ORIGINAL ARTICLE

Consensus on diagnosis and management of hereditary angioedema in Greece

Diagnosis and treatment of angioedema

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Summary

HAE is a rare disease manifesting with recurrent attacks of disabling and potentially life-threatening angioedema for which early diagnosis and effective therapy are critical. Recent scientific progress and the development of novel therapeutic options has engendered multiple important changes in the diagnosis and management of the disease. In an attempt to encourage and facilitate the use of this progress for all patients, the Hellenic Society of Angioedema has undertaken the effort to develop consensus recommendations for the diagnosis, treatment and management of hereditary angioedema in special patients' groups. To this aim a panel of 11 experts was assembled

and a modified Delphi method was used. After a comprehensive review of relevant literature from the last five years retrieved from Medline, the initial text of the recommendations was formulated and consensus was sought among the experts. The consensus included statements that were agreed by more than 80% of the experts. This article presents the 24 consensus recommendations that were finally formulated.

Key words

C1-esterase inhibitor deficiency; hereditary angioedema; recommendations; short-term prophylaxis; unknown hereditary angioedema.

1. Introduction

The term angioedema describes a clinical phenotype characterized by localized and self-limiting oedema of subcutaneous and submucosal tissues, caused by the transient release of vasoactive mediators and subsequent increase in vascular permeability. In the majority of cases, the appearance of angioedema is accompanied by wheals, either within the context of allergic reactions or in patients with acute or chronic urticaria. Less commonly, this phenotype occurs in the absence of urticaria, manifesting as recurrent episodes of oedema lasting up to 5 days, in which case the term angioedema refers to a distinct disease, which may be hereditary or acquired (2).

The most common cause of HAE is mutations in the *SERPING1* gene, which encodes the production of the C1INH inhibitor. C1INH is a regulatory protein of the complement system, the contact system, coagulation, and fibrinolysis. C1INH deficiency due to mutations in *SERPING1*, results in the overproduction of bradykinin, leading to increased sudden, vascular permeability and the formation of localized edema that is self-limiting (3, 4).

Mutations associated with HAE-C1INH in the *SERPING1* gene result in the production of a protein that is not effectively secreted, leading to reduced concentrations of C1INH in the plasma. This specific disorder characterizes 80-85% of cases reported as HAE Type I. In the remaining 15-20% of cases, mutations are primarily located in the region encoding the enzymatic center of C1INH, resulting in the production of a dysfunctional C1INH protein. In these cases, the antigenic levels of C1INH in the plasma are normal, but the levels of the protein, measured based on its functionality, are reduced. The type of disease caused by these mutations is referred to as HAE Type II (3, 4).

The age of HAE-C1INH onset, the frequency, localization, and severity of episodes are unpredictable and vary widely both among different patients, even if they belong to the same family, and throughout the life of each individual patient. As a result, the disease significantly impacts the quality of life for patients and their families. Particularly dangerous is the involvement of the upper respiratory tract, which can lead to death from asphyxiation, as well as intra-abdominal localization, mainly affecting the intestinal wall, often resulting in misdiagnoses or unnecessary surgical interventions (5).

In addition to HAE caused by C1INH deficiency, there are forms of the disease characterized by normal antigenic and functional levels of the protein, referred to as HAE with normal C1INH (HAE-nC1INH) (6, 7). The responsible genetic defect has been identified in a small percentage of these cases. The most commonly recognized causes of HAE-nC1INH are mutations in *F12*, the gene for coagulation factor XII and *PLG*, the gene for plasminogen, while cases in individual families have also been identified, members of which suffer from HAE attributed to mutations in the *ANGPT1*, the gene for angiopoietin-1; *KNG1*, the gene for kininogen-1; *MYOF*, the gene for myoferlin; *HS3ST6*, the gene for heparan sulfate glucosamine 3-O-sulfotransferase-6;

CPN, the gene for carboxypeptidase N, and *DAB2IP*, the gene for disabled homolog 2 interacting protein. In the majority of cases of HAE-nC1INH (possibly around 75%), however, the underlying genetic defect has not yet been determined. These cases are collectively referred to as angioedema of unknown cause (AE-UNK) (8, 9).

