Review article

Uncovering the true burden of hereditary angioedema due to C1-inhibitor deficiency: A focus on the Asia-Pacific region

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Hereditary angioedema (HAE) due to C1-inhibitor deficiency or dysfunction is a rare genetic disorder that causes recurrent episodes of swelling in various parts of the body. Treatment goals of HAE aim to "normalize" life for all patients; however, lack of diagnostic facilities and limited access to effective treatment options in developing nations cause delays in diagnosis and place a significant burden on patients. In this review, we aim to highlight the burden of disease caused by C1-inhibitor HAE across the Asia-Pacific region, considering its epidemiology, morbidity and mortality, and socioeconomic and psychological impact. We also review the availability of guideline-recommended diagnostic facilities and treatments, and how patients are currently managed. Data were collected from published literature and HAE experts in the region, who provided information regarding diagnosis and management in their countries. Current practice was reviewed against international guidelines, as well as local guidelines/consensus used in Australia, Japan, and China. Suggestions are provided for improving the time to diagnosis in the region, increasing access to guideline-recommended treatments, and providing support to reduce the burden on patients and caregivers. There is an urgent need to improve HAE services and provide access to life-saving treatment in developing countries, and efforts should be made to increase awareness of guideline recommendations in high-income economies that do not currently provide long-term prophylactic treatments. (J Allergy Clin Immunol 2024;153:42-54.)

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Hereditary angioedema (HAE) due to C1-esterase inhibitor deficiency or dysfunction (C1-INH-HAE) is a rare, potentially life-threatening disease characterized by recurrent acute attacks of skin and/or mucosal edema.[1,2] The disease is primarily driven by deficiency or dysfunction in C1-INH protein (HAE types 1 and 2, respectively), which leads to dysregulation of the kallikrein-kinin pathway and overproduction of bradykinin, a potent mediator of the inflammatory cascade responsible for vasodilation and vascular permeability.[1,2]

C1-INH-HAE is a chronic disorder with high morbidity and negative impact on patient quality of life (QoL) because of repeated attacks of angioedema, which may be fatal when localized to the larynx.[3] Without access to effective acute and prophylactic treatments, mortality caused by laryngeal edema is high.[4] Historical mortality rates before effective treatments in Western populations were approximately 30%,[4] which reflects current trends in developing Asian nations. Median age of those who died from C1-INH-HAE in a recent Chinese survey was 46 years (interquartile range: 35-53 years).[5] However, because access to guideline-recommended treatments has increased, mortality in C1-INH-HAE has been lowered significantly, although, at the present time, this reduction is limited to high-income countries.[2,6]

In developing countries across the Asia-Pacific (APAC) region, early recognition and timely intervention with guideline-recommended treatment are crucial areas of unmet need.[2] In particular, because of the cost of disease-specific treatment such as plasma-derived C1-INH (pdC1-INH) or recombinant C1-INH, lanadelumab, berotralstat, ecallantide, and icatibant, many developing countries have little to no access to guideline-recommended options.[2,5,7]

This review aims to highlight the true burden of disease caused by C1-INH-HAE across the APAC region, considering its epidemiology, morbidity and mortality, socioeconomic and psychological impact, and availability of guideline-recommended treatments. The authors will uncover areas that require significant attention from governments and health authorities and outline potential action points that can have the greatest positive impact on patients.

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Abbreviations used

APAAACI: Asia Pacific Association of Allergy, Asthma and Clinical Immunology
APAC: Asia-Pacific
C1-INH: C1 esterase inhibitor
C1-INH-HAE: Hereditary angioedema due to C1-esterase inhibitor deficiency or dysfunction
C4: Complement component 4
EAACI: European Academy of Allergy and Clinical Immunology
FFP: Fresh frozen plasma
GDP: Gross domestic product
HAE: Hereditary angioedema
IV: Intravenous
pd: Plasma-derived
QoL: Quality of life
SC: Subcutaneous
TA: Tranexamic acid
WAO: World Allergy Organization

HAE IS RARE BUT ITS EXACT PREVALENCE IS UNKNOWN ACROSS THE APAC REGION

Worldwide, the prevalence of HAE is thought to be approximately 1:50,000, although this estimate ranges between 1:10,000 and 1:150,000.[1] In developing nations across the APAC region, a recent survey estimated a median overall prevalence of 0.02 per 100,000; however, a large range was observed between countries, with some estimates as high as 0.33 to1.00 per 100,000 (in Singapore and New Zealand) and as low as 0.02 per 100,000 (India).[8]

Given the large population in this area of the world (roughly 46% of the global population),[8] it is likely that there are a significant number of people living with undiagnosed HAE (Fig 1).[2,8-12] Vast heterogeneity has also been noted among regions with similar ethnic backgrounds, for example, in Han Chinese-predominant regions such as Hong Kong (China) and Mainland China, with an estimated prevalence of 0.60 and 0.04 per 100,000 population, respectively.[8] Even in developed Asian nations, such as Japan, HAE is not well documented, with estimates for prevalence ranging significantly, from 0.02 per 100,000 to as many as 1 in 10,000, with exact patient numbers unknown.[8,13] In Hong Kong, following implementation of a systematic family screening program, the estimated point prevalence of C1-INH-HAE increased from 0.16 to 0.60 per 100,000 within a span of 2 years.[14] This demonstrates the potential of improving diagnostic capacity and family screening in the APAC region.[14]

The APAC region is densely populated and is likely home to the largest number of undiagnosed patients with HAE in the world.[2,8,9]

These data suggest that many patients across the region are living with undiagnosed C1-INH-HAE, especially in low-income countries: up to 99% of patients remain undiagnosed in India versus roughly 50% in Australia and New Zealand.[2,10]

UNDIAGNOSED PATIENTS WITH C1-INH-HAE SUFFER INCREASED MORBIDITY AND MORTALITY

Because of the relative availability and accessibility of modern diagnostic methods and treatments in Western nations, mortality due to HAE has been significantly reduced.[2,15] However, morbidity and mortality in undiagnosed patients have been found to be much higher than in diagnosed patients.[1,2,15]

Delay in diagnosis is a problem, even in developed nations. Although the median delay in diagnosis has improved recently to 2.6 years for C1-INH-HAE (reduced from 12.8 years a decade ago),[5,16] the variation in delay in diagnosis is still very large, ranging from 0.13 years to 17.3 years.[17] Even in situations in which a patient had a family member with C1-INH-HAE, the time to diagnosis may not be reduced versus that for those with a negative history, suggesting that patients may not be aware of the hereditary nature of the disease or may fail to come forward for diagnosis for other reasons, such as previous lack of benefit from medical services.[16] This delay in diagnosis puts patients at greatly increased risk of premature death from asphyxiation, as well as exposes them to the social and economic consequences of untreated C1-INH-HAE.[16] Unpublished observations from India suggest that delay in diagnosis is the most important factor leading to mortality in patients with C1-INH-HAE. Undiagnosed HAE or an "uncertain diagnosis" of HAE also leads to elevated anxiety in both symptomatic patients and asymptomatic family members, which can be alleviated after allergist/immunologist assessment and advice.[14]

