

REVIEW ARTICLE

The dermatology view of hereditary angio-oedema: practical diagnostic and management considerations

M. Maurer,^{†,*} L.C. Parish[‡][†]Department of Dermatology, Venereology and Allergy, Charité - University Medicine, Berlin, Germany[‡]Department of Dermatology and Cutaneous Biology, Jefferson Medical College of Thomas Jefferson University, Philadelphia, PA, USA

*Correspondence: M. Maurer. E-mail: marcus.maurer@charite.de

Abstract

Hereditary angio-oedema (HAE) is characterized by recurrent, localized, non-pitting, non-pruritic, non-urticarial oedema. Nearly all patients experience skin swelling as a feature of HAE. There may be painful abdominal attacks, accompanied by nausea and vomiting. The disease is life-threatening should laryngeal oedema occur. HAE results from a deficiency or dysfunction of C1 inhibitor, a plasma protein with an important role in regulating the contact, complement and fibrinolytic systems. Effective management of HAE should include a plan for treatment of attacks, as well as routine and preprocedure prevention. Acute and prophylactic therapy with C1 inhibitor therapy for correcting the underlying deficiency in HAE is a valuable option.

Received: 19 December 2011; Accepted: 4 April 2012

Conflict of interest

M. Maurer has been a paid consultant, has received unrestricted or educational grants and has received funding to support the work on this project; L.C. Parish has been a paid consultant, has received unrestricted or educational grants, has received funding to support the work on this project and has received a grant for participating in the writing of a manuscript on this subject.

Funding source

None.

Introduction

Hereditary angio-oedema (HAE) is a rare autosomal-dominant disease caused by mutation in the C1 inhibitor gene, resulting in deficiency or dysfunction in C1 inhibitor, a human plasma protein with an important role in regulating the contact, complement and fibrinolytic systems.^{1–6} The disorder is characterized by intense, diffuse subcutaneous or submucosal oedema, which can involve the face, extremities, trunk, larynx, abdomen or genitalia. Attacks are typically recurrent and, in most cases, unpredictable. Cutaneous manifestations are a common feature of HAE, and in many patients, the oedema is of such severity that it results in temporary disability (e.g. inability to write or hold objects in the case of hand oedema). Abdominal attacks are associated with transient oedema of the bowel wall and usually present with crampy or colicky pain, vomiting, diarrhoea, intestinal obstruction and occasionally ascites.⁷ HAE may be life-threatening, when swelling occurs in the upper airway, with asphyxiation from laryngeal attacks, being the most common cause of mortality.^{8–10} Approximately half of all patients with HAE experience a laryngeal attack during their lifetime.⁸

Although the exact incidence of HAE is unknown, prevalence is estimated to be 1 in 50 000.^{11,12} There are approximately 1500 known cases of HAE in Germany, alone.¹³ No sex or race predominance is noted.⁴ Signs may appear at any age, although most cases of HAE present in childhood, with attacks worsening during puberty.^{14,15} Signs typically persist throughout life, but the frequency and severity of attacks are difficult to predict.¹⁴ Observational studies suggest that trauma can precipitate swelling, although angio-oedema often occurs without an apparent trigger.

The consequences of HAE are substantial. It is estimated that up to 30 000 visits to the emergency department in the United States are attributed to HAE each year.^{16,17} Patients who present to emergency departments for severe swelling may be mistakenly identified as having allergic reactions or even acute gastrointestinal conditions, possibly leading to inappropriate surgical procedures in up to 1/3 of patients.^{16–19} Unfortunately, endoscopy to evaluate acute abdominal pain or indeed any instrumentation of the oropharynx can worsen the clinical manifestations and produce potentially fatal results.⁴

HAE also has a dramatic negative impact on a patient's quality of life.²⁰ Cutaneous swelling is often painful and disabling, preventing patients from working or going to school. Individuals with HAE are often incapacitated for as many as 20–100 days, annually,¹ and up to 42% of patients with HAE may develop depression.²⁰ Patients trying to manage severe abdominal pain are known to develop narcotic dependence.²¹ In addition, misdiagnosis leads to years of ineffective medical therapy and markedly diminished quality of life, as patients continue to experience untreated attacks.^{6,11,16,22}

Almost all adults with HAE experience cutaneous swelling, with the upper extremities most commonly affected.¹⁴ In one analysis of 221 German patients with C1 inhibitor deficiency, 97% of reported oedema episodes involved skin swelling of the extremities, face, genitals and trunk;¹⁴ another study reported skin involvement in 91% of 226 HAE patients.¹⁸ Subcutaneous oedema is the most common and earliest manifestation in paediatric patients with HAE.²³ Cutaneous attacks are especially disturbing for HAE patients, because oedema associated with facial or extremity attacks can be disfiguring and disabling. Cutaneous oedema is the cardinal sign of HAE for which the dermatologist may be consulted early in the course of the disease. Awareness of HAE can contribute to a more timely diagnosis and use of effective treatments.

C1 inhibitor gene mutation

The general condition of angio-oedema was described by John Laws Milton in 1876,²⁴ and findings of a hereditary component to the disease were published by William Osler in 1888.²⁵ Nearly a century later, deficiency of C1 inhibitor as the underlying defect of HAE was elucidated in a seminal study by Virginia Donaldson and Richard Evans.³ Since that time, understanding of the pathophysiology and genetic basis of HAE has expanded considerably. C1 inhibitor is a serine protease inhibitor, belonging to the same family that includes antitrypsin and antithrombin. It is primarily synthesized by hepatocytes.⁴ The main function of C1 inhibitor is regulation of the contact (kallikrein–kinin) system, complement cascade and intrinsic coagulation cascade.^{2,26}

As a primary regulator of both the contact and complement systems, C1 inhibitor modulates a number of steps that lead to the production of bradykinin^{2,6} (Fig. 1). Because patients with HAE have low functional C1 inhibitor, the complement and contact cascades become unregulated during an attack, as C1 inhibitor is irreversibly consumed in each enzymatic interaction.^{6,8} Bradykinin is subsequently overproduced as a result of diminished C1 inhibitor function, leading to increased vascular permeability, extravasation and uncontrolled oedema.

