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Special Article

International consensus on hereditary and acquired angioedema

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A R T I C L E   I N F O

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**Introduction**

In light of the remarkable progress recently achieved in our understanding of angioedema, the American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology, European Association of Allergy and Clinical Immunology, and World Allergy Organization have joined together to promote communication about diagnosis and management of angioedema on a global scale. Within the framework of this collaboration, termed the International Collaboration in Asthma, Allergy, and Immunology (ICAALL), a series of International Consensus (ICON) documents are being developed to serve as a resource and to support physicians and other health care professionals in caring for patients with allergic and immunologic disorders.

This document was developed by an international workgroup, formed to develop an ICON document in which the pathogenesis, prevalence, clinical manifestations, diagnosis, and management of angioedema are described. Angioedema may occur with or without concomitant hives. The consensus of the leadership of the 4 societies and the author group was that based on improvements in our understanding of hereditary angioedema (HAE) in recent years and the recent introduction of 5 HAE-specific drugs, the goals of ICAALL would best be served by focusing this ICON on angioedema occurring without concomitant hives and more specifically by concentrating primarily on C1 inhibitor (C1INH) deficiency syndromes. The author group was subdivided based on topic preference to generate specific sections of the ICON. Content was derived from literature searches, published guidelines, and clinical expertise. Drafts of the ICON were peer reviewed within the author group and subsequently by a steering group of the 4 societies. Where evidence gaps were encountered, content was determined by consensus of the author group.

**Definition and Pathogenesis**

Angioedema is a vascular reaction of the deeper layers of the skin and mucous membranes, with localized blood vessel dilatation and increased permeability that result in tissue swelling.\(^1\) The swelling is asymmetric, nondependent, and nonpitting and resolves without scarring or discoloration. The angioedema is caused by a temporary increase in vascular permeability mediated by release of one or more mediators. The specific cellular mechanisms that increase endothelial permeability during angioedema have not been determined. However, histamine and bradykinin, the mediators responsible for most angioedema, act through G protein–coupled receptors expressed on cell membranes. Bradykinin enhances vascular permeability via phosphorylation of vascular endothelial cell cadherin and activation of phospholipase, leading to intracellular calcium mobilization and eventually allowing flow of plasma from the vascular to the interstitial compartment and edema formation.\(^2,3\) Angioedema can involve virtually any site, including extremities, genitourinary tract, bowel, face, oropharynx, or larynx.\(^4\)

Bradykinin is the mediator responsible for angioedema in patients with HAE.\(^4\) High levels of bradykinin are present in plasma from patients with angioedema due to C1INH deficiency.\(^4\) Bradykinin is cleaved from high-molecular-weight kininogen by plasma kallikrein, which is physiologically generated from its zymogen by activated factor XII (FXII) on contact system activation.\(^5\) The mechanism leading to contact system activation in vivo has not been determined. C1INH intervenes at several steps in controlling contact system activation, being an important inhibitor of FXII and plasma kallikrein. Reduced levels or impaired function of C1INH can lead to excessive bradykinin release and angioedema.\(^5,6\)

Bradykinin–mediated angioedema can be either hereditary or acquired (Table 1). Two forms of HAE have been defined\(^3-9\): (1) HAE due to C1INH deficiency and (2) HAE with normal or near-normal antigenic and functional levels of C1INH. HAE due to C1INH deficiency can be further divided based on the C1INH antigenic level: type I HAE (HAE-1) is characterized by low antigenic and functional C1INH levels, whereas type II HAE (HAE-2) is due to C1INH dysfunction and is characterized by normal (or elevated) antigenic but low functional C1INH levels. There are also 2 subtypes of HAE with normal C1INH, either associated with a mutation in the FXII gene or of unknown cause. Mutations of the FXII gene have been identified in some families, but the pathophysiology is still undefined. Acquired C1INH deficiency (ACID) is frequently associated with lymphoproliferative diseases and/or autoantibodies against C1INH that may be responsible for C1INH consumption. Autoimmune disorders (eg, systemic lupus erythematosus) have also been described in association with ACID. Angioedema may also be caused by an angiotensin-converting enzyme inhibitor (ACEI), which interferes with bradykinin degradation.\(^4\)

