

# Hereditary Angioedema patient experiences of medication use and emergency care

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## ABSTRACT

**Background:** Hereditary angioedema (HAE) is a rare inherited illness characterised by recurrent swellings. Four percent of HAE attacks are life threatening throat swellings requiring urgent medical intervention. The aim of this study was to gain an in depth understanding of patient experiences of use of treatment and emergency care. **Methods:** 65 participants completed an online survey including open ended questions about their experiences and/or completed an in-depth interview. Interview participants were asked to share and talk about up to five images that they felt best represented their life experiences with HAE. Data were analysed using reflexive thematic analysis.

**Results:** Treatment experiences highlighted the life changing nature of new treatments and benefits for quality of life, but also illustrated common barriers to treatment administration. Emergency care experiences illustrated how throat attacks and fear of their future occurrence could be traumatic.

**Discussion:** Findings indicate that HAE patients need psychological support to process fears and negative experiences. In addition, psychological barriers to treatment administration must be addressed to ensure treatment is used effectively. Education for emergency practitioners is also needed to improve emergency treatment and reduce the psychological burden of delayed emergency care.

## 1. Introduction

Hereditary angioedema (HAE) is a rare inherited illness with prevalence estimated to be 1 in 50–150,000 occurring across all ethnic groups [1]. The condition is characterised by recurrent swellings affecting almost any part of the body, although the usual sites include limbs, genitals, face, mouth, and abdomen [2]. Attacks are often unpredictable impacting on quality of life and mental health, as well as education, career progression, and work productivity [1]. The use of medication to manage HAE has the potential to improve quality of life [3].

Around four percent of HAE attacks are life threatening with throat swellings requiring urgent medical intervention [4]. It is estimated that 33–56% of these attacks result in death by asphyxia if left untreated [5], and it is proposed that delays in emergency care and administration of drug therapies within emergency departments contribute to these deaths [6]. It is therefore essential that patients receive quick and efficient

treatment when presenting at emergency departments (ED).

Historically, misdiagnosis or inappropriate treatments for HAE were common [7]. However, in the past few decades the management has undergone major changes and there are now effective agents for the prevention and management of acute attacks [3,8]. These agents include those infused intravenously, subcutaneous agents such as Firazyr, a synthetic bradykinin inhibitor, and most recently, Lanadelumab, a synthetic kallikrein inhibitor. Lanadelumab [9], Ruconest [10] and Cinryze [11] when used regularly as prophylactics, have been shown to prevent symptom onset.

Acute attacks have serious implications for patients; upper airway swellings present risk of asphyxiation, abdominal attacks can cause severe debilitating pain, and peripheral attacks of limbs impair functioning in activities of daily life [3]. On demand treatments such as Berinert [12] and Firazyr [13] can be used when patients experience acute attacks. For many, these medications can be self-administered at home increasing patient control over treatment and improving quality of

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life [3]. Early administration of on demand treatments for acute attacks speeds the resolution of symptoms and can reduce attack severity [3]. International guidance recommends that on demand treatment is considered for all acute attacks and is mandatory for attacks affecting the upper airway [3].

While evidence indicates that these agents are effective in the management of HAE [2,14] little is known about patients' own perceptions and experiences of self-administering medications or receiving treatment in emergency care settings. One qualitative study conducted in the United States of America (USA) with patients using subcutaneous C1 inhibitor replacement therapy for prophylaxis, reported that access to treatment reduced frequency of symptoms, had a significant impact on patients' lives, and decreased levels of HAE-related worry and anxiety. Participants also highlighted how access to medication for self-administration gave them independence and freedom to plan their own lives as they wished, including more freedom to work and travel [15]. The USA healthcare system is funded through a complex mix of private insurance and government subsidies, while the United Kingdom (UK) provides a national system of healthcare funded through taxation [16]. It is therefore expected that patient experiences in the UK differ to patients in the USA. To date no research has been conducted to explore the treatment experiences of HAE patients in the UK.

Qualitative methods are a valuable tool for understanding the human and organizational factors that influence the quality and safety of health care [17] and facilitate understanding of the patient journey, a critical endeavor for informing the delivery of care [18]. Qualitative research is of value to the allergy and immunology community, can provide insights that cannot be achieved with quantitative research, and should be used to inform national and international guidelines [19]. For this paper, qualitative data on patient use and perceptions of treatment and emergency care services in the UK were collected as part of a wider study exploring the lived experience of HAE. Data were analysed to develop an understanding of patient experience and these experiences are presented with the aim of making recommendations for improving treatment use and the quality of emergency care.

