international guidelines only recommend androgens as second-line treatment for LTP and do not recommend

TABLE VI. Treatment choice for long-term prophylaxis (LTP) in HAE and AAE-C1-INH

	HAE		AAE-C1-INH	
LTP therapy option	n	%*	n	%†
Androgens only	288	55	17	47
Tranexamic acid only	94	18	17	47
Cinryze (plasma-derived C1-INH) only	30	6	0	0
Berinert (plasma-derived C1-INH) only	39	7	0	0
Ruconest (recombinant C1-INH) only	3	1	0	0
Androgens and tranexamic acid combined	32	6	2	6
Oral medication and C1 inhibitor	22	4	0	0
C1 inhibitor (unspecified) only	3	1	0	0

AAE-C1-INH, Acquired angioedema due to C1 inhibitor deficiency; *HAE*, hereditary angioedema.
*Based on the total number of patients with HAE reported as receiving LTP (n = 524)—note that there was a discrepancy of 13 between the total number of patients reported as receiving LTP and the numbers reported for individual treatment options (n = 511).
†Based on the total number of patients with AAE-C1-INH receiving LTP (n = 36).

TABLE VII. Available therapeutic options according to center policy (N = 37)

	Availability	
Treatment options	No. of centers	Percentage of responding centers
Danazol	34	92
Oxandrolone	17	46
Tranexamic acid	36	97
Cinryze (plasma derived C1-INH)	32	86
Berinert (plasma derived C1-INH)	37	100
Ruconest (recombinant C1-INH)	22	59
Icatibant	36	97

C1-INH, C1-esterase inhibitor.

tranexamic acid,[10] at the time of the survey, C1-INH was the only other LTP treatment option available and English national commissioning policy[20] restricted this to patients with 2 or more attacks per week while taking oral prophylaxis (or if oral prophylaxis is contraindicated or not tolerated).

The figures for C1-INH usage (8% of all people with HAE in the survey) give a crude indication as to the proportion of people with HAE who have very severe disease in view of the English national commissioning policy[20] restricting C1-INH LTP use for patients with 2 or more attacks per week.

At the time of the survey, lanadelumab and berotralstat were not available in the United Kingdom, and it would be interesting to collect follow-up data to see how LTP usage changes with this. It is likely that some patients would switch to or start on lanadelumab or berotralstat, given the ease of administration and/or side effect profile compared with available options for LTP.

Service provision and organization

The data showed that 10 centers had only 1 consultant seeing patients with HAE and 8 centers had only 1 specialist nurse seeing these patients. However, national service specifications[21] recommend that centers should have at least 2 consultants caring for these patients, as this would provide greater resilience. It would be worth exploring whether added resource can be provided to increase staff coverage in centers where only a single consultant or nurse is providing care.

TABLE VIII. Services available for patients with HAE managed in each center (N = 37)

Services available	No. of centers	Percentage
In-center training for C1 inhibitor self-administration	30	81
Outsourced training for C1 inhibitor self-administration	9	24
In-center training for icatibant self-administration	36	97
Outsourced training for icatibant self-administration	12	32
Home delivery for C1 inhibitor	21	57
Home delivery for icatibant	25	68

HAE, Hereditary angioedema.

Apart from access to Berinert, there was variability in which medications centers had access to and what services they were able to provide.

Of particular significance, only about two-thirds of centers were able to provide home delivery of on-demand therapies. This significantly affects patients who have to travel long distances to access a specialist center to collect their medication. This is despite an English national service specifications contract,[21] indicating that home therapy delivery services should be available to patients with HAE.

The variation in available services is worth exploring further to determine the reasons why these exist and what can be done to improve this.

Challenges identified

The survey has identified challenges in the care of patients. Although provision of therapy for acute attacks was generally good, only 61% of patients with HAE were able to self-administer this, and these data require further exploration to determine the reasons and whether this can be improved. Data on LTP agents showed significant usage of androgens and tranexamic acid, which are not first-line agents in international guidelines.[10] This is due to a combination of what medications were available at the time of the study and current commissioning policy, but would be important to look at again, given the availability of more medication since the survey.

The survey also identified variation in the provision of care, both in the number of staff and available services between different centers. All centers providing HAE care in the United Kingdom are nationally commissioned specialized centers with defined service specifications. Further work to determine why this variation exists and how overall standards can be raised is important.

Limitations of the data

Although this survey includes almost all centers treating HAE in the United Kingdom, there were a small number of centers that did not participate in the survey. To our knowledge, there is no difference in these centers that would significantly bias the overall results of the survey. Another limitation of the survey is that it does not provide data about disease severity or control, or patient satisfaction with their level of care. This would have required collecting individual patient level data to analyze and

would have been a significantly more complicated undertaking. The survey also did not ask for the reasons for the variation in service provision or therapies used, which would have been helpful to know. These areas are all things that are important to address in future work.

CONCLUSIONS

In conclusion, this survey has provided a comprehensive set of data on current numbers of patients with HAE and AAE-C1-INH in the United Kingdom, as well as the treatments used and services available to them. This data will be useful for planning and commissioning services for patients with HAE and AAE-C1-INH and may be particularly useful with the number of new medications currently in the development pipeline. We have also demonstrated that it is possible to collect data on a national level and have learned lessons about data collection, and the need to balance obtaining data from as many centers as possible versus the level of detail provided in the data. This survey also identified that there is a potential need for better routine processes to capture data on this group of patients for improved understanding and care, and ideally more complete recruitment to the national registry may be the best solution. Finally, the survey identifies areas where the care of this group of patients is done well but also areas where there may be room for further improvement. It is hoped that this survey and other future efforts will help provide information and form the basis for decision-making, to ultimately provide the best care for this group of patients.

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