

Enzymatic pathways in the pathogenesis of hereditary angioedema: The role of C1 inhibitor therapy

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A functional abnormality of C1 inhibitor (C1INH) is present in types I and II hereditary angioedema (HAE), and normal C1INH may be rendered ineffective in the newly described type III HAE. C1INH inhibits factor XIIa, factor XII fragment (XII_f), kallikrein, and plasmin. Thus, in its absence, there is marked activation of the bradykinin-forming cascade resulting in severe angioedema. Factor XII may autoactivate on binding to endothelial cell surface gC1qR (receptor for the globular heads of C1q) thus initiating the cascade. Alternatively, stimuli that activate endothelial cells may liberate (or express at the cell surface) heat shock protein 90 or the enzyme prolylcarboxypeptidase, either of which can interact with the prekallikrein–high-molecular-weight kininogen complex to convert prekallikrein to kallikrein stoichiometrically. The kallikrein produced can cleave high-molecular-weight kininogen to produce bradykinin and also recruit factor XII by enzymatically activating it. Patients with type I or II HAE have mutant C1INH so that control of C1 activation is lost.

Autoactivation of C1r in the absence of C1INH leads to C1s activation followed by C4 cleavage and depletion. An attack of swelling is accompanied by conversion of factor XIIa to factor XII_f and further enzymatic activation of C1r so that C4 levels drop further and C2 is depleted. New therapies for HAE focus on the bradykinin-forming cascade and include a kallikrein inhibitor and a bradykinin B-2 receptor antagonist in addition to administration of purified C1INH. (*J Allergy Clin Immunol* 2010;■■■:■■■-■■■.)

Key words: Angioedema, bradykinin, kallikrein, kininogen, factor XII, endothelial cells

Hereditary angioedema (HAE) is a potentially life-threatening disorder resulting from a mutation in the gene controlling the synthesis of C1-inhibitor (C1INH), a serine protease inhibitor that blocks the activity of various components of the complement, fibrinolytic, and, in particular, the contact (bradykinin-forming) systems.¹ It is a relatively rare disorder that nevertheless results in significant morbidity and mortality. This review provides an

Abbreviations used

C1INH: C1 inhibitor
gC1qR: Receptor for the globular heads of C1q
HAE: Hereditary angioedema
HK: High-molecular-weight kininogen
HSP-90: Heat shock protein 90
XII_f: XII fragment

overview of the current understanding of the underlying pathophysiologic defect in HAE, the unraveling of which has been a key element in helping to develop more targeted approaches to pharmacologic intervention.

GENETIC AND MOLECULAR BASIS OF HAE

Hereditary angioedema is an autosomal-dominant disorder in which the gene defect results in a biochemical abnormality in the levels or functionality of C1 esterase inhibitor (C1INH). The mutations, of which over 200 have so far been described,² are located on chromosome 11 (11q11-q13.1), with the relative position within the gene dictating the type of HAE that results.³ Two main types of HAE have been described.⁴ These are symptomatically indistinguishable, but the physiologic defect is distinctive in each case. Type 1 HAE, which accounts for 80% to 85% of all cases, is defined by reduced circulating C1INH concentrations (with levels around 5% to 30% of expected values).⁵ Type 1 HAE mutations occur throughout the gene, resulting in the production of abnormal proteins that are not secreted. In contrast, type 2 HAE (15% to 20% of cases), in which the mutations are typically single amino acid substitutions, mainly at exon 8 (at or near the active site), demonstrates relatively normal, or even raised, levels of circulating C1INH. In this case, however, the protein secreted is dysfunctional. It should also be noted that, although HAE is primarily inherited, it is estimated that 20% to 25% of cases result from a new spontaneous mutation,⁶ with implications for diagnosis, because an accurate family history is an important element. More recently, a third presentation of HAE has been described, predominantly (but not exclusively) in female subjects. This is not related to C1INH deficiency, but a subpopulation of patients have a missense mutation in the factor XII gene⁷⁻⁹ at position 309 in which a threonine is replaced either by lysine or arginine. Excessive bradykinin formation may be responsible for angioedema because acute attacks have been successfully treated with a B-2 receptor antagonist,¹⁰ but a detailed mechanism has not been elucidated, and the factor XII mutation is not evident in all such patients.⁷ Thus, some controversy exists in sorting out the details. A decreased level of either angiotensin-converting enzyme or aminopeptidase P may be an additional predisposing factor apart from estrogen or trauma.¹¹ A family history is essential to make

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the clinical diagnosis, otherwise an isolated patient's condition would resemble idiopathic angioedema (Table 1) but with a greater potential to have attacks that can lead to respiratory compromise. One form of idiopathic anaphylaxis¹² resembles this clinical presentation as well.

