



Special Article

International consensus on hereditary and acquired angioedema

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Outline

1. Introduction	396
2. Definition and Pathogenesis	396
3. Prevalence	396
4. Epidemiology	396
5. Clinical Manifestations	397
5.1. HAE-1/2	397
5.2. HAE with normal C1INH	397
5.3. ACID	397
5.4. ACEI-associated angioedema	397
6. Diagnosis	397
7. Treatment	398
7.1. Treatment of attacks	398
7.2. Long-term prophylaxis	398
7.3. Short-term prophylaxis	398
7.4. Treatment in special groups: children, women, and pregnant women	399
7.5. ACID	399
7.6. Angioedema associated with ACEIs	399
8. Unmet Needs: Diagnosis and Management in Resource-Limited Environments	400
Acknowledgment	401
References	401

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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.¹

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 defined⁵⁻⁹: (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

Table 1
Classification of angioedema^a

Category	Bradykinin mediated				Mast cell mediated, normal C1INH		Idiopathic, normal C1INH, negative inheritance
	C1INH deficiency/defect		Normal C1INH		IgE mediated	Non-IgE mediated	
	Positive inheritance	Negative inheritance	Positive inheritance	Negative inheritance			
Disease	HAE-1, HAE-2	ACID	HAE with normal C1INH	Drug-induced AE (eg ACEI), nonclassified AE	Anaphylaxis, IgE-mediated urticaria	Chronic spontaneous urticaria, inducible urticarias, nonclassified AE	Nonclassified AE
Occurrence of superficial wheals	Negative	Negative	Negative	Negative	Positive/negative	Positive/negative	Negative

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).

^aMast 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.

(132 patients), China (133 patients), and Brazil (210 patients) suggest a lower HAE prevalence in these countries than in Europe and North America.¹¹ 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.¹²

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.^{13,14} 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.¹² The frequency of attacks is highly variable. Most often, patients present with symptoms during childhood,^{15–17} with a worsening of symptoms around puberty.¹³ 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.^{13,17} 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

Table 2
Clinical clues for angioedema diagnosis

Angioedema characteristic	Clinical association
Accompanied by hives	May be IgE mediated, non-IgE mediated, or nonclassified ^a ; generally due to mast cell degranulation
Duration of swelling	Mast cell-mediated angioedema typically lasts <48 hours; bradykinin-mediated angioedema often lasts ≥72 hours
Angioedema of bowel	Very frequent in HAE-1/2 or ACID; less common but may occur in HAE with normal C1-INH level; uncommon but may occur with ACEI-associated angioedema; very uncommon in mast cell-mediated angioedema
Predilection for the face, mouth, upper airway	Suggestive of ACEI-induced angioedema or HAE with normal C1INH level
Prodromal symptoms	Characteristic of HAE, especially erythema marginatum; occurs in up to 50% of HAE patients
Family history of angioedema	Present in 75% of patients with HAE due to C1INH deficiency; a required element for diagnosis of HAE with normal C1INH who lack FXII mutation

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).

^aNonclassified implies that no cause has been identified.

preceding attacks, and an older age of symptom onset.^{18–20} 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.²¹

ACEI-associated angioedema

Angioedema related to ACEIs has a strong predilection to involve the face, lips, and tongue.²² 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.^{22–25} 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.²⁶

Diagnosis

Elucidating the cause of angioedema involves a detailed history, careful physical examination, and appropriate laboratory testing. Despite this, many cases are idiopathic.²⁷

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.^{1,10,13,22} 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.^{28,29} 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.^{9,30,31}

In ACID, the C1q level, which is normal in HAE patients with rare exceptions, is low in most cases.^{10,13} 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.

Table 3
Complement levels in the diagnosis of HAE

Type of angioedema	C1INH antigenic level	C1INH functional level	C4 level	C1q level
HAE-1	Low	Low	Low	Normal
HAE-2	NI	Low	Low	Normal
HAE with normal C1INH	Normal	Normal	Normal	Normal
ACID	Low	Low	Low	Low
Angioedema due to ACEI	Normal	Normal	Normal	Normal
Nonclassified angioedema ^a	Normal	Normal	Normal	Normal

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

^aNonclassified implies that no cause has been identified.