## 2. Methods

### 2.1. Design

A mixed methods design combining an online quantitative and qualitative survey with follow up in-depth interviews was employed. The study was approved by Staffordshire University School of Health, Science and Wellbeing Ethics Committee.

### 2.2. Procedure

A convenience sample was recruited via HAE UK, a specialist UK charity group for individuals affected by HAE, using the incentive of a prize draw for shopping vouchers. The following inclusion criteria applied: over 18 years, confirmed diagnosis of HAE with C1 inhibitor deficiency, and able to converse in English. Information about the study was shared via the charity email mailing list and social media. Following informed consent participants completed an online Qualtrics® [20] survey with open and closed questions. At the end of the survey participants were also offered the option to complete an additional in-depth interview in return for a £15 shopping voucher.

Following a second consent process interview participants were emailed an outline of the interview schedule and asked to share up to five images that they felt best represented their life experiences with HAE. This photo-elicitation process is an empowering approach that enables participants to lead discussions about their own perceptions and experiences of health issues [21,22]. Participants were informed that the photographs chosen could be anything they felt would help the researchers understand their experiences with HAE. One participant chose not to share any images.

Due to the geographical variability, interviews were conducted and recorded using Microsoft Teams or telephone and a dictaphone. Interviews were conducted by AB, I L-W, JE and DH. AB was the project lead and has substantial experience with the use of qualitative methods and conduct of research interviews and acted as supervisory lead for all interviews conducted. None of the interviewers had any lived experience or knowledge of HAE prior to conducting the research.

The interviews lasted up to two hours and were guided by an interview schedule, beginning with the participant's background (e.g., the onset of HAE symptoms and diagnosis experience) before moving on to their current life with HAE. Each image was then discussed in turn. Questioning was kept deliberately generic to facilitate discussion of issues important to the participants themselves. Both participant and researcher had a copy of the photographs in front of them to aid discussion of the images. At the end of the interview participants were asked questions regarding their treatment and coping, support network, and their future with HAE. Participants were fully debriefed and provided with details of support organisations.

The interview process was piloted with the first participant and no changes were made for further participants. Interviewers met regularly to discuss the conduct of the interviews and any field notes or observations. Data were collected between September 2021 and April 2022.

### 2.3. Analysis

Interview data were transcribed and anonymised using pseudonyms. Themes were developed from open question survey responses and interview transcripts using reflexive thematic analysis [23]. Reflexive thematic analysis is a method for identifying themes and patterns of meaning. Analysis took an inductive and experiential approach which generates analysis from the data, giving emphasis to the participants voice and experience.

Braun and Clarke recommend a five-step analysis process [23]: 1.) Data familiarisation and making familiarisation notes, 2.) Systematic data coding, 3.) Generating initial themes from coded and collection data, 4.) Developing and reviewing themes, 5.) Refining, defining, and naming themes. The researchers adopted a critical realist perspective to the data collection and analysis [24] recognising that it is possible to acquire an insight into people's experiences through their accounts, but also that we as researchers have a role in constructing knowledge.

To conduct the analysis transcripts were divided between AB, I L-W, DH and AO. In step 1 the researchers read and familiarised themselves with their allocated transcripts and completed systematic data coding electronically using Microsoft Word. In step 2 each analyst generated initial themes from their data set and recorded these in tables. In step 3 the authors met to discuss the developing themes and a shared document was created capturing all themes identified across the data set. During these discussions some themes from different authors were merged or subsumed into each other. In step 4, I L-W used this list of themes to review all the transcripts and extract data representing each theme into separate word documents. In step 5 AB reviewed these word documents alongside the full transcripts and produced a short paragraph summarising the content for each theme before using this summary and rich example quotes from the data to produce a theme narrative. This narrative was reviewed and edited by all authors to produce the final theme narrative presented in this paper.