The delay in diagnosis varies widely in Asian nations, with patients being diagnosed as young as at birth and as old as at 72 years,[8] if indeed they are diagnosed at all. In India, for example, although 1 study reported a mean delay in diagnosis of 6.5 years (range, 0-28 years),[2] the authors acknowledged that this estimate is likely inaccurate given that there are only 130 confirmed cases in a country of approximately 1.38 billion people, and that it is typical for older generations to receive their diagnosis only after their grandchildren have been diagnosed.[2] In South Korea, it took 7.75 ± 10.54 years for a definitive diagnosis.[18,19] One study in China reported a mean delay in diagnosis of 11.04 to 12.64 years, and in Japan (arguably the most developed Asian nation as far as HAE is concerned),[5,20] the delay was particularly long, at 15.6 ± 13.3 years.[18] Interestingly, in China, it was found that the decade in which patients started to experience symptoms, there was a significant impact on the diagnostic delay ($P < .001$), with those who had symptom onset before 1999 experiencing a delay of 19.75 years, between 2000 and 2009 a delay of 8.67 years, and between 2010 and 2017 a delay of 3.79 years.[20]

Factors that contribute to the delay in diagnosis in the APAC region

Awareness of HAE among physicians and the public is notably low,[2] with a survey conducted in Japan including more than 9000 physicians documenting that only 44.8% had any degree of awareness regarding HAE.[21]

In terms of trained allergists/immunologists, several Asian nations have inadequate numbers of these essential clinicians.[2] Specifically, India has a single training program in pediatric immunology, with only 11 physicians completing their training as of 2021.[2] Hong Kong initiated its inaugural training center for immunology and allergy in 2021 and currently has just 2 practicing specialists in this domain. Singapore does not maintain a dedicated specialty for immunology and allergy; instead, it relies on rheumatology specialists to cultivate subspecialty interests in this area.

FIG 1. Estimates of possible numbers of HAE cases and confirmed cases throughout the APAC region.[2,8-12] This illustration includes only the estimated prevalence and confirmed diagnoses data for the location of the participating authors. The number of possible patients was estimated using prevalence of 1:50,000 and population in 2020 for each location.

Testing for C1-INH function in the laboratory is not generally available in developing Asian nations, which could account for the lack of diagnosed patients.[2] Diagnostic facilities for HAE, including genetic testing, are limited and mostly available only at large tertiary centers or university hospitals, even in more developed nations.[2,8] Testing complement component 4 (C4) levels is the most widely available test in the region, but pitfalls include suboptimal sensitivity and specificity.[8] Where testing for C1-INH levels is available, tests are challenging to conduct because of a lack of local technical expertise and the need for careful sample handling.[2,13]

In Japan, for example, evaluation of the antigenic level of C1-INH is not covered by the national health insurance system, and so diagnosis of C1-INH-HAE is obtained on the basis of clinical history and measurement of C4 and (preferably) C1-INH function, which is usually available only in reference centers and may be subject to sample-handling error. Availability of genetic testing for HAE is variable; for example, only 20% of Japanese patients with suspected HAE receive genetic testing, which can be useful in instances wherein standard test results are inconclusive, prenatal or early postnatal diagnosis is required, or wherein sample transport issues preclude the use of standard tests.[18]

In China, the evaluation of antigenic levels of C4 and C1-INH is covered by the National Health Insurance System. Although C4 is widely tested in most hospitals, antigenic testing of C1-INH levels is available in fewer than 10 centers. Testing for functional C1-INH has not been approved and is used only in research when a patient is suspected to have HAE type 2.

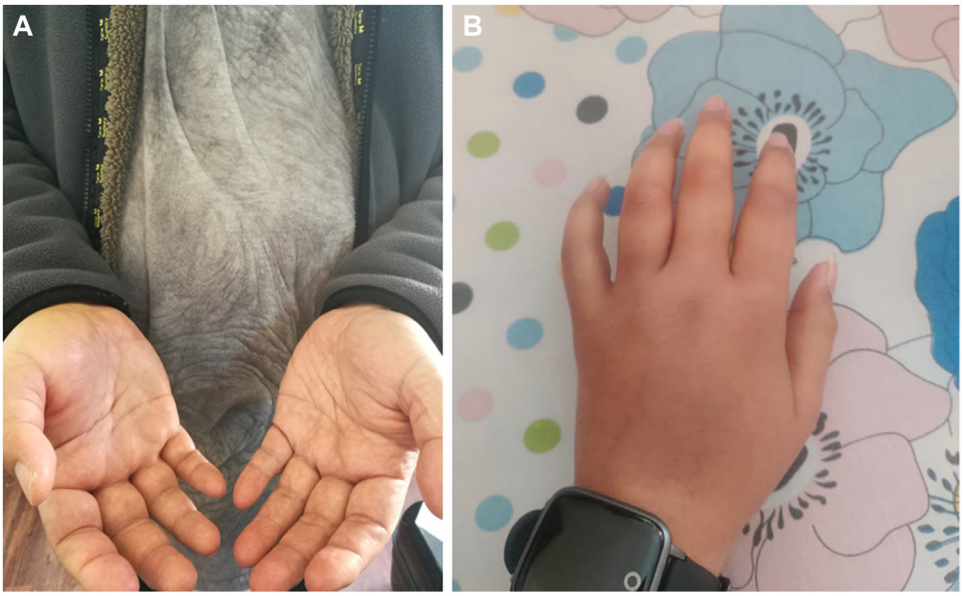

FIG 2. A and **B,** Cutaneous edema of the extremities, involving nonpruritic swelling of the skin caused by small vessels in deep SC tissue. The swollen areas generally have indistinct borders, do not resemble an allergic reaction mediated by IgE, and do not respond to antihistamines or corticosteroids.[22] Images courtesy of Dr Philip Li and Dr Ankur Jindal.

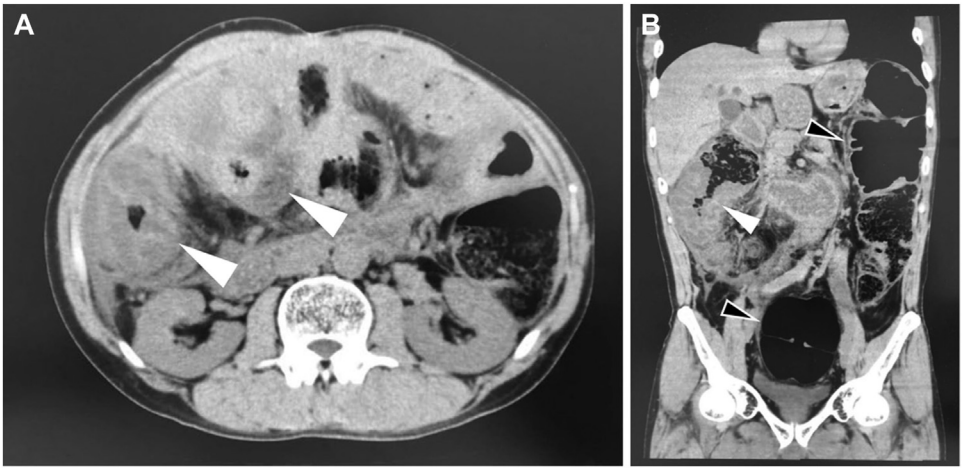

FIG 3. A and **B**, Abdominal computed tomography scan in a patient with HAE during an acute attack: axial section (*A*) and coronal section (*B*). Submucosal edema of the intestinal tracts is observed during an acute attack (*white arrows*). Colectasia is observed (*B*), which was probably caused by the attenuation of peristalsis due to 11 previous surgical procedures (*black arrows*). Images reproduced with permission from Honda et al.[23]