Treatment

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^{32–38} 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 generally effective in treating acute attacks of angioedema³⁹; however, sometimes it lacks efficacy or can cause sudden worsening of symptoms. FFP also carries a risk of viral transmission.³⁹

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.³³ The additional agents that can be used for long-term prophylaxis are listed in Table 5. Treatment with oral 17 α -alkylated androgens^{40–43} 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 17 α -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; Xanodyne Pharmaceuticals, Newport, Kentucky) for long-term prophylaxis of HAE.^{42–45} Another antifibrinolytic drug, tranexamic acid (Cyklokapron, Transamin; Pfizer Inc, New York, New York), has also been widely used in Europe for long-term prophylaxis of HAE⁴⁵ 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.^{46–48} High-dose 17 α -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.^{49,50} 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

Table 4
HAE-specific agents^a

Drug	EMA and FDA indications	Recommended dosage	Mechanism	Potential adverse effects
Plasma-derived nanofiltered C1INH (Berinert-P; CSL Behring, King of Prussia, Pennsylvania)	Acute attacks	20 U/kg intravenous	Deficiency replacement	Theoretical: transmission of infectious agent
Plasma-derived nanofiltered C1INH (Cinryze; ViroPharma, Exton, Pennsylvania)	Long-term prophylaxis in United States and Europe, also short-term prophylaxis and on-demand in Europe	1,000 U intravenous every 3–4 days	Deficiency replacement	Theoretical: transmission of infectious agent
Recombinant human C1INH (Rhucin; Pharming, Leiden, The Netherlands)	Acute attacks (pending in United States, approved in Europe)	50 U/kg intravenous	Deficiency replacement	Uncommon: risk of anaphylaxis in rabbit sensitized individuals
Ecallantide (Kalbitor; Dyax, Burlington, Massachusetts)	Acute attacks (in United States, not approved in Europe)	30 mg subcutaneous (administered as 3 injections of 10 mg/mL each)	Inhibits plasma kallikrein	Uncommon: antidrug antibodies, injection site reactions, risk of anaphylaxis
Icatibant (Firazyr; Shire, St. Helier, New Jersey)	Acute attacks	30 mg subcutaneous	Bradykinin B2-receptor antagonist	Common: injection site reactions

Abbreviations: EMA, European Medicines Agency; FDA, US Food and Drug Administration.

^aRegistration and availability of these drugs differ from country to country.

Table 5
Drugs commonly used for long-term HAE prophylaxis^a

Drug	Adult dosage (usual, range)	Pediatric dosage (usual, range)	FDA approved/ HAE indication	Adverse effects
17α-Alkylated androgens				
Danazol (Danocrine; Sanofi-Synthelabs, Inc, Barcelonata, Puerto Rico)	Minimal effective dose do not exceed 200 mg/d	Not recommended; if absolutely necessary do not exceed 2.5 mg/kg/d (50 mg/wk to 200 mg/d)	Yes/yes	Common: weight gain, virilization, acne, altered libido, muscle pains and cramps, headaches, depression, fatigue, nausea, constipation, menstrual abnormalities and increase in liver enzymes,
Stanozolol (Winstrol; Bayer, Leverkusen, Germany)	Minimal effective dose do not exceed 2 mg/d	0.5 mg/d (0.5 mg/wk to 2 mg/d)	Yes/yes	hypertension, alterations in lipid profile
Oxandrolone (Oxandrin; Pfizer Inc, New York, New York)	Minimal effective dose do not exceed 10 mg/d	0.1 mg/kg/d (2.5 mg/wk to 7.5 mg/d)	Yes/no	Unusual: Decreased growth rate in children, masculinization of the female fetus, cholestatic jaundice, peliosis hepatis and hepatocellular adenoma
Antifibrinolytics				
ϵ -Aminocaproic acid (Amicar; Xanodyne Pharmaceuticals, Inc, Newport, Kentucky)	2 g 3 times daily (1 g twice daily to 4 g 3 times daily)	0.05 g/kg twice daily (0.02 g/kg twice daily to 0.1 g/kg twice daily)	Yes/no	Common: nausea, vertigo, diarrhea, postural hypotension, fatigue, muscle cramps with increased muscle enzymes
Tranexamic acid (Cyklocapron, Transamin; Pfizer Inc, Lysteda; Ferring Pharmaceuticals, Parsippany, New Jersey)	1 g twice daily (0.25 g twice daily to 1.5 g twice daily)	20 mg/kg twice daily (10 mg/kg twice daily to 25 mg/kg 3 times daily)	Yes/no	Unusual: enhanced thrombosis

Abbreviations: FDA, US Food and Drug Administration; HAE, hereditary angioedema.

