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Consensus on diagnosis and management of Hereditary Angioedema in the Middle East: A Delphi initiative

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ABSTRACT

Background: Hereditary angioedema (HAE), a potentially life-threatening genetic disorder due to C1 inhibitor deficiency in most cases, is characterized by sudden and/or recurrent attacks of angioedema (subcutaneous/submucosal swellings). The global World Allergy Organization (WAO)/European Academy of Allergy and Clinical Immunology (EAACI) International guideline for HAE management is comprehensive, but the implementation of this guideline may require regional adaptation considering the diversity in disease awareness, type of medical care systems, and access to diagnostics and treatment. The aim of this Delphi initiative was to build on the global guideline and provide regional adaptation to address the concerns and specific needs in the Middle East.

Methods: The Consensus panel comprised 13 experts from the Middle East (3 from the United Arab Emirates, 3 from Saudi Arabia, 2 from Lebanon, 2 from Kuwait, 2 from Oman and 1 from Qatar) who have more than 2 decades of experience in allergy and immunology and are actively involved in managing HAE patients. The process that was carried out to reach the consensus recommendation included: 1.) A systematic literature review for articles related to HAE management using Ovid MEDLINE. 2.) The development of a questionnaire by an internationally acclaimed expert, with 10 questions specific to HAE management in the Middle East. 3.) Experts received the questionnaire via email individually and their answers were recorded (email/interview). 4.) A virtual consensus meeting was organized to discuss the questionnaire, make amends if needed, vote, and achieve consensus.

Results: The questionnaire comprised 10 questions, each with 2 or more statements/recommendations on which the regional experts voted. A consensus was reached based on a 70% agreement between the participants. The key highlights include: 1) HAE experts in the Middle East emphasized the importance of a positive family history for arriving at a diagnosis of HAE. 2) The number of episodes per month or per 6-month period and severity should be used, together with other markers, to determine the need for prophylaxis. 3) Disease status should be monitored by

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periodic visits and the use of patient-reported outcome measures such as the angioedema activity score and the angioedema control test. 4) Attenuated androgens and tranexamic acid may be considered for long-term prophylaxis, if lanadelumab, C1-Inhibitor or berotralstat are not available.

Conclusion: This consensus recommendation may help to educate healthcare practitioners in the Middle East and unify their approach to the diagnosis and management of HAE.

Keywords: Hereditary angioedema, Middle east, Delphi consensus

INTRODUCTION

Hereditary angioedema (HAE) is a rare genetic disorder with an approximate global incidence of 1:10,000–1:50,000.[1-4] Thereby, the estimated number of patients affected in the Middle East region would be ~9527 to 47,638 (estimated total population, Middle East [2022]: ~4 476,377,851[5]). HAE can be categorized into 3 types based on C1 inhibitor (C1–INH) gene function and/or levels. Type I and type II HAE are due to mutations that affect C1–INH inheritance and are autosomal dominant. Patients with type I HAE have low levels of C1–INH protein and function;[6–9] whereas patients with type II HAE have normal C1–INH protein levels but impaired C1–INH function.[10] Patients with non-type I/II HAE have normal levels of C1–INH protein and function, collectively called normal C1–INH HAE (nC1-INH-HAE).[11-13] Patients with HAE have compromised quality of life due to characteristic recurrent angioedema attacks, wherein swelling (subcutaneous or submucosal) can affect 1 or multiple sites in the body including internal organs like intestine, urinary tract, and larynx. Acute attacks require immediate treatment and may be potentially fatal if the upper airway is involved.[14,15] The lack of awareness even among treating physicians and difficulty to interpret HAE manifestations, including swelling and recurrent abdominal pain, may lead to delayed diagnosis and consequently poor management of HAE. It is important to rule out other types of angioedema, for example, excluding non-HAE patients unresponsive to H1-antagonists and other treatments recommended for histamine-induced angioedema.[16] Therefore, the most crucial steps in the management of HAE are early diagnosis, effective treatment of acute attacks, and short- and long-term prophylaxis.