CLINICAL PRESENTATION OF HAE

More than 45 years have passed since the initial identification of C1INH deficiency as the primary defect in HAE, and much research has been carried out over the years to elucidate further the mechanisms involved. Before describing the pathophysiologic pathways in more detail, however, a review of the clinical presentation of the disease is in order.

The earliest description of angioedema was by Milton¹³ in 1876, with the first report of a hereditary form of the disease published over a decade later by Sir William Osler (1888).¹⁴ It was not until 1963, however, that the biochemical basis of HAE (ie, the defect in C1INH) was first elucidated by Donaldson and Evans.¹⁵

As already noted, it is a relatively rare condition, with a prevalence estimated at between 1 in 10,000 and 1 in 50,000 individuals.¹⁶ Disease onset is relatively early, with symptoms commonly appearing first during childhood and increasing through puberty. There may be identifiable precipitating factors (for example, drugs, infections, trauma, hormones, surgical/dental procedures), but a triggering event for individual episodes may not be evident.

The site of the angioedema attack in HAE is variable, not just between patients but also within the same patient. Most typically HAE presents as a marked diffuse edema in the skin, with the extremities most commonly affected. Swelling can, however, also occur in the face (lips, eyelids, tongue) and genitalia. Although not life-threatening, edema in these locations can be disfiguring and even functionally disabling. Of greater concern is submucosal edema in the gastrointestinal and respiratory tracts. Recurrent abdominal attacks (presenting as acute pain, often with associated nausea and vomiting and occasionally with diarrhea) are common, and a quarter of patients are thought to have abdominal symptoms as the dominant presentation.¹⁷ Ascites may be evident on MRI evaluation. Furthermore, these painful abdominal attacks can be misdiagnosed as an acute abdomen, a consequence of which may be unnecessary surgery.^{6,18} Edema of the airways is the most significant presentation of HAE, with swelling of the larynx and upper respiratory tract having the potential to cause death by asphyxiation. Laryngeal attacks are relatively common, and it has been estimated that approximately 50% of patients will experience at least 1 attack in their lifetime.¹⁹ Death from asphyxiation is a serious risk, even in patients with no previous history of laryngeal involvement.²⁰ Mortality from undiagnosed disease is high (30% to 40%), and this is most often a result of upper airway obstruction.²⁰

Hereditary angioedema is a disease with a significant impact on quality of life, social and physical functioning, and health care costs. Attacks in untreated patients can last between 2 and 5 days and, although these often resolve spontaneously, they can be disabling, affecting work and social activities. It has been estimated that repeated attacks can result in between 20 and 100 days of incapacity per year.²¹ In the United States alone, HAE attacks are thought to lead to around 15,000 to 30,000 emergency department visits annually.²² The ability to diagnose this disease and to treat or, more importantly, prevent attacks is clearly a major goal of management. Newer, more targeted pharmacologic agents

have been developed that will provide better management options, and an important driver of this development has been a better understanding of the underlying molecular processes in HAE.

ENZYMATIC CASCADE AND INHIBITION BY C1INH

There is evidence for activation of a number of systems during attacks of HAE: the contact (bradykinin-forming) system, the factor XII-dependent fibrinolytic cascade and the complement pathway. Which of these is responsible for symptom mediation in HAE has been the matter of much debate and research, but the evidence accumulated over nearly 50 years of research clearly points to the bradykinin-forming system being the most important.

