

The Humanistic, Societal, and Pharmaco-economic Burden of Angioedema

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Abstract Hereditary angioedema due to C1 inhibitor deficiency (C1-INH-HAE) is a rare disorder characterized by intermittent and unpredictable episodes of swelling which cause disfigurement, disability, pain, or, in case of laryngeal swelling, risk of death. Historical factors, including the intermittent nature of the disorder, the lack of awareness of this ultra-rare condition amongst medical personnel, lack of specialist centers, and limited treatment options have contributed to under-diagnosis and under-treatment of the condition. Incorrect treatment of attacks has been common, even when medical help is sought. This has led to reduced health-seeking behavior and alternative coping strategies, sometimes even denial, in many families, while a minority of HAE-affected patients have become serial emergency room attenders with chronic pain and ongoing requirement for opiate-based painkillers. Both strategies have incurred not only physical but also psychological and economic consequences.

In the last 10 years, new and effective acute therapies have been made available, some of which have also provided short-term and long-term prophylaxis options, together with a better understanding of older prophylactic drugs. Improved awareness of HAE amongst the general public, family members, and physicians has reduced the long delay in diagnosis and

increased the number of patients receiving effective and up-to-date therapies to improve the physical impact of the disorder.

Data on the impact of treatment on the psychological outcomes is scarce, but the limited information available suggests that access to specialist advice and treatment leads to psychological as well as physical improvement.

HAE also has profound effects on individual and family economic output, directly via absenteeism from school or work and indirectly via lost opportunities. Economic improvements associated with better treatments are offset by the high cost of new acute treatments, resulting in difficult pharmaco-economic calculations. Worldwide, cost considerations present potentially insurmountable barriers to treatment for many patients, depending on the healthcare system in the individual country.

Keywords Hereditary angioedema · C1 inhibitor deficiency · Pharmaco-economic · Long-term condition · Quality of life · Integrated care

Burden of Illness on Individual Patients with HAE

Several studies have attempted to quantify the burden of HAE on the individual. Methodologies are listed in Table 1. A questionnaire-based survey of 457 American patients affiliated to the American Patient Organization HAEA in 2007–2008, before the widespread availability of new treatments, showed reduced quality of life as measured by the generic short form-12 (SF-12) consisting of 12 questions about health-related physical and psychological functioning over the previous 4 weeks [1]. Patients were moderately affected with a mean of 27 HAE attacks per year at the time of the survey. Results showed significant quality of life impairment in all physical and mental components. Impairment was more

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Table 1 Surveys and methodologies on quality of life (QoL) in hereditary angioedema (HAE) type I/II

1. EQ5D-5L: EuroQoL 5 Dimensions 5 Levels
2. HAHA: US Hereditary Angioedema Association
3. HAS: Hamilton Anxiety Scale
4. HDI-SF: Hamilton Depression Inventory-short form
5. HDRS: Hamilton Depression Rating Scale
6. MCS: mental component summary
7. PCS: physical component summary
8. SF-12: short form-12 (generic health-related quality of life questionnaire)
9. SF-36: short form-36
10. VAS: visual analogue scale
11. WPAI-GH: Work Productivity and Activity Impairment – General Health