The currently revised global WAO/EAACI HAE guideline (2021)[17] provides comprehensive guidance on the diagnosis and management of HAE. However, implementing this international guideline across the globe can be challenging considering the peculiarities of geographic regions. In the Middle East, many organizations are still working towards increasing HAE disease awareness to decrease the time to diagnosis and treatment. Additionally, modern self-administered HAE treatments are not yet approved or have become available only recently in the Middle East, and access is limited. As a result, there are only few experienced HAE treating physicians and specialist nurses to train patients, as compared to other regions such as Europe or North America, which have long-standing experience in training patients to treat and prevent attacks using self-administrable treatment.[18] Limited availability of diagnostic tests for HAE is another challenge in the Middle East.

Thus, it is paramount to adapt the global guideline and have region-specific, evidence-based and real-world expert recommendations for the diagnosis and management of HAE. For this purpose, we bring forth these consensus recommendations around the diagnosis and management of HAE for the Middle East region.

MATERIALS AND METHODS

The Middle East HAE consensus recommendations were generated following a 4-step process, using a modified Delphi Method.

Facilitator and panel selection: An expert panel of 13 members, representative of the Middle East region, was assembled (3 from the United Arab Emirates, 3 from Saudi Arabia, 2 from Lebanon, 2 from Kuwait, 2 from Oman, and 1 from Qatar), and

an international expert in HAE management, who led a global Delphi consensus on treatment goals in HAE[19] as well as the update and revision of the WAO/EAACI HAE guideline, moderated the process.

The modified Delphi process involved the following steps:

1. Systematic literature review: A clinical researcher conducted a systematic literature search related to HAE management. The search engine used was Ovid MEDLINE and the keywords included were long- and short-term prophylaxis and acute treatment of attacks in HAE-1, HAE-2, or HAE nC1-INH. International guidelines and results of randomized controlled trials were included in the literature search.
2. Questionnaire development: The moderator helped to develop a questionnaire specific to HAE management in the Middle East based on this systematic literature review and regional expert opinions. Questionnaire development was carried out from July 2021 to September 2021.
3. Questionnaire dissemination and collection of responses: A questionnaire with 10 questions was disseminated via email to the 13 regional HAE experts in October 2021. The experts were asked to provide individual input in regard to the different recommendations based on their clinical expertise. The responses to the questionnaire were recorded via email or interview within 90 days of dissemination.
4. Consensus meeting: A virtual consensus meeting was organized on January 8, 2022 wherein the experts voted on each consensus recommendation statement for HAE management in the Middle East. Statements that received an agreement of $\geq$70% of participating experts were included in the consensus. Statements that participants did not agree on were discussed to understand whether this was due to the ambiguity of the wording or other reasons. Where applicable, changes were implemented, and another round of voting was performed for the reworded statements. This process was carried out using anonymous polling.

This study was conducted in accordance with the principles in the Declaration of Helsinki.[20]

RESULTS

All experts on the Delphi panel were allergists-immunologists with vast experience in managing HAE patients, on average 26 years (range: 20–32 years). The consensus questions and/or statements were divided into 4 parts: 1) Diagnosis and monitoring of HAE, 2) Treatment of acute attacks, 3) Short-term and long-term prophylactic treatment, and 4) Diagnosis and treatment of special populations: women (especially during pregnancy, lactation, reproductive age, menopause) and children.

Diagnosis and monitoring of HAE

There was unanimous agreement in support of a rigorous diagnostic approach to ensure early diagnosis and reduce misdiagnoses. A thorough family history (immediate and extended) was considered crucial in the diagnostic approach in patients suspected to have HAE, due to high rates of consanguineous marriages in the Middle East. Children with a positive family history are advised to be tested for HAE. Testing for C4, C1–INH level and function at the same time was the recommended diagnostic approach. Genetic testing was recommended in the case of strong clinical suspicion of HAE in the presence of normal C1–INH levels and function. If accessible, genetic testing can currently be performed for 6 genes (FXII, ANGP1, PLG, KNG, MYOF, HS). Physicians are encouraged to refer patients with HAE with normal C1–INH to an angioedema center of reference and excellence (ACARE), in their country or region, where all of these mutations can be assessed.[21] Currently, the Middle East has 5 ACAREs in the region (United Arab Emirates/Abu Dhabi, Qatar, Kuwait, Saudia Arabia, and Oman). Additionally, checking C1q levels is recommended for patients with symptoms of HAE with no family history and/or have low C4 and low C1–INH level and function, to rule out acquired angioedema, especially in case of late-onset symptoms or age 40 and above. It was highlighted by the experts that type 1 HAE patients exhibit both, low C1–INH protein levels and function. C1–INH levels lower than 30% of normal levels during an attack and between 30% and 50% of normal values outside of an attack are indicative of HAE.[22] In case of inconclusive laboratory results, repeated testing is recommended, preferably during an attack

until the diagnosis is either confirmed or ruled out. The statements that did not reach consensus were: 1) C4, C1–INH level and function should be checked in the stated sequence rather than all at once. 2) Diagnostic workup should be prompted by prodromal signs and symptoms that precede attacks of angioedema. Here, it was noted that not all HAE attacks are preceded by prodromal signs and symptoms. 3) Disease activity should be assessed based on location of attacks alone.