Strong evidence supports that the pathogenetic mechanism of some forms of HAE-nC1INH (e.g., HAE-FXII) is directly involved in the metabolism of bradykinin. In contrast, in other forms (e.g., HAE-ANGPT1, HAE-MYOF, HAE-HS3OST6), there seems to be no direct involvement of bradykinin, but genetic defects imply some dysfunction of the endothelium (10).

Although at the population level, patients with HAE-nC1INH, compared to those with HAE-C1INH, exhibit some differences in the clinical manifestation of the disease, at an individual level, these two forms are practically indistinguishable (11).

Diagnostic challenges also arise regarding the differentiation of HAE from acquired forms of angioedema. The most common form of AAE is associated with drug intake, primarily ACE inhibitors (AAE-ACEI). AAE-ACEI is not dose-dependent, may appear even years after the start of treatment, is characterized by normal levels of C4 and antigenic and functional C1INH, while episodes may persist for months after discontinuation of the drug (12).

Less commonly, AAE is due to acquired deficiency of C1INH, either because of increased consumption, which is usually associated with lymphoproliferative disorders, or due to its inactivation by autoantibodies against C1INH. In many cases of AAE, the appearance of angioedema precedes, even for several years, the manifestation of the primary disease (13, 14).

The difficulty in interpreting manifestations of HAE or/and AAE, including oedema and relapsing abdominal pain, can lead to delayed diagnosis and, consequently, ineffective management of the disease. Therefore, early diagnosis, effective treatment of acute episodes, and short-term and long-term prevention are critical steps in managing HAE.

2. Materials & Methods

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

Facilitator and panel selection: An expert panel of 10 members, representative of Greece and an international expert in HAE management, who 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 in January 2023. The search engine used was Ovid MEDLINE and the keywords included were long- and short-term prophylaxis and acute treatment of attacks in HAE Type I, HAE Type II, or HAE-nC1INH.

Studies were limited to English language publications that were published and indexed in MEDLINE. The complete search strategy and inclusion criteria include:

- English language publications
- Original results published in an indexed journal referring to:
    - Disease: type I or type II hereditary angioedema or hereditary angioedema
    - Type of publication: guidelines referring to (at least one of):
        - Acute treatment

- Long-term prophylaxis
- Short-term prophylaxis

169 unique results were identified in the search, and two reviewers independently applied the predetermined inclusion criteria to the titles and abstracts. If either reviewer indicated that a result required further consideration at the title and abstract review stage, the full text document was retrieved and reviewed.

103 results were retrieved and reviewed in full text. 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 Greece based on this systematic literature review and expert opinions. Questionnaire development was carried out from July 2023 to September 2023.

3. Questionnaire dissemination and collection of responses: A questionnaire with 10 questions was disseminated via email to the 10 HAE experts in September 2023. The experts were asked to provide individual input regarding the different recommendations based on their clinical expertise. The responses to the questionnaire were recorded via email.

4. Consensus meeting: A virtual consensus meeting was organized on October 23rd, 2023 wherein the experts voted on each consensus recommendation statement for HAE management in Greece. Statements that received an agreement of >80% 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. This process was carried out using anonymous polling.

3. Results

All experts on the Delphi panel were allergists-immunologists with vast experience in managing HAE patients. 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.

RECOMMENDATIONS FOR DIAGNOSIS OF HAE

3.1. What should prompt the diagnostic workup of HAE?

Recommendation 1: Indications for appropriate laboratory testing for HAE include:

a. A positive family history

b. Recurrent episodes/unprovoked episodes of non-pitting, non-pruritic oedema affecting three main areas: subcutaneous tissue (face, upper or lower extremities, genitals), abdominal organs (stomach, intestines, bladder), and the upper airway (larynx, tongue)

c. Unexplained recurrent abdominal pain.

d. Absence of wheals. (Note: Patients with HAE often have erythema marginatum).

e. Failure of attacks to respond to antihistamines, glucocorticoids, or epinephrine.

f. Swelling attacks that are triggered by minor physical trauma such as dental work, prolonged sitting or standing, medications.

g. Difficulty in breathing due to airway swelling (edema) especially if triggered by trauma e.g., intubation.

h. Exploratory laparotomy with unrevealing diagnosis.

i. Onset of symptoms in childhood/adolescence and worsening at puberty.