**Prevalence**

HAE-1/2 is a rare autosomal dominant disorder that affects approximately 1:50,000 individuals, with reported ranges from 10,000 to 1:150,000.\(^10\) Many different mutations of the SERPING1, which codes for C1INH, are known to cause HAE-1/2. Approximately 85% of the mutations result in HAE-1, and 15% of them result in HAE-2; de novo mutations of SERPING1 account for approximately 20% to 25% of cases.\(^10\) HAE with normal C1INH is less frequent than HAE-1/2.

**Epidemiology**

There is no sex predominance in HAE-1/2.\(^10\) Most cases of HAE with normal C1INH are female. Data from recent studies in Japan

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Table 1: Classification of angioedema\(^4\)

<table>
<thead>
<tr>
<th>Category</th>
<th>Bradykinin mediated</th>
<th>Mast cell mediated, normal C1INH</th>
<th>Idiopathic, normal C1INH, negative inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C1INH deficiency/defect</td>
<td>Normal C1INH</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Positive inheritance</td>
<td>Negative inheritance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Positive inheritance</td>
<td>Negative inheritance</td>
<td></td>
</tr>
<tr>
<td>Disease</td>
<td>HAE-1, HAE-2</td>
<td>ACID</td>
<td>Drug-induced urticaria</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anaphylaxis, IgE-mediated urticaria</td>
</tr>
<tr>
<td>Occurrence of superficial wheals</td>
<td>Negative</td>
<td>Negative</td>
<td>Nonclassifed AE</td>
</tr>
<tr>
<td></td>
<td>Positive/negative</td>
<td>Positive/negative</td>
<td>Positive/negative</td>
</tr>
</tbody>
</table>

**Abbreviations:** ACEI, angiotensin-converting enzyme inhibitor; ACID, acquired angioedema due to C1 inhibitor deficiency; AE, angioedema; C1INH, C1 inhibitor; HAE-1, hereditary angioedema type 1 (due to C1 inhibitor deficiency); HAE-2, hereditary angioedema type 2 (due to C1 inhibitor defect).

\(^*\) Mast cell–mediated angioedema may occur with concomitant hives. Nonclassified implies that no cause has been identified. High-quality evidence indicates bradykinin is the mediator responsible for angioedema in HAE-1/2 and in association with ACEI; for HAE with normal C1INH levels, the role of bradykinin is assumed, and additional evidence is required to support this.
Abbreviations: ACID, acquired angioedema due to C1INH deficiency; ACEI, angiotensin-converting enzyme inhibitor; C1INH; C1 inhibitor; FXII, factor XII; HAE-1, hereditary angioedema type 1 (due to C1 inhibitor deficiency); HAE-2, hereditary angioedema type 2 (due to C1 inhibitor defect).

(132 patients), China (133 patients), and Brazil (210 patients) suggest a lower HAE prevalence in these countries than in Europe and North America. The reasons are unknown but may include underdiagnosis or a lower prevalence in Asian populations. HAE severity varies considerably, even in family members with the same gene mutation. The mean age at onset of symptoms is 8 to 12 years; 75% experience their first attack by the age of 15 years.

**Clinical Manifestations**

Compared with urticarial swelling, the swelling of angioedema is deeper and longer lasting, is nonpruritic, and may be painful. Although the appearance of the angioedema itself cannot establish the cause or specific diagnosis, details of the swelling may aid the clinician in distinguishing the different causes of angioedema. Table 1 and Table 2 list pertinent characteristics of angioedema as clues for potential diagnoses.