### 2.4. Participants

In total 65 participants completed the online survey and 37 requested information about the follow up interview, of these 11 (30%) arranged an interview. Survey participants ranged in age from 19 to 79 (mean age 47) and interview participants from 28 to 76 (mean age 53). On average symptom onset began at age 12 for survey respondents and 10 interviewees, and mean age of diagnosis was 22 for survey respondents and 30 for interviewees. 78% of survey participants and 82%

of interviewees were prescribed prophylactic treatments, the most prescribed were Berinert and Danazol. Most participants had treatments available at home (85% survey; 100% interview). The most used on demand attack management treatments were Berinert and Icatibant. Further demographic details can be seen in Table 1.

### 3. Results

Four themes were developed relating to the experiences of treatment use and use of emergency care. Treatment use experiences highlighted the life changing nature of treatment and the associated benefits for quality of life. However, participants also discussed reasons for delaying treatment administration including attributing symptoms to other causes, concerns about being a drain on NHS financial resources, and circumstances in which participants were unable to administer their own treatment. Emergency care experiences were captured within two themes illustrating the terrifying experience of throat attacks and fear of their future occurrence, and traumatic and upsetting experiences of accessing emergency care (Fig. 1). Example quotes can be found in Table 2.

#### 3.1. Life changing treatment: “HAE doesn’t control me anymore”

Treatments were life changing for participants; [‘Treatments] changed my life’ (Megan, 22, F, Survey) and HAE medication was described as “really amazing” (Ben, 30, M, Interview) and “my lifeline” (Maria, 51, F, Interview). Older participants, with experience of living with HAE when no effective options for treatment were available, explained how access to medication improved their lives (Example 1).

**Table 1**  
Participant characteristics.

Characteristic	Survey Participants*	Interview Participants
Number; (% female)	42 (78%)	11 (55%)
Age: range, mean (SD)	19–79, 46.75 (16.57)	28–76, 53.09 (18.82)
Age of Symptom onset: mean (SD)	12.57 (8.9)	9.82 (6.32)
Age of diagnosis: mean (SD)	22.08 (14.93)	29.64 (19.93)
Hospital admissions in the last 12 months: mean (SD)	0–20, 0.73 (2.85)	0–1, 0.36 (0.50)
Average number of attacks per month in the last 12 months: range, mean (SD)	0–36, 3.62 (6.80)	0–13, 3.45 (4.45)
<b>Prescribed prophylactic treatments**</b>		
Berinert	9 (14%)	1 (9%)
Cinryze	6 (9%)	1 (9%)
Lanadelumab	5 (8%)	–
Danazol	10 (15%)	2 (18%)
Berotrastat	5 (8%)	2 (18%)
Tranexamic Acid	7 (11%)	1 (9%)
Icatibant	4 (6%)	–
Other	5 (8%)	–
None	14 (22%)	2 (18%)
<b>Access to at home treatment</b>		
Treatment available at home	55 (85%)	11 (100%)
No treatment at home, attends hospital for treatment	5 (8%)	–
Other	5 (8%)	–
<b>On demand medications***</b>		
None	2 (3%)	1 (9%)
Berinert	16 (25%)	6 (55%)
Ruconest	1 (2%)	–
Icatibant	27 (42%)	6 (55%)
Cinryze	5 (8%)	1 (9%)
Danazol	7 (11%)	1 (9%)
Tranexamic acid	6 (9%)	1 (9%)
Other	1 (2%)	–

\* Statistics include data from participants who also took part in interviews.

\*\* Some participants had access to more than one medication type.

\*\*\* Treatments for acute attacks administered either at home or in medical settings, some participants had access to more than one medication type.

85% of participants reported access to treatments for home administration. This access gave a sense of freedom and control over a condition that was otherwise seen as challenging, intrusive, and unpredictable (Example 2). Treatment access was essential and empowered participants to feel in control of HAE and able to live their lives as they wished. However, there were times when barriers to treatment administration or access arose.

#### 3.2. Delaying treatment: “I was leaving it too late”

Most acknowledged that delaying treatment following the onset of an attack could lead to more severe symptoms, slowed recovery and sometimes recurrence. Despite this participants detailed reasons for delayed or non-use of medication including not attributing symptoms to HAE, concerns about treatment costs, and difficulties accessing support for treatment administration.