HAE results from mutations in the C1 inhibitor gene located on chromosome 11; more than 200 different mutations have been identified in patients with HAE.^{1,27–29} The disorder is autosomally dominant, although 25% of cases are attributed to spontaneous mutation in individuals with no family history of HAE.^{4,30}

There are two major forms of HAE.⁸ Type I is characterized by a deficiency in C1 inhibitor production, resulting in reduced levels of both functional and antigenic C1 inhibitor;^{3,5,31} approximately 85% of patients with HAE have type I. Approximately 15% of patients with HAE have type II, which results in secretion of a mutant C1 inhibitor protein that is dysfunctional. Patients with type II HAE have normal (or slightly higher than normal) antigenic C1 inhibitor levels, but low functional C1 inhibitor levels.^{6,32} Types I and II HAE have indistinguishable clinical presentations.

A third form, type III, is very rare and has been described in patients who have normal antigenic and functional C1 inhibitor levels. This type primarily occurs in women with a family history of angio-oedema.^{33,34} Although similar to types I and II HAE, type III may be associated with a defect in coagulation factor XII gene.

Clinical presentation and diagnosis

HAE is a rare condition, and many physicians may never encounter a patient with this disorder. Due to its variable clinical presentation, the differential diagnosis may be confusing. The time until the diagnosis is made on average ranges from 8 to 22 years after the initial attack.^{22,35,36} The frequency of attacks is extremely unpredictable and may vary from fewer than one attack per year to more than one attack per week, and the frequency of recurrences can fluctuate during different life stages.^{8,18,37} Attacks may occur in multiple locations or start in one area and spread to another location before resolving spontaneously after 2–5 days (up to 1 week).¹⁴ The features of HAE include a history of recurrent angio-oedema that is non-urticarial and non-pruritic, lasts longer than 24 h and is unresponsive to antihistamines³⁸ (Table 1). Other diagnostic features include unexplained abdominal pain and early onset of signs (typically <18 years of age when first attack occurs). HAE should be suspected in patients presenting with any of the characteristic signs, especially in the presence of a positive family history. Attacks may occur without a trigger; however, precipitating factors that contribute to the onset of an attack include stress, trauma, infection, menstruation and pregnancy.^{8,39,40} In addition, some medications, such as oestrogen-containing agents and angiotensin-converting enzyme (ACE) inhibitors, may also induce HAE attacks. In some patients, angio-oedema is preceded by prodromes, such as a tingling sensation and erythema marginatum, a non-raised, serpiginous eruption, which is reported in up to 50% of patients with HAE.^{35,40–42} Nearly all patients present with cutaneous swellings, most commonly of the hands, arms, legs, feet, trunk, face and genitalia, with non-pitting oedema characterized by ill-defined margins^{4,7,14,15,35,40} (Fig. 2a). Submucosal intestinal oedema or laryngeal swelling also may occur. When oedema affects the viscera, varying degrees of abdominal obstruction may occur (Fig. 2b). Typical gastrointestinal manifestations include cramps (that can be sudden and severe), anorexia, nausea, vomiting, diarrhoea and tenderness upon palpation. Ascites with fluid accumulation in the peritoneal cavity may be observed. In the case of laryngeal or facial