pronounced in those taking androgen therapy, although the study could not address any question of causality. However, 457 patients represented a response rate of only 19 % of those surveyed. In a prospective study published in 2011, 286 patients from 11 different countries were assessed by the SF-36 showing lower physical component summary (PCS) and mental component summary (MCS) compared with population norms [2]. In a 2013 sub-study of this work, 35 Brazilian patients, with limited or no access to acute treatments or C1 inhibitor prophylaxis, recorded impairment in all eight dimensions investigated, with vitality and social aspects of QoL being most severely affected. Over 90 % showed significant impairment, despite over half describing their HAE as ‘well-controlled’ [3]. As with the American cohort, use of danazol was associated with worse QoL impairment [3]. In a 2012 UK national audit of patients with improved (albeit variable) access to acute treatments and an average attack rate of 13 per year, QoL was reported by physicians to be ‘moderately’ or ‘severely’ impacted in 37 % of cases [4]. In a cohort of 64 adults Danish patients, more than half of patients felt that HAE had significant negative psychological impact on their lives and restricted their physical activities [5]. Sixty-one percent of these patients worried about risk of suffocation, and 42 % worried about possible side effects of HAE treatment. The SF-36 was applied in 193 French HAE patients and compared with allergic patients over a 12-month period [6]. Patients with HAE had lower QoL compared with healthy controls, and with allergic patients, except for the physical aspects (physical component summary). QoL impairment correlated with attack frequency, being significantly worse in those with more than five attacks per year. In a recent paper from 2015, 134 self-identified American HAE subjects showed significant improvement in QoL with regard to psychological/emotional status, ability to carry out daily activities, fear of suffocation, and medication side effects after introduction of newer therapies [7]. However, significant burden of illness remained. Table 2 summarizes quality of life studies published in the field of hereditary angioedema.

Anxiety and Depression

Patients with HAE experience higher levels of anxiety and depression than the unaffected population. Using the Hamilton Depression Inventory-short form (HDI-SF) American patients completing a 2007 survey, 43 % of patients had scores indicating clinically significant depression, compared with 16 % of the unaffected population [1]. An American survey conducted in a different center after availability of acute treatments showed continued high levels of depression, with 39 % of 26 adult HAE patients having clinically significant symptoms and 15 % of patients having anxiety [8].

The 2011, ‘Burden of illness in hereditary angioedema’ survey assessed 186 European HAE patients with access to acute treatment and androgens, anti-fibrinolytics, or C1 inhibitor prophylaxis [9]. Using the hospital anxiety and depression scale (HADS), 23 % of Spanish, 8 % of German, and 10 % of Danish patients had clinically significant depression [10]. Significantly, at that time, the German and Danish patients had better access to the full range of therapies, including well-established self-administration programs [11–13], perhaps suggesting that prevalence of depression in HAE can be reduced by improvements in therapy. The same survey showed continuing high levels of anxiety: 46, 23, and 24 % of Spanish, German, and Danish patients respectively had clinically significant anxiety [10]. Levels of anxiety and depression correlate with HAE disease severity [1, 10]. Pain of the most recent attack showed close correlation with severity of anxiety about future attacks, distress about HAE, sudden feelings of panic, and anxiety about passing HAE onto children in the European study [10]. Factors such as severity, frequency, duration of swelling, and country of residence were also found to be significant.

In contrast to the full physical recovery between HAE attacks, emotional and QoL impairment continues even between attacks [1, 10, 14] as has been described for other episodic disorders such as migraine [15]. In-depth interviews in a subset of the European study patients highlighted fear of attacks and of asphyxiation, interruption to normal activities, and concerns about genetic transmission of the condition to their children as particular sources of anxiety [16]. Adolescent and young adult participants experienced unique anxieties related to perceived inability to participate in peer group activities such as sports, and anxieties about the impact of HAE on their future ability to achieve educational and social goals [16] (Fig. 1).

Fouche and coworkers reported the additional distress experienced by American patients when medical professionals failed to recognize the severity or physical nature of their pain and when their suggestions for diagnosis were not taken into account [8]. Such experiences added to the stress associated with the unpredictability of the HAE and its future course.

Table 2 Surveys and methodologies on quality of life (QoL) in hereditary angioedema (HAE)