**HAE-1/2**

Angioedema attacks typically involve the extremities, genitourinary tract, bowel, face, oropharynx, or larynx. Attacks may last for 72 to 96 hours, are often severe and disabling, and may be associated with significant morbidity and risk for mortality. Extremity and abdominal attacks each account for almost 50% of all attacks, and more than 50% of patients experience at least one upper airway attack with risk for asphyxiation during their lifetime. The frequency of attacks is highly variable. Most often, patients present with symptoms during childhood, with a worsening of symptoms around puberty. Prodromal symptoms, such as fatigue, irritability, weakness, nausea, and erythema marginatum, precede an angioedema attack by several hours or up to a day in up to 50% of HAE patients. Symptoms may be worsened by stress, trauma, exogenous estrogens, ACEIs, menses, and possibly infections.

**HAE with normal C1INH**

The clinical presentation of HAE with normal C1INH resembles that of HAE-1/2, with the following key differences: fewer attacks with more attack-free intervals, higher percentage of cutaneous and facial attacks, lower percentage of abdominal attacks, lower percentage of multisite attacks, no erythema marginatum preceding attacks, and an older age of symptom onset. As noted in Table 1, evidence indicates the angioedema in HAE1/2 and angioedema associated with ACEIs are mediated by bradykinin; for HAE with normal C1-INH, the role of bradykinin is assumed. States of increased estrogen exposure due to either pregnancy or exogenous estrogen administration frequently exacerbate HAE with normal C1INH. Disease severity is typically more pronounced in women compared with men. Inheritance suggests an autosomal dominant pattern; however, penetrance appears to be lower than with HAE-1/2.

**ACID**

ACID is analogous in its presentation to HAE-1/2, except that a family history is lacking and angioedema generally develops after the age of 40 years.

**ACEI-associated angioedema**

Angioedema related to ACEIs has a strong predilection to involve the face, lips, and tongue. Angioedema affecting the bowels or extremities is less common. Risk of angioedema from ACEIs is higher in smokers, African Americans, and women; diabetes has been associated with lower risk. Angioedema most commonly occurs in the first month of treatment; however, more than 25% of patients experience their first attack of angioedema 6 months or longer after beginning ACEI therapy; some patients have received ACEIs for years before their first episode. Nearly 50% have angioedema recurrences, which may continue for months after ACEI withdrawal.

**Diagnosis**

Elucidating the cause of angioedema involves a detailed history, careful physical examination, and appropriate laboratory testing. Despite this, many cases are idiopathic.

As indicated in Table 1, the differential diagnosis of HAE or ACID includes chronic spontaneous angioedema, IgE-mediated angioedema, and ACEI-associated angioedema. These conditions can be suspected based on exposure history. IgE-mediated angioedema can be confirmed by cutaneous or in vitro testing for immediate hypersensitivity, but routine testing without a suspected allergen is not indicated. Clinical clues for angioedema diagnosis are described in Table 2.

C1INH deficiency merits investigation in patients with recurrent angioedema without concomitant hives, including patients with ACEI-associated angioedema. A diagnosis of C1INH deficiency requires laboratory confirmation with measurement of the C4 level, C1INH antigenic level, and C1INH functional level. Table 3 gives the complement profiles in various forms of recurrent angioedema. C4 is an excellent screening test for C1INH deficiency; most patients with C1INH deficiency have a reduced C4 level. This reduced C4 level is found in nearly 100% of cases during attacks. C4 is a normal C4 level during an attack of angioedema strongly supports an alternative diagnosis.

If C1INH deficiency cannot be confirmed by laboratory testing, a strong family history of angioedema without concomitant hives, not responsive to high-dose antihistamines, supports a diagnosis of HAE with normal C1INH. Search for the FXII mutation can be performed in these patients and if detected can confirm a diagnosis of HAE with normal C1INH; however, lack of FXII mutation does not rule out this diagnosis.

In ACID, the C1q level, which is normal in HAE patients with rare exceptions, is low in most cases. Presence of an underlying malignant tumor or detection of C1INH autoantibodies strongly supports a diagnosis of ACID. The diagnosis of idiopathic angioedema is based on the exclusion of known causes of angioedema, including C1INH deficiency.
The treatment of HAE can be categorized as treatment of attacks (on-demand treatment) and prophylactic treatment (short term and long term). All patients with C1INH deficiency should have an established plan on how to respond and effective drugs immediately available.