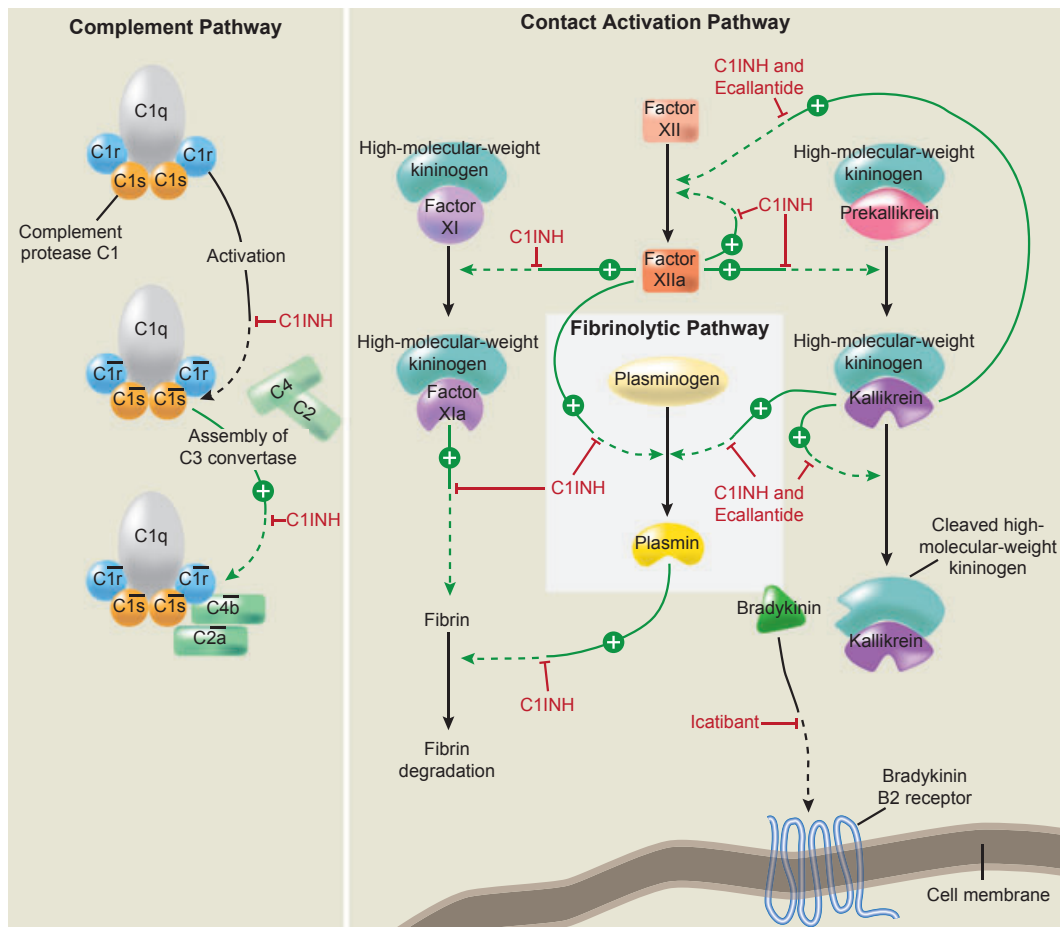


Figure 1 Pathways inhibited by C1 inhibitor (C1 INH) (reproduced from Ref. 6, with permission).

Table 1 Clinical features of hereditary angio-oedema

• Recurrent, non-pitting, non-pruritic angio-oedema
• Angio-oedema lasting longer than 24 h
• Unresponsive to antihistamines or corticosteroids
• No weals
• Unexplained abdominal pain (sudden/severe cramps, anorexia, nausea, vomiting, diarrhoea, tenderness upon palpation)
• Angio-oedema preceded by a prodrome (tingling sensation, erythema marginatum)
• Signs gradually worsen over 24–36 h; spontaneously resolve after 2–5 days
• Family history of angio-oedema
• Signs first appear during first or second decade
• Unknown triggers

swelling, risk of asphyxiation is as high as 40% in untreated patients.^{4,10}

Conditions resembling HAE, but with a different underlying pathology, include acquired C1 inhibitor deficiency, allergic angio-oedema, ACE inhibitor-induced angio-oedema and chronic

idiopathic angio-oedema^{43,44} (Table 2). Acquired C1 inhibitor deficiency is most similar to HAE, except for the absence of a genetic component.^{45,46} Acquired C1 inhibitor deficiency is often the result of a lymphoproliferative disorder and is caused by increased C1 inhibitor catabolism.³⁹ Onset of acquired C1 inhibitor deficiency tends to occur in middle age, and there is no family history. Allergic reactions are the most common form of angio-oedema, in which a known trigger (e.g. allergy to a bee sting, food, latex) causes weals and/or pruritus. Allergic attacks are mediated by histamine and other proinflammatory mediators, released by mast cells in response to IgE receptor activation and respond to treatment with antihistamines, corticosteroids or epinephrine; however, these medical interventions are of no clinical benefit in HAE.⁸ ACE inhibitor-induced angio-oedema typically affects the lips, face and tongue and is not associated with pruritus or urticaria. The inhibition of ACE inhibitors leads to accumulation of bradykinin,⁴⁷ with discontinuation of the ACE inhibitor being the treatment of choice.⁶ The use of ACE inhibitors should be avoided in patients with HAE. Chronic idiopathic angio-oedema may be diagnosed in individuals who experience

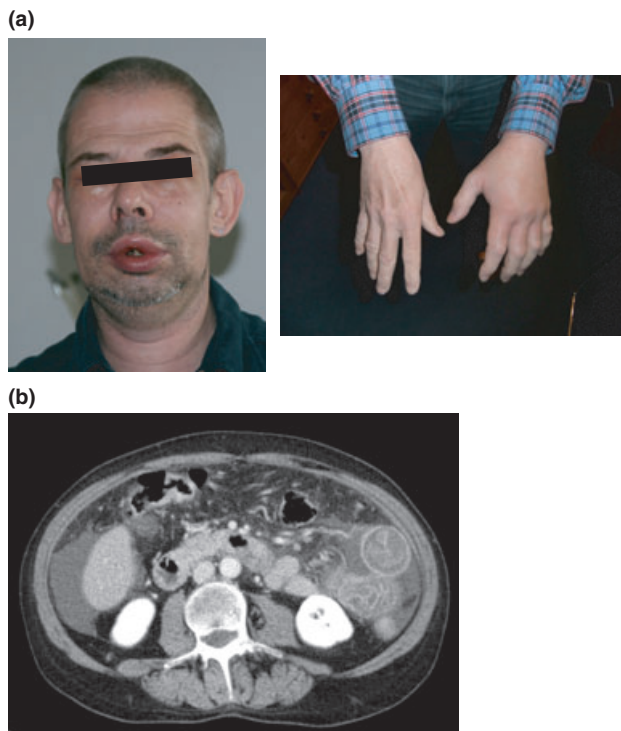


Figure 2 (a) Photographs showing facial and extremity swelling during an attack of hereditary angio-oedema (HAE). (b) CT scan during abdominal HAE attack shows oedematous bowel wall; the gut lumen is closed.

three or more episodes per year of angio-oedema in which the pathology is indeterminant.⁶

In addition to careful medical and family history, measurement of biochemical markers is necessary to confirm the diagnosis of HAE⁴⁸ (Table 3). Serum complement factor 4 (C4) levels may be used to screen for HAE.^{21,37} C4 levels are low in symptomatic HAE patients and low in more than 90% of asymptomatic patients. If C4 levels are in the normal range at initial screening, the test should be repeated during an attack. Measurement of antigenic and functional C1 inhibitor levels distinguishes between type I (low antigenic and functional C1 inhibitor levels) and type II (normal or elevated antigenic C1 inhibitor level, low functional C1 inhibitor activity) HAE. Measurement of complement proteolytic protein, C1q, differentiates HAE from acquired C1 inhibitor deficiency, because C1q levels are normal in HAE and typically low in acquired C1 inhibitor deficiency. Serum complement proteins are normal in allergic, ACE inhibitor-induced and chronic idiopathic forms of angio-oedema.