As for monitoring disease status, this consensus proposes to monitor HAE activity with robust tools such as the angioedema activity score (AAS), which includes the assessment of attack numbers, and to monitor disease control with the help of the Angioedema Control Test (AECT). Disease status and the need for treatment optimization may also be assessed by documentation of the effect of the attacks on normal function and routine activities, the requirement for intensive care/hospitalization and quality of life impairment (eg., by use of the Angioedema Quality of Life Questionnaire). The experts emphasized that disease activity in patients with HAE can be difficult to classify since the sum of problems over a specified period may alter and often fluctuates. The assessment of disease status by the use of patient-reported outcome measure should be complemented by discussing with patients their subjective symptoms and perceptions of the impact on quality of life and daily activities.[23] Overall, the Middle East consensus recommendations on diagnosis and management of HAE are in line with those of the global guideline (Table 1).

Treatment of HAE

The decision of selecting a choice of treatment is multifactorial and it varies based on age, gender, co-morbidities, etc. Therefore, it is important to know the available treatment choices and their efficacy and safety profiles. In addition, it is important to determine the type of treatment most suitable for the patient at any given point of time by taking into account patient preference through a shared decision-making process. For example, acute attacks require aggressive on-demand treatment while known triggers drive consideration of short-term prophylaxis (STP). Furthermore, considering the unpredictable nature of the disease, the monitoring techniques discussed earlier should be used at every patient visit, to guide decisions on long-term prophylaxis (LTP) treatment. It is important to note that the cost of medication was not considered a contributing factor to decide on these treatment options. Table 4 lists all the HAE treatment management available in the Middle East region at the time of this publication.

On-demand treatment of an acute attack of HAE

The on-demand treatment of HAE attacks is recommended to be performed using any of the following agents:1) C1–INH concentrate, 2) Icatibant, a synthetic bradykinin B2-receptor antagonist, 3) Ecallantide, a recombinant plasma kallikrein inhibitor, and 4) Fresh frozen plasma (FFP) if 1–3 are not available. It is important to highlight that ecallantide is selectively available in some healthcare centers of the Middle East region. Therefore, another treatment option should be considered immediately if ecallantide is unavailable, to avoid any delay in treatment of acute attacks. Additionally, patients are recommended to have 2 doses of either intravenous auto-infusion or subcutaneous administration as a part of acute treatment. The experts agreed that danazol and tranexamic acid should not be used in case of acute attacks.

Short-term and long-term prophylaxis

Short-term prophylaxis (STP) is recommended to reduce and/or prevent angioedema attacks during or after any surgical procedure and/or stressful trigger. Consensus was reached around the need to use STP in all HAE patients who face medical interventions, endoscopic interventions, surgery or otherwise, with an increased risk of having an angioedema attack and/or whenever the upper airway is manipulated regardless of long-term prophylaxis (LTP) application. The recommended first-line STP option is plasma-derived C1-inhibitor (pd-C1-INH) or recombinant C1–INH (Table 2).

Long-term prophylaxis, in the Middle East, is indicated in patients whose on-demand therapy has inadequately minimized the manifestations and the suffering related to HAE.[24]

The choice of treatment for LTP is lanadelumab (monoclonal antibody targeting plasma kallikrein) or pd-C1-INH (IV or SC) or berotralstat (oral,