^aRegistration and availability of these drugs differ from country to country.

readily available), omission of preprocedural treatment with on-demand treatment contingent on any signs of an attack is an alternative management approach.

Treatment in special groups: children, women, and pregnant women

Changes in estrogen in association with puberty, menopause, or hormone replacement therapy, oral contraceptive use, or pregnancy can provoke or exacerbate a tendency for more frequent and/or severe attacks in some women with C1INH deficiency.⁵¹ For pregnant patients with more serious flares of HAE, long-term prophylaxis is an appropriate intervention because the potential for benefit exceeds the potential for harm and burden associated with this treatment.⁵² The decision to prescribe long-term prophylaxis during pregnancy should be considered carefully on an individualized basis and involve the patient in the decision-making process. Because treatment with androgens is contraindicated during pregnancy,⁵³ plasma-derived C1INH is preferred and may also be considered for women desiring to become pregnant.⁵⁴ Angioedema attacks during labor and delivery are relatively rare.⁵² This can be managed expectantly by having an on-demand HAE-specific agent available should an episode of angioedema occur. Clinical trials investigating the efficacy and safety of these novel agents for children are lacking. However, clinical experience with C1INH replacement therapy in children implies these agents are favorable from the standpoint of balancing the potential for benefit with the potential for harm or burden in properly selected patients.⁵⁵

ACID

Because the pathogenesis of ACID entails low levels of C1INH due to increased catabolism, either related to a malignant tumor (eg, lymphoma) or an autoimmune disorder (eg, systemic lupus erythematosus), treatment of such an underlying condition can result in improvement in ACID.²¹ Compared with HAE, anecdotal evidence implies these patients may be less responsive to attenuated androgens but exhibit greater response to treatment with antifibrinolytic agents.⁷ Response to plasma-derived C1INH may be less reliable based on the presence of C1INH antibodies.⁵⁶ Icatibant and ecallantide have been reported to be efficacious for treatment of attacks.^{57,58}

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.²² 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.⁵⁹

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.^{22,60} The presence of concomitant genetic variants affecting function of other bradykinin-degrading enzymes may be necessary for development of ACEI-induced angioedema.⁶¹ 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.⁶²

Angioedema has also been reported in association with angiotensin receptor blockers (ARBs) and with aliskiren, a renin inhibitor.^{63,64} The rate of angioedema in patients receiving an ARB is substantially lower compared with patients treated with an ACEI.⁶³ 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.⁶⁴

Management of angioedema associated with ACEIs entails ACEI suspension.²² 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.^{65,66} Icatibant and FFP^{67,68} 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 ARB⁶³; however, most can receive ARB treatment without angioedema recurrence. One study⁶⁹ found no statistically significant difference in recurrence rates of angioedema comparing subsequent treatment with an ARB and a calcium channel antagonist. A meta-analysis⁷⁰ 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-analysis⁶³ 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.⁷¹ 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).²⁶ 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.⁷² 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 (Hiok 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.^{12,28,29}

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.⁷³ 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.⁷⁴ FFP is still used in some countries, such as China, for prophylaxis before surgical or dental procedures and for acute attacks.^{75,76} 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.⁷⁷ 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 Report⁷⁸ 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 developed countries, patients with chronic conditions have adherence rates of 50% to 60%, despite evidence that medication improves quality of life and prevents death.⁷⁹ 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.⁸⁰ Refusal to receive continuous therapy can lead to higher morbidity and mortality in HAE.^{49,53}

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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References