PATIENTS WITH HAE SUFFER UNPREDICTABLE AND POTENTIALLY LIFE-THREATENING ATTACKS

In HAE, acute attacks of angioedema can be localized anywhere on the body; however, the most common sites are the extremities (Fig 2),[22] gastrointestinal tract (Fig 3),[23] face and larynx (Fig 4), and genitals. Single-site attacks occur most frequently, but migratory, simultaneous, or closely spaced attacks can also occur.[22]

In C1-INH-HAE, C1-INH deficiency or dysfunction is present at birth; however, most symptoms begin at school age, in the first or second decade of life.[22] The frequency of attacks is extremely variable, and may even vary considerably for the same individual, depending on their stage of life.[22]

The symptoms of HAE are caused by the extravasation of plasma into the deeper cutaneous or mucosal tissue layers.[22] Cutaneous and abdominal attacks are the most common in HAE, with abdominal attacks often being accompanied by severe pain and other concomitant symptoms.[1] It has been reported, however, that the frequency and severity of abdominal attacks are lower among Asian patients than among those in Western nations.[24]

Recurrent edema of the gastrointestinal wall is reported by 70% to 80% of patients, usually accompanied by acute pain, which can

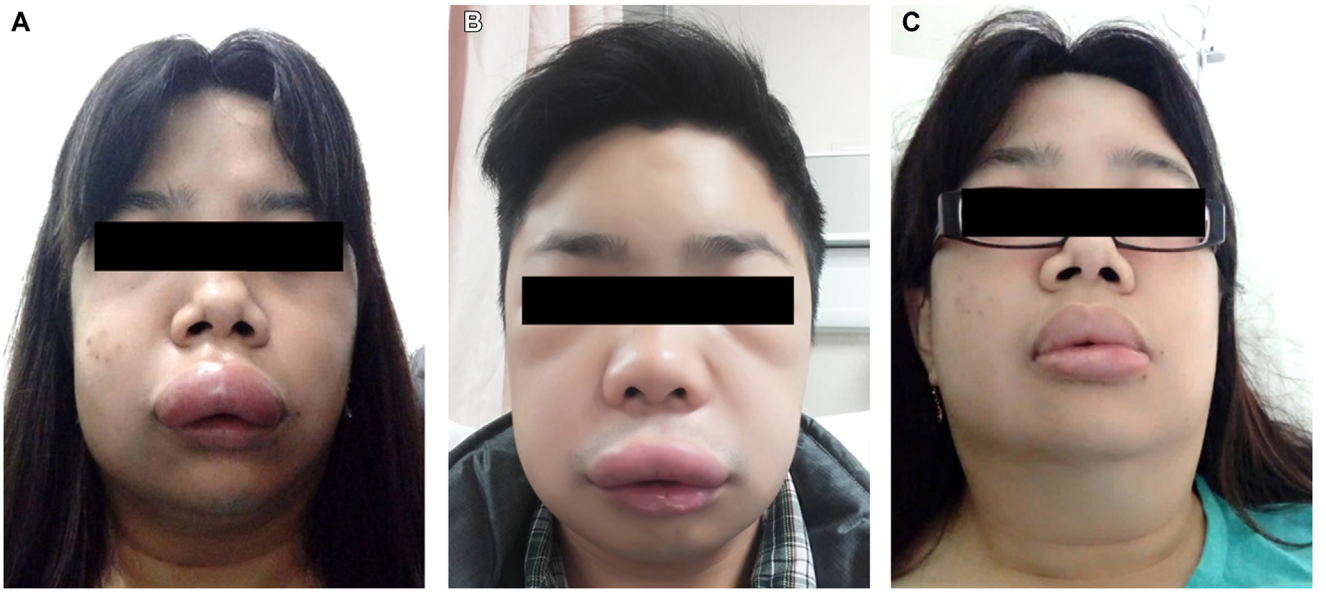

FIG 4. A-C, Edema in the patient's face (*A* and *B*) and subcutaneous edema of the neck (*C*) in a patient who also had laryngeal edema (not shown). Images courtesy of Dr Philip Li.

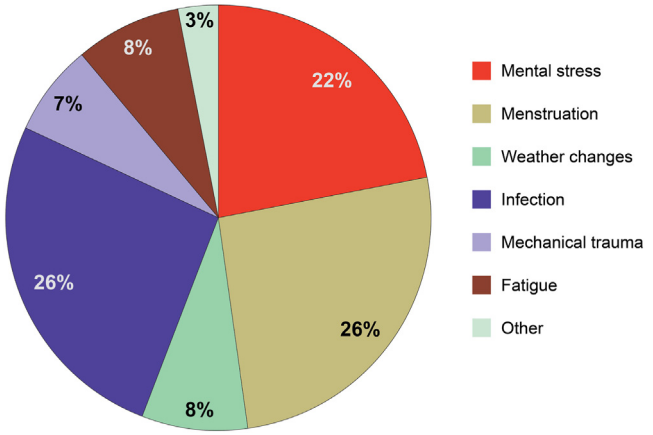

FIG 5. Distribution of trigger factors involved in edema of the upper airway. Adapted from Zotter et al.[27]

vary from mild discomfort to severe, intractable pain.[22] Concomitant symptoms may include ascites, vomiting, and/or diarrhea.[22] Fluid loss, plasma extravasation, and vasodilation can result in hypovolemia, which can progress to hypovolemic shock.[22] Bowel angioedema often resembles abdominal emergencies, resulting in approximately one-third of patients with undiagnosed HAE undergoing unnecessary surgery during abdominal attacks.[22,25]

Laryngeal edema is the most dramatic and life-threatening event for patients with HAE, with half the patients experiencing it at least once in their lives.[22] A history of repeated episodes of suffocation due to laryngeal edema is not uncommon, and some patients carry permanent tracheal cannulae as a result.[22] In environments in which effective diagnosis and treatments are not available, between 25% and 30% of patients with HAE die from laryngeal attacks.[26] Mortality from asphyxiation is high, with historical genealogic information showing up to 30% mortality among patients with HAE.[4] Data in Asian populations are scarce, but of 103 Chinese patients with HAE surveyed, 223 family members reported angioedema symptoms, of whom 30 died of laryngeal edema.[5]

Factors triggering attacks of angioedema

The exact role of trigger factors in the onset of attacks in C1-INH-HAE is still not fully understood.[27] There are a number of triggers with a known association with HAE, such as treatment with angiotensin-converting enzyme inhibitors, dental procedures, medical procedures that result in mechanical trauma, estrogen-containing oral contraception, and estrogen hormone replacement therapy.[1,27] Arguably of greater concern are the more indeterminate triggers that are less easy to predict or avoid, such as mental stress, fatigue, menstruation/hormonal changes, infection, and even changes in the weather, which have been associated with edema of the upper airway (Fig 5).[27]

Where it does not interfere with healthy lifestyle, patients should be instructed to avoid trigger factors and be assisted in this endeavor, for example, by using progesterone-only oral contraceptive pills.[1] In cases in which triggers are unavoidable, they should be anticipated with preprocedural prophylactic treatment.[1]

Socioeconomic and environmental conditions in the APAC region are very different from those in the regions reporting on HAE triggers. Conditions also differ between and within individual nations in the APAC region. Data on the prevalence and role of trigger factors for the APAC region will most likely contribute to our understanding of C1-INH-HAE and may provide insights into the apparent differences in affected body sites.