Consensus Statement	Consensus Percentage
I-What should prompt the diagnostic workup of HAE so that a patient of HAE is NOT missed?	
1. A positive family history.	100
2. Recurrent episodes/unprovoked episodes of non-pitting, non-pruritic edema affecting three main areas: *subcutaneous tissue* (face, upper or lower extremities, genitals), *abdominal organs* (stomach, intestines, bladder), and *the upper airway* (larynx, tongue).	100
3. Unexplained recurrent abdominal pain.	100
4. Absence of wheals. (Note: Patients with HAE often have erythema marginatum).	100
5. Failure of attacks to respond to antihistamines, glucocorticoids, or epinephrine.	100
6. Swelling attacks that are triggered by minor physical trauma such as dental work, prolonged sitting or standing, medications.	100
7. Difficulty in breathing due to airway swelling (edema) especially if triggered by trauma e.g., ex-intubation.	75
8. Exploratory laparotomy with unrevealing diagnosis.	75
9. Onset of symptoms in childhood/adolescence and worsening at puberty.	83
II-How should disease activity of HAE be assessed in order to reach appropriate decisions for treatment and prophylaxis?	
1. Frequency of attacks.	100
2. Angioedema activity score (AAS).	100
3. Angioedema Control Test (AECT).	92
4. Effect of the attacks on normal function and routine activities (e.g., school, work, ability to perform house chores, hobbies, sports etc.).	83
5. Requiring intensive care/Hospitalization.	83
6. Quality of life impairment (e.g. Angioedema Quality of Life Questionnaire).	83
7. Severity of attacks (need for emergency room visits or on demand therapy).	75
III-Part 1: What should be the diagnostic approach to confirm HAE, Part 1: HAE type I/ II?	

(continued)

Consensus Statement	Consensus Percentage
1. Check C4, C1 inhibitor level and function	83
2. Test results indicative of HAE type I/II should be confirmed by retesting.	100
III-Part 2: What should be the diagnostic approach to confirm HAE, Part 2: HAE non type I/II? Differential diagnosis	
1. If test results are negative for HAE type I/II and there is strong clinical suspicion of HAE non Type I/II, genetic testing including Factor XII mutation analysis should be considered.	100
2. Check C1q level if symptoms started with no family history, & low C4, low C1–INH level, low C1–INH function. Low serum C1q suggests acquired angioedema & should prompt diagnostic workup for underlying autoimmune, hematological or myeloproliferative disorder.	100
IV-How should patients be monitored for the course of their disease including treatment responses?	
The following parameters should be considered for monitoring patients on prophylaxis	
1. Clinical Activity judged by periodic visits.	92
2. Keep a diary of symptoms and actions taken, and review diary at each visit.	92
3. An angioedema activity score (e.g. the AAS).	92
4. The angioedema control test (AECT).	92
5. The use of on demand treatment.	92
6. Side effects.	92
7. An Angioedema Quality of Life Questionnaire (e.g. the AE-QoL).	85

Table 1. (Continued) Middle East Consensus recommendations for the diagnosis and monitoring of HAE (percentage agreement)

synthetic, small-molecule plasma kallikrein inhibitor). Attenuated androgens can be considered if these three medications are unavailable, and tranexamic acid treatment is a last resort (Table 2). Despite being on LTP, acute attacks can still occur and therefore patients are advised to have two doses of on-demand treatment available at all times.

Statements that did not reach consensus include: 1) Cost of medication is the determining factor for choosing on-demand or prophylactic treatment. 2) Short-term prophylaxis should be considered for patients who are not on prophylaxis or are on long-term prophylaxis.

Special populations

There was a detailed discussion related to HAE management in special populations namely a) women, especially during pregnancy, lactation, reproductive age, and menopause, and b) children.

Consensus Statement	Consensus Percentage
V-How can one determine whether treatment should be on-demand only or include prophylactic treatment?	
The following parameters should be used to determine the need for prophylaxis	
1. Number of episodes per month or per 6-month period.	100
2. Severity of episodes.	100
3. QoL impairment.	100
4. Use of and need for on-demand treatment.	100
5. Availability and ability to administer the on-demand treatment.	92
6. Presence of triggering factors (e.g., at work or at school).	83
7. Sites involved in attack.	77
8. Response to on-demand treatment.	75
9. Patient preference	75
10. Comorbid conditions.	75
VI-What should be the on-demand treatment for an acute attack of HAE? (any of the below)	
1. C1-INH concentrate.	100
2. Icatibant, a synthetic bradykinin B2-receptor antagonist.	92
3. Ecallantide, a recombinant plasma kallikrein inhibitor.	85
4. Fresh frozen plasma if 1–3 are not available.	100
VII-When should we initiate short-term prophylaxis? What to use?	
Short-term prophylaxis should be considered:	
1. In patients who face medical interventions, surgery or otherwise increased risk of having an angioedema attack.	100
2. Whenever the upper airway is manipulated.	92
Short-term prophylaxis should be done with:	
1. C1- inhibitor.	100
2. If 1 is not available, fresh frozen plasma, danazol or tranexamic acid.	85
VIII-What should be the preferred option for long-term prophylaxis? (any of the below)	
1. Lanadelumab.	100
2. C1-INH.	92