Fig 1 depicts the initiating steps involved in the activation of the cascade. Factor XII circulates as a proenzyme with no detectable activity, but autoactivation on binding to certain negatively charged surfaces (reaction 1) converts factor XII to an active enzyme, factor XIIa. This reaction is relatively slow. It is assumed that a trace of factor XIIa is present in normal plasma (less than 0.01% of the total factor XII content), which is sufficient to initiate the cascade. However, positive feedbacks exist such that products resulting from factor XII activation such as kallikrein or plasmin (reactions 2 and 3) rapidly convert factor XII to factor XIIa. An additional cleavage of factor XIIa (molecular weight, 80,000) converts it to factor XII fragment (factor XII_f; molecular weight, 28,500-30,000), which retains the ability to convert prekallikrein to kallikrein (Fig 2) but is relatively ineffective in continuing the intrinsic coagulation cascade—that is, factor XIIa effectively converts coagulation factor XI to factor XIa, but factor XII_f does not. However, factor XII_f possesses the ability to activate the C1r subcomponent of the first component of complement (which factor XIIa cannot effect) and provides a link between the bradykinin-forming cascade and complement.²³ Activated C1r converts C1s to activated C1s, and activated C1s will activate C4 and C2. This may account for the further lowering of C4 levels and the decline in C2 observed during attacks of swelling patients with hereditary angioedema.

Fig 2 depicts the conversion of prekallikrein to kallikrein by either factor XIIa or factor XII_f. The substrates of kallikrein are shown, which include high-molecular-weight kininogen (HK), from which bradykinin is derived, and a link to fibrinolysis. Kallikrein activates the small amount of prourokinase present in plasma, and the urokinase produced converts plasminogen to plasmin. Kallikrein can also directly convert plasminogen to plasmin, but it is far less effective than urokinase.

Activation of normal plasma generates factor XIIa, primarily, and the major feedback activation of factor XII is a result of kallikrein (Fig 1) rather than plasmin. However, in the absence of C1INH (which inhibits factor XIIa, factor XII_f, kallikrein, and plasmin), formation of factor XII_f is facilitated, and the role of plasmin appears more prominent.²⁴ Fibrinolysis is enhanced as a result of endothelial cell activation by bradykinin (Fig 3) to release tissue plasminogen activator as well as kallikrein activation of prourokinase (Fig 2); the plasmin thus generated can contribute to bradykinin formation by activating factor XII (Fig 1).

BRADYKININ FORMATION AT THE CELL SURFACE

Bradykinin binds to, and activates, the bradykinin B2 receptor, causing vasodilatation, increased vascular permeability, and smooth muscle contraction, all of which lead to the tissue swelling that characterizes HAE.

TABLE I. Angioedema types: diagnostic features and laboratory findings

Type	Presenting symptoms	General features	Family history	Onset	Laboratory findings		
					C1INH	C4	C1q
HAE type I	Edema in extremities, GI tract, respiratory tract; life-threatening laryngeal edema a major concern; abdominal swelling accompanied by pain, vomiting, diarrhea; no urticaria (prodromal nonpruritic eruption of erythema marginatum may be present)	Autosomal-dominant inherited disorder; no sex or race pattern; triggers often unknown; 80% to 85% of HAE cases	Yes (but approximately 20% to 25% spontaneous mutation)	2nd decade or earlier (severity may ↑ postpuberty)	↓ Function normal	↓	N
HAE type II	As for HAE type I	As above; 15% to 20% of HAE cases	As above	As above	N or ↑ abnormal function	↓	N
HAE type III	As for types I and II	Recurrent angioedema in a female population Etiology unclear—mutation in factor XII identified in a subpopulation, suggesting bradykinin as the mediator	Yes	Unclear	N	N	N
Acquired C1INH deficiency, type I	Similar to HAE	Linked to underlying lymphoproliferative disorder (B-cell) or rheumatologic disorders	No	Typically later—4th decade	↓	↓	↓
Acquired C1INH deficiency, type II	Similar to HAE	Anti-C1INH antibodies (mainly IgG but occasional IgA/IgM) bind to active site Increasingly identified in patients designated as type I	No	Typically later—4th decade	↓	↓	↓
Allergic angioedema	Edema (most often face or throat); often with urticaria	Most common form of angioedema; triggers (eg, food, drugs, bee sting, cold/heat) provoke IgE-mediated histamine response			N	N	N
ACE inhibitor–induced angioedema	Edema at all sites—upper airways obstruction as seen in HAE; no urticaria	Possibly up to 8% of angioedema cases Increased susceptibility in black subjects		Typically within first 3 mo of treatment; often within first few weeks	N	N	N
Chronic idiopathic angioedema	Edema (all sites, common on face)	Unclear etiology; persistent symptoms	No	Varies	N	N	N

ACE, angiotensin converting enzyme; GI, gastrointestinal; N, Normal.