Treatment considerations

Because HAE is mediated by bradykinin, treatments used for other forms of angio-oedema (e.g. corticosteroids, antihistamines) are not effective. Obviously, patients with HAE should avoid known

triggers that precipitate attacks.⁶ For example, ACE inhibitors are contraindicated, and women should not take exogenous oestrogens, including oral contraceptives.

Acute treatment

Acute treatment options for HAE include C1 inhibitor replacement therapy (human or recombinant) and targeted therapies that act at specific points in the kallikrein-kinin (contact) system, including icatibant (Firazyr®), a selective competitive bradykinin type 2-receptor antagonist^{49,50}, and ecallantide (Kalbitor®), a recombinant kallikrein inhibitor⁵¹ (Table 4). Rapid replacement of C1 inhibitor is a good option for managing acute HAE attacks, including laryngeal oedema,^{11,48,52} with signs beginning to abate within 30–60 min of infusion.^{53–58} With proper training, selected patients may have the option to self-administer C1 inhibitor therapy.⁵⁹

Routine prevention of HAE attacks

Patients with HAE may benefit from routine prophylactic therapy, if they have frequent or severe attacks, poor quality of life, or history of laryngeal attacks.^{13,15,21,37} Mortality from HAE has decreased with the use of prophylactic therapy.^{10,18} Attenuated androgens, antifibrinolytic agents and nanofiltered C1 inhibitor are options for routine prevention⁴⁸ (Fig. 3).

Attenuated androgens, such as danazol, oxandrolone and stanazolol, have been used to manage HAE since the 1960s and have been considered the gold standard for prophylaxis in many countries.⁶⁰ Androgens may be administered orally to reduce both the frequency and severity of attacks,⁶¹ although slow onset of action (~48 h) limits utility during an attack. They may also be difficult to administer during abdominal attacks. Androgens are known to increase hepatic synthesis of C1 inhibitor, although the exact mechanism is unclear.¹² International consensus guidelines propose two options for therapeutic dosing with an aim of maintaining HAE control and minimizing adverse effects: (1) achieving initial control of attacks with higher doses (400–600 mg daily) and gradually tapering to a dose that maintains effective control or (2) starting with a low dose and gradually increasing until an effective dose is achieved.^{11,12,37} Danazol 200 mg once daily is recommended as the highest long-term dosage for HAE prevention.⁴⁸ There are a number of drawbacks with androgen therapy in terms of anabolic (weight gain, increased skeletal muscle mass, increased haematopoiesis, increased bone density, salt and water retention and abnormal lipid metabolism) and androgenic (development of male sex characteristics, increased hair growth, acne, behavioural changes and infertility) side-effects.^{12,13} These agents should not be used in pregnant or lactating women or individuals with renal, hepatic or cardiac dysfunction. Androgen therapy is not recommended for children due to the potential for androgens to affect behaviour, as well as growth and development, namely premature closure of epiphyseal plates.^{6,23} In Germany, androgenic derivatives, including danazol, are not approved for HAE and are

Table 2 Comparison of angio-oedema types (adapted from Ref.⁴⁴, with permission)

Type	Features	Clinical presentation	Laboratory findings
HAE type I	80–85% of HAE cases Autosomal-dominant inherited disorder, family history in majority (approximately 20–25% spontaneous mutation) No sex or race pattern Signs appear second decade (or earlier)–severity may increase postpuberty Triggers often unknown	Oedema present in extremities, GI tract, respiratory tract Life-threatening laryngeal oedema a major concern Abdominal swelling accompanied by pain, vomiting, diarrhoea Urticaria absent	C1 INH low (antigenic and functional) C4 low C1q normal (compare AAE)
HAE type II	15–20% of HAE cases (family history, sex/race pattern, triggers as above)	As for HAE type I	C1 INH normal/elevated but dysfunctional C4 low; C1q normal (compare AAE)
HAE type III	Recurrent AE in female population Origin unclear may involve abnormal expression of factor XII gene, leading to increased generation of bradykinin	Indistinguishable from types I and II	C1 INH normal (antigenic and functional) C4 normal
AAE type I	Linked to underlying lymphoproliferative disorder (B cell) No family history/genetic link Signs appear later in life (typically fourth decade)	Signs similar to HAE	C1 INH/C4 low C1q reduced (compare HAE)
AAE type II	Autoantibodies produced against C1 INH (mainly IgG but IgA/IgM have been noted) bind to active site No family history/genetic link Signs appear later in life (typically fourth decade)	Signs similar to HAE	C1 INH/C4 low C1q reduced (compare HAE)
Allergic AE	Most common form of AE triggers (e.g. food, chemicals, drug, bee sting, cold/heat provoke histamine response)	Oedema (most often face or throat) Urticaria may be present	Normal
ACE inhibitor-induced AE	Possibly up to 8% of AE cases ACE Onset normally within first week of therapy but delayed presentation has been noted	Oedema at all sites; airway and tongue very common Urticaria may occur but not common	Normal
Chronic idiopathic AE	Unclear origin; persistent signs No family history Age of onset any time	Oedema at all sites – especially face and lips – normally accompanied by urticaria	Normal

AAE, acquired C1 inhibitor deficiency; ACE, angiotensin-converting enzyme; AE, angio-oedema; C1 INH, C1 inhibitor; C4, complement factor 4; GI, gastrointestinal; HAE, hereditary angio-oedema.

not marketed. Import and use of androgens in Germany require justification by the prescribing physician. In other countries, including Austria and Switzerland, danazol is licensed for use in HAE.

Antifibrinolytic agents are rarely used for routine prophylaxis of HAE, because these agents reduce the number and severity of attacks in only about 30% of patients with HAE;²¹ however, antifibrinolytics may be considered for patients intolerant of androgen therapy or in children and pregnant women.^{11,21} The mechanism of action of antifibrinolytics in HAE is unknown, and there is no observable effect on C1 inhibitor levels.³⁷ Tranexamic acid is

approved for prophylactic treatment of HAE and is administered as an oral dose of 20–50 mg/kg/day.^{6,13,15} Common side-effects of antifibrinolytics include nausea, vertigo, diarrhoea, postural hypotension, fatigue and muscle cramps.