HAE attacks place a considerable burden on patients and carers

Patients with C1-INH-HAE, even in Western nations with access to guideline-recommended treatments, continue to experience a substantial burden from their disease, particularly those with a high frequency of attacks or poor disease control.[3,28] In studies of patients in the United States (N = 445)[3] and Europe,

Canada, and Australia (N = 242),[29] C1-INH-HAE was found to be a significant burden on patients, despite the relatively high availability of guideline-recommended first-line treatments versus nations in the APAC region.[2] In these studies, most patients had an angioedema attack in the last month (78.7% and 79.7%, respectively), and almost half had an attack in the last week (41.8% and 47.1%, respectively).[3,29] Attack durations varied from 6 hours or less to more than 3 days, with 33.9% to 42% of patients reporting attacks that lasted 2 days or longer.[3,29]

A worrying percentage of attacks affected the face (12.4%-15.8%) and throat/mouth (8.0%-10.3%),[3,29] with these locations being associated with lower QoL scores relative to attacks affecting the extremities,[3] as well as a risk of mortality due to asphyxiation.[1] Education of patients and families to seek help for facial attacks, which may progress to involve the larynx, or for laryngeal attacks immediately after onset, may minimize mortality, but is no substitute for effective and accessible at-home self-administered treatment.[2] Depending on what acute treatments are available, and especially in countries where first-line prophylaxis is not available, educating patients and caregivers on self-administration is likely to increase in importance.

A more recent study from Australia highlighted the continued burden of disease experienced by patients, even when receiving guideline-recommended treatment for HAE, including C1-INH and lanadelumab as long-term prophylaxis.[28] In this study, 50 patients with C1-INH-HAE who were enrolled over 11 months between 2019 and 2020 experienced a total of 463 recorded attacks, resulting in the administration of 238 doses of icatibant and 75 doses of intravenous (IV) C1-INH.[28] The authors found that although attacks still occurred for patients taking prophylaxis, the use of prophylactic treatments greatly reduced the frequency of attacks from pretreatment baseline levels.[28]

Data from Japan tell a similar story, with patients suffering an average of 15.7 ± 26.4 attacks per year, with more than 1 in 4 patients suffering more than 20 attacks per year (26.1%; n = 28 of 69).[18] Among the study participants, a total of 960 attacks were recorded, of which only 53.1% were treated.[18] It should be noted that because this study was conducted when home self-treatment was not available in Japan, patients may have decided not to seek treatment if their attacks were not severe enough.

In another study that investigated the effect of HAE on caregivers (primarily family members), it was found that acute attacks had a significant impact on caregivers as well as patients, resulting in absenteeism from work, which increased as in line with the pain severity of attacks.[30] For patients with more frequent attacks, absenteeism increased for both them and their caregivers, with caregivers missing an average of 3.3, 3.6, and 10.1 days of work per month when caring for patients who had less than 1 attack per month, 1 or more attacks per month, and 1 or more attacks per week, respectively.[30]

PATIENTS WITH C1-INH-HAE ARE FREQUENTLY HOSPITALIZED AND REQUIRE TREATMENT IN EMERGENCY DEPARTMENTS

Visits to emergency departments and extended periods of hospitalization are high for patients with HAE, representing a significant burden to patients and health systems, both financially and logistically.[3,29] In 2 non-APAC studies of the burden of C1-INH-HAE on patients, in the 12 months before data collection, 9.2% to 37.6% of patients visited an emergency department or urgent care facility, with a mean of 5.2 visits to emergency care, between 12.8% and 19.4% were hospitalized, for a mean stay of 7.4 nights, and 6.3% reported undergoing at least 1 surgical procedure related to HAE symptoms.[3,29] Hospitalizations were highest for patients living in countries that had a low availability of long-term prophylactic treatments.[29]

In another US study that investigated the hospitalizations and emergency department visits of patients with C1-INH-HAE and patients with allergic angioedema, although the overall hospital utilization was greater for allergic angioedema than for HAE because of higher prevalence in the population, the relative rates were much higher for HAE, with 45% of patients with HAE requiring hospitalization versus 18.3% of patients with allergic angioedema.[31]

Hospitalization data from Australia

In Australia, guideline-recommended treatment and prophylaxis are generally available to patients, although there are still restrictions in place. Despite this, a recent study showed that 5% of attacks still necessitated presentation to the emergency department, predominantly for facial/laryngeal edema.[28] Of the 9 patients requiring hospitalization in this study, 6 were receiving older prophylaxis treatment (danazol or tranexamic acid [TA]) or on-demand therapy only at the time of the attack.[28] This study highlighted the benefit of guideline-recommended prophylactic treatments, with most of the attacks occurring in individuals on older prophylaxis or solely on-demand treatments.[28]

Hospitalization data from Japan

With, until recently, a lack of guideline-recommended long-term prophylaxis options in Japan and acute treatment with pdC1-INH being administered exclusively in hospitals (when available),[2,9] patients with HAE were frequently hospitalized and experienced delays in receiving effective treatment, even when already diagnosed.[13,18] A recent survey of 63 patients with HAE showed that 39.7% used emergency services (ambulance) in their prediagnosis period, decreasing only slightly to 34.9% after diagnosis.[32]

In another survey conducted in Japan, it was found that the medical departments most frequently visited before diagnosis were general medicine (76%), gastroenterological medicine (44%), and dermatology (35%).[18] In addition, almost a quarter of patients reported visiting the emergency department or the intensive care unit.[18]

This study also reported a high rate of hospitalization before diagnosis, with patients spending a mean of 14.3 ± 5.3 days per year in hospital before being diagnosed, and a mean of 4.3 ± 1.3 days per year in hospital after being diagnosed.[18] Although this shows a significant decrease in the number of days hospitalized after the diagnosis ($P = .0074$), as many as 41.3% of patients still needed to be hospitalized for a day or longer, even after diagnosis.[18] Many patients with HAE in Japan remain undiagnosed despite up to a mean of 4.7 emergency department visits per year, with nearly one-quarter undergoing treatment for anaphylaxis.[13]

Access to first-line, highly effective prophylactic and acute attack treatments in Japan is rapidly improving and, on the basis of experience elsewhere, is likely to lead to reductions in emergency health care requirement. Effect on diagnosis rates is less well documented, and it will be interesting to see whether

TABLE I. WAO/EAACI guidelines: Summary of recommendations for treatments[1]

Treatment type	Primary recommendations	Other recommendations
Acute treatment	IV C1-INH, ecallantide, and icatibant recommended first-line. SDP should be used in the absence of these. FFP should be used in the absence of SDP.	The use of antifibrinolytics (TA) or androgens (danazol) is not recommended.
Short-term prophylaxis	IV pdC1-INH concentrate recommended first-line. FFP may be used as second-line treatment, where safe. Androgens may be used (5 d before and 2-3 d after).	TA is not recommended for short-term prophylaxis.
Long-term prophylaxis	SC pdC1-INH, lanadelumab, or berotralstat is preferred first-line recommendation. Where these are not available, IV C1-INH may be used. Androgens are recommended as a second-line option.	TA is not recommended for long-term prophylaxis.