**Treatment of attacks**

Standard angioedema treatment modalities, such as epinephrine, corticosteroids, or antihistamines, do not have a salutary effect and are not recommended. Currently approved treatments for attacks are listed in Table 4. These agents are efficacious and safe for on-demand treatment and are most effective when administered early in an attack.

Fresh frozen plasma (FFP) should be used to treat attacks of HAE when no other treatment proven to be effective is available. FFP is safe for on-demand treatment and are most effective when administered early in an attack.

**Long-term prophylaxis**

Patients not treated successfully with on-demand therapy should be considered for long-term prophylaxis. Attack frequency and severity, location of and access to acute care, other comorbid conditions, individual circumstances, and patient values and preferences may all influence the decision to undergo treatment with long-term prophylaxis. In addition to being efficacious for on-demand treatment of attacks, plasma-derived C1INH has also been reported to be effective for long-term prophylaxis. The additional agents that can be used for long-term prophylaxis are listed in Table 5. Treatment with oral 17α-alkylated androgens has been reported to decrease the frequency and severity of HAE attacks, but long-term use may be associated with more potential for harm. Both the efficacy and adverse effects of 17α-alkylated androgens are dose related; for this reason, these agents are recommended at the lowest dose that achieves control of attacks. Although generally less efficacious than attenuated androgens, some patients benefit with the antifibrinolytic drug ε-aminocaproic acid (Amicar; Xenodyne Pharmaceuticals, Newport, Kentucky) for long-term prophylaxis of HAE. Another antifibrinolytic drug, tranexamic acid (Cyclokapron; Transamin; Pfizer Inc, New York, New York), has also been widely used in Europe for long-term prophylaxis of HAE and has recently become available in oral form in the United States (Lysteda 650; Ferring Pharmaceuticals, Parsippany, New Jersey).

**Short-term prophylaxis**

Short-term prophylaxis can be achieved with administration of 1,000-2,000 U of plasma-derived C1INH or, if plasma-derived C1-INH is not available, infusion of 2 U (10 mL/kg for children) of solvent or detergent-treated plasma or FFP several (up to 6) hours before a scheduled procedure. High-dose 17α-alkylated androgens (6-10 mg/kg/day in divided doses to a maximum of 200 mg 3 times daily of danazol per day or equivalent) taken for 5 to 7 days before and 2 days after the procedure is an alternative strategy for short-term prophylaxis. Because there are no studies assessing the comparative efficacy of these drugs for short-term prophylaxis, our recommendations are based on expert opinion and small, uncontrolled, observational studies. For emergency procedures and in pregnant patients, administration of plasma-derived C1INH is preferred. A dose of on-demand short-term treatment drug (C1INH, ecallantide, or icatibant) should be readily available, particularly for dental procedures or surgical procedures that require intubation. In selected situations (eg, when trauma is expected to be minimal and on-demand therapy is inadequate), continuing on-demand therapy may be considered during the procedure.
Angioedema associated with ACEIs

Angioedema, with a predilection for the face and tongue, has been observed in 0.1% to 0.7% of patients treated with ACEIs. Because ACEIs are commonly prescribed, angioedema from ACEIs is encountered more frequently than angioedema from C1INH deficiency. Bradykinin levels are elevated during episodes of angioedema.

ACE is a dipeptidylcarboxypeptidase that converts angiotensin I to angiotensin II. ACE is also a kininase II, an enzyme that catabolizes bradykinin into inactive peptides. When ACE is inhibited, bradykinin degradation can be prolonged. The presence of concomitant genetic variants affecting function of other bradykinin-degrading enzymes may be necessary for development of ACEI-induced angioedema. Consistent with this hypothesis, reduction in activity of another kininase, dipeptidyl peptidase IV, in the context of immunosuppressive therapy for organ transplantation has been associated with an increase in angioedema in patients concomitantly taking an ACEI.