3.2. How should disease activity of HAE be assessed?

Recommendation 2: Criteria for assessing the severity of the disease are:

a. Frequency of attacks.

b. Effect of the attacks on normal function and routine activities (e.g., school, work, ability to perform house chores, hobbies, sports etc.).

c. Requiring hospitalization.

d. Severity of attacks (need for emergency room visits or on demand therapy).

3.3. What should be the diagnostic approach to confirm HAE?

Recommendation 3: Based on clinical indications, laboratory investigation for HAE should begin with determining the plasma concentration of C4 and the antigenic and functional levels of C1INH

HAE-C1INH is significantly more common than HAE-nC1INH. Therefore, based on clinical indications, laboratory testing should initially focus on diagnosing HAE-C1INH.

Determining the concentration of C4 is useful when the measurement of C1INH concentration is not readily available. Usually, C4 is found to be decreased even during intervals between episodes, although there are reported cases of HAE-C1INH with normal C4 (15). In cases where the concentration of C4 is determined within normal

limits, the measurement should be repeated during an episode. However, the evaluation of C4 concentration values should be approached with caution, given the relatively common deficiency and high thermal sensitivity of the factor, and considering that decreased C4 levels are found in many other conditions.

To confirm the diagnosis of HAE-C1INH, it requires determining the functional concentration of C1INH in the plasma and retrieving it at levels below 50% of normal (16). By determining the levels of C1INH, the distinction between HAE Type I and HAE Type II is also achieved. In HAE Type I, along with the functional concentration, the antigenic concentration of the protein is also decreased, whereas in HAE Type II, it is normal or even increased.

When assessing the functional levels of C1INH, the method of determination should be taken into account, as the chromogenic assay has a positive predictive value of 98% and a negative predictive value of 100%, while the corresponding values for ELISA are 100% and 62% (17).

Recommendation 4: For the diagnosis of HAE-C1INH, it is necessary to find reduced levels of C4 and antigenic or functional levels of C1INH in the plasma. In patients who test positive, repeated testing is suggested to confirm the diagnosis.

Recommendation 5: All children with a family history of HAE should be tested for HAE.

When one of the parents has HAE-C1INH, their children have a 50% chance of having the disease. In most cases, HAE-C1INH manifests during childhood or adolescence. However, there are cases where the disease first appears at a much older age. Early diagnosis of C1INH deficiency can protect the children of families with a history of

angioedema from the potential risk of asphyxia or unnecessary surgical interventions during the initial onset of the disease.

In children under one year of age, concentrations of C4 and C1INH are typically lower than those found in adults. Therefore, corresponding assessments should be made after the age of one.

Recommendation 6: Individuals with a family history of HAE and reduced concentrations of C4 and antigenic and/or functional C1INH who do not exhibit clinical symptoms of the disease should be classified as having C1INH deficiency rather than HAE-C1INH.

Recommendation 7: Check C1q level if symptoms are late onset and there is no family history, and if C4 level is low, C1INH level is low, C1INH function is low. Low serum C1q suggests acquired angioedema and should prompt diagnostic workup for underlying autoimmune, hematological or myeloproliferative disorder.

In patients with a diagnostic challenge between hereditary and acquired C1INH deficiency, the determination of C1q is useful, as its concentration is reduced in 75% of cases of acquired angioedema with C1INH (18, 19). However, there have been reported cases of HAE-C1INH where C1q is reduced, and transient C1q deficiency is also observed due to the circulation of autoantibodies against the factor and during the course of viral infections (20-22).

3.4. When is genetic testing required?

Recommendation 8: In most cases, genetic testing is not required for the diagnosis of HAE-C1INH.

