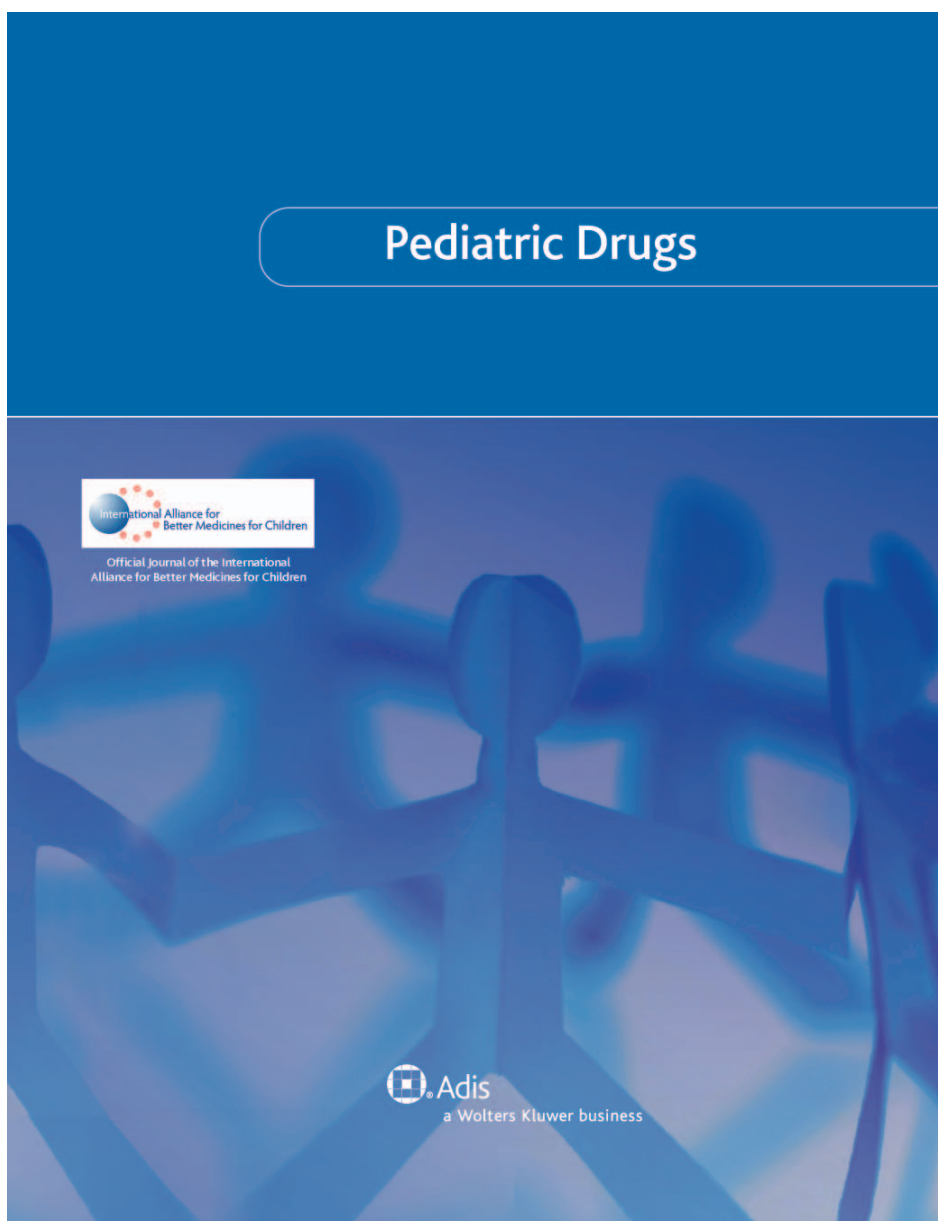


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Hereditary Angioedema in Childhood