##### 3.2.1. “Maybe it’s something else”

All survey participants were asked to explain how they knew when they needed to administer their treatment and responses included “pain” (38%), “swelling” (25%), skin changes such as feeling “hot and itchy” (20%), gastro symptoms such as feeling “bloated and uncomfortable” (15%), “tiredness” or “exhaustion” (15%), “pins and needles” (9%), “nausea” or “dizziness” (9%), “mood changes” such as “irritability”, “loneliness” or “depression” (6%), “red markings” or “rash” (7%) “stiffness” or “weakness” (6%). Some also reported “no warning” (12%) or a “general feeling” or a feeling that was “hard to describe” (7%).

This variability in symptoms and warning signs led to understandable uncertainty. Participants sometimes reported delaying treatment administration due to attributing the bodily sensations they were experiencing to something other than HAE (Example 3). Participants explained that the uncertainty relating to identifying symptoms could change over time. For example, some described how they had previously delayed treatment administration but with experience had developed more awareness of when treatment was needed and the risks of delay including worsening of symptoms (Example 4).

Experience of attacks helped some participants learn to recognize the symptoms, and ‘mistakes’ with delayed treatment administration highlighted the importance of taking medications when symptoms began. However, other participants did not illustrate the same awareness and instead continued to delay treatment as they perceived that medications should only be used for ‘serious’ attacks (Example 5). For these participants treatment would only be administered where the attack was too painful to leave untreated, they were at risk of a more serious attack, or they perceived that the attack would prevent them from engaging in usual activities of daily living.

##### 3.2.2. “Always worried that it costs so much”

Many participants expressed concern over the expense of their treatment and cost to the National Health Service (NHS). This worry was used to rationalize delaying treatment administration (Example 6). When interview participants were asked how they had come to know treatment costs, this was often through contact with healthcare professionals (HCPs) or through taking part in drug trials. One participant stated that on several visits to the ED for throat swellings they had been “constantly reminded do you know how expensive this treatment is? [imitating HCP] ‘do you know these vials cost five hundred pounds each? and you’re having three of them’” (Maria, 51, F, Interview).

Several participants who had been worried about the cost of their treatment, had been reassured by HCPs to use their treatment at the first sign on an attack (Example 7). This highlights how, although participants came to learn about the cost of their medication through contact with HCPs, HCPs were also able to reassure them, ease worry and guilt, and encourage early use of treatments.

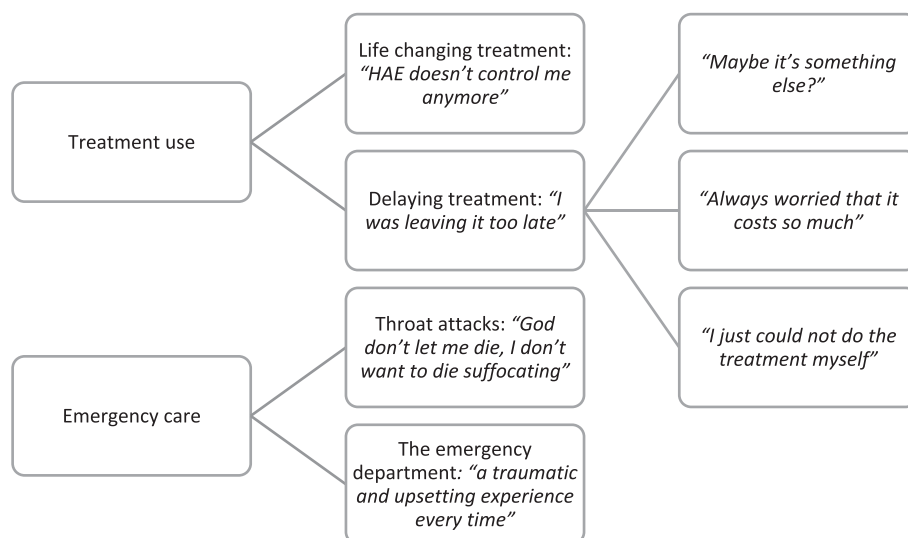


Fig. 1. Theme diagram.

### 3.2.3. "I just could not do the treatment myself"

Some participants had struggled with needle phobias, did not like administering their treatment themselves, and discussed a need to rely on others around them to administer medications. There were also occasions where participants were unable to administer medication themselves and could not access support needed from either HCPs or family. For example, one participant who became symptomatic during pregnancy, described a time when she was unable to administer her treatment and was unable to access support through her immunology team, GP, or district nurses (Example 8). A lack of community resource for support with treatment administration could lead to delaying treatment, a serious risk for some participants. Others also experienced practical barriers with treatment administration, such as struggling to access training for using the treatment (Example 9). Sometimes participants had no warning signs for an attack and sudden swelling of the hands or fingers, prevented them from being able to administer medication for themselves. In other circumstances participants did not have the confidence to administer medications. These participants often relied on family members (Example 10). For these participants, if family members were unavailable, they had no choice but to attend EDs.