Finding reduced levels of C4 and functional C1INH diagnoses C1INH deficiency with a specificity of 98%-100% (23) and negative prognostic value of 96% (24). On the other hand, identifying the pathogenic mutation through the examination of the *SERPING1* gene, is not feasible in a percentage ranging from 3.8% to 17.9% (4). The failure rate of determining the pathogenic mutation of *SERPING1* depends, in part, on the use of methods specifically designed to analyze the entire length of this particular gene (25). Following these, genetic testing offers no advantage in diagnosing HAE-C1INH.

However, genetic testing of the *SERPING1* gene may prove useful in the following cases (26): 1) When the results of C4 measurements or/and antigenic and functional C1INH are unclear. 2) In children under one year of age. 3) To confirm the diagnosis of C1INH deficiency in asymptomatic individuals. 4) To confirm the diagnosis of HAE-C1INH in patients with a negative family history. 5) To exclude the diagnosis of acquired angioedema, especially in patients with normal C1q concentrations. 6) Pre-implantation testing.

Recommendation 9: Patients with a strong clinical suspicion of HAE and normal levels of functional C1INH should undergo genetic testing to search for mutations associated with HAE-nC1INH.

The diagnosis of HAE-nC1INH forms due to mutations in the *F12, PLG, ANGPT1, KNG1, MYOF, HS3OST6, CPN* and *DAB2IP* genes can only be made through genetic testing. Since mutations in the *ANGPT1, KNG1, MYOF*, *HS3OST6, CPN* and *DAB2IP* genes have been identified only in individuals from isolated families, genetic testing for suspected HAE-nC1INH is sufficient to focus on searching for mutations in the *F12*

and *PLG* genes. After genetic testing, the diagnosis of HAE-FXII and HAE-PLG has been confirmed in many cases, initially classified as acquired idiopathic non-histaminergic angioedema or AE-UNK (27-29).

RECOMMENDATIONS FOR HAE TREATMENT

Since the severity of the disease shows significant variability over time, the most appropriate treatment for each patient should be determined at each specific moment. The choice of suitable therapy is multifactorial and depends on the severity of the disease, age, gender, comorbidities, and patient preferences. Regular revision of the treatment approach is advised to be considered due to disease variability.

It is important to provide information on all available treatment options, their effectiveness, and safety. Table I lists all available therapies in Greece.

The decision of selecting a choice of treatment is multifactorial and it varies based on age, gender, co-morbidities, patient preference etc. Therefore, it is important to know the available treatment choices and their efficacy and safety profiles. The route and ease of administration should also be carefully considered. Table I lists all the HAE treatment management available in Greece at the time of this publication.

3.5. How should patients be monitored for the course of their disease?

Recommendation 10: The course of the disease and the response to prophylactic treatment are monitored through regular patient examinations and the use of a diary. Particular attention is given to the need for therapeutic intervention during disease episodes and the occurrence of drug-related adverse events.

4.1. How can one determine whether treatment should be on-demand?

When and how is on-demand treatment administered for angioedema episodes?

Recommendation 11: All angioedema episodes are eligible for on-demand treatment.

The goal of treating episodes is to minimize morbidity, prevent life-threatening situations, and improve quality of life. The decision regarding which episodes require treatment should be based on these goals rather than solely on identifying the episode (30, 31).

Recommendation 12: Episodes involving the upper airways should be addressed promptly. In cases of progressively worsening laryngeal oedema, even with immediate pharmacological intervention, intubation or cricothyrotomy/tracheostomy is recommended.

Oedema of the upper airways is an emergency situation as it can lead to asphyxia (32-34). In Greece, at least 15 cases of deaths from laryngeal oedema in patients with HAE have been recorded (35). Immediate administration of treatment is absolutely necessary, while emergency airway management may be required through intubation or surgical intervention (36).

Recommendation 13: Episodes should be treated as quickly as possible. Self-administration of drugs significantly reduces the treatment delay. All patients should always have with them medications to address at least 2 episodes.

Early treatment of acute episodes achieves more effective management compared to delayed administration (37-39). As early treatment is facilitated by self-administration,

patient education in this regard is encouraged. All available episode treatment options in Greece have studies and approval for self-administration (40, 41).

Since the frequency of episodes may vary over time, it is important for patients to always carry all necessary medications with them. It is recommended to always have a supply for the management of at least 2 episodes (42).