An Approach to Management

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Abstract

Hereditary angioedema (HAE) is an inherited disorder characterized by recurrent, circumscribed, non-pitting, non-pruritic, and rather painful subepithelial swelling of sudden onset, which fades during the course of 48–72 hours, but can persist for up to 1 week. Lesions can be solitary or multiple, and primarily involve the extremities, larynx, face, esophagus, and bowel wall. Patients with HAE experience angioedema because of a defective control of the plasma kinin-forming cascade that is activated through contact with negatively charged endothelial macromolecules leading to binding and auto-activation of coagulation factor XII, activation of prekallikrein to kallikrein by factor XIIa, and cleavage of high-molecular-weight kininogen by kallikrein to release the highly potent vasodilator bradykinin. Three forms of HAE have currently been described. Type I and type II HAE are rare autosomal dominant diseases due to mutations in the C1-inhibitor gene (*SERPING1*). C1-inhibitor mutations that cause type I HAE occur throughout the gene and result in truncated or misfolded proteins with a deficiency in the levels of antigenic and functional C1-inhibitor. Mutations that cause type II HAE generally involve exon 8 at or adjacent to the active site, resulting in an antigenically intact but dysfunctional mutant protein. In contrast, type III HAE (also called estrogen-dependent HAE) is characterized by normal C1-inhibitor activity. The diagnosis of HAE is suggested by a positive family history, the absence of accompanying pruritus or urticaria, the presence of recurrent gastrointestinal attacks of colic, and episodes of laryngeal edema. Estrogens may exacerbate attacks, and in some patients attacks are precipitated by trauma, inflammation, or psychological stress. For type I and type II HAE, diminished C4 concentrations are highly suggestive for the diagnosis. Further laboratory diagnosis depends on demonstrating a deficiency of C1-inhibitor antigen (type I) in most kindreds, but some kindreds have an antigenically intact but dysfunctional protein (type II) and require a functional assay to establish the diagnosis. There are no particular laboratory findings in type III HAE.

Prophylactic administration of either 17 α -alkylated androgens or synthetic antifibrinolytic agents has proven useful in reducing the frequency or severity of attacks. Plasma-derived C1-inhibitor concentrate, recombinant C1-inhibitor, ecallantide (DX88; a plasma kallikrein inhibitor) and icatibant (a bradykinin B₂ receptor antagonist) have demonstrated significant efficacy in the treatment of acute attacks, whereas the C1-inhibitor concentrate has also provided a significant benefit as long-term prophylaxis. However, these drugs are not licensed in all countries and are not always readily available.

1. Background

Hereditary angioedema (HAE) was first described by Heinrich Quincke in 1882^[1] and, in 1888, its inheritable nature was demonstrated by Osler.^[2] About 2 decades later, in 1917, Crowder and Crowder further defined HAE as an autosomal dominant disease.^[3] Today it has been demonstrated that type I and type II HAE result from heterogeneous mutations in *SERPING1*, the C1-inhibitor gene located in the chromosomal region 11q12–q13.1. *SERPING1* mutations that cause type I HAE occur throughout the gene and result in truncated or misfolded proteins with a deficiency of antigenic recognition and functional C1-inhibitor activity (quantitative deficit). Today over 150 mutations have been described in unrelated patients that cause type II HAE and that generally involve exon 8 at or adjacent to the active site, resulting in an antigenically intact but dysfunctional mutant protein (qualitative deficit).^[4–9] The incidence of HAE in the general population is about 1 in 50 000 without known differences between ethnic groups.^[10] The biochemical alteration in HAE, i.e. a decreased level of C1-inhibitor, was discovered by Donaldson et al. in 1963.^[11]

The objective of this article is to review the available data on hereditary angioedema with particular focus on the diagnosis and management in childhood. English language papers were identified through a MEDLINE search and by reviewing the bibliographies of the identified papers.

2. Biology

C1-inhibitor, an α_2 -neuraminoglycoprotein of 105 kDa, is synthesized primarily by hepatocytes and monocytes, and is present at normal serum concentrations of approximately 30 mg/dL. As a member of the serpin superfamily of protease inhibitors, its spectrum of inhibitory activity is defined by a 444 arginine-445 threonine dipeptide at its reactive center. The target proteins of C1-inhibitor include the proteases C1r and C1s (classical pathway of the complement system), mannose-binding lectin (MBL)-associated serine protease (MASP) 1 and 2 (mannose-binding pathway of the complement system),

factor XIIa and kallikrein (contact system), and factors XIa, XIIa, and XIIf (coagulation cascade), and plasmin (fibrinolysis).^[12–17] The four protease systems (see figure 1) are, to various extents, activated during bouts of angioedema in HAE that occur when the serum C1-inhibitor concentration drops below a crucial threshold of approximately 30% of the normal value. There has been considerable controversy about the mediator(s) responsible for the increased vascular permeability causing the bouts of angioedema in HAE. The mechanisms of HAE have recently been extensively and comprehensively reviewed.^[18–20] Accumulated data strongly indicate that attacks are mediated by bradykinin generated via activation of the contact system (figure 1). Bradykinin, a nonapeptide cleaved from its inactive precursor, high-molecular-weight kininogen, by plasma and tissue kallikrein, potentially increases vascular permeability by binding to its cognate receptor, the bradykinin 2 receptor (Bk2R).^[21–24] As evidenced from figure 1, accumulation of bradykinin is also responsible for the angioedema sometimes observed in patients treated with ACE inhibitors.^[24,25] Since the four C1-inhibitor-controlled protease systems release different vasoactive peptides upon cleavage of their components, it seems unlikely that symptoms in HAE are solely due to bradykinin. Another candidate mediator is a kinin-like peptide released from C2 during activation of complement.^[19]