### 3.3. Throat attacks: "God don't let me die, I don't wanna die suffocating"

When asked about their worst experience with HAE, seven of the interview participants discussed experiencing a throat swelling. Participants who had experienced throat swelling often described living in fear of throat attacks (Example 11). Many lived in a constant state of awareness of the life-threatening nature of HAE often influenced by the loss of a family member with HAE who experienced a throat swelling (Example 12). Even for those who had not lost a family member to HAE, the experience of a throat attack could be extremely traumatic, with participants experiencing thoughts that they were going to die (Example 13). Throat swelling experiences were described as traumatic. For many this was exacerbated by their experiences with EDs.

### 3.4. Visiting the emergency department "a traumatic and upsetting experience every time"

Participants provided detailed accounts of ED encounters where they felt their own knowledge of their bodies and condition was ignored or overlooked, evidence of their condition in the form of letters was not trusted, and delays in getting treatment led to increasingly severe symptoms and slowed recovery.

Many described having an official letter that explained their condition and treatment requirements or had taken their own medications to EDs. However, their accounts suggested that often this self-advocation by patients was felt to be ignored or mistrusted by the healthcare professionals they encountered, and even carrying their own medication to EDs did not guarantee timely administration (Example 14).

For some this experience could be avoided by availability of medications at home and access to training to administer these. However, sometimes ED visits were essential and there was a consensus that the condition was not well understood by staff. This lack of awareness could result in unnecessary distress (Example 15). These experiences highlight how lived experience of having throat attacks and negative experiences in EDs could contribute to participants' fear of future throat attacks.

While most participants described negative experiences in EDs there were some accounts of more positive experiences (Example 16). These examples illustrate how the combination of clear communication, respect for the patient's knowledge about the condition, and quick decision making by staff could improve the experience of emergency care.

## 4. Discussion

This qualitative study explored the treatment and emergency care experiences of 65 participants living with Hereditary Angioedema (HAE) in the UK. Through the analysis of data collected using novel mixed methods four themes were developed: 1) the life changing experience of treatment which gave participants control over a challenging and unpredictable life with HAE; 2) reasons for delaying treatment including uncertainty about symptoms, concerns about costs to the NHS, and practical barriers to treatment administration; 3) the terrifying experience of life-threatening throat attacks; and 4) traumatic and upsetting encounters with emergency care. These findings provide important new insights into the experience of patients with HAE in the United Kingdom (UK) and highlight opportunities for improving the quality of patient care.

The first two themes relate to the experience of using HAE treatments. Participants described access to self-managed treatments as life changing. These showed physical and psychological benefits and facilitated many to feel empowered to have more control over their condition. These findings mirror those of participants in the USA who experienced access to prophylactic medications as beneficial for facilitating independence and freedom and easing worry and anxiety [15]. However, in this UK based sample it was also evident that several context specific factors could contribute to delayed use of on demand

**Table 2**

Example participant quotes for each theme.

Theme	Subtheme	Example	Quotes
Life changing treatment: "HAE doesn't control me anymore"		1	It's made a huge difference because it's removed almost entirely the worry aspect of saying what happens if I get an attack of HAE? Because I can't tell you how revolutionary these drugs have been [...] as soon as those drugs started to become available any anxiety at all virtually disappeared (Owen, M, 72, Interview)
		2	In my younger years before diagnosis my life was very poor health wise but as I now have medication, I feel happier. (Sarah, F, 65, Survey)
Delaying treatment: "I was leaving it too late"	"Maybe it's something else"	3	It's kind of made me realise that although I have got a condition, with that treatment it's controllable. It doesn't control me anymore. (Sasha, 28, F, Interview)
		4	Life is much improved as an HAE sufferer since being given Icatibant to use at home. Much less interruption to your life, especially when travelling abroad. It allows me to continue work, social activities etc, as I always have an injection available, allowing me to administer to myself anywhere, anytime that is convenient for me (Elizabeth, 61, F, Survey)
		3	At first when [the swelling is] not that bad you think, 'well is it maybe something else, is it maybe I've just eaten something that, it's given me a bit of a tummy ache or is maybe period pain or is it...?', you try to rationalise it to anything else, you'll think 'oh it's fine, it will go away by itself'. (Sophie, 34, F, Interview)
		4	If the pain comes on very quickly - like a light switch being turned on - then I know it is HAE. If the pain is mild and dull, it may be that I don't realise it is HAE until a day or two. (Alison, 52, F, Survey)
		3	I was leaving it too late and putting it off just thinking 'oh, it's not an attack' and tricking myself, even though I knew the pain was bad. But now, the past few years I'm pretty confident with 'yep this is bad inject