Recommendation 14: The on-demand treatment for an acute attack of HAE in Greece should be:
a. C1–INH concentrate.
b. Icatibant, a synthetic bradykinin B2-receptor antagonist.
c. Fresh frozen plasma (FFP) if none of the above is available.

For the treatment of acute episodes, pdC1INH is administered intravenously, and icatibant is given subcutaneously. These are highly effective medications for managing episodes with rapid onset of action (usually within 30 minutes) and favorable safety profiles (43, 44). The basic characteristics of these medications are listed in Table I. In Greece, they are prescribed through the electronic prescription system, along with the necessary medical certificate. They are provided free of charge by special pharmacies of EOPYY (National Organization for Healthcare Services Provision) or hospital pharmacies. In case neither of the two mentioned drugs is available, the administration of FFP (Fresh Frozen Plasma) is recommended (45). Androgens and anti-fibrinolytic agents have NO role in the treatment of acute episodes (46).

Although controlled randomized studies have not been conducted for the treatment of HAE-nC1INH, there are reports suggesting the effectiveness of treatments used in HAE-C1INH (47, 48). Specifically, icatibant appears to be effective in bradykinin-mediated forms of angioedema (49).

4.2. When should we initiate short-term prophylaxis? What to use?

Recommendation 15: Short-term prophylaxis should be considered:

a. In patients who face medical interventions, surgery or otherwise increased risk of having an angioedema attack.

b. Whenever the upper airway is manipulated.

In particular, trauma and stress are known triggering factors for angioedema attacks. Dental surgical procedures in the oral cavity, in particular, can cause airway obstruction (50). Prophylactic treatment reduces the risk of developing angioedema (51, 52).

STP is required before interventional medical or dental procedures. The extent of local trauma may influence the decision to administer prophylactic treatment. STP may also be required before stressful events.

Recommendation 16: Short-term prophylaxis should be done with:

a. pdC1INH at a dose of 1000 units or 20 units/kg.

b. FFP and androgens can be used as second-line STP only if pdC1INH is not available."

Although data on its effectiveness are not sufficient, IV administration of pdC1INH is recommended as the first-line treatment for STP. Nevertheless, most reports confirm that the use of STP with pdC1INH is effective (51-54). The administration should take place as close to the intervention as possible, ideally 1-6 hours before. The exact dosage is not fully determined, but most experts consider that 1000 units or 20 units/kg provide satisfactory prophylaxis (55).

Attenuated androgens have been used in the past for STP. Danazol is used at a dose of 400-600 mg/day, starting administration 5-7 days before, and then continuing for another 2-5 days after the intervention or stress-inducing event (54, 56). Often,

prophylactic treatment regimens with androgens may cause significant adverse effects over time.

FFP can be used when there is no access to pdC1INH, and there is no time for androgen use. Tranexamic acid, which was used in the past, is no longer recommended by most guidelines (56, 57).

For HAE-nC1INH, there are no data at all regarding STP.

4.3. What should be the preferred option for long-term prophylaxis?

Recommendation 17: The goal of the treatment is complete control of the disease and improvement of the patients' quality of life.

The absence of episodes and complete control of the disease should be the ultimate goal of the treatment (58). Improvement in the quality of life, in some patients, is achieved only with LTP, meaning the administration of a stable medication regimen that reduces the frequency of episodes and diminishes the disease burden (59).

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

Recommendation 18: The following parameters should be used to determine the need for LTP:

a. Number of episodes

b. Severity of episodes.

c. QoL impairment.

d. Availability and ability to administer the on-demand treatment.

e. Presence of triggering factors (e.g., at work or at school).

f. Sites involved in attack.

g. Response to on-demand treatment.

h. Patient preference

i. Comorbid conditions.

The decision to start LTP must be individualized, addressing each patient's specific needs, and not relying on absolute criteria. Factors such as the frequency and severity of episodes, access to on-demand treatments, and comorbidities should be carefully evaluated. The disease burden and its impact on patients' quality of life should be systematically assessed. The use of certified tools to monitor disease activity and quality of life, such as Angioedema Activity Score (AAS), Angioedema Control Test (AECT) Angioedema Quality of life Questionnaire (AE-QoL), Hereditary Angioedema Clinical Questionnaire (HAE-CQ), is encouraged, and these tools have been translated and validated in Greek (59-63).