Study	No. of patients	Instrument	Comments	Outcome
Banerjee 2015	149	Asking for impact of HAE on QoL	Cross-sectional study self-selected patients HAEA summit	72 % had a significant impact on QoL
Bouillet 2013	193	SF-36 v.2.0	1 year data	Lower QoL than allergic patients and healthy controls, except PCS
Bygum 2014	64	HAE-specific questions	Comparison with allergic patients Prospective Danish cohort study	More than half of patients had significant negative psychological impact on their lives and restriction in physical activities 61 % worried about risk of suffocation 42 % worried about possible adverse effects of HAE therapies Development of conceptual model
Bygum 2015	30	Open-ended qualitative interviews	Multicenter study (Denmark, Germany, Spain)	
Caballero 2011	286 (257)	SF-36 v.2.0	Prospective multicenter cohort study, 11 countries	PCS: <47.28> lower than population norms MCS: <45.33> lower than population norms
Caballero 2014	186	HADS HAE-specific questions	Cross-sectional with retrospective data, multicenter burden of illness study (Denmark, Germany, Spain)	38 % anxiety 14 % depression
Christiansen 2015	107	HAE-specific questions	Cross-sectional, retrospective data Self-selected patients HAEA summit	Significant improvement in psychological status, ability to carry out daily activities, fear of suffocation and medication side effects after introduction of newer therapies
Fouche 2014	26	HDRS + HAS	Telephone interviews	39 % depression 14 % anxiety
Gomide 2013	35	SF-36 v. 2.0	Brazilian part of Caballero 2011	90 % had scores <70
Jolles 2014	223 adults 29 children	Impact on QoL (none, mild, moderate, or severe)	National audit in UK	37 % of adult patients had a moderate or severe impact of HAE on QoL
Lumry 2010	457	SF-12 WPAI-GH HDI-SF	Online survey HAEA 19 % participation rate	Lower scores all domains compared population norms (~severe asthma or Crohn's disease) 34 % overall work impairment<3.3 days lost/last attack>43 % depressive symptoms
Lumry 2014	16	SF-36 v. 1.0	Clinical trial setting C1-inhibitor (C1-INH) prophylaxis 12+12 weeks Paper-based survey	PCS: 36.41 → 43.92 (placebo 37.06) MCS: 49.90 → 54.00 (placebo 44.98) EQ5D today <0.83> EQ5D attack <0.51>
Nordenfelt 2014	103	EQ5D-5L VAS 0–100		
Aabom 2014	27	SF-36 v. 2.0	Danish part of Caballero 2011	Scores corresponded to population norms