Activation pathways have been described that differ from that depicted in Figs 1 and 2 because they can bypass factor XII and activate the prekallikrein-HK complex directly on endothelial cells. Prolylcarboxypeptidase and/or heat shock protein 90 (HSP-90)²⁵ bind to prekallikrein-HK and convert prekallikrein to kallikrein stoichiometrically—for example, the amount of kallikrein produced equals the molar input of HSP-90. Thus direct endothelial cell activation of circulating factor XII may explain the HAE response to trauma (for example, during surgery or dental procedures), during which large areas of endothelium are exposed. Stress-induced release of HSP-90 is also a possibility. Once a small amount of kallikrein is produced, cleavage of factor XII by

kallikrein will trigger the usual kinin-forming cascade. This is shown in Fig 3, in which activation of an endothelial cell (eg, by histamine, the cytokine milieu, hypoxia) liberates vasodilators such as nitric oxide or prostaglandin E₂ as well as HSP-90 and prolylcarboxypeptidase to generate kallikrein. A second endothelial cell is shown below with the kinin-forming cascade activated along the cell surface. Although factor XII can autoactivate on binding to the receptor for the globular heads of C1q (gC1qR) to start the cascade,²⁶ kallikrein might initiate it by cleavage of factor XII.

Because various forms of physical stress or psychic stress can initiate attacks of swelling in patients with HAE, there is the possibility of induction of B1 receptors by cytokines such as IL-1

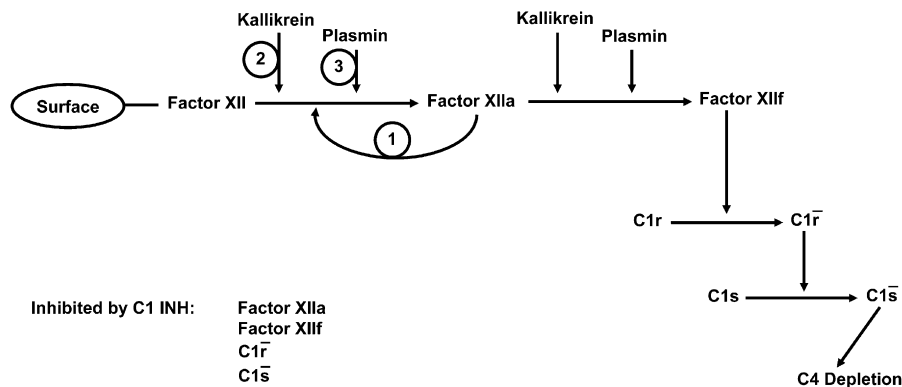


FIG 1. Factor XII-dependent reactions. Initiation begins with factor XII autoactivation (reaction 1) cleavage of surface-bound factor XII by factor XIIa followed by feedback activation by kallikrein (reaction 2). Plasmin activates factor XII similarly (reaction 3) but may not contribute significantly unless plasma is deficient in C1INH. Factor XIIf activates complement.

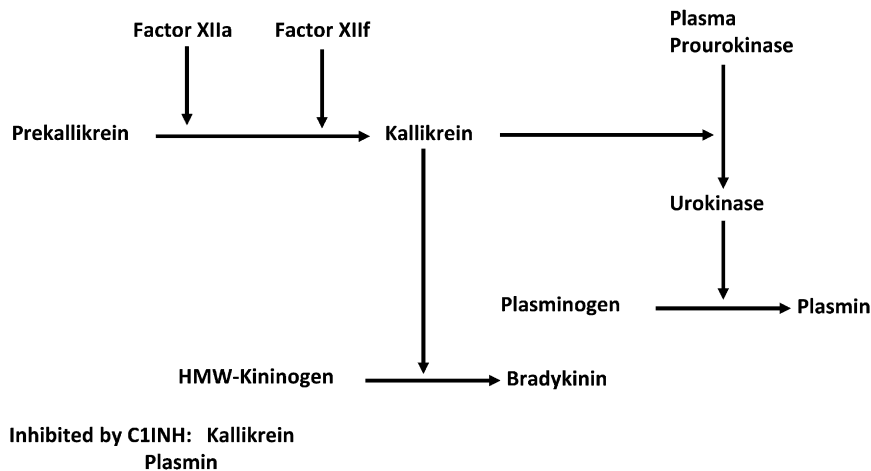


FIG 2. Kallikrein-dependent reactions to produce bradykinin and augment fibrinolysis. *HMW*, high molecular weight.