Successful LTP requires a high degree of compliance, and therefore, patient preferences should be taken into account (64). Since the severity of the disease varies over time, the need for initiating as well as discontinuing LTP should be regularly reevaluated.

Recommendation 19: For LTP, the following drugs are available:

a. pdC1INH

b. Lanadelumab

c. Berotralstat

d. Attenuated androgens, if the above options are not available.

e. Tranexamic Acid, if the above options are not available (a-c)

The drugs for LTP are divided into two categories:1) 1st line treatments including pdC1INH, Lanadelumab and Berotralstat, and 2) 2nd line treatments than can be considered if these three medications are unavailable, including attenuated androgens, and tranexamic acid treatment. The main characteristics of these drugs are mentioned in Table I.

The pdC1INH is administered either intravenously or subcutaneously. It is an effective and safe prophylactic treatment that reduces episodes and improves the quality of life (65, 66). Subcutaneous administration is superior in terms of side effects related to frequent venipunctures and is recommended for long-term use (67).

Lanadelumab is a human monoclonal antibody that inhibits plasma kallikrein, administered subcutaneously, and has been proven to be effective with good safety characteristics. Angioedema episodes and the need for on-demand treatments are significantly reduced (68, 69).

Berotralstat is a potent inhibitor of plasma kallikrein that works by binding to plasma kallikrein and blocking its proteolytic activity. It is administered orally and is suitable for long-term prophylaxis. It is an effective and safe drug with gastrointestinal side effects being the most common (70, 71).

In Greece, the supply of first-line therapies for long-term prophylaxis is done through pharmacies affiliated with the EOPYY and hospitals. This is facilitated through the electronic approval system, where a panel of specialists approves the necessity of their administration based on a request from the treating physician.

Attenuated androgens traditionally constituted the cornerstone of LTP, albeit not without serious dose-dependent side effects (72-74). In a study from the Greek

population, adverse effects were observed in approximately 70% of HAE patients receiving androgens for LTP (35). When used, they should be administered at the lowest possible dose. Their use in children and women should be avoided (75, 76). These are now considered second-line treatments, and their administration is limited to cases where first-line treatments are not available.

Anti-fibrinolytic agents, such as tranexamic acid, have been used in the past with relative success in LTP, especially in patients for whom androgens are contraindicated or have adverse effects (77, 78). They are not very effective, but they have good safety profiles. They are now considered second-line drugs and are used when no other LTP option is available.

LTP for patients with HAE-nC1INH has not been studied in randomized controlled trials. Despite the lack of experience, the need for long-term prophylaxis in these patients should be evaluated based on the specific circumstances of recommendation 18. Treatment with progestins in women, antifibrinolytics, pdC1INH, and Lanadelumab have been tested with conflicting results. Probably, HAE-nC1INH due to different mutations may require a separate approach due to the different mechanisms that cause angioedema (79-81).

RECOMMENDATIONS FOR SPECIAL POPULATIONS

5.1. What should be done differently in women with HAE, especially during pregnancy, lactation, reproductive age, menopause?

Recommendation 20: pdC1INH is the treatment of choice, both for acute episodes and for short-term and long-term prophylaxis in pregnant and lactating women.

C1 inhibitor is the treatment of choice in pregnant and lactating women.

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 (82).

Recommendation 21: Contraceptives and hormone replacement therapy with estrogen are contraindicated in women with HAE.

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 (83).

Experiencing angioedema attacks in young age is mostly associated with increased frequency and severity of attacks during pregnancy (84). In addition, women who reported mechanical trauma-triggered attacks before pregnancy experience more attacks during all three trimesters of pregnancy. The abdomen is a frequently reported site for attacks in pregnancy, potentially secondary to stretching of the uterus or fetal movement (85, 86).