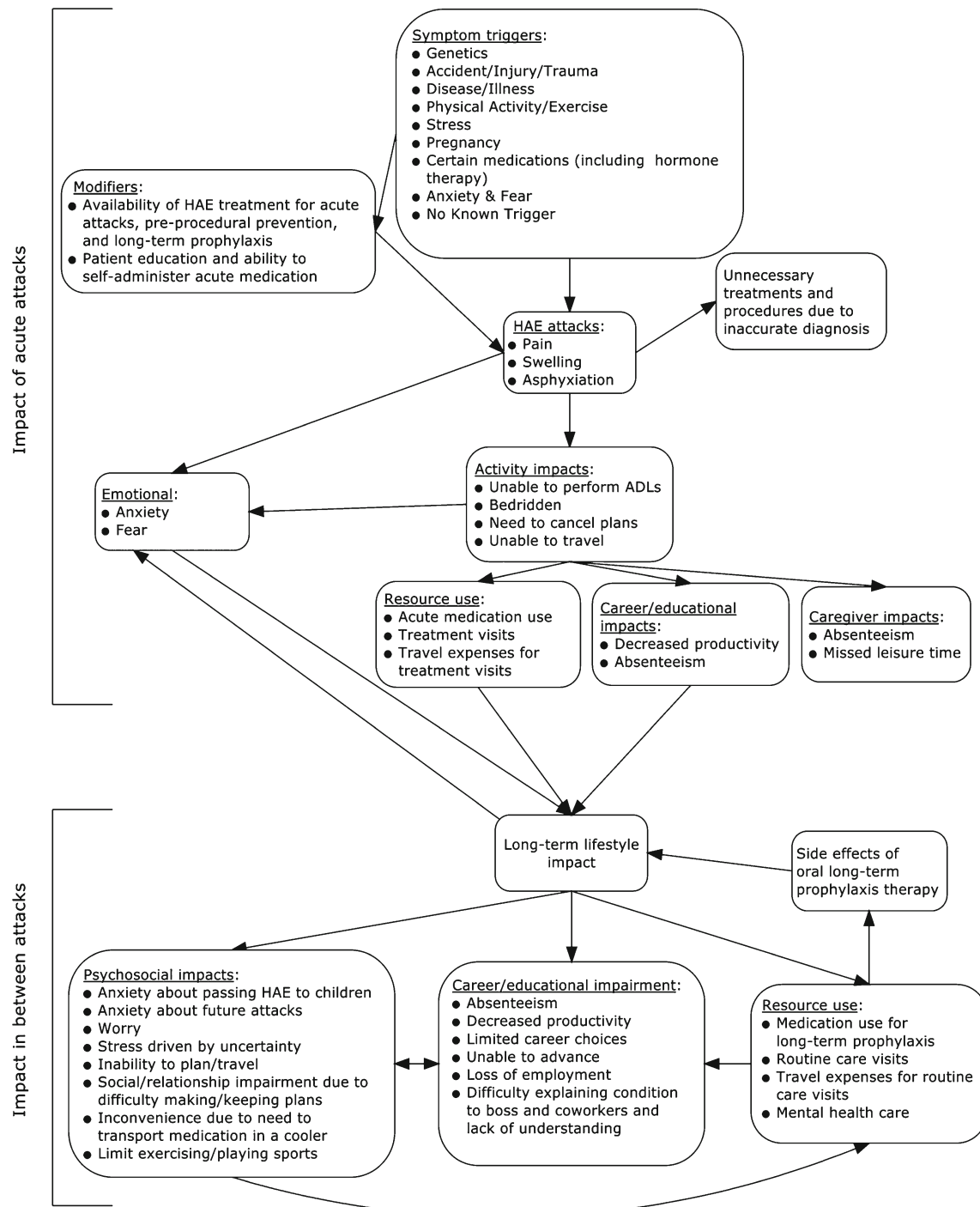


Fig. 1 Burden of illness in hereditary angioedema: conceptual model. [Reproduced with kind permission from Acta Derm Venereol 2015; 95: 706–710]. ADL activities of daily living; HAE hereditary angioedema

Patients reported that stress, anxiety, and low mood could trigger attacks, thus leading to a vicious circle of angioedema triggering further anxiety and yet more angioedema. One interesting theory is that poor control of the inflammatory process in HAE, in particular raised interleukin 1B levels, confers an additional physical risk factor for depression [8, 17]. Factors contributing to anxiety and depression in the era of

accessible acute treatment were remarkably similar to those reported earlier. Encouragingly, more recently surveyed patients reported that access to acute attack treatment, especially if self administered, and access to short- and long-term prophylaxis had improved their sense of self control and eased anxiety [7, 16]. However, a survey of patients attending the 2013 US Hereditary Angioedema summit reported continued

impact on QoL, despite a high prevalence (88 %) of availability of acute treatment [18]. As well as the individual loss of QoL, a substantial emotional burden for those family members or caregivers who do not have HAE has recently been recognized [16].

Societal Burden

The societal burden of hereditary angioedema can be considerable and is borne not only by the patient but also by his or her family and other caregivers, employers, and by the wider society because of lost productivity, lost opportunities, burden of care, and pharmaco-economic cost.