or TNF- α . The B1 receptor is preferentially stimulated by des-arg⁹ bradykinin formed by removal of the C-terminal arg of bradykinin by plasma carboxypeptidase N (kininase 1/anaphylatoxin inactivator) or cellular carboxypeptidase M. A recent study of vascular leakage (*in vitro* and *in vivo*) using HAE plasma obtained during attacks of swelling reported a role for the B1 receptor²⁷ in mediating vascular leakage, perhaps induced by a cytokine in the HAE plasma. However, an antibody to the HK binding site of gC1qR inhibited the expression of vascular permeability. Thus, if the HAE plasma has high kallikrein levels (which is undoubtedly so), it may digest HK bound to the endothelial cell gC1qR, generating bradykinin, which in the time frame of the experiment is partially converted to des-arg⁹ bradykinin. Thus, the result may reflect not only the kinin profile of the HAE plasma but also kinins generated by the experimental protocol. Direct measurement of the kinins in the HAE plasma will be needed to determine the quantity and role of any B1 receptor agonist.

COMPLEMENT CASCADE: SOME HISTORICAL PERSPECTIVE AND UTILITY IN DIAGNOSIS

Early studies investigating the possible source of kinin-like activity in plasma from patients with HAE suggested that the low

levels of complement component C2 in HAE plasma during attacks of swelling are consistent with a role for C2 cleavage products as vasoactive factors,²⁸ and plasmin cleavage of C2b was reported to produce a kinin with contractile activity. It was subsequently shown, however, that activation of C2 followed by cleavage of C2a or C2b with trypsin, kallikrein, or plasmin did not generate kinin contractile activity.²⁹ In addition, bradykinin was shown to be generated, seemingly spontaneously, on incubation of HAE (but not normal) plasma.³⁰ Although this was assumed to represent activation of the factor XII-dependent bradykinin cascade depicted in Figs 1 and 2, in retrospect, it could be a result of digestion of HK by prekallikrein because prekallikrein has been shown recently to have proteolytic activity without conversion to kallikrein that is suppressed when C1INH is present.³¹ Further research using bradykinin receptor antagonists, as well as amino acid sequencing of the kinin produced on activation of HAE plasma, corroborated these observations and also demonstrated conclusively that bradykinin is the major mediator of enhanced vascular permeability in HAE.³²⁻³⁴

Although the products of the complement cascade are no longer believed to play a role in the development of HAE, it is clear that they are invaluable for the distinction of HAE from other forms of angioedema that are not a result of C1INH