International consensus algorithms include C1 inhibitors for routine prophylaxis of HAE,^{11,12,48,52} particularly for individuals who cannot tolerate (or have contraindications to) androgen or antifibrinolytic therapy. Candidates for routine prevention include patients with significant anxiety; those with more than one attack per month; previous intubation, intensive care unit stay, or laryngeal swelling; those with more than 10 days lost from school or

Table 3 Laboratory diagnosis of hereditary angio-oedema (HAE)

• If HAE is suspected based on clinical features, diagnosis should be confirmed with laboratory analysis of complement components (C4, C1 INH, C1q)
• Begin screening by measuring serum C4 levels and quantifying C1 inhibitor antigenically and functionally – If serum C4 levels are normal, repeat screen during an attack – If serum C4 levels are normal during an attack, consider other causes for angio-oedema – If serum C4 levels are decreased, quantifying C1 inhibitor antigenically and functionally will distinguish between types I and II HAE – type I: low antigenic and functional C1 INH – type II: normal or elevated antigenic C1 INH, low functional C1 INH
• C1q levels are normal in HAE and reduced in acquired angio-oedema

C1 INH, C1 inhibitor; C4, complement factor 4.

work per year; a significantly decreased quality of life; narcotic dependence; and individuals with limited access to healthcare or with rapid onset of attacks.^{21,59} C1 inhibitors are efficacious for routine prevention, consistently reducing frequency of attacks.^{56,62–65} A study in patients with severe HAE, defined as presence of severe abdominal, urogenital and/or laryngeal attacks at least once a week or at least 52 attacks per year in any location, and who were refractory to long-term prophylaxis with attenuated androgens, demonstrated that C1 inhibitor therapy significantly reduced incidence of attacks ($P < 0.001$) and had a positive impact on quality-of-life measures.⁶⁶

Recently, nanofiltered C1 inhibitor (Cinryze®) was approved in the EU for routine and preprocedure prevention of HAE attacks, as well as treatment for acute attacks. Treatment with prophylactic nanofiltered C1 inhibitor concentrate resulted in a greater than

twofold reduction in the number of attacks compared with placebo.⁵⁷ In this double-blind, crossover trial, 22 patients with HAE were randomly assigned to prophylactic twice-weekly injections of nanofiltered C1 inhibitor (1000 U) or placebo for two 12-week periods; each patient acted as his or her own control. The number of attacks of angio-oedema per period was 6.3 in the nanofiltered C1 inhibitor group compared with 12.8 in the placebo group ($P < 0.001$). Severity of attacks (measured on a 3-point scale, with 1 indicating mild, 2 moderate and 3 severe) was significantly lower with nanofiltered C1 inhibitor prophylaxis (mean 1.3 ± 0.85) compared with placebo (1.9 ± 0.36 ; $P < 0.001$). Nanofiltered C1 inhibitor prophylaxis reduced duration of attacks compared with placebo (2.1 ± 1.13 vs. 3.4 ± 1.39 days; $P = 0.002$) and was associated with fewer days of swelling (10.1 ± 10.73 vs. 29.6 ± 16.9 days; $P < 0.001$). These findings were confirmed in an open-label trial, where 146 patients with HAE and who had one or more attacks per month or a history of laryngeal oedema were enrolled.⁶⁷ Nanofiltered C1 inhibitor therapy (1000 U) was administered every 3–7 days (median of 1.4 days/week). Median HAE attacks were reduced from a rate of 3.0 per month to 0.2 per month; 86% of patients experienced an average of less than one attack per month, and 35% reported no attacks during the study.⁶⁷ The most common adverse effects reported in this study were headache, nausea, dermatitis, erythema and diarrhoea.

Preprocedure prevention of HAE attacks

Preprocedure prevention of attacks before medical, dental or surgical procedures is the third component of disease management for patients with HAE. Laryngeal oedema and death from asphyxiation have occurred in patients with HAE following dental and medical procedures.⁹ Consensus guidelines recommend prophylactic treatment with C1 inhibitor administered 1–6 h prior to a

Table 4 Drugs used for acute treatment and prevention of hereditary angio-oedema (HAE) attacks^{13,15}

Product name	Indication	Adult dosage and administration
C1 inhibitor		
Pasteurized (Berinert® P; CSL Behring)	Acute	20 U/kg IV
Nanofiltered (Cinryze®; ViroPharma SPRL)	Acute/Prevention	Acute: 1000 U IV; second 1000 U if no response within 60 min Routine: 1000 U IV every 3–4 days Preprocedure: 1000 U IV within 24 h before procedure
Recombinant (Ruconest®; Pharming Group N.V.)	Acute	50 U/kg IV; 4200 U IV in adults >84 kg
Icatibant (Firazyr®; Shire)	Acute	30 mg SC
Ecallantide (Kalbitor®; Dyax Corp)	Acute*	30 mg SC; administered in three 10 mg injections
Tranexamic acid (Cyklokapron®; Pfizer)	Prevention	20–50 mg/kg/d PO split BID or TID
Danazol	Prevention†	100 mg PO every 3 days; up to 600 mg QD

BID, twice daily; IV, intravenous; PO, by mouth; QD, once daily; SC, subcutaneous; TID, 3 times daily; U, units.

*Approved in the United States; under review in Europe.

†Used for prophylactic therapy in other countries, including Austria and Switzerland, but not approved in Germany.