Each attack impacts on the ability to work, in proportion to its severity. A survey from the USA conducted in 2007–2008 showed that workers had missed a mean of 3.3 days work because of their most recent attack [1, 19]. The proportion of patients missing work increased with severity of attack: from 19.8 % for mild attacks to 78.2 % of severe attacks. Severe attacks typically resulted in more days off than mild attacks, with a mean of 5.5 days missed, compared with a mean of 2.2 days if mild. In addition to the loss of days worked, patients reported significant HAE attack-related impairment while at work, estimated at a mean of 33.5 % by the Work Productivity and Activity Impairment – General Health (WPAI-GH) questionnaire [19]. These indirect costs accounted for 64–75 % of overall cost for patients with mild and moderate attacks. Despite having relatively frequent attacks, with a mean of 27 attacks per year, only 30 % had sought immediate medical attention for their most recent attack. This may reflect the relative unavailability of effective acute treatment in 2007/2008: only 14.2 % of respondents had received C1 inhibitor and a further 3.5 % fresh frozen plasma, the remainder receiving palliative or no treatments in the year prior to the survey. The more recent 2011 European Burden of Illness study reports better access to acute treatment, albeit related to attack frequency, with 100 % of attacks being treated in participants experiencing attacks weekly or more frequently, compared with 41 % of attacks in those for whom attacks occurred monthly or less frequently [20]. Although, only 23 % had sought medical care for their most recent attack, 66 % had received HAE-specific treatment with either C1 inhibitor or icatibant, many via self-administration [20]. As with the American survey, attack frequency was high with a mean of 33 attacks per year.

Despite better access to treatment, 56 % patients reported missing work or education during their most recent attack: For those in employment, days missed depended on attack frequency, ranging from 2.2 to 11.6 days per year. Work productivity was impaired in between attacks also, with degree of impairment being proportionate to attack frequency. Similarly, a Swedish study reported that 44 % of 74 patients

had missed work during their most recent HAE attack, with severe attacks resulting in absenteeism in 81 % of cases [14]. Interestingly, the time of complete disablement was longer for peripheral attacks (median 4 to 12 h) than abdominal attacks (2 to 4 h) despite the perception of peripheral attacks as a milder manifestation of the disorder [20]. A minority of attacks are multisite, usually affecting peripheries and abdomen, airway, or a second peripheral site. Multisite attacks were associated with the greatest duration of complete disablement at 12 to 24 h [20].

In Japan, where acute treatment is available in hospital, a physician-completed questionnaire indicated that 21.1 % had required overnight hospital admission and 28.7 % of patients had been absent from work or education because of HAE [21]. In the UK in 2005/2006, 1257 hospital admissions for HAE were recorded, 40 % of which were estimated to result in a prolonged stay of 3–5 days [22].

Unpredictable disability, impaired performance, and work/education absenteeism has long-term consequences. A Swedish study found that 57 % of patients experiencing attacks once a month or more and 41 % experiencing attacks less frequently reported that HAE had hindered their career or educational advancement [14]. These data were similar to those reported in the earlier American cohort, where 48.4–54.5 % had experienced a variety of educational and career limitations [1]. Overall impact was comparable to that for patients with severe asthma or Crohn's disease.

The impact of HAE is not limited to affected family members. Caregivers, usually family members, required time off work to care for their affected relative in 52 % of attacks [20]. Caregiver work time missed was proportional to attack severity and estimated at 2.1 vs 1.2 days for severe or mild attacks, respectively. Annual caregiver days off work also depended on attack frequency and ranged from 2.2 to 10.1 days per year. Thus, caregiver absenteeism was comparable with that of the affected relative [20]. The American survey did not capture caregiver absenteeism but recognized a childcare cost for a minority of patients [1]. This may be an underestimate of the true societal cost, as it does not include unpaid care given by relatives. Parents of affected children may be particularly impacted [23].

Leisure time was also impacted, with 59 % of patients missing leisure days [1]. The number of leisure days missed (mean 2.7) was similar to those lost to work or education. Indirect effects included reluctance to travel or to take part in sports, certain hobbies, or social activities [16].

Economic Impact

Medication costs for patients are highly variable as they depend on the number and frequency of attacks, treatment modalities, and need for supportive care. The new HAE-specific

drugs are orphan drugs with high costs but a substantially better benefit-to-risk ratio than androgens and anti-fibrinolytics. In fact it has been stated that Cinryze® has the highest annual cost of any drug on the market in the USA [24]. In a web-based survey conducted in the USA before approval of the new acute treatment modalities, the economic burden of HAE was assessed based on direct treatment costs of acute attacks and routine care as well as indirect costs, such as travel, child care, missed work, and reduced productivity. The average annual direct and indirect costs per patient were estimated to be 42,000 USD, ranging from 14,000 to 96,000 USD [1]. Costs however did not include the considerable cost of HAE-associated depression and anxiety nor did they include the cost of the subsequently licensed acute treatments.