The levels of C1INH decrease during pregnancy and return to normal after childbirth. Diagnosing new cases of HAE during pregnancy should be done with great caution, and diagnostic tests should be repeated after childbirth (87-89).

Intravenous pdC1INH is the drug of choice for both on-demand treatment of episodes and short-term or long-term prophylaxis during pregnancy. Although there is insufficient data, the continuation of LTP with subcutaneous pdC1INH should be done at the lowest effective dose (86, 90).

Androgens should be discontinued immediately upon confirmation of pregnancy, while tranexamic acid can continue to be used in cases where it is administered for LTP and is effective (91).

The use of lanadelumab and berotralstat during pregnancy is off-label and not recommended.

Although not recommended during pregnancy (see Table I), icatibant has been used in isolated cases without reported adverse reactions to the embryo (92). It can be used in emergency cases when pdC1INH is not available.

In cases where short-term prophylaxis is required, and pdC1INH is not available, FFP may be used (93, 94).

The care of a pregnant woman with HAE requires interdisciplinary collaboration among multiple specialties (treating physician, obstetrician, and anesthesiologist) who need to develop a specific plan with clear guidelines for cases where urgent management of an episode or STP is required before delivery. Although each case must be individualized, prophylactic treatment is generally not required in a normal delivery (85). pdC1INH must always be available during delivery and for at least 48 hours afterward.

Recommendation 22: In case of a cesarean section, pdC1INH should be given prophylactically.

In case of a cesarean section, pdC1INH should be given prophylactically. Epidural anesthesia is preferred over general anesthesia to avoid potential airway injuries from intubation (86).

Breastfeeding is often accompanied by an increase in the frequency of the mother's episodes, the management of which should be individualized, taking into account the impact of treatment on the newborn (94).

For patients with HAE-nC1INH, there are no clinical data. Successful LTP with pdC1INH during pregnancy has been reported in 3 patients (2 with HAE-FXII and 1 with AE-UNK) (95). There are also reports of successful LTP with tranexamic acid in patients with HAE-FXII.

5.2. What should be the approach to the Diagnosis and Management of HAE in children?

Although the genetic defect is present from birth, its clinical expression is very rare in newborns and infants. Episodes can occur at any time, but more commonly begin during childhood or adolescence (96, 97). The frequency and severity of episodes typically increase during adolescence (97).

Data from the Greek patient registry indicated that approximately half of the patients experienced angioedema attacks at an age younger than 8 years old (35). The fact that in more than half of the children, the first episodes were abdominal makes the suspicion of diagnosis particularly challenging, especially in cases without a family history.

The erythema marginatum, a fleeting serpiginous erythema that develops as a prodromal sign, appears more frequently in children and is often mistakenly perceived as urticarial rash (98, 99).

Therapeutic management in children, as well as in adults, includes on-demand treatment for episodes, short-term and long-term prophylaxis with medications indicated for pediatric use. The dosage regimens of these medications are detailed in

Table I. It is noted that new clinical studies are constantly being conducted, modifying downward the age limits for these drugs (100).

HAE-nC1INH rarely occurs in childhood. However, approximately 10% of patients with HAE-FXII exhibit symptoms before the age of 12 (101).

Recommendation 23: The treatment of episodes in children should be done with pdC1INH or icatibant (above 2 years old).

A specific written treatment plan in collaboration with the parents is necessary. Both pdC1INH and icatibant are effective and safe medications for children. Supportive treatment with fluid replacement for intestinal angioedema and airway management for laryngeal angioedema may be required (102, 103).

Family education about triggering factors and the treatment of acute episodes is crucial. The goal of treatment is the complete normalization of children's lives and their participation in all age-appropriate activities. When selecting sports, both the children's desires and the specifics of the condition should be taken into account. School educators and healthcare personnel must be informed about the disease and have a written management plan. pdC1INH and icatibant should always be available at home, school, on trips, and during travels.

Prophylactic strategies may be utilized for both short-term and long-term management. The objective of short-term prophylaxis is to minimize the risk of edema in pediatric patients exposed to stressors or undergoing procedures (e.g., medical, dental, or surgical interventions) that may provoke an episode. In contrast, long-term prophylaxis is directed toward reducing the incidence, severity, and cumulative impact of angioedema episodes.