In type III HAE, which was first described in 2000 and predominantly affects women, patients have normal antigenic and functional C1-inhibitor.^[26,27] In some female patients with type III HAE, angioedema can be explained by gain-of-function mutations of the coagulation factor XII gene,^[28,29] which has estrogen-responsive elements in its promoter region.^[30] Factor XII, a zymogen form of factor XIIa, is activated by contact with negatively charged surfaces. Factor XIIa cleaves plasma prekallikrein to form kallikrein, which, in turn, generates bradykinin from high-molecular-weight kininogen.^[31] Under physiological conditions, C1-inhibitor controls this 'contact activation cascade' by inactivating factor XIIa and plasma kallikrein. Interestingly, there have been reports about individual families with type III HAE and normal C1-inhibitor antigen and function in which men are also affected.^[32–34]

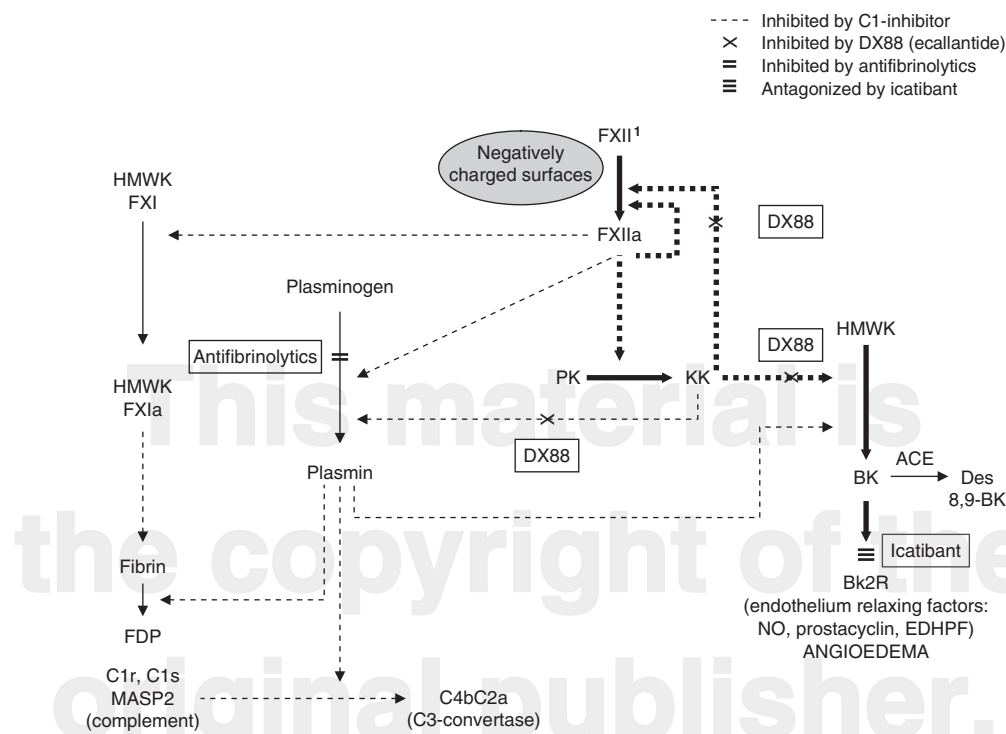


Fig. 1. Pathomechanism of angioedema in hereditary angioedema. Bold arrows indicate the major pathogenic pathway of angioedema in hereditary angioedema. **1** The FXII gene has estrogen-responsive elements in its promoter region. **BK** = bradykinin; **Bk2R** = bradykinin 2B receptor; **DX88** = ecallantide; **EDHPF** = endothelium-derived hyperpolarizing factor; **FDP** = fibrin degradation products; **HMWK** = high-molecular-weight kininogen; **KK** = kallikrein; **MAASP** = mannose-binding lectin-associated serine protease; **NO** = nitric oxide; **PK** = prekallikrein.