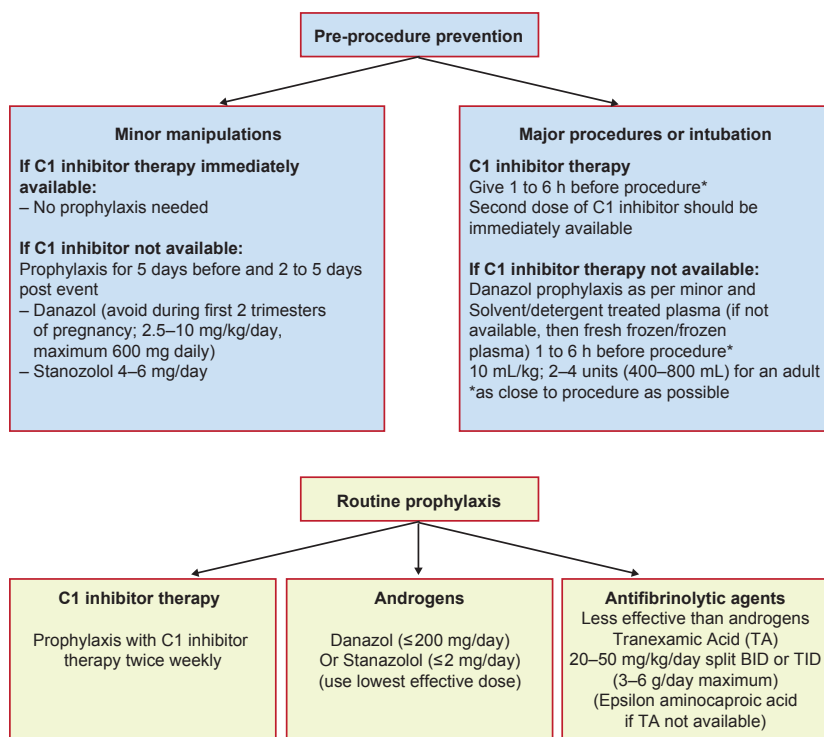


Figure 3 Prophylaxis algorithm for management of hereditary angio-oedema (HAE).⁴⁸ BID, twice daily; TID, 3 times daily.

major procedure or intubation.^{11,12,48} C1 inhibitors have been used successfully prior to surgical procedures and during pregnancy.^{68–73} For minor procedures, prophylaxis may not be needed if C1 inhibitor therapy is immediately available. Nanofiltered C1 inhibitor was administered within 24 h prior to a total of 91 medical, dental or surgical procedures (40 procedures in children and 51 procedures in adults). For 98% of procedures, no HAE attacks were reported within 72 h after the dose.⁷¹ It is recommended that nanofiltered C1 inhibitor be administered within 24 h before a medical, dental or surgical procedure. Other options include treatment with an attenuated androgen, such as danazol (maximum dose of 600 mg daily) for 5 days before and 2–5 days after the procedure.^{48,74} Fresh frozen plasma administered 1–6 h before the procedure has also shown efficacy.³⁷

Conclusions

HAE is a potentially life-threatening genetic disorder characterized by marked, diffuse oedema. HAE can have a significant negative impact on quality of life. Because many patients present initially for assessment of cutaneous manifestations, dermatologists should recognize HAE and know how to manage effectively this condition. Proper diagnosis and treatment can minimize the significant morbidity and mortality associated with HAE, including prevention of unnecessary medical procedures. C1 inhibitor therapy and drugs targeted to the contact activation pathway provide valuable options for both acute and prophylactic management of HAE.

Effective therapy should reduce the number of attacks and minimize the impact of HAE on the patient's daily life.

Acknowledgements

Scientific Therapeutics Information, Inc. (Springfield, New Jersey, USA) provided editorial assistance. Funding for editorial assistance was provided by ViroPharma Incorporated (Exton, Pennsylvania, USA).

References

- Cicardi M, Agostoni A. Hereditary angioedema [editorial]. *N Engl J Med* 1996; **334**: 1666–1667.
- Davis AE III. The pathophysiology of hereditary angioedema. *Clin Immunol* 2005; **114**: 3–9.
- Donaldson VH, Evans RR. A biochemical abnormality in hereditary angioneurotic edema: absence of serum inhibitor of C' 1-esterase. *Am J Med* 1963; **35**: 37–44.
- Nzeako UC, Frigas E, Tremaine WJ. Hereditary angioedema: a broad review for clinicians. *Arch Intern Med* 2001; **161**: 2417–2429.
- Rosen FS, Pensky J, Donaldson V, Charache P. Hereditary angioneurotic edema: two genetic variants. *Science* 1965; **148**: 957–958.
- Zuraw BL. Hereditary angioedema. *N Engl J Med* 2008; **359**: 1027–1036.
- Bork K, Staubach P, Eckardt A, Hardt J. Symptoms, course, and complications of abdominal attacks in hereditary angioedema due to C1 inhibitor deficiency. *Am J Gastroenterol* 2006; **101**: 619–627.
- Agostoni A, Aygören-Pürsün 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**(Suppl.): S51–S131.