The orphan drugs marketed for treatment of HAE in Europe are expensive and prices of icatibant, plasma-derived C1 inhibitor concentrates (Berinert® or Cinryze®), or recombinant C1 inhibitor concentrate (Ruconest®/conestat alpha) vary considerably. An English National Health Service (NHS) evaluation in 2013 calculated the annual cost to be 1.2–7.7M GBP (1.73–11.07M USD) for plasma-derived C1 inhibitor concentrate or icatibant, or 6.3–26.3M GBP (9.06–37.8M USD) for recombinant C1 inhibitor concentrate based on certain conditions [21]. Wholesale acquisition costs in the USA are higher: 3117 USD for a single dose of ecallantide (a *kallikrein* inhibitor not marketed in Europe), 6800 USD for icatibant, and 5671 USD for plasma-derived C1 inhibitor concentrate (Berinert, based on bodyweight of 75 kg) in 2012 [25].

Overall healthcare burden, both financial and human, can be considerable, especially if hospital treatment is required. UK National Health Service costs were significantly higher for people with HAE compared to the general population, even when high cost specialist HAE treatments were excluded, with increases of 160 % for primary and 447 % for secondary care [26]. The US cost of a single ecallantide treatment rises from 3117 to 9540 USD per dose when administration costs are taken into account [27] and overall HAE drug costs have more than doubled in the USA between 2012 and 2014 [28].

Economic data using cost-utilities (cost per quality year of life gained) and cost-effectiveness (cost per attack prevented) are needed. A Polish cost-utility analysis of a hospital-based C1 inhibitor treatment program to treat life-threatening HAE attacks, estimated a quality-adjusted life year (QALY) cost of 15,226 Euro (16,658 USD) for recombinant C1 inhibitor (Ruconest) and 27,786 Euro (30,399 USD) for plasma-derived C1 inhibitor (Berinert) [29]. Potential European acute drug costs have been estimated at 15,318 Euro (16,766 USD) per patient per year, with hospital costs minimized by self-administration programs [5, 30] (Longhurst personal communication).

The personal disruption, QoL, economic disadvantage and drug costs of acute attacks can partially be prevented by use of

long-term prophylaxis [31, 32]. Older prophylactic agents including attenuated androgens (danazol, stanozolol, or oxandrolone) or anti-fibrinolytics (tranexamic acid or epsilon aminocaproic acid) are relatively cheap. C1 inhibitor (Cinryze), given intravenously, has been shown to be effective in prophylaxis and is used where contraindications, incomplete efficacy, adverse effects, or patient choice preclude the other options [32]. Patients participating in a double blind, placebo controlled crossover trial of healthcare provider-administered C1 inhibitor prophylaxis, 1000 U twice weekly, experienced significantly better QoL in all mental and physical domains, measured by the SF-36, while on the 12-week treatment arm, compared with placebo [33]. In contrast, use of attenuated androgens has been associated with worse QoL [1, 3]. However, these uncontrolled studies are expected to have been subject to considerable confounding.

Prophylactic Cinryze costs an average of 350,000 USD per patient per year in the USA and is used by an estimated 852 patients, or 28 % of those known to have HAE [25].