For children and adolescents, lanadelumab, pdC1-INH I (s.c.) and berotralstat are approved as LTP as analyze in table I.

Recommendation 24: All patients with HAE should be vaccinated for hepatitis A and B

Since all patients with HAE are candidates for plasma-derived product therapy, they should be vaccinated for hepatitis A and B (97, 104, 105).

Table I. Characteristics of the HAE treatments available in Greece

4. Discussion and conclusions

Differences between countries in terms of the epidemiology of angioedema, the availability of drugs and especially the access of patients to health services, require the adaptation of international recommendations on the disease to the conditions of each country. The rapid research developments in this field have accentuated this need. We believe that the above recommendations will help Greek physicians managing patients with angioedema to provide them with the most up-to-date diagnostic and therapeutic support.

Compliance with Ethical Standards statements:

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Table I. Characteristics of the HAE treatments available in Greece

Drug	Indication	Dose	Mechanism	Possible side effects
pdC1-INH IV[+]	Episode	Adults and children 20 units/kg	Replacement, beneficial impact on all systems where C1INH acts	Very rarely: Hypersensitivity reactions- Anaphylaxis Thromboembolic events have been reported with very high doses Theoretically: Risk of transmission of infectious agents Complications from frequent venipuncture when using IV for LTP Administration is allowed during pregnancy and lactation
	STP	1000 units ή 20 units/kg once 1-6 hours before		
	LTP	1000 U every 3-4 days Doses >2500 U IV in proportion to the response, corresponding measures may be required		
pdC1INH SC[++]	LTP	60 IU/kg SC twice a week		
Icatibant [@]	Episode	Adults and children >65 kg 30 mg/3 ml SC (the dose can be repeated in 6 hours - up to 3 administrations per 24 hours) Children >2 years and >12 kg from 10-25 mg, depending on body weight	Selective antagonist of type 2 bradykinin receptor	Very frequently: Injection site reactions Caution in patients with acute ischemic heart disease, unstable angina and very recent stroke Not indicated in pregnancy and lactation
Lanadelumab[#]	LTP	300 mg SC every 2 weeks for adults and adolescents >12 years of age. Possible increase of the interval to 4 weeks if the patient is episode free for 6 months.	Monoclonal antibody Plasma kallikrein inhibitor	Very frequently: Injection site reactions Rarely: Hypersensitivity reactions, immunogenicity, development of neutralizing antibodies (ADA), transaminase

Drug	Indication	Dose	Mechanism	Possible side effects
		There is recent (2023) FDA approval for children >2 years of age [98]		elevation, aPTT elevation without bleeding - related adverse events Not indicated in pregnancy and lactation
Berotralstat[$]	LTP	150 mg per os daily Adults and adolescents >12 years of age weighing ≥40 kg	Plasma kallikrein inhibitor	Very frequently: Side effects from gastrointestinal, headache Rarely: Increase in transaminases, QT prolongation and interaction with cyclosporine, BCRP inhibitors and drugs metabolized on CYP3A4 Not indicated in pregnancy and lactation Contraindicated in children
Danazol [71]	Second - line LTP	Adults: The lowest possible dose is recommended 200 mg/per os daily (from 100 mg/per os) from 100 mg every 3 days to 600 mg/day)	Unknown	Very frequently: Virilization, weight gain, acne, menstrual disorders Frequently: Headache, myalgia, libido disorders, increased transaminases, hyperlipidemia, hypertension Rarely: Hepatitis, cholestatic

Drug	Indication	Dose	Mechanism	Possible side effects
				jaundice, hepatocellular adenoma Not indicated in pregnancy and lactation
Tranexamic acid [103]	Second - line LTP	Adults: 1 g per os 2 times a day (from 500-4000 mg total daily) Children: 20 mg/kg 2 times daily From 20 mg/kg to 75 mg/kg total daily)	Inhibition of plasminogen activation and plasmin activation	Frequenly: Nausea, gastrointestinal disorders, myalgia increase in CPK Theoretically: Risk of thrombosis