- 9 Bork K, Barnstedt SE. Laryngeal edema and death from asphyxiation after tooth extraction in four patients with hereditary angioedema. *JADA* 2003; **134**: 1088–1094.
- 10 Bork K, Siedlecki K, Bosch S *et al*. Asphyxiation by laryngeal edema in patients with hereditary angioedema. *Mayo Clin Proc* 2000; **75**: 349–354.
- 11 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**(Suppl. 2): S30–S40.
- 12 Gompels MM, Lock RJ, Abinun M *et al*. C1 inhibitor deficiency: consensus document. *Clin Exp Immunol* 2005; **139**: 379–394.
- 13 Maurer M, Magerl M. Long-term prophylaxis of hereditary angioedema with androgen derivatives: a critical appraisal and potential alternatives. *J Dtsch Dermatol Ges* 2011; **9**: 99–107.
- 14 Bork K, Meng G, Staubach P, Hardt J. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. *Am J Med* 2006; **119**: 267–274.
- 15 Gower RG, Busse PJ, Aygören-Pürsün E *et al*. Hereditary angioedema caused by C1-esterase inhibitor deficiency: a literature-based analysis and clinical commentary on prophylaxis treatment strategies. *WAO J* 2011; **4**(Suppl): S9–S21.
- 16 Moore GP, Hurley WT, Pace SA. Hereditary angioedema. *Ann Emerg Med* 1988; **17**: 1082–1086.
- 17 Wilson DA, Bork K, Shea EP *et al*. Economic costs associated with acute attacks and long-term management of hereditary angioedema. *Ann Allergy Asthma Immunol* 2010; **104**: 314–320.
- 18 Agostoni A, Cicardi M. Hereditary and acquired C1 inhibitor deficiency: biological and clinical characteristics in 235 patients. *Medicine (Baltimore)* 1992; **71**: 206–215.
- 19 Zilberberg M, Jacobsen T, Tillotson G. The burden of hospitalizations and emergency department visits with hereditary angioedema and angioedema in the United States, 2007. *Allergy Asthma Proc* 2010; **31**: 511–519.
- 20 Lumry WR, Castaldo AJ, Vernon MK *et al*. The humanistic burden of hereditary angioedema: impact on health-related quality of life, productivity, and depression. *Allergy Asthma Proc* 2010; **31**: 407–414.
- 21 Craig T, Riedl M, Dykewicz MS *et al*. When is prophylaxis for hereditary angioedema necessary? *Ann Allergy Asthma Immunol* 2009; **102**: 366–372.
- 22 Lunn ML, Santos CB, Craig TJ. Is there a need for clinical guidelines in the United States for the diagnosis of hereditary angioedema and the screening of family members of affected patients? *Ann Allergy Asthma Immunol* 2010; **104**: 211–214.
- 23 Farkas H. Pediatric hereditary angioedema due to C1 inhibitor deficiency. *Allergy Asthma Clin Immunol* 2010; **6**: 18.
- 24 Milton JL. On giant urticaria. *Edinburgh Med J* 1876; **22**: 513–526.
- 25 Osler W. Hereditary angio-neurotic oedema. *Am J Med Sci* 1888; **95**: 362–367.
- 26 Davis AE III, Mejia P, Lu F. Biological activities of C1 inhibitor. *Mol Immunol* 2008; **45**: 4057–4063.
- 27 Cugno M, Zanichelli A, Foieni F *et al*. C1 inhibitor deficiency and angioedema: molecular mechanisms and clinical progress. *Trends Mol Med* 2009; **15**: 69–78.
- 28 HAEdb-C1 inhibitor gene mutation database. *Statistics of the HAEdb. Current Version: 2005.2.0. Last Entry Submitted 2008-07-18.*. Available at: <http://hae.enzim.hu/stat.php> (accessed 29.11.10).
- 29 Kalmár L, Hegedüs T, Farkas H *et al*. HAEdb: a novel interactive, locus-specific mutation database for the C1 inhibitor gene. *Hum Mutat* 2005; **25**: 1–5.
- 30 Pappalardo E, Cicardi M, Duponchel C *et al*. Frequent de novo mutations and exon deletions in the *C1inhibitor* gene of patients with angioedema. *J Allergy Clin Immunol* 2000; **106**: 1147–1154.
- 31 Davis AE III. C1 inhibitor and hereditary angioneurotic edema. *Annu Rev Immunol* 1988; **6**: 595–628.
- 32 Bork K, Barnstedt SE. Treatment of 193 episodes of laryngeal edema with C1 inhibitor concentrate in patients with hereditary angioedema. *Arch Intern Med* 2001; **161**: 714–718.
- 33 Bork K. Hereditary angioedema with normal c1 inhibition. *Curr Allergy Asthma Rep* 2009; **9**: 280–285.
- 34 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.
- 35 Bygum A. Hereditary angio-oedema in Denmark: a nationwide survey. *Br J Dermatol* 2009; **161**: 1153–1158.
- 36 Roche O, Blanch A, Caballero T *et al*. Hereditary angioedema due to C1 inhibitor deficiency: patient registry and approach to the prevalence in Spain. *Ann Allergy Asthma Immunol* 2005; **94**: 498–503.
- 37 Zuraw BL. Hereditary angioedema: a current state-of-the-art review, IV: short- and long-term treatment of hereditary angioedema. Out with the old and in with the new? *Ann Allergy Asthma Immunol* 2008; **100**(Suppl. 2): S13–S18.
- 38 Gompels MM, Lock RJ, On behalf of the Advisory Group. C1 inhibitor deficiency: diagnosis. *Clin Exp Dermatol* 2005; **30**: 460–462.
- 39 Bork K. Recurrent angioedema and the threat of asphyxiation. *Dtsch Arztebl Int* 2010; **107**: 408–414.
- 40 Frank MM. Hereditary angioedema: the clinical syndrome and its management in the United States. *Immunol Allergy Clin North Am* 2006; **26**: 653–668.
- 41 Kemp JG, Craig TJ. Variability of prodromal signs and symptoms associated with hereditary angioedema attacks: a literature review. *Allergy Asthma Proc* 2009; **30**: 493–499.
- 42 Starr JC, Brasher GW. Erythema marginatum preceding hereditary angioedema. *J Allergy Clin Immunol* 1974; **53**: 352–355.
- 43 Kaplan AP, Greaves MW. Angioedema. *J Am Acad Dermatol* 2005; **53**: 373–388.
- 44 Parish LC. Hereditary angioedema: diagnosis and management – a perspective for the dermatologist. *J Am Acad Dermatol* 2011; **65**: 843–850.
- 45 Cicardi M, Zingale LC, Pappalardo E *et al*. Autoantibodies and lymphoproliferative diseases in acquired C1 inhibitor deficiencies. *Medicine* 2003; **82**: 274–281.
- 46 Cugno M, Castelli R, Cicardi M. Angioedema due to acquired C1 inhibitor deficiency: a bridging condition between autoimmunity and lymphoproliferation. *Autoimmun Rev* 2008; **8**: 156–159.
- 47 Byrd JB, Adam A, Brown NJ. Angiotensin-converting enzyme inhibitor-associated angioedema. *Immunol Allergy Clin North Am* 2006; **26**: 725–737.
- 48 Bowen T, Cicardi M, Farkas H *et al*. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. *Allergy Asthma Clin Immunol* 2010; **6**: 24.
- 49 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.
- 50 Krause K, Metz M, Zuberbier T *et al*. Successful treatment of hereditary angioedema with bradykinin B2-receptor antagonist icatibant. *J Dtsch Dermatol Ges* 2010; **8**: 272–274.
- 51 Cicardi M, Levy RJ, McNeil DL *et al*. Ecallantide for the treatment of acute attacks of hereditary angioedema. *N Engl J Med* 2010; **363**: 523–531.
- 52 Cicardi M, Bork T, Caballero T *et al*. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group. *Allergy* 2012; **67**: 147–157.
- 53 Bork K, Staubach P, Hardt J. Treatment of skin swellings with C1 inhibitor concentrate in patients with hereditary angio-oedema. *Allergy* 2008; **63**: 751–757.
- 54 Bork K, Meng G, Staubach P, Hardt J. Treatment with C1 inhibitor concentrate in abdominal pain attacks of patients with hereditary angioedema. *Transfusion* 2005; **45**: 1774–1784.
- 55 Farkas H, Jakab L, Temesszentandrás G *et al*. Hereditary angioedema: a decade of human C1 inhibitor concentrate therapy. *J Allergy Clin Immunol* 2007; **120**: 941–947.