Then and Now: QoL for Those with Hereditary Angioedema

The past decade has seen unprecedented advances in the treatment options open to those with hereditary angioedema [34]. In 2005, plasma-derived C1 inhibitor for acute treatment was limited to a small number of specialist centers in Western Europe. Since this time, two plasma-derived C1 inhibitors, a recombinant C1 inhibitor, and novel agents targeting *kallikrein* or the *bradykinin* receptor have proved safe, effective, and are widely available, at least in the more affluent nations [31]. Prophylaxis with intravenous C1 inhibitor has been shown to improve QoL, in contrast to previously available oral options [33]. Evidence to guide dosage and timing of treatment has contributed to faster resolution of attacks [6–35]. Perhaps even more importantly, logistical improvements have transformed the patient experience: the expert patient advocacy movement, led by the patient group HAE international (HAEI) and national patients' associations, has collaborated with healthcare professionals in producing guidelines to modernize protocols, to promote improved evidence-based treatments [32], and to raise awareness, thus improving the previously dire and, for patients, dangerous under-diagnosis [4, 10, 36–42]. Comprehensive care centers, inspired by the hemophilia model, have focused on providing access to expert medical advice, patient education and a range of specialist treatments. Coordination of care and treatment logistics by specialist staff has enabled truly patient-centered integrated care [5, 30, 43, 44].

In particular, the move from healthcare provider-based to home-based treatments has enabled a transformation of ambition from relief of the sick, disabled patient to prevention of

disability by early, patient-controlled treatment [11, 45–47]. When trained to self-administer C1 inhibitor, patients experienced a significant improvement in quality of life, measured by the Dermatology Life Quality Index (DLQI) and SF-36 compared with their own historical control data [11]. An early adopter of home therapy, the Frankfurt HAE center, reported results of 28 years of HAE care in 2010 [45]. At this time, 55 % of 450 adults and 24 % of 107 pediatric patients were practicing home therapy. Those with frequent attacks used an individual replacement treatment (IRT) approach, receiving C1 inhibitor at the very first symptoms of an attack, usually twice weekly, an approach which effectively provided prophylaxis for severe or laryngeal attacks. Those changing from danazol prophylaxis, because of poor control or intolerable side effects, to C1 inhibitor IRT noted improved QoL [48]. Approval of icatibant, a subcutaneous treatment, has further increased access and thus treatment outcomes, particularly for those with less frequent attacks, or where the patient lacks confidence or skill to master intravenous cannulation technique [47, 49–51]. Ecallantide has not been approved for self-administration because of anaphylactoid reactions but is administered by a nurse at the patient's home under a program that prioritizes early treatment [52].

These advances have contributed to a steady increase in uptake of therapies. Use of plasma-derived C1 inhibitor concentrates increased from 0.2 treatments per patient per year in 1980–2002 to 3.6 treatments per patient per year in 2004–2008, in an Italian cohort experiencing 7.9–8.9 attacks per year [53]. Amongst HAE patients attending the Danish National HAE Centre for the first time, 34 % had ever received plasma-derived C1 inhibitor concentrate or icatibant treatment for one or more acute attacks compared with 80 % of patients at latest follow-up visit in 2012 [5]. In this patient cohort, number of treated attacks increased from 12 to 36 per year in patients on home therapy.

A single extended family's experience, set in the context of the history of HAE, movingly illustrates the changes experienced over this remarkable time period [54].

Economic Benefits of Newer Treatment Paradigms

A study of ecallantide given by a specialist nurse at the patient's home showed a cost saving of 648,147 USD for 50 patients experiencing 249 attacks over 5 months, largely due to the reduced cost of a home nurse (150 USD per visit) compared with emergency room attendance (2600 USD per visit) [25]. A cost minimization analysis carried out by the manufacturer of icatibant estimated savings of 600–813 GBP (861–1167 USD) per attack, based on an undisclosed icatibant price, for self-administered icatibant, compared with in-hospital C1 inhibitor at licensed dose (Berinert) [22]. In a wider-ranging assessment, a Spanish group estimated that

self-administration of icatibant could save 80–170 Euro (88–186 USD) per attack, or up to 2.3M Euro (2.52M USD) annually in direct and indirect costs, compared with hospital treatment, while improving social outcomes [55].