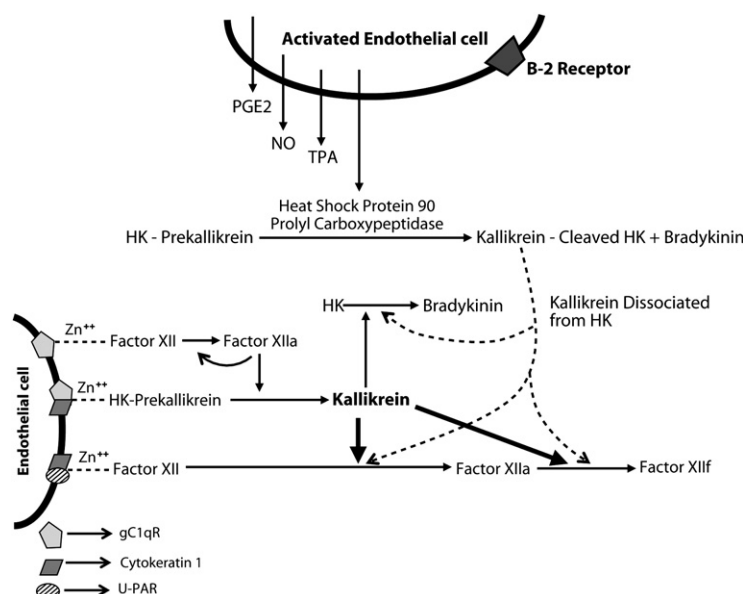


FIG 3. Assembly and activation of the kinin-forming cascade on endothelial cells. Activated endothelial cells present HSP-90 or prolylcarboxypeptidase independent of any factor XII present to generate bradykinin stoichiometrically. The reaction is facilitated when C1INH is absent. Kallikrein thus formed (dotted lines) can initiate factor XII-dependent activation at adjacent cells. PGE2, prostaglandin E2; TPA, tissue plasminogen activator; U-PAR, urokinase plasminogen activator receptor.

deficiency. C1 (the most important complement protein with respect to HAE) is a complex of C1q, C1r, and C1s components. C1 is unstable in the absence of C1INH such that C1r autoactivates leading to activation of C1s which, in turn, cleaves and activates C4. This is why there is a low C4 level in 95% of patients with HAE even when they are asymptomatic.

Acquired C1INH deficiency is caused by C1INH depletion or inactivation associated with other diseases, with lymphoma the most prominent.^{35,36} This disorder was originally divided into type I disease with immune complex activation of C1 and secondary depletion (consumption) of C1INH, and type II disease with IgG antibody to C1INH,³⁷ which interferes with its inhibition of proteases.³⁸ The latter mechanism, however, appears prominent in most cases, indicating that the distinction of types I and II is not always clear and the disorder can be viewed as one of B-cell hyperreactivity³⁹ most typically expressed as B-cell lymphoma or monoclonal gammopathy. Cryoglobulinemia is an example of a massive circulating immune complex associated with very low C4 levels because of binding of C1q, yet angioedema is rarely, if ever, seen. The degree to which C1INH is consumed in this instance is not known. The mechanism of inactivation of proteases by C1INH involves cleavage of the C1INH molecule itself, resulting in a conformational change, with inhibition of enzyme activity resulting from active site distortion.⁴⁰ In acquired C1INH deficiency, the antibody-bound C1INH is digested by proteases, which decreases its molecular weight, but the cleaved inhibitor is unable to inactivate the protease.

C1INH normally acts across multiple systems and at multiple sites. It is the primary regulator of the classical complement pathway (via inactivation of C1r and C1s), and it also inhibits the alternative pathway (by binding to C3b). C1INH contributes to inactivation of plasmin, but the major fast-acting plasmin inhibitor is α_2 antiplasmin. In relation to HAE, the most important

actions of C1INH are to inhibit the bradykinin-forming contact system, where it inactivates kallikrein, factor XIIa and factor XIIIf, each of which is an important antecedent to bradykinin production.

Diagnosis of HAE is commonly missed or delayed, and it has been reported that the average time from symptom appearance to diagnosis can be as long as 20 or more years.⁴¹ A diagnosis of HAE should be suspected in cases in which there is a history of recurrent attacks of peripheral angioedema (nonpruritic, nonpitting) and/or abdominal pain in the absence of urticaria. The swelling can be seen affecting many parts of the body, most commonly the extremities, face, or genitalia.

The genetic basis of HAE means that family history is an important starting point in diagnosing the disease. Yet approximately 20% to 25% of affected individuals have C1INH deficiency resulting from a new mutation, so that lack of HAE in other family members cannot rule out the diagnosis. Laboratory testing based on a C4 determination and C1INH levels (quantitative and functional) allows differentiation of HAE from angioedema of different etiologies. C1q levels remain normal in HAE, allowing differentiation from acquired C1INH deficiency in which levels are reduced in about 70% of patients. Table I lists the most common conditions (allergic as well as nonallergic) in which angioedema is a prominent presenting symptom, with the key diagnostic indicators in each case. (The distinctions between forms of angioedema are reviewed in more detail elsewhere.⁴²) The necessity of basing diagnosis on a combination of family and clinical history, symptoms, and laboratory tests is immediately apparent, with no individual factor serving as a clear differentiator. The differences in etiology also point to a need for different treatment approaches; for example, antihistamines are a mainstay of treatment in allergic angioedema but have no role in managing HAE, in which histamine has no role.