- 56 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.
- 57 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.
- 58 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.
- 59 Dagen C, Craig TJ. Treatment of hereditary angioedema: items that need to be addressed in practice parameter. *Allergy Asthma Clin Immunol* 2010; **6**: 11.
- 60 Banerji A, Sloane DE, Sheffer AL. Hereditary angioedema: a current state-of-the-art review. V: attenuated androgens for the treatment of hereditary angioedema. *Ann Allergy Asthma Immunol* 2008; **100**(Suppl. 2): S19–S22.
- 61 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.
- 62 Bork K, Hardt J. Hereditary angioedema: long-term treatment with one or more injections of C1 inhibitor concentrate per week. *Int Arch Allergy Immunol* 2011; **154**: 81–88.
- 63 Bork K, Witzke G. Long-term prophylaxis with C1 inhibitor (C1 INH) concentrate in patients with recurrent angioedema caused by hereditary and acquired C1 inhibitor deficiency. *J Allergy Clin Immunol* 1989; **83**: 677–682.
- 64 De Serres J, Gröner A, Lindner J. Safety and efficacy of pasteurized C1 inhibitor concentrate (Berinert® P) in hereditary angioedema: a review. *Transfus Apher Sci* 2003; **29**: 247–254.
- 65 Martinez-Saguer I, Heller C, Fischer D *et al*. Prophylactic treatment with pasteurized C1 inhibitor in hereditary angioedema (HAE): a prospective 32 months follow-up [abstract #1032]. *Blood* 1999; **94**(Suppl. 1): 233a.
- 66 Kreuz W, Martinez-Saguer I, Aygören-Pürsün E *et al*. C1 inhibitor concentrate for individual replacement therapy in patients with severe hereditary angioedema refractory to danazol prophylaxis. *Transfusion* 2009; **49**: 1987–1995.
- 67 Zuraw B, Baker J, Hurewitz D *et al*, and the Cinryze Study Group. Open-label use of nanofiltered C1 esterase inhibitor (human) (Cinryze) for the prophylaxis of hereditary angioedema (HAE) attacks [poster #P262]. Presented at the 2010 Annual Scientific Meeting of the American College of Allergy, Asthma, and Immunology, November 11–16, 2010, Phoenix, AZ.
- 68 Alvarez JM. Successful use of C1 esterase inhibitor protein in a patient with hereditary angioneurotic edema requiring coronary artery bypass surgery. *J Thorac Cardiovasc Surg* 2000; **119**: 168–171.
- 69 Baker J, Ried M, Banerji A *et al*, and Cinryze Study Group. Open-label use of nanofiltered C1 esterase inhibitor (human) (nf-C1 INH) for the treatment or prophylaxis of acute attacks of hereditary angioedema (HAE) in pregnant subjects [poster #2010]. Presented at the WAO International Scientific Conference, December 5–8, 2010, Dubai, UAE.
- 70 Cicardi M, Zingale LC, Zanichelli A *et al*. The use of plasma-derived C1 inhibitor in the treatment of hereditary angioedema. *Expert Opin Pharmacother* 2007; **8**: 3173–3181.
- 71 Lumry W, Busse P, Baker J *et al*, the Cinryze Study Group. Pre-procedural administration of nanofiltered C1 esterase inhibitor (human) (Cinryze) for the prevention of hereditary angioedema (HAE) attacks after medical, dental, or surgical procedures [poster #903]. Presented at the American Academy of Allergy, Asthma, and Immunology Annual Meeting, March 18–22, 2011, San Francisco, CA.
- 72 McGlinchey PG, Golchin K, McCluskey DR. Life-threatening laryngeal oedema in a pregnant woman with hereditary angioedema. *Ulster Med J* 2000; **69**: 54–57.
- 73 Nathani F, Sullivan H, Churchill D. Pregnancy and C1 esterase inhibitor deficiency: a successful outcome. *Arch Gynecol Obstet* 2006; **274**: 381–384.
- 74 Farkas H, Gyeney L, Gidófalvy E *et al*. The efficacy of short-term danazol prophylaxis in hereditary angioedema patients undergoing maxillofacial and dental procedures. *J Oral Maxillofac Surg* 1999; **57**: 404–408.