Adapted from Maurer et al.[1]
SDP, Solvent detergent-treated plasma.

improvements in available treatments result in more affected people coming forward for medical advice.

Hospitalization data from China

Patients with HAE in China experienced significant hospitalization, visiting numerous clinical departments for HAE symptoms. The most frequently visited by patients with HAE were the emergency department (90.6%), dermatology department (71.9%), allergy clinics (61.5%), gastroenterology department (52.1%), health centers or clinics (42.7%), rheumatology department (34.4%), and otolaryngology department (34.4%).[20]

INCREASING THE USE OF GUIDELINE-RECOMMENDED TREATMENTS

An HAE attack is unpredictable and may occur at any time and be followed by another attack in short succession.[1] For this reason, the World Allergy Organization/European Academy of Allergy and Clinical Immunology (WAO/EAACI) guidelines recommend that patients should be provided with on-demand medication and carry enough medication with them for the treatment of at least 2 attacks.[1]

For C1-INH-HAE, IV C1-INH, icatibant, and ecallantide are the recommended on-demand treatments of choice, with early treatment providing a better response than late treatment.[1] Treatment with C1-INH, icatibant, or ecallantide should, therefore, be provided as early as possible.[1] For the on-demand treatment attacks where first-line treatments are not available, solvent detergent-treated plasma should be used.[1] If it is not available, HAE attacks should be treated with fresh frozen plasma (FFP) of which there is a safe supply available.[1] The guidelines recommend against using antifibrinolytics such as TA or attenuated androgens such as danazol, because these treatments show minimal or no benefit for treatment of established acute HAE attacks (Table I). However, when first-line treatments are unavailable, patients report anecdotally that attenuated androgens or TA taken during prodromal or very early symptoms can abort the attack or reduce attack severity.[1,2]

In addition to on-demand treatment, similar recommendations are also given for patients who may be exposed to specific angioedema-inducing situations.[1] Short-term prophylactic treatment of people with HAE is done with the intent to minimize the risk of angioedema during situations of surgical trauma, dental surgery, or other procedures associated with mechanical impact, especially of the upper aerodigestive tract.[1] The guidelines recommend the use of IV pdC1-INH as first-line preprocedural prophylaxis.[1] FFP is also recommended for short-term prophylaxis as a second-line agent, with the guidelines noting the risk of blood-borne disease transmission and allosensitization.[1] Attenuated androgens such as danazol have been recommended in the past, but the guidelines note that currently pdC1-INH is the agent of choice in preprocedural situations.[1] TA is not recommended by most guideline experts (Table I).[1]

Guideline recommendations regarding long-term prophylaxis are built on the goal of achieving complete control of HAE and normalizing patients' lives, which, in a measurable sense, translates to patients no longer experiencing attacks.[1] Guidelines recommend that long-term prophylaxis should be considered in all patients with C1-INH-HAE and individualized to their needs, taking into consideration disease activity, QoL, availability of health care resources, the level of control achieved by using on-demand treatments, and patient preference.[1]

The preferred first-line agents for long-term prophylaxis of C1-INH-HAE are subcutaneous (SC) pdC1-INH, lanadelumab, a human anti–plasma kallikrein mAb, and berotralstat, an oral plasma kallikrein inhibitor.[1] The guidelines recommend any of these 3 medications for the first-line long-term prophylactic treatment of patients with C1-INH-HAE on the basis of their efficacy and administration route (Table I).[1] In instances wherein all of these medications are available, the choice of treatment should be made by shared decision-making, because there is not enough evidence to recommend any of these options over each other.[1] When none of these treatments is available, efforts should be made to change this as a priority.[1] Of the 3 preferred first-line treatments for long-term prophylaxis, pdC1-INH is the only recommended option in special populations, such as children younger than 12 years, women who are pregnant or planning to become pregnant, and lactating women (the use of lanadelumab and berotralstat in pregnancy is off-label and not recommended).[1]

Attenuated androgens, although traditionally used for long-term prophylaxis of C1-INH-HAE, must be regarded critically because of their adverse androgenic and anabolic effects, drug interactions, contraindications, and side effects.[1] They cannot be used in pregnant or lactating women or in children or adolescents.[1] For this reason, among others related to use in special populations and children/adolescents, androgens are not recommended as a first-line option, and should be considered only as a second-line option.[1]

Antifibrinolytics such as TA are not recommended by the WAO/EAACI guidelines for long-term prophylaxis because of lack of efficacy. However, the guidelines recognize that these treatments are used where first-line treatments are not available

TABLE II. Available HAE treatments in APAC countries[2]

Country	Acute treatments	Short-term prophylaxis	Long-term prophylaxis
Australia	pdC1-INH, icatibant	pdC1-INH, icatibant	pdC1-INH, lanadelumab, TA
Bangladesh	FFP	Danazol, FFP	Danazol, TA
Hong Kong (China)	pdC1-INH, FFP	pdC1-INH, FFP	Danazol, lanadelumab, TA
India	FFP	Danazol, FFP, stanozolol	Danazol, stanozolol, TA
Indonesia	—	FFP	—
Japan	pdC1-INH, icatibant	pdC1-INH	Berotralstat, C1-INH, danazol, lanadelumab TA
New Zealand	pdC1-INH, icatibant	pdC1-IN	pdC1-INH (from 2024), stanozolol, TA
Singapore	pdC1-INH,* FFP	pdC1-INH, FFP	Danazol, TA
South Korea	FFP, icatibant	Danazol	Danazol, TA
China	FFP	Danazol, TA	Danazol, lanadelumab,* TA
Malaysia	FFP	FFP	—
Philippines	FFP	FFP	—

Adapted from Jindal et al,[2] with updates provided by authors.
*Self-funded/funded via discretionary medical fund.