In 2007, prior to the introduction of acute treatments, US data indicated that 45 % of patients presenting to healthcare facilities with HAE were hospitalized [56]. Current treatment paradigms have the potential to improve this, as illustrated by the Danish experience, reported in 2014. In Denmark, a well-established, centrally administered, patient-centered HAE program has enabled major reductions in healthcare burden. Forty-nine percent of patients practiced self-administration of C1 inhibitor or icatibant for acute attacks, with an 84 % reduction in emergency hospital visits, from a mean of 3.8 to 0.6 visits per patient per year over an 11-year period. There were no deaths or tracheotomies and patients reported reduced impact of HAE in all physical and psychological domains, except concerns about the hereditary nature of the disorder as assessed by the McNemar test. Although these impressive results required a 300 % increased use of high cost treatments to treat a mean of 36 attacks per year, annual costs remained manageable at an estimated average of 15,318 Euro (16,766 USD) per patient [5, 22] (Longhurst personal communication).

Inequalities

Despite great progress, huge inequities remain. Global differences in national income, healthcare infrastructure, and reimbursement schemes have left many patients unable to benefit from the improvements enjoyed by the most fortunate. In most Western European countries and Israel, government-sponsored insurance or national healthcare schemes ensure reasonable access to diagnosis, expert advice, and acute treatment options. In the USA, the situation is more complex; insurance costs and co-payments can vary massively depending on the drug and its place of administration. Nevertheless, a variety of initiatives brokered by the HAEA, the US patients' association, with support from the pharmaceutical companies, currently ensures reasonable availability of care [25]. However, even within the European Union, there is variability. Patients in Greece have only limited access to hospital-based acute treatment for severe attacks [41]. Much of Eastern Europe has only recently gained access to hospital-only treatment for life-threatening attacks, courtesy of a partnership between patient associations, governments, and pharmaceutical companies [57]. Unsurprisingly in a global world, inequities can affect patient's wellbeing: a recent survey of Greek HAE patients reported that QoL was reduced in all patients, 86 % 'greatly' or 'significantly' [41].

Other nations may have more limited access to diagnosis, acute treatments, and even to the cheaper oral prophylactic options. In Brazil, acute HAE treatments

are not reimbursed and danazol is classified as a high cost drug [3], while in Argentina both icatibant and C1 inhibitor are available and accessible by 82 % patients, with home therapy practiced by 29 % [58]. The international patients' organization is coordinating a global access program to enable named patients to receive acute treatment in countries where these medications are not otherwise available [57].

Access to home therapy, essential for minimizing healthcare usage, work absenteeism, and other adverse impacts, is even more limited, even in affluent countries. For example, in Japan, acute treatments are exclusively hospital-based and limited to C1 inhibitor (HAE Japan, personal communication). Elsewhere, guidance to patients may vary. Some patients, even if self-administering, are taught to wait until the attack is severe, thus limiting options for preventing disability [6]. Others are subject to national guidelines that may be interpreted differently by payers, patients, and physicians [22, 59]. Local differences in management may affect particular groups: children are often disadvantaged by a belief that HAE is less severe, therefore less disabling and by the lack of licensed treatment options in this group. Nevertheless, there is a pressing need for expert care and access to medication, not least because future social and healthcare behaviors are developed in this vulnerable group [23].

Looking Towards a Better Future

HAE is a lifelong disorder, and adverse HAE-related experience in childhood, adolescence, or earlier adult life is likely to have long-term consequences, even in the absence of ongoing uncontrolled symptoms. In this context, the QoL improvements noted in the past few years are extremely encouraging and further improvements should be expected from the cohort of children and young people currently benefiting from modern management. Newly developed angioedema activity measurement tools should facilitate assessment of disease activity and guide intensity of treatment [60] and an angioedema-specific quality of life tool will provide more specific data on outcomes [61].

Fast upon the heels of the revolution in acute treatments, new prophylactic treatments are in development, reviewed earlier in this volume [31], with preliminary results suggesting unprecedented levels of convenience, efficacy, and safety. These have the potential to further transform the patient experience but, of course, are likely to present substantial pharmaco-economic challenges. If these logistical and financial challenges can be overcome, we can look forward to future generations of HAE sufferers free from physical, psychological, and economic burden.

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