- [1] Kaplan AP, Greaves MW. Angioedema. *J Am Acad Dermatol*. 2005;53:373–392.
- [2] Mehta D, Malik AB. Signaling mechanisms regulating endothelial permeability. *Physiol Rev*. 2006;86:279–367.
- [3] Sandoval R, Malik AB, Minshall RD, Kouklis P, Ellis CA, Tirupathi C. Ca(2+) signalling and PKCalpha activate increased endothelial permeability by disassembly of VE-cadherin junctions. *J Physiol*. 2001;533(pt 2):433–445.
- [4] Cugno M, Zanichelli A, Foienni F, Caccia S, Cicardi M. C1-inhibitor deficiency and angioedema: molecular mechanisms and clinical progress. *Trends Mol Med*. 2009;15:69–78.
- [5] Cugno M, Nussberger J, Cicardi M, Agostoni A. Bradykinin and the pathophysiology of angioedema. *Int Immunopharmacol*. 2003;3:311–317.
- [6] Kaplan AP, Joseph K. The bradykinin-forming cascade and its role in hereditary angioedema. *Ann Allergy Asthma Immunol*. 2010;104:193–204.
- [7] Cicardi M, Zanichelli A. The acquired deficiency of C1-inhibitor: lymphoproliferation and angioedema. *Curr Mol Med*. 2010;10:354–360.
- [8] Bork K, Wulff K, Hardt J, Witzke G, Staubach P. Hereditary angioedema caused by missense mutations in the factor XII gene: clinical features, trigger factors, and therapy. *J Allergy Clin Immunol*. 2009;124:129–134.
- [9] Cichon S, Martin L, Hennies HC, et al. Increased activity of coagulation factor XII (Hageman factor) causes hereditary angioedema type III. *Am J Hum Genet*. 2006;79:1098–1104.
- [10] Zuraw BL. Clinical practice: hereditary angioedema. *N Engl J Med*. 2008;359:1027–1036.
- [11] Grumach AS, Valle SO, Toledo E, et al, on behalf of group interested on HAE (GINHA). Hereditary angioedema: first report of the Brazilian registry and challenges [published online ahead of print August 7, 2012]. *J Eur Acad Dermatol Venereol*. doi: 10.1111/j.1468-3083.2012.04670.x.
- [12] Bork K, Meng G, Staubach P, Hardt J. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. *Am J Med*. 2006;119:267.
- [13] Frank MM, Gelfand JA, Atkinson JP. Hereditary angioedema: the clinical syndrome and its management. *Ann Intern Med*. 1976;84:586–593.
- [14] Bowen T, Cicardi M, Bork K, et al. Hereditary angioedema: a current state-of-the-art review, VII: Canadian Hungarian 2007 International Consensus Algorithm for the Diagnosis, Therapy, and Management of Hereditary Angioedema. *Ann Allergy Asthma Immunol*. 2008;100(1 suppl 2):S30–S40.
- [15] Farkas H, Varga L, Szeplaki G, Visy B, Harmat G, Bowen T. Management of hereditary angioedema in pediatric patients. *Pediatrics*. 2007;120:e713–e722.
- [16] Agostoni A, Cicardi M. Hereditary and acquired C1-inhibitor deficiency: biological and clinical characteristics in 235 patients. *Medicine (Baltimore)*. 1992;71:206–215.
- [17] Prematta MJ, Kemp JG, Gibbs JG, Mende C, Rhoads C, Craig TJ. Frequency, timing, and type of prodromal symptoms associated with hereditary angioedema attacks. *Allergy Asthma Proc*. 2009;30:506–511.
- [18] Bork K. Diagnosis and treatment of hereditary angioedema with normal C1 inhibitor. *Allergy Asthma Clin Immunol*. 2010;6:15.
- [19] Bork K. Hereditary angioedema with normal C1 inhibition. *Curr Allergy Asthma Rep*. 2009;9:280–285.
- [20] Bork K, Gul D, Hardt J, Dewald G. Hereditary angioedema with normal C1 inhibitor: clinical symptoms and course. *Am J Med*. 2007;120:987–992.
- [21] Zingale LC, Castelli R, Zanichelli A, Cicardi M. Acquired deficiency of the inhibitor of the first complement component: presentation, diagnosis, course, and conventional management. *Immunol Allergy Clin North Am*. 2006;26:669–690.
- [22] Byrd JB, Adam A, Brown NJ. Angiotensin-converting enzyme inhibitor-associated angioedema. *Immunol Allergy Clin North Am*. 2006;26:725–737.
- [23] Brown NJ, Ray WA, Snowden M, Griffin MR. Black Americans have an increased rate of angiotensin converting enzyme inhibitor-associated angioedema. *Clin Pharmacol Ther*. 1996;60:8–13.
- [24] Gibbs C, Lip G, Beevers D. Angioedema due to ACE inhibitors: increased risk in patients of African origin. *Br J Pharmacol*. 1999;48:861–865.
- [25] Miller D, Oliveria S, Berlowitz D, Fincke B, Stang P, Lillienfeld D. Angioedema incidence in US veterans initiating angiotensin converting enzyme inhibitors. *Hypertension*. 2008;51:1624–1630.
- [26] Beltrami L, Zanichelli A, Zingale L, Vacchini R, Carugo S, Cicardi M. Long term follow up of 111 patients with angiotensin converting enzyme inhibitor related angioedema. *J Hyperten*. 2011;29:2273–2277.