TABLE III. Regional guideline recommendations in Australia, Japan, and China[33-35]

Australasian Society of Clinical Immunology and Allergy: Hereditary Angioedema Position Paper 2022[33]	
Acute treatment	IV C1-INH or SC icatibant is available for use in the hospital setting, and may be made available to patients after adequate training for self-administration. C1-INH and icatibant are available for adult and pediatric patients.
Short-term prophylaxis	IV C1-INH is recommended for short-term prophylaxis of major dental procedures and intubation, administered 1-6 h before the procedure. Danazol may be used when C1-INH is not available or for prophylaxis of minor dental and medical procedures.
Long-term prophylaxis*	SC C1-INH concentrate and lanadelumab are recommended for long-term prophylaxis. Danazol and TA have historically been used for long-term prophylaxis, but their use is limited by side effects and relative lack of efficacy.
Japanese Association for Complement Research: Guideline for Hereditary Angioedema 2019†[34]	
Acute treatment	C1-INH or icatibant is recommended, with intubation or surgical intervention of the airway considered in cases of asphyxiation during laryngeal attacks.
Short-term prophylaxis	Pretreatment prophylaxis with C1-INH is recommended for all medical, surgical, and dental procedures related to mechanical irritation to the upper aerodigestive tract.
Long-term prophylaxis*	C1-INH is recommended, but at the time of publication, was undergoing regulatory approval for long-term prophylaxis (berotralstat and lanadelumab were not available at the time of publication of these guidelines).† Danazol and TA can also be considered, but caution should be exercised because of side effects (danazol) and lack of efficacy (TA).
Chinese Society of Allergy and Chinese College of Allergy and Asthma Hereditary Angioedema Consensus (2019)[35]	
Acute treatment	FFP is recommended, with tracheotomy in cases of asphyxiation during laryngeal attacks. Icatibant is recommended once it is approved (icatibant was approved in 2021).‡
Short-term prophylaxis	Danazol and TA are recommended for short-term prophylaxis of dental procedures and other medical procedures, administered 5 d before the procedure and continued for 2 d after.
Long-term prophylaxis*	Danazol and TA are recommended for long-term prophylaxis, but it is important to monitor the side effects of danazol and the lack of efficacy of TA. TA is mainly recommended for children. Lanadelumab is recommended for long-term prophylaxis once it is approved (lanadelumab was approved in 2020).‡

*The treatment options recommended by the Australasian Society of Clinical Immunology and Allergy for long-term prophylaxis (SC C1-INH and lanadelumab) are not currently available in New Zealand (SC C1-INH has been available from 2023 for severely-affected patients).
†Although the 2019 Clinical Guidelines do not mention SC C1-INH, lanadelumab, or berotralstat, because these were not approved in 2019, these treatments are now available in some centers.
‡Under the Chinese Government Rare Disease Policy, lanadelumab has been available from December 2020 and icatibant from April 2021 before clinical trial in China. Icatibant has been covered by the National Health Insurance system from March 2022 and lanadelumab from March 2023. There are no policy restrictions to prescribe them.

and androgens are contraindicated, for acquired C1 inhibitor deficiency and some cases of HAE with normal C1 inhibitor.[1,2]

Clinical practice evidence of guideline adherence in Asian and Western countries

In contrast to many developed countries, there are limited options for the management of C1-INH-HAE in the APAC region, especially, but not exclusively, among developing nations, and first-line options are either completely unavailable or their use is limited to the provision of acute treatment in a hospital setting.[2] Patients with C1-INH-HAE in most Asian countries are frequently managed prophylactically using attenuated androgens or TA, and for preprocedural prophylaxis or on-demand treatment attenuated androgens and FFP are used.[2] As a result, it is common to see avoidable HAE-related morbidity in these countries (Table II).[2]

In a recent study on the epidemiology, management, and treatment access of HAE in the APAC region, only around half of the APAC countries had registered on-demand medications, and only one-third had prophylactic medications available, highlighting the disparity when compared with Western nations.[8] Moreover, international guidelines or consensus is rarely adhered to in the region, and regional guidelines are largely unavailable, with Australia, Japan, and China being the only countries that implement any guideline-recommended clinical practice, with

several variations in place in these local guidelines/consensus versus the WAO/EAACI guidelines (Table III).[8,33-35]

Although access to guideline-recommended treatments is relatively high in Western nations (such as Australia, Austria, Canada, France, Germany, Spain, Switzerland, the United Kingdom, and the United States), only around two-thirds of patients in these countries (62.4%-68.5%) are taking medication to prevent attacks on an ongoing basis (long-term prophylaxis).[3,29]

The importance of providing access to effective long-term prophylaxis has been shown by the stratification of treatment type by the number of attacks among Western patients with C1-INH-HAE.[29] In this subgroup of patients, long-term prophylaxis use was the highest among those who experienced no attacks, and the lowest for patients experiencing 13 or more attacks in a 6-month period (85.7% vs 49.4%, respectively).[29] These results suggest that long-term prophylaxis was generally effective, with the C1-INH found to be the most commonly used long-term prophylactic agent in Western nations (45.7%) followed by androgens (34.4%), TA (17.9%), and others (5.3%).[29] This is likely due to widespread compliance to international guidelines among Western nations, which have recommended pdC1-INH for long-term prophylaxis consistently since 2004.[22]

In Japan, a study found that only 53% of attacks were treated with on-demand therapy, although this survey was conducted at a time when home therapy by self-injection was not yet available.[18] The patients surveyed had a rate of long-term prophylaxis use comparable with that of Western patients (60%),[18] but most were prescribed TA, a treatment that is not recommended by international guidelines,[1] but can be considered as per the local Japanese guidelines.[36] In this study population, 11.4% of patients took prophylactic treatment when they felt an attack was likely, and 18.6% of patients took no prophylactic medication at all, regardless of symptoms.[18] Among Japanese patients, oral TA has been the most commonly used treatment for long-term prophylaxis (77.6%), followed by danazol (20.4%), with only 2.0% of patients using C1-INH concentrate (although this is likely to change given updated guideline recommendations in 2019, with C1-INH, lanadelumab, and berotralstat now available in Japan).[18,36] Only a small number of patients in this cohort reported that their prophylactic treatment was either "very effective" or "effective" (7.1% and 21.4%, respectively), with patients experiencing an average of 15.7 ± 26.4 attacks per year (total patient population).[18] There was no difference in the use of prophylactic treatments between the high attack– and low attack–frequency groups.[18]

TREATMENT-RELATED CHALLENGES IN DEVELOPING APAC NATIONS AND STRATEGIES FOR IMPROVING C1-INH-HAE MANAGEMENT

In developing countries in the APAC region, where timely acute treatment is often not available, risk benefit is weighed toward a greater adoption of prophylaxis.[2] However, there are a number of other challenges in these countries that also need to be addressed.