(continued)

Consensus Statement	Consensus Percentage
3. Berotralstat.	100
4. Attenuated androgens, if 1–3 are not available.	100
5. Tranexamic Acid, if 1–3 are not available.	85

Table 2. (Continued) Middle East consensus recommendations for the treatment of HAE (percentage agreement)

In women, menstruation can be a trigger for HAE attacks, and nearly one-third of women have increased number of attacks during and after menopause.[25] However, in ~55% of female patients with HAE, menopause does not alter the disease activity. It is recommended to avoid menopausal hormone replacement therapy in females with HAE as estrogens may exacerbate the condition. Estrogens should also be avoided for contraception. Instead, barrier methods, intrauterine devices, and progestin can be used.[26]

Experiencing angioedema attacks in young age is mostly associated with increased frequency and severity of attacks during pregnancy.[27,28] In addition, women with C1–INH-HAE who reported mechanical trauma-triggered attacks before pregnancy experience more attacks during all 3

Consensus Statement	Consensus Percentage
IX-What should be done differently in women with HAE, especially during pregnancy, lactation, reproductive age, menopause?	
1. C1 inhibitor is the treatment of choice in pregnant and lactating women.	100
2. Attenuated androgens should not be used during pregnancy as they cross the placenta and may result in virilization of the foetus.	100
X-What should be the approach to the Diagnosis and Management of HAE in children? What would be the key differences as compared to adults?	
1. The diagnostic workup in children suspected to have HAE is the one used in adults.	100
2. All children with a family history of HAE should be tested for HAE.	100

Table 3. HAE consensus recommendations for Middle East: Special population (percentage agreement)

Region / Availability of Medicine	UAE	Lebanon*	Qatar	Oman	Kuwait	KSA
Tranexamic Acid	✓	✓	✓	✓	✓	✓
Danazol	✓	✓	✓	✓	✓	✓
Lanadelumab	✓	✓	✓	✓	✓	✓
Icatibant	✓			✓	✓	✓
C1 esterase inhibitor	✓		✓	✓	✓	✓
Berotralstat	✓					✓
* In Lebanon, Lanadelumab is registered but not yet available at the time of submission, C1 esterase inhibitor can be imported on special request and case by case						

Table 4. HAE treatment options available in Middle East

trimesters of pregnancy. Furthermore, pregnant women with C1–INH-HAE reported a higher frequency of angioedema attacks during the last trimester.[27] The abdomen is a frequently reported site for attacks in pregnancy, potentially secondary to stretching of the uterus or fetal movement. Pregnant women with abdominal HAE attacks need to be counselled to maintain a low threshold to contact their obstetrician.[27,29]

Multidisciplinary care is important and should include the treating physician, obstetrician, midwife, and anesthesiologist. An individualized treatment plan or strategy for each HAE patient with clear recommendations should be sent to the obstetrician if STP is to be considered prior to delivery. Home delivery should be avoided to minimize the risk for mother and newborn. While STP is not routinely indicated prior to vaginal delivery, this will depend on the severity of patient's symptoms. The C1–INH concentrate should be available during delivery in case acute symptoms develop and for at least 48 h thereafter. At least 2 doses of on-demand C1–INH should be available during and after childbirth. If the delivery requires vacuum or forceps, a dose of intravenous pd-C1-INH concentrate should be considered. If a planned caesarean delivery is required for patients with HAE, a dose of pd-C1-INH concentrate should be given, and general anesthesia (GA) with endotracheal intubation should be avoided, if possible, as it may produce laryngeal edema. Intubation and GA should be avoided, and epidural anesthesia is preferred.[29] Lanadelumab and berotralstat are not approved for pregnant women as LTP (Table 3).