CURRENT THERAPY

Patients living with HAE face a number of challenges, and they live with uncertainty about when their next attack will come. Although many attacks resolve spontaneously, the variability of the disease (including severity and site of attack) and common lack of identifiable triggers mean that most patients with HAE cannot confidently predict when, where, and how severe their next attack will be. Management approaches need, therefore, to consider 3 main areas: (1) routine prophylaxis, in which the goal is to decrease the frequency, duration, and severity of attacks; (2) procedural prophylaxis, which is directed at preventing attacks that may result from predictable trauma (eg, surgery or a significant dental procedure), and (3) treatment of acute attacks.

Craig⁴³ recently reviewed the evidence for defining which patients are likely to need routine prophylaxis and concluded that those with a history of frequent and/or severe attacks (including laryngeal attacks), loss of social function and quality of life, or significant anxiety should be considered for prophylaxis.

In the United States, until recently (see “New and Investigational Interventions”), there have been no approved effective agents for acute treatment of C1INH-related angioedema. Because the angioedema in HAE is not histamine-mediated, antihistamines or corticosteroids are ineffective in acute management, and even adrenaline given subcutaneously is unreliable and only occasionally provides some benefit. Attacks that involve the extremities and are not disabling or life-threatening will normally be considered self-limited, and acute treatment if any would be aimed at symptom control. Acute management of the more severe abdominal and upper airway manifestations is essential. In the absence of effective pharmacologic agents, abdominal attacks tend to be managed with fluid replacement and pain relief. Laryngeal edema, with the potential for asphyxiation, may require hospitalization with a potential need for intubation or tracheostomy.

Androgens such as methyltestosterone have been in use since the 1960s; however, poor tolerability of the basic molecules drove the development of attenuated forms (eg, 17- α -alkylated anabolic androgens such as danazol, stanozolol) with better safety profiles.⁴² The mechanism of action of androgens in alleviating HAE symptoms is unclear, although androgens can cause an increase in C4 or C1INH levels in plasma. However, they have been shown to be effective clinically at lower doses than might be required to upregulate C1INH gene expression to normal levels; therefore, dosage for routine prophylaxis needs to be titrated down to the lowest dose at which there is a clinical effect rather than being based on normalization of levels of C1INH/C4⁴³ or even some incremental increase from baseline. Androgens have been shown to play a role in kinin catabolism (by increasing levels of aminopeptidase P), which may contribute to symptom improvement.

Clinical use of androgens is mostly confined to prophylaxis, both routine (dose-titrated) and procedural (eg, high-dose danazol for 1 week before the planned procedure). The onset of effect (1–2 days) means that androgens are not generally used as acute treatment, although increasing the maintenance dose during an attack is an option. When used prophylactically, the duration can be for a lifetime, and androgenic side effects are a concern.

Antifibrinolytic agents such as ϵ -aminocaproic acid or tranexamic acid inhibit the conversion of plasminogen to plasmin (and also inhibit plasmin) and have been used in the routine

prophylaxis of HAE with some (but limited) efficacy. The mechanism of action is unclear because they do not increase plasma C1INH levels, but inhibition of some effect of plasmin on bradykinin formation is implied. Kallikrein converts plasma prourokinase to urokinase, which in turn converts plasminogen to plasmin.⁴⁴ Also, bradykinin stimulation of endothelial cells releases tissue plasminogen activator. Thus, high plasmin levels are found during attacks of swelling in HAE,⁴⁵ and plasmin activation of factor XII⁴⁶ may be the mechanism by which it augments bradykinin formation. There is also some anecdotal evidence (not supported by published evidence) for use of ϵ -aminocaproic acid in treating acute attacks.⁴⁷ They are generally less preferred (and less effective) than androgens, and in the United States, its role has been limited to those for whom androgens are contraindicated. In Europe, tranexamic acid has been favored for prophylaxis in children.⁴⁸

Fresh frozen plasma has been used in preference to high-dose androgens in procedural prophylaxis, with an infusion given several hours before the procedure. Fresh frozen plasma has also been used in acute attacks, with the aim of replacing plasma C1INH. However, there is a theoretical risk that concomitant replenishment of plasma proteases and substrates involved in angioedema formation will worsen the swelling, and examples of this have been reported.