Improve access to allergists/immunologists and diagnostic resources

Although most nations across the region have allergists/immunologists with relevant expertise in diagnosing patients with HAE,[8] there is a severe lack of awareness of HAE among general physicians and patients,[2,13,18] limited access to diagnostic facilities and treatments, and sometimes little to no standardized care because of lack of adherence to any clinical guidelines.[2,18] In addition, in the first worldwide survey on perspectives about the allergy and immunology specialty, it was found that only 29.8% of responders in APAC considered allergy and clinical immunology as a "recognized specialty" versus 61.4% and 71.8% in North America and Europe, respectively, and more than 1 in 10 did not recognize it as a specialty, subspecialty, or even an area of postgraduate medical training.[37]

In Hong Kong, for example, training in allergy is done as part of training in pediatric immunology and infectious disease, which is a robust program, but does not include adult immunology—an area in which there has not been a local trainee for more than 2 decades.[38] As of 2023, there are only 5 immunology and allergy specialists listed in the Hong Kong Medical Council Specialist Register, putting the number of allergists per head of population at roughly 1:1,170,000, but of these only 3 are currently practicing and have experience with managing HAE.[39] This paucity of allergists is reflected across other countries in the region, with Thailand and Malaysia having 1 allergist per 1,000,000 and 1 allergist per 25,000,000 people, respectively.[38,40]

In India, there may be very few trained allergists/immunologists, with limited medical educational centers to provide relevant training in pediatric immunology.[2] For example, despite its population and potential prevalence of HAE, there are only approximately 11 physicians in India with the expertise required to identify and manage patients.[2]

When it comes to diagnostic resources for investigating C1-INH-HAE, although all centers in the Asia Pacific Association of Allergy, Asthma and Clinical Immunology (APAAACI) Survey across the region had access to tests for C4 levels, relatively few could measure C1-INH level and function, and a small minority could perform *SERPING1* genotyping.[8] Measuring C1-INH level and function is arguably the most important change to implement, because this has been associated with significantly lower age at diagnosis ($P = .017$),[8] but these tests require careful sample handling and a high level of technical expertise, which may not be generally available, presenting an additional challenge to diagnosing HAE type 2.[2]

Create patient support and HAE advocacy groups

In the APAAACI Survey, only half of the countries or territories surveyed had patient support groups.[8] Countries that did have patient support groups were found to be significantly more likely to have C1-INH replacement therapy and prophylactic medications registered than those without patient support groups ($P = .018$ and .002, respectively).[8]

Patient support groups are key to improving patient awareness and can help lobby governments and pharmaceutical companies to develop and increase access to medicines for rare diseases such as HAE.[8] This is exemplified by recent advances in the availability of HAE medication in Hong Kong, which previously had no registered HAE-specific treatments until advocacy and lobbying by their local patient support group.[8] In the span of just 3 years, patients gained access to C1-INH replacement, icatibant, and lanadelumab.[8]

TABLE IV. Long-term prophylaxis availability (2021) by country and GDP/capita[2,36,44]

Country	GDP/capita ($)	Available long-term prophylaxis
APAC		
Singapore	64,582	Danazol, TA
Australia	57,374	pdC1-INH, lanadelumab, TA
Hong Kong (China)	48,676	Danazol, lanadelumab, TA
New Zealand	41,945	pdC1-INH (2023), stanozolol, TA
Japan	39,290	Berotralstat,* C1-INH,† danazol, lanadelumab,* TA
South Korea	31,363	Danazol, TA
China	12,551	Danazol, lanadelumab, TA
Indonesia	3,894	None
Rest of world		
United States	62,795	pdC1-INH, danazol, lanadelumab, TA
Germany	47,603	pdC1-INH, danazol, lanadelumab, oxandrolone, TA
Italy	34,483	pdC1-INH, danazol, lanadelumab
Spain	30,371	pdC1-INH, danazol, stanozolol, TA
Turkey	9,370	pdC1-INH, danazol, TA

Adapted from Jindal et al.[2]
*Berotralstat and lanadelumab were not licensed at the time of data collection for this table.
†C1-INH was not approved for long-term prophylaxis in Japan at this time.

Improve adoption of regional or international guidelines

It should also be noted that in many countries and regions, such as India, Indonesia, Bangladesh, Hong Kong, Singapore, and South Korea, there is no adoption of clinical guidelines (local or international), and therefore little to no compliance with guidelines when it comes to management recommendations.[2] In the APAAACI Survey, only one-third (33%) of nations surveyed used regional guidelines.[8] Even in countries with local guidelines in place, such as Japan, New Zealand, and Australia, compliance with HAE treatment guidelines is low.[2]

As well as being important for the standardization of clinical practice, implementation of clinical guidelines has been shown to improve access to medication, with the APAAACI Survey revealing that countries with guidelines in place were significantly more likely to have on-demand medications versus those without ($P = .015$).[8]

Improve funding for, and access to, HAE treatments

In developing Asian nations, management of C1-INH-HAE can be daunting for patients, families, and physicians from a financial point of view, with most patients having to personally bear the cost of therapy.[2] First-line on-demand treatments such as C1-INH, ecallantide, and icatibant are often not available or, if they are, their cost is prohibitively expensive for almost all patients, with a lack of universal health cover.[41] As a result, options may be limited to FFP and attenuated androgens.[2]

In some regions, such as Singapore, lack of government subsidies for treatments for rare genetic diseases has resulted in the establishment of organizations such as the Rare Disorders Society and the Rare Disease Fund, which provide financial support to patients through a combination of community donations and 3:1 government matching.[42] Cover currently includes treatments for Gaucher disease, hyperphenylalaninemia due to tetrahydrobiopterin (BH4) deficiency, Pompe disease, and primary bile acid synthesis disorder, but not long-term treatments for HAE.[42] However, it is worth noting that the Medication Assistance Fund subsidy in Singapore is available for on-demand treatment with IV C1-INH for acute attacks.[42] In India, the Rare Disease Policy of the Government of India represents a potentially promising option for patients with HAE to access first-line on-demand treatment. In China, however, first-line treatments for acute attacks and prophylaxis are now available under the Rare Disease Policy and covered by the National Health Insurance system.

Across developed nations in the region, the reimbursement process for drugs for rare diseases can be inconsistent, with very few countries having a dedicated process.[43] In Japan, for example, government-subsidized HAE treatments may be limited to large university hospitals or regional hospital hubs,[18] even for on-demand treatment of attacks, subjecting patients to long wait times.[18] In Australia, although first-line guideline-recommended treatments for long-term prophylaxis, such as SC C1-INH concentrate, are funded through the Australian National Blood Authority, routine long-term prophylaxis is funded only for patients experiencing the equivalent of 2 (lanadelumab) or 8 (scC1-INH) or more acute attacks per month, potentially creating barriers for many patients who would still benefit from funded access.[33]

Improve access to long-term prophylaxis

In developing countries in the APAC region, where on-demand treatment may not be readily available, and there is little to no standardized care because of lack of clinical guidelines, there are significant challenges in place with respect to the availability of first-line treatments.[2] Despite a lack of recommendation from international guidelines and paucity of evidence, antifibrinolytic agents (TA, 30-50 mg/kg/d in 2-3 divided doses up to 3 g/d) are used for long-term prophylaxis.[2] This is largely due to the better tolerability of these treatments compared with attenuated androgens, especially in children and adolescents and potentially in pregnancy.[2]

Although many nations in the APAC region may not necessarily have the means with which to enable access to first-line HAE treatments to patients through conventional routes, there are a number of Asian countries that have equivalent gross domestic product per capita (GDP/capita) to Western nations yet provide a lower level of care (Table IV).[2,44] Even among many developed nations in Asia, international and local guidelines are not adopted or adhered to, except for Japan (where guideline-recommended first-