Angioedema has also been reported in association with angiotensin receptor blockers (ARBs) and with aliskiren, a renin inhibitor. The rate of angioedema in patients receiving an ARB is substantially lower compared with patients treated with an ACEI. A 0.4% rate of angioedema (relative risk, 0.31; 95% confidence interval, 0.07–1.47, for 150 mg; relative risk, 0.57; 95% confidence interval, 0.17–1.89, for 300 mg) has been observed with aliskiren.

Management of angioedema associated with ACEIs entails ACEI suspension. Because angioedema related to ACEI is a class effect, all ACEIs should henceforth be avoided. As with management of acute angioedema in patients with C1INH deficiency, administration of antihistamines, corticosteroids, or epinephrine is not associated with benefit and is not recommended. For severe angioedema episodes, hospitalization may be required; life-threatening airway obstruction may develop that mandates intensive care management. Deaths from ACEI-induced laryngeal edema have been reported. Icatibant and FPR have been associated with salutary effects for treatment of ACEI-associated angioedema; however, no data beyond these observational reports have been published. No evidence exists at this time to guide management of acute angioedema associated with either an ARB or aliskiren.
Patients with a history of angioedema during treatment with an ACEI may be at elevated risk if switched to aliskiren as an alternative antihypertensive agent, and aliskiren should be avoided if feasible in these patients. A modest risk for angioedema to recur exists in patients who are switched to an ARB; however, most can receive ARB treatment without angioedema recurrence. One study found no statistically significant difference in recurrence rates of angioedema comparing subsequent treatment with an ARB and a calcium channel antagonist. A meta-analysis estimated a 2% to 17% risk of recurrence of angioedema in patients who had ACEI-induced angioedema and were switched to an ARB, whereas a pooled analysis of 2 randomized controlled trials and a meta-analysis generated an estimate of angioedema recurrence of 10% or less and reported that recurrent episodes of angioedema tended to be less severe and developed earlier in therapy. A persistent tendency to experience angioedema, irrespective of subsequent drug exposures, may exist in some patients despite ACEI suspension. Additional studies with sufficiently large sample size will be required to more accurately define the potential for ongoing angioedema in patients with ACEI-associated angioedema and to guide proper pharmacologic management of these patients. The decision to switch to an ARB (or to aliskiren) when suspending ACEI use due to angioedema should be considered in the context of a careful assessment of potential harm (recurrent angioedema, which may be serious or even life-threatening) compared with benefit (therapeutic need for angiotensin/renin inhibition, which in some patients may be associated with increased survival). This decision should be made in the context of patient circumstances and include patient values and preferences in the decision-making process.

Unmet Needs: Diagnosis and Management in Resource-Limited Environments

The unpredictable nature and severity of HAE may be associated with physical, emotional, and economic burdens for patients and their families. To obtain a clearer understanding of the burden of HAE and unmet needs for its diagnosis and management in resource-limited areas, a survey of health care professionals in the Asia-Pacific region was performed (Hikoo Hee Chng, MD, unpublished data, September 2012).

Although recent advances in our understanding of C1INH deficiency syndromes and the introduction of the 5 novel medications listed in Table 4 carry the promise of improved health care outcomes for patients with HAE, these advances have not translated into improved outcomes for many patients with HAE and ACID in resource-limited environments. There are several factors that appear to be contributing to this.

First, there is a lack of awareness by patients of the nature of their condition. Consequently, patients may fail to seek medical attention based on symptoms that are infrequent, mild, or both. Moreover, based on misconceptions regarding their symptoms, they may assume their angioedema is caused by allergy. Second, misdiagnosis by health care professionals can lead to mislabeling of patients with HAE or ACID as having angioedema caused by allergy. The most serious consequence of this mislabeling is that patients with laryngeal attacks who are at risk of death might receive treatment with epinephrine, antihistamines, and corticosteroids.