**Table 2 (continued)**

Theme	Subtheme	Example	Quotes
		5	now', it's much better than the pain you'll get if you don't, or the ongoing problem afterwards. (Ben, 30, M, Interview)
		5	As the years have gone on what I'm finding is, if I don't inject for my foot it'll start in my stomach, so my foot will go down and my stomach will start. So what I do now is when I feel it's starting, I just think right just let's inject, let's stop it now before it gets any worse, before obviously [my foot] gets that fat I can't get a shoe on, and then it's going to affect my work, it's gonna affect me hobbling around the house or, you know, being laid up in bed for a bit. Just let's do it because it's gonna stop a further attack as well. (Maria, 51, F, Interview)
	"Always worried that it costs so much"	6	I only take the extra treatment (Danazol) if it is a severe attack and/or I have to leave the house for an important event. (Penny, 54, F, Survey)
		6	[I administer treatment] when I am at work and cannot permit myself to be unwell, or when I sense the episode is going to be worse than usual. (Ian, 23, M, Survey)
		6	You know that the treatment is very, very expensive so you potentially don't want to be taking it unnecessarily if it is something else. [...] I suppose it's a cost to all of us, isn't it? We all pay into our NHS, so knowing each infusion costs £1,650, like it's a lot of money per time [...] Part of me I suppose does feel very guilty. (Sophie, 34, F, Interview)
		7	I just take when it's extreme, probably... absolute extreme - my face, my throat, whatever. Otherwise, I don't take it [...] they are very, very expensive, apparently. So, I don't take it, I don't take it on a regular basis, not at all. And if it's in my hands or my feet or wherever, other part of my body, forget about it. (Rosanna, 74, F, Interview)
		7	I wouldn't use the injection right, and they - because I was always worried that it costs so much - and they told me that I shouldn't worry, I

(continued on next page)

Table 2 (continued)

Theme	Subtheme	Example	Quotes
			should worry about my health, not about what I was using. So, it was just in conversation that, you know, [I learnt that] that the injections were expensive. (Kevin, 75, M, Interview)
	"I just could not do the treatment myself"	8	It's very, very rarely that I would ask for help with [IV infusions], but there was one time I couldn't for whatever reason, get IV access, I'd tried several times over, I just could not do the treatment myself. And I was home alone, I was very unwell, and I'd phoned to get help with it. And my immunology team, their nurse specialist wasn't available, there wasn't anybody in the day ward that day. So, I'd phoned the GP, who'd passed me onto the district nurses because they were too busy. The district nurses said it was out of their remit, that they wouldn't, they didn't know the drug, they wouldn't do anything with that either. So basically there was nobody within a community setting that was able to help me if I couldn't help myself with it, there was no other support available and I was advised just to go to A&E. [...] I didn't go to A&E, I just waited the few hours until my husband came home from work and I just waited for my husband to be able to help me with infusion, by which point it's obviously another couple of hours down the line and I felt even more unwell than I felt in the first place (Sophie, 34, F, Interview)
		9	As I have never been trained to self-administer intravenous serum, my GP usually did this as necessary and then only very occasionally. However, GP refuses to do this now so if required I have to go to A&E. My GP still cannot tell me where I can get training on self-injecting the serum, apart from me going to [a hospital] some 70 miles away. [...] Currently I have no one I can turn to locally if I need the serum and feel that my only option in an emergency is to find a local drug addict! (Julia, 67, F, Survey)

Table 2 (continued)