- [27] Zingale LC, Beltrami L, Zanichelli A, et al. Angioedema without urticaria: a large clinical survey. *CMAJ*. 2006;175:1065–1070.
- [28] Zuraw BL, Sugimoto S, Curd JG. The value of rocket immunoelectrophoresis for C4 activation in the evaluation of patients with angioedema or C1-inhibitor deficiency. *J Allergy Clin Immunol*. 1986;78:1115–1120.
- [29] Gompels MM, Lock RJ, Morgan JE, Osborne J, Brown A, Virgo PF. A multicentre evaluation of the diagnostic efficiency of serological investigations for C1 inhibitor deficiency. *J Clin Pathol*. 2002;55:145–147.
- [30] Dewald G, Bork K. Missense mutations in the coagulation factor XII (Hageman factor) gene in hereditary angioedema with normal C1 inhibitor. *Biochem Biophys Res Commun*. 2006;343:1286–1289.
- [31] Duan QL, Binkley K, Rouleau GA. Genetic analysis of Factor XII and bradykinin catabolic enzymes in a family with estrogen-dependent inherited angioedema. *J Allergy Clin Immunol*. 2009;123:906–910.
- [32] Craig TJ, Levy RJ, Wasserman RL, et al. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. *J Allergy Clin Immunol*. 2009;124:801–808.
- [33] Zuraw BL, Busse PJ, White M, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *N Engl J Med*. 2010;363:513–522.
- [34] Cicardi M, Banerji A, Bracho F, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. *N Engl J Med*. 2010;363:532–541.
- [35] Lumry WR, Li HH, Levy RJ, et al. Randomized placebo-controlled trial of the bradykinin B receptor antagonist icatibant for the treatment of acute attacks of hereditary angioedema: the FAST-3 trial. *Ann Allergy Asthma Immunol*. 2011;107:529–537.
- [36] Zuraw B, Cicardi M, Levy RJ, et al. Recombinant human C1-inhibitor for the treatment of acute angioedema attacks in patients with hereditary angioedema. *J Allergy Clin Immunol*. 2010;126:821–827, e14.
- [37] Waytes AT, Rosen FS, Frank MM. Treatment of hereditary angioedema with a vapor-heated C1 inhibitor concentrate. *N Engl J Med*. 1996;334:1630–1634.
- [38] Kunschak M, Engl W, Maritsch F, et al. A randomized, controlled trial to study the efficacy and safety of C1 inhibitor concentrate in treating hereditary angioedema. *Transfusion*. 1998;38:540–549.
- [39] Prematta M, Gibbs JG, Pratt EL, Stoughton TR, Craig TJ. Fresh frozen plasma for the treatment of hereditary angioedema. *Ann Allergy Asthma Immunol*. 2007;98:383–388.
- [40] Bork K, Bygum A, Hardt J. Benefits and risks of danazol in hereditary angioedema: a long-term survey of 118 patients. *Ann Allergy Asthma Immunol*. 2008;100:153–161.
- [41] Cicardi M, Castelli R, Zingale LC, Agostoni A. Side effects of long-term prophylaxis with attenuated androgens in hereditary angioedema: comparison of treated and untreated patients. *J Allergy Clin Immunol*. 1997;99:194–196.
- [42] Sloane DE, Lee CW, Sheffer AL. Hereditary angioedema: safety of long-term stanozolol therapy. *J Allergy Clin Immunol*. 2007;120:654–658.
- [43] Gompels MM, Lock RJ, Abinun M, et al. C1 inhibitor deficiency: consensus document. *Clin Exp Immunol*. 2005;139:379–394.
- [44] Frank MM, Sergeant JS, Kane MA, Alling DW. Epsilon aminocaproic acid therapy of hereditary angioneurotic edema: a double-blind study. *N Engl J Med*. 1972;286(15):808–812.
- [45] Agostoni A, Aygoren-Pursun E, Binkley KE, et al. Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. *J Allergy Clin Immunol*. 2004;114(3 suppl):S51–S131.
- [46] Jaffe CJ, Atkinson JP, Gelfand JA, Frank MM. Hereditary angioedema: the use of fresh frozen plasma for prophylaxis in patients undergoing oral surgery. *J Allergy Clin Immunol*. 1975;55:386–393.
- [47] Bork K, Hardt J, Staubach-Renz P, Witzke G. Risk of laryngeal edema and facial swellings after tooth extraction in patients with hereditary angioedema with and without prophylaxis with C1 inhibitor concentrate: a retrospective study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2011;112:58–64.
- [48] De Serres J, Groner A, Lindner J. Safety and efficacy of pasteurized C1 inhibitor concentrate in hereditary angioedema: a review. *Transfus Apher Sci*. 2003;29:247–254.
- [49] Gelfand JA, Sherins RJ, Alling DW, Frank MM. Treatment of hereditary angioedema with danazol: reversal of clinical and biochemical abnormalities. *N Engl J Med*. 1976;295:1444–1448.