NEW AND INVESTIGATIONAL INTERVENTIONS

Alternatives have been sought for prophylaxis as well as for treatment of acute attacks that target the bradykinin-forming cascade. The 2 main areas for development are C1INH replacement therapy directed against the fundamental defect in HAE, and agents directed downstream at the contact (bradykinin-forming) system. The rationale for the various approaches is described here; a thorough review of the clinical evidence for the various agents is outside the scope of this article, but the reader is referred to Krassilnikova et al,⁴¹ Frank,⁴⁹ and Bernstein⁵⁰ for more detailed reviews.

C1INH REPLACEMENT THERAPY

Recognition of C1INH deficiency and/or dysfunction as the primary cause of HAE has led to the development of direct replacement therapy, an approach that has been widely used in Europe, Canada, and Australia for over 20 years but which, until recently, has not been available in the United States. A number of different pharmaceutical approaches have been taken in the development of C1INH replacements, resulting in C1INH concentrates derived from human plasma as well as recombinant human C1INH produced in rabbits.

Plasma-derived C1INH concentrates are perhaps the most physiologic approach, because these directly replace the normal protein to act at all steps in the various cascades described, but there is a theoretical possibility of transmission of infectious agents such as viruses or prions. The manufacturing process therefore includes steps to remove sources of infection via nanofiltration and pasteurization. An alternative approach is the production of recombinant human C1INH in rabbits, with the benefit of a theoretically limitless supply of C1INH that is unlikely to contain human pathogens. There is, however, a potential for the development of hypersensitivity reaction to the

nonhuman allergens, and the short half life limits its potential use to acute episodes but not prophylaxis.

At the time of this writing, the US Food and Drug Administration has approved (as of late 2008) a C1INH (Cinryze; Viro-Pharma, Exton, Pa) for use in routine prophylaxis of HAE. More recently, they have also approved a C1INH (Berinert; CSL Behring, King of Prussia, Pa) for acute management of facial and abdominal attacks in adolescents and adults. (Non-US guidelines have, in fact, been recommending use of plasma-derived C1INH for routine and procedural prophylaxis as well as treatment of acute attacks for some time.^{16,51}) Data from initial clinical studies with these agents are reviewed elsewhere,^{41,49,50} and a recent study of Cinryze use for acute therapy or prophylaxis has just been published.⁵²

KININ-PATHWAY MODULATORS

These agents act at a point further downstream in the contact system, to inhibit either the formation of or the action of bradykinin, and 2 approaches have thus far been taken. A recombinant kallikrein inhibitor (DX-88 [ecallantide]) has been developed with the aim of blocking production of bradykinin.⁵³ Acting still further downstream is a direct antagonist of the bradykinin B2 receptor (icatibant),⁵⁴ which is a synthetic decapeptide structurally analogous to bradykinin with a similar receptor affinity.

Both agents have been developed for subcutaneous, rather than intravenous, administration, and both are synthetic, which may minimize the risk of infection as a result of blood-borne agents. As with all foreign peptides, however, there is a theoretical risk of allergy because of sensitization with repeated administration. There is also limited knowledge about the long-term effects of direct bradykinin inhibition, with some cardiac effects seen in animal models, although because these agents are intended for acute use rather than routine prophylaxis, this is perhaps of less concern.⁴⁹ Clinical trials have been completed for both agents in acute attacks^{41,50} and, at the time of writing, Ecallantide has been approved in the United States for acute treatment of HAE attacks,⁵⁵ whereas icatibant has been approved in Europe and Brazil.⁵⁶

Future approaches suggested by recent data include blockade of the B1 receptor, if the findings of Bossi et al²⁷ are confirmed, or blockade of gC1qR^{25,27} to inhibit activation at the cell surface.

HAE is a rare but debilitating—and potentially fatal—disorder for which current treatment strategies are not entirely satisfactory; there are significant risks of side effects (especially in pregnancy and in the young), and no treatment can be said to be optimally effective, especially in the area of treatment of acute attacks. Improved understanding of the underlying physiologic processes in HAE has, however, led to the development of new targeted therapies that ideally will revolutionize both the routine and acute management of this distressing condition.

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