Third, diagnostic tests are either not available or beyond the reach of the average patient. Although a C4 level is often readily available and affordable in many countries, the same may not be true for C1q and C1INH antigenic and functional levels. Laboratories provide services based on demand and cost recovery. In the Asia-Pacific region, C1q, C1INH antigenic, and C1INH functional levels are not available in India, Indonesia, Thailand, Philippines, and Vietnam, and both C1INH antigenic and functional levels are not available in Taiwan. South American countries have access to quantitative C1INH evaluation, but access is limited in Central American countries. In countries in South and Central America, C1INH functional level determination is available in only a few locations. The cost of C1q and C1INH assays are deemed to be not affordable to the average patient even in developed countries such as Singapore and Hong Kong. Interestingly, these 4 laboratory tests are available in Pakistan to patients seen at specialty centers.

Health care professionals practicing in locations where one or more tests are not available or affordable may use a thorough history to aid in reaching a diagnosis. Measurement of C4 levels is a cost-effective screening test to rule out HAE, although the C4 level may be normal between attacks.

It is understandable that costs of drug registration and cost recovery from sales in any country are important to a pharmaceutical company. In the case of rare conditions, such as HAE and ACID, low use may discourage new drug applications. Health care professionals who support coverage of medical expenses play an important role. At the time of this writing, C1INH replacement therapy, ecallantide, and icatibant were not available in many countries in the Asia-Pacific region, including India, Indonesia, Philippines, Pakistan, Thailand, Sri Lanka, Singapore, and Taiwan, whereas ecallantide and icatibant were not available in Hong Kong, Japan, and Korea. In the Latin American countries, Argentina has C1INH replacement therapy, and icatibant is available in Brazil and Mexico. Even the United States has had access to new therapies for acute attacks only recently.

Attenuated androgens, danazol and stanozolol, and tranexamic acid are more widely available and generally affordable. In several Latin American countries, however, attenuated androgens are not available and/or are costly (these drugs are supported by the government in Brazil). In many areas of the world, treatment of HAE and ACID focuses on routine long-term prophylaxis because effective short-term treatment is not available; for example, more than half of Brazilian HAE patients are treated with danazol. FFP is still used in some countries, such as China, for prophylaxis before surgical or dental procedures and for acute attacks. Even in countries where on-demand treatment for attacks is available, FFP has been used due to restricted access related to cost reimbursement.

Where HAE-specific drugs for acute attacks are not available, emphasis must be placed on patient education for avoidance of triggers, such as minor trauma (including dental procedures), vigorous exercise, emotional stress, the use of estrogen-containing medications (eg, hormone replacement therapy and contraceptives), alcohol, infection, and ACEIs in patients with HAE and ACID.

For patients with ACID, treatment of the primary disease (if identified) may be effective in preventing recurrence of angioedema. This finding should be emphasized, especially where effective new therapies for acute attacks are lacking or not affordable.

A patient’s acceptance of the disease and adherence to treatment and medical follow-up is an even more important component of treatment success in developing countries. A World Health Report affirmed that “medication non-adherence is so great and the consequences are of such concern that more people worldwide would benefit from efforts to improve medication adherence than from development of new medical treatments.” In developing countries, patients with chronic conditions have adherence rates of 50% to 60%, despite evidence that medication improves quality of life and prevents death. In economically challenged countries, with poor access to health care, a lack of diagnostic assays, and limited availability of medications taken into account, poor adherence threatens all efforts to treat chronic conditions, such as diabetes, depression, and HIV/AIDS.
Because even a history of asphyxia in one’s family may not lead some patients to seek medical care, it is likely that adherence in HAE, although not formally evaluated, is a major challenge.

The authors of this ICON recommend a public health initiative, particularly in resource-limited areas, for HAE, to include the following:

- Educational programs for the public and health care professionals
- Improved access to laboratory tests
- Establishment of reference centers in each country or region
- Comprehensive access to evidence-based therapies, with governmental support
- Expanded activities of patient support groups to reach out to health care professionals and affected patients and their families.

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