- [50] Craig TJ. Appraisal of danazol prophylaxis for hereditary angioedema. *Allergy Asthma Proc.* 2008;29:225–231.
- [51] Bouillet L, Longhurst H, Boccon-Gibod I, et al. Disease expression in women with hereditary angioedema. *Am J Obstet Gynecol.* 2008;199:484, e1–4.
- [52] Czaller I, Visy B, Csuka D, Fust G, Toth F, Farkas H. The natural history of hereditary angioedema and the impact of treatment with human C1-inhibitor concentrate during pregnancy: a long-term survey. *Eur J Obstet Gynecol Reprod Biol.* 2010;152:44–49.
- [53] Sheffer AL, Fearon DT, Austen KF. Hereditary angioedema: a decade of management with stanazolol. *J Allergy Clin Immunol.* 1987;80:855–860.
- [54] Farkas H, Jakab L, Temesszentandrási G, et al. Hereditary angioedema: a decade of human C1-inhibitor concentrate therapy. *J Allergy Clin Immunol.* 2007;120:941–947.
- [55] Kreuz W, Rusicke E, Martinez-Saguer I, Aygoren-Pursun E, Heller C, Klingebiel T. Home therapy with intravenous human C1-inhibitor in children and adolescents with hereditary angioedema. *Transfusion.* 2012;52:100–107.
- [56] Levi M, Choi G, Picavet C, Hack C. Self-administration of C1-inhibitor concentrate in patients with hereditary or acquired angioedema caused by C1-inhibitor deficiency. *J Allergy Clin Immunol.* 2006;117:904–908.
- [57] Zanichelli A, Badini M, Nataloni I, Montano N, Cicardi M. Treatment of acquired angioedema with icatibant: a case report. *Intern Emerg Med.* 2011;6:279–280.
- [58] Cicardi M, Zanichelli A. Acquired angioedema. *Allergy Asthma Clin Immunol.* 2010;6:14.
- [59] Nussberger J, Cugno M, Amstutz C, Cicardi M, Pellacani A, Agostoni A. Plasma bradykinin in angio-oedema. *Lancet.* 1998;351:1693–1697.
- [60] Blais C Jr, Rouleau JL, Brown NJ, et al. Serum metabolism of bradykinin and des-Arg9-bradykinin in patients with angiotensin-converting enzyme inhibitor-associated angioedema. *Immunopharmacology.* 1999;43:293–302.
- [61] Adam A, Cugno M, Molinaro G, Perez M, Lepage Y, Agostoni A. Aminopeptidase P in individuals with a history of angio-oedema on ACE inhibitors. *Lancet.* 2002;359:2088–2089.
- [62] Byrd JB, Woodard-Grice A, Stone E, et al. Association of angiotensin-converting enzyme inhibitor-associated angioedema with transplant and immunosuppressant use. *Allergy.* 2010;65:1381–1387.
- [63] Beavers CJ, Dunn SP, Macaulay TE. The role of angiotensin receptor blockers in patients with angiotensin-converting enzyme inhibitor-induced angioedema. *Ann Pharmacotherapy.* 2011;45:520–524.
- [64] White WB, Bresalier R, Kaplan AP, et al. Safety and tolerability of the direct renin inhibitor aliskiren: a pooled analysis of clinical experience in more than 12,000 patients with hypertension. *J Clin Hypertens (Greenwich).* 2010;12:765–775.
- [65] Jason DR. Fatal angioedema associated with captopril. *J Forensic Sci.* 1992;37:1418–1421.