Theme	Subtheme	Example	Quotes
		10	My husband has had to administer c1 estrase IV on several occasions which was very stressful (Jane, 55, F, Survey) My son-in-law has got so used to giving [injections] to his wife that he gave me one once. [...] I don't [self-administer], I've never had to cause there's always been somebody else to do it. (Carolyn, 76, F, Interview)
Throat attacks: "God don't let me die, I don't wanna die suffocating"		11	I really do have sleepless nights because I don't want to go to sleep, you know? I can quite often be sat up downstairs because I don't want to nod off in case a throat swell, you know? And it creates this sort of almost anxiety that you're gonna get a swelling even though nothing might happen. (Warren, 41, M, Interview) It is a condition that still people still die from, you know? And we're very conscious, or any patient is always very conscious about [that], you know? [...] Now that's the only time I've ever had a throat swelling, only once ever. But it's, that's the potentially the most dangerous thing you know? and that's what my Mum died from, which is why I'm always quite conscious of it. (Alan, 57, M, Interview)
		12	There was no air [imitates struggled breathing], I was gasping for air, I couldn't [breathe], there was no air you know, it happened. And just to let you know ... there are a few people in my family, not immediate family but cousins and uncles and so on, who have the same things. And three of them died from that, died of that, died! (Rosanna, 74, F, Interview) My father died from laryngeal edema when I was 6 months old. His father (my grandfather) died of this when my father was 6 months old. The feeling I had when I woke up in hospital after my throat closed was one of relief, in that I had survived and knew how it progressed when my father and grandfather had died. (Archie, 79, M, Survey)

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Table 2 (continued)

Theme	Subtheme	Example	Quotes
Visiting the emergency department “a traumatic and upsetting experience every time”		13	All I was thinking was ‘oh God don’t let me die, I don’t wanna die suffocating, being aware I’m suffocating’... and I remember them coming and saying ‘if it doesn’t start going down, we’re gonna have to sedate you and incubate [sic] you’, and all I wrote on this pad was ‘please don’t let me die’, that was my only thought in my head was ‘please don’t let me die’. (Maria, 51, F, Interview)
		14	[My most severe HAE episode was] lips and throat when I was 21. I went to hospital that’s when I was finally diagnosed, I was crying and thought I was going to die. (Helen, 46, F, Survey)
		15	I’ve got this letter that says Mr [redacted]’s got HAE, this is how you do the injections, there’s literally a flowchart on there [that says] ‘do this’, and you’d think you could say, I don’t know, ‘I’m having a throat swell’ or something, ‘here’s the thing, do this’, and they’d get straight on it. But they don’t, they faff about for ages, phoning everybody and his dog up and trying to find out where they put the C1 esterase inhibitor, and you can be four or five hours before anything actually happens and that’s really frustrating (Alan, 57, M, Interview)
			In the past I have experienced lots of probing of my abdomen and delayed infusion of the Berinert I bring with me (really wish I could learn to do this myself at home and not go to A&E) as the medical staff don’t seem to believe what I am saying. (Theresa, 59, F Survey)
			Staff don’t understand HAE and can be heard googling it and discussing it in the corridor. Don’t have medication in hospital pharmacy, or if night-time it is locked up. Can only get icatibant sent over from [another hospital] by taxi (icatibant doesn’t work for me and gives severe and prolonged skin reaction). Left in waiting room for hours. [...]. A traumatic and upsetting experience every time. (Emma, 46, F, Survey)

Table 2 (continued)

Theme	Subtheme	Example	Quotes
		16	[My most severe HAE episode was] sudden onset of severe facial swelling, extending below jaw line. Feeling of panic as soft tissue in throat affected. Attended A&E, treated as a domestic violence victim and husband subjected to critical interview at triage before the situation treated seriously. (Elizabeth, 61, F, Survey)
			My local hospital is very quick to treat me when I present myself to A&E. I normally carry my laminated card but only on the odd occasion will I have problems getting treated immediately. (Sam, 30, M, Survey)
			The most severe attack would probably be one of my throat swells. [...] My throat began to tingle, and I knew that I had to go to A&E. thankfully I only lived a 5 min drive from the hospital [...] I checked in and explained what the problem was and was told to take a seat in the waiting room and I would be triaged. I explained that I needed urgent C1 and the receptionist said I would be a priority. I sat in the chair and tried not to panic as my throat tingled and I could feel restriction in my throat. I knew that stress is not helpful to HAE and so I took deep breaths and tried to remain calm. My husband then came in and I was called through to triage. The nurse sent me straight through to resus to get C1 immediately. It was very scary. (Karen, 44, F, Survey)

medication potentially leading to poorer attack outcomes.