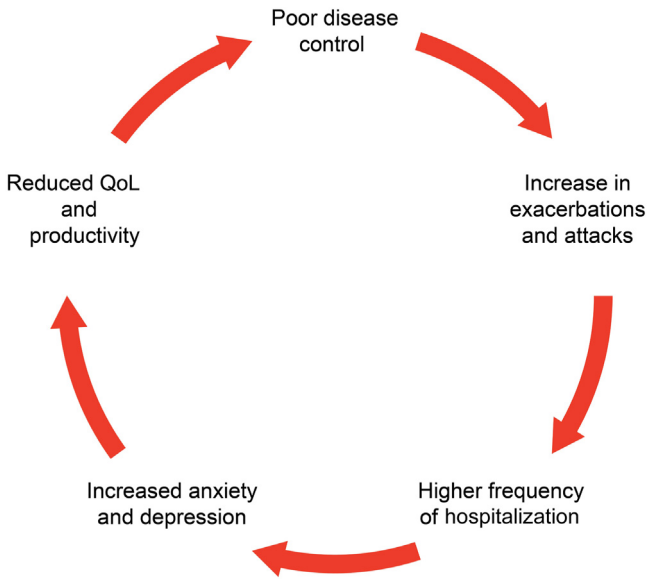

FIG 6. The cycle of disease burden in C1-INH-HAE. Adapted from Banerji et al,[3] Mendivil et al,[29] and Liu et al.[41]

line prophylaxis treatments have started to become available), China (with the recent availability of lanadelumab), and Australia.

In the management of C1-INH-HAE, only a minority of countries, all with GDP/capita of more than US $40,000, have the resources to fully comply with international guidelines; however, there are a number of steps that can be taken to improve outcomes for patients and confer the greatest risk/benefit.[2]

Improving management of C1-INH-HAE can have a positive impact on mental health and QoL

In general, the mental health of patients with HAE is poorer than that of the overall population.[29] This is exacerbated in instances where patients suffer anxiety and depression as a result of poorly managed C1-INH-HAE, with a high frequency of attacks (Fig 6).[29] A lack of control over their disease was associated with greater reported anxiety and depression, with the lowest Angioedema Control Test scores being reported by patients with the severest anxiety and depression.[3,29] Even when patients are relatively well controlled, simply being "troubled by attacks" can be interpreted as a mental health burden.[32] In a recent survey conducted in Japan by Yamamoto et al,[32] this burden was seen more frequently in patients who experienced a high rate of attacks (36.8%), but was also present in low-attack and no-attack groups (10.3% and 14.3%, respectively). Attack frequency with anxiety and depression have been shown to be drivers of poor disease control.[29]

Low health-related QoL scores have been shown to correlate with higher frequency of attacks, and across the globe, health-related QoL scores have been shown to be lower among patients with C1-INH-HAE than among the general population.[3,29,41]

C1-INH-HAE AFFECTS DAILY LIFE AND LEADS TO REDUCED PRODUCTIVITY AND ACTIVITY IMPAIRMENT

HAE has negative impacts that extend from early education in a patient's life to career opportunities. Typically presenting in the first or second decade of life, HAE can have a significant effect on a patient's development from a young child all the way to adulthood. Loss of education and career opportunities is common among patients, with 100% of patients feeling like their educational advancement was hindered by their disease, 69% feeling their career choices had been limited, and 57% feeling their career progression was hindered.[45]

A recent survey conducted in Japan noted that anxiety around HAE attacks has an impact on whether a patient feels able to work or not, what sort of work they seek, whether they feel safe working alone, and also on their travel plans and daily life activities.[32] Disease activity can worsen these effects as well, with patients who experienced high attack rates (13 or more attacks in 6 months) reporting a considerable effect on their ability to accomplish basic activities of daily living, compared with those who remained attack-free (67.0% vs 6.7%).[3] Similar to daily activity impairment, mean work productivity loss was shown to be over 10 times higher in patients with 13 or more attacks per year versus those with no attacks (39.9% vs 3.3%).[3] The numerous unmet needs shown in this survey serve to highlight the necessity to advance HAE management and lessen disease burden.

The effect of HAE on a person's career opportunities brings into question the wider economic impacts of the disease, including the direct cost of administering treatment. When disease-specific therapies for HAE were not available in the United States, as is the case in many countries in Asia today, patients were found to experience an average of 26.9 swelling attacks per year, with an average cost per patient of $44,597.[45] Although health care costs in the United States are higher than elsewhere, it should be noted that most of these costs were associated with hospitalization ($17,381), emergency care ($2,827), and outpatient care ($3,777), rather than the price of treatment itself ($5,194).[45]

The provision of long-term prophylaxis for patients with C1-INH-HAE has the potential to reduce the economic burden of treating HAE-related attacks, even in countries with a lower relative GDP/capita, through reducing the number of attacks patients experience per year and the associated health service usage.

Data on socioeconomic impacts in the APAC region countries are largely lacking. Although it is likely that there will be significant detriment, region-specific data are urgently needed, especially in view of the differences in socioeconomic environment.

Conclusions

It should be noted that basing clinical decisions solely on the economic benefit of providing treatment raises ethical questions, and as stated in the clinical guidelines for the management of C1-INH-HAE, all patients should be considered for prophylaxis, wherever they are located and whatever the financial cost.[1]

Increasing the availability of guideline-recommended effective drugs for the prophylactic treatment of C1-INH-HAE in the APAC region would almost certainly provide benefits for patients, caregivers, and society as a whole.[3,29] The uncertainty faced by patients regarding the unpredictable nature of their condition is a significant source of anxiety, and the effect that prophylaxis has on decreasing attack rates is likely to have a positive impact on stress and anxiety about future attacks.[3] This, in turn, would likely result in a positive benefit to the patient's QoL through

greater freedom, improved productivity, and participation in sports and social activities.

It is well documented that C1-INH-HAE affects a patient's ability to go to school or work.[3,29,45] Access to long-term prophylactic treatment may decrease absenteeism and lost productivity and could improve the patient's chance at achieving their education or career goals.[45] In the case of caregivers for younger patients, reducing the frequency of attacks can help with their ability to work and reduce absenteeism.

There are significant challenges in C1-INH-HAE management, particularly in developing Asian nations. Low disease awareness leads to lengthy delays in diagnosis, and where treatments are available, they tend to be weighted toward suboptimal on-demand options. Patients in low-income countries simply do not have access to life-saving treatments, effective prophylaxis, or even specialist physicians and related services.[2] In these nations, there is an urgent need to improve HAE services and provide access to life-saving treatment.

Many high-income economies in the Asia region, such as New Zealand, Hong Kong, South Korea, and Singapore, do not currently provide guideline-recommended long-term prophylactic treatments, despite having the equivalent means to do so as other nations that do adhere to the guidelines.[2] The only exception is Japan, where patients are now able to access prophylactic treatment with berotralstat, SC C1-INH, and lanadelumab.

In these locations, every effort should be made to increase awareness of the guideline recommendations and to highlight the burden placed on patients, carers, health providers, and health care services when management of C1-INH-HAE is not optimal, which may require lobbying at the government level. Drugs for the treatment and prevention of rare diseases, such as HAE, provide significant value to patients and society in terms of improvements in health, increased productivity, reduced morbidity and health care utilization, QoL, and survival.[45] The availability of specific therapies for treating C1-INH-HAE has dramatically decreased the burden of this disease on patients in countries that have adopted those treatments and has the potential to do so in the Asia region as well.

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