- [66] Cupido C, Rayner B. Life-threatening angio-oedema and death associated with the ACE inhibitor enalapril. *S Afr Med J.* 2007;97:244–245.
- [67] Bas M, Greve J, Stelter K, et al. Therapeutic efficacy of icatibant in angioedema induced by angiotensin-converting enzyme inhibitors: a case series. *Ann Emerg Med.* 2010;56:278–282.
- [68] Schmidt PW, Hirschl MM, Trautinger F. Treatment of angiotensin-converting enzyme inhibitor-related angioedema with the bradykinin B2 receptor antagonist icatibant. *J Am Acad Derm.* 2010;63:913–914.
- [69] Cicardi M, Zingale LC, Bergamaschini L, Agostoni A. Angioedema associated with angiotensin-converting enzyme inhibitor use: outcome after switching to a different treatment. *Arch Intern Med.* 2004;164:910–913.
- [70] Haymore BR, Yoon J, Mikita CP, Klote MM, DeZee KJ. Risk of angioedema with angiotensin receptor blockers in patients with prior angioedema associated with angiotensin-converting enzyme inhibitors: a meta-analysis. *Ann Allergy Asthma Immunol.* 2008;101:495–499.
- [71] Lumry WR, Castaldo AJ, Vernon MK, Blaustein MB, Wilson DA, Horn PT. The humanistic burden of hereditary angioedema: impact on health-related quality of life, productivity, and depression. *Allergy Asthma Proc.* 2010;31:407–414.
- [72] Khalil ME, Basher AW, Brown EJ, Alhaddad IA. A remarkable medical story: benefits of angiotensin converting enzyme inhibitors in cardiac patients. *J Am Coll Cardiol.* 2001;37:1757–1764.
- [73] Huggett B. Companies line up for hereditary angioedema market. *Nat Biotechnol.* 2008;26:364–365.
- [74] Grumach AS, Valle SOR, Toledo E, et al, on behalf of group interested on HAE (GINHA). First report of 210 patients with hereditary angioedema from Brazilian registry [published online ahead of print August 7, 2012]. *J Eur Acad Dermatol Venereol.* doi: 10.1111/j.1468–3083.2012.04670.x.
- [75] en HL, Zhang HY. Clinical features of hereditary angioedema: analysis of 133 cases [in Chinese]. *Zhonghua Yi Xue Za Zhi.* 2007;87:2772–2776.
- [76] Tang R, Chen S, Zhang HY. Fresh frozen plasma for the treatment of hereditary angioedema acute attacks. *Chin Med Sci J.* 2012;27:92–95.
- [77] Markovic SN, Inwards DJ, Frigas EA, Phyllyk RP. Acquired C1 inhibitor deficiency. *Ann Intern Med.* 2000;132:144–150.
- [78] van Dulmen S, Sluijs E, van Dijk L, Ridder D, Heerdink R, Bensing J. Patient adherence to medical treatment: a review of reviews. *BMC Health Serv Res.* 2007;7:55–67.
- [79] Wood B. Medication Adherence: The real problem when treating chronic conditions. *US Pharm.* 2012;37(4 Compliance suppl):3–6.
- [80] World Health Organization. Adherence to long-term therapies: evidence for action. www.who.int/hiv/pub/prev_care/lttherapies/en/index.html. Accessed August 1, 2012.