Some participants reported not adhering to treatments. This is not an unexpected finding, according to a systematic review of medication adherence around 20–50% of patients do not adhere to prescribed treatment leading to higher healthcare costs, more emergency care use and poorer outcomes for patients [25]. For HAE patients, early administration of medications for acute attacks improves patient outcomes and is recommended by international HAE guidance [3], therefore exploration of the reasons for treatment delay can help to inform adherence interventions. The most discussed influence on medication adherence was cost to the NHS, something that participants had become aware of through discussions with healthcare professionals or through participation in medical trials. Participants described feelings of concern and guilt over the costs of their medication, and this could lead to non-use or delayed administration in some circumstances.

Very little research has explored patient perceptions of NHS resource allocation. One study with oncologists and terminal cancer patients also

found that patients became aware of medication funding through discussions with healthcare professionals and expressed guilt about their use. Furthermore, oncologists reported personal conflict and decision-making challenges regarding resource allocation [26]. These findings illustrate that HAE patients, who are not in end-of-life care, also experience guilt about medication costs and this can have important implications for their medication adherence. This warrants further investigation to better understand patient and immunologist perceptions of the issue and to find ways to reduce the impact on medication delay.

For some, the concern over cost was overcome by reassurance or guidance from a healthcare professional. Healthcare professional-patient communication is therefore a vital component in treatment adherence for HAE. Evidence from a range of conditions indicates that poor ratings of physician communication increases medication non-adherence [27] and patient-provider focused interventions have potential to improve patient health and patient and provider experience [28]. Facilitators and barriers to effective communication between providers and HAE patients should be explored to enable targeted intervention.

Another key barrier to treatment administration was practical. Some patients could self-administer while others relied on community healthcare professionals, family members or EDs. Some had no training in self-administration, others had training but experienced psychological barriers to treatment administration. These findings suggest that UK provision for HAE patients is not adhering to international recommendations for comprehensive and integrated care or that all patients provided with on demand treatments should be taught to self-administer [3].

Many participants recounted memories of unpleasant encounters within EDs. Often this was on occasions where a patient had begun to experience symptoms of throat attack. Despite the use of consultant letters by patients, delays regarding the provision of appropriate medication could be highly distressing. This distress continued post discharge through fear of recurrent throat attacks. As HAE is a rare condition, it is quite possible that many ED professionals have never encountered a similar presentation during their working lives and therefore have limited experiential evidence to draw upon when assisting HAE patients. Targeted training of ED professionals is needed to improve emergency care. Measures should also be taken to ensure that all patients are treated by specialists with specific expertise in managing HAE as per international recommendations [3].

Strengths of this study include the mixed methods approach to data collection, the range of responses collected, and the use of a participant led photo-elicitation technique to empower participants to lead the interviews about their experiences. However, it should be noted that participants were recruited via a UK based charity for persons affected by HAE. This was a useful platform for recruiting participants, however it does mean that participants were limited to those who had chosen to be a member of this charity group and those who do not access the charity's resources, such as their Facebook group and mailing lists, may not be represented. In addition, while the number of survey responses was high, only 11 of these took part in in-depth interviews and there could be a difference in experiences between those who agreed to be interviewed and those who did not.

## 5. Conclusions

HAE patients need psychological support to process fears and negative experiences. Psychological barriers to treatment administration must also be addressed to ensure treatment is used effectively. In addition, targeted education for emergency practitioners is needed to improve emergency treatment and reduce the psychological burden of delayed emergency care.

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## Data sharing statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

## CRediT authorship contribution statement

**Amy Elizabeth Burton:** Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Isobel Lindsay-Wiles:** Formal analysis, Investigation, Data curation, Writing – review & editing, Project administration. **Daniel Herron:** Formal analysis, Investigation, Data curation, Writing – review & editing. **Alison Owen:** Formal analysis, Investigation, Data curation, Writing – review & editing. **Jade Elliott:** Formal analysis, Investigation, Data curation, Writing – review & editing. **Angela Metcalfe:** Investigation, Conceptualization, Writing – review & editing. **Lavanya Diwakar:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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