The experts discussed that, in children, recurrent abdominal pain or documented soft tissue swelling by endoscopy/radiological studies or angioedema without wheals should encourage suspicion of HAE. It is also important to remember that erythema marginatum is frequent in the pediatric population. If a child is diagnosed with HAE, education of pediatric patients and their family members about HAE symptoms, precautions, and when to seek medical advice is essential[30] (Table 3).

In regards to treatment of HAE in children, pd-C1-INH can be used for the treatment of acute attacks.[31] Icatibant is also approved for children aged 2 years and above with modified dosage based on body weight. If pd-C1-INH or Icatibant are not available, solvent/detergent-treated plasma (SDP) is preferred over FFP; however, both can be considered. FFP (10–15 ml/kg) can be used at any age.[32] Androgens should be avoided in children with HAE, and anti-fibrinolytics (tranexamic acid 2–40 mg/kg) are preferred over androgens due to their superior safety profile.[28] In regard to LTP, the indications for treatment in adolescents are the same as in adults. Lanadelumab or berotralstat may be used for patients aged 12 years and above. Lanadelumab is administered at a dose of 300 mg every 2 weeks and extended to every 4 weeks in asymptomatic patients. Berotralstat's recommended maximum dosage is 150 mg once daily.[33,34]

Overall, the Middle East consensus recommendations on diagnosis and management of HAE are in line with those of the global guideline.

DISCUSSION

These consensus recommendations address a unique set of challenges in the Middle East region related to patient awareness, diagnostic setup, treatment availability, and accessibility for HAE management.

Our recommendations, therefore, provide detailed guidance for the diagnostic work-up and management of HAE, empowering the healthcare professionals to act timely and thereby reduce the interval between onset of symptoms, diagnostic confirmation, and treatment initiation.

We encourage experts in other geographical regions to execute a similar process and develop regional adaptions of the global WAO/EAACI guideline. This can help to address specific regional challenges for achieving the highest treatment goal, that is, to minimize the HAE attack frequency and intensity and restore better quality of life to patients with HAE.

Finally, timely updates to these recommendations based on emerging clinical trial data and real-world evidence are warranted.

CONCLUSION

To our knowledge, this is the first consensus recommendation for HAE diagnosis and

management in the Middle East. Having a Middle East-specific adaptation of the global guideline promises to improve the approach to HAE management and healthcare for patients with HAE across the region.

Abbreviations

AAS; Angioedema activity score, AECT; Angioedema Control Test, AE-QoL; Angioedema Quality of Life Questionnaire, C1–INH; C1 Inhibitor, FFP; Fresh Frozen Plasma, GA; General Anesthesia, HAE; Hereditary Angioedema, LTP; Long-Term Prophylaxis, nC1-INH-HAE; Normal C1–INH HAE, pd-C1-INH; Plasma-Derived C1-Inhibitor, SDP; Solvent/Detergent-Treated Plasma, STP; Short-Term Prophylaxis, UAE; United Arab Emirates, WAO/EAACI Guideline; World Allergy Organization (WAO)/European Academy of Allergy and Clinical Immunology (EAACI) Guideline.

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Role of contributors

Prof. M Maurer was responsible for the concept and design of the Delphi voting process, moderating the voting panel, and preparation of the manuscript.
Dr. M Abuzakouk, Dr. M Al Ahmad, Dr. W Al-Herz, Dr. H Alrayes, Dr. S Al-Tamemi, Dr. R Arnaout, Dr. H Binghadeer, Dr. R Gutta, Dr. C Irani, Dr. H Mobayed, Dr. I Nasr, Dr. H Shendi, Dr. F Zaitoun were involved as a Delphi voting member and responsible for Delphi outcome data analysis and interpretation, Critical input and revision of the manuscript.
All authors have approved the final version of manuscript and all authors take responsibility for all aspects of this work ensuring accuracy and integrity of work.

Declaration of competing interest

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Ethics statement

The authors declare that the study was conducted in accordance with the principles in the Declaration of Helsinki (7th version, 2013). The patient consent to participate is not applicable here.

Availability of data and materials

The data related to HAE recommendation statements reaching consensus is incorporated in the manuscript (Tables 1–3). Data related to HAE recommendation statements that did not reach consensus is available in supplementary material. No other additional data was generated besides these.

Submission declaration

We confirm that the manuscript is original, has not been published before, is not currently being considered for publication elsewhere. All authors agree to the publication.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.waojou.2022.100729.

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