3. Clinical Manifestations

HAE is characterized by attacks of circumscribed, non-pitting, and non-pruritic but rather painful sudden-onset angioedema, which fully develops within a few hours and resolves over 48–72 hours, but can persist for up to 1 week. Attacks are often heralded by a prodrome that usually consists of a feeling of tingling for about 1 hour or more in the area where edema will develop. The frequency of the attacks varies considerably from less than one to over 30 per year, and some patients may remain completely asymptomatic.^[10,35,36] A large-scale survey conducted by Bork et al.^[37] revealed that the annual number of attacks is almost twice as high in patients with HAE onset before the age of 5 years, compared with those who develop HAE after the age of 15 years. Moreover, it was revealed that the initial symptoms of HAE appear during the first decade of life in 50% of the patients, during the second decade in 35% of the patients, and after the age of 20 years in the remaining 15% of patients.^[35,37] However, HAE can develop as early as the first year of life.^[38–44] Lesions can be solitary or multiple, and primarily involve the extremities, larynx, face, and bowel wall.^[37] Angioedema often recurs with a highly variable and fluctuating severity^[45,46] that is independent of the plasma

C1-inhibitor levels. Generally, it resolves without harm, but laryngeal and/or tracheal angioedema may result in rapid asphyxiation and remains a principal cause of life-long morbidity and mortality. Before the advent of therapy, HAE-related mortality was as high as 30%.^[35,47]

Abdominal symptoms (e.g. colic pain, nausea, vomiting, watery diarrhea, abdominal distension, and ascites) caused by intestinal wall edema, which at times are severe, may be the sole clinical manifestation of the disease.^[37,43,47–53] The diarrhea is caused by intraluminal fluid loss in the edematous gut. Hypotension, tachycardia, hemoconcentration, and pre-renal renal failure can result from intravascular volume depletion.^[47] The extreme importance of recognizing abdominal HAE in childhood cannot be stressed enough. These abdominal symptoms may mimic infantile colic, acute appendicitis, or other forms of acute abdomen, and can lead to unnecessary surgery.^[37,43] The absence of fever and symptom improvement after infusions of C1-inhibitor concentrate can help in the differential diagnosis of HAE.^[37]

Upper airway edema, an important feature of HAE, has the potential to be fatal because of impending suffocation that can ensue rapidly. Laryngeal attacks are uncommon before the age of 3 years and tend to appear later than other symptoms.^[35,43,45] However, small children are particularly at risk for asphyxiation



Fig. 2. Serpentine-like rash that can herald angioedema in hereditary angioedema (reproduced from De Knop et al.,^[57] with permission).

because of the small diameter of the upper airways. In children, edema formation has a propensity for the face and neck and can eventually progress to involve the epiglottis, uvula and the soft palate. Laryngeal edema frequently worsens around puberty and finally afflicts about half of the patients.^[35,43,47] Clinical manifestations of laryngeal edema are hoarseness, stridor, globus sensation, dyspnea, dysphagia, and voice distortion.

CNS symptoms suggestive of focal cerebral or cerebellar edema (such as headaches, seizures, or hemiparesis) may occur, and represent a medical emergency.^[43,47,54,55] Other organs such as the urinary bladder, kidney, esophagus, and muscles, joints, and the chest may be involved.^[43,45,56] Urticaria is not a feature of HAE and, if present, may be suggestive of another diagnosis. However, HAE attacks may be associated with some erythema, or an annular or serpentine-like (figure 2) rash may herald these attacks.

Well known precipitating events that trigger HAE attacks are mental or physical stress, (minor) trauma, insect stings, food (e.g. alcohol), dental or surgical procedures (e.g. ventilation), and intercurrent infection (e.g. *Helicobacter pylori*). However, in about half of the patients no precipitating event can be identified.^[47] There are no distinguishing features for type III HAE, except that a higher percentage of the attacks are facial. Autoimmunity, especially glomerulonephritis, is more prevalent among patients with C1-inhibitor deficiency.^[58,59]

Acquired angioedema (AAE) differs from HAE in that it lacks a family history, generally has a late onset of symptoms, is usually associated with decreased complement C1q levels, and responds differently to therapy. Patients with AAE show refractoriness to C1-inhibitor replacement due to catabolism of the protease inhibitor and an increased prophylactic response to antifibrinolytics than to androgens.^[17,60]

4. Diagnosis

Early diagnosis of HAE is an absolute prerequisite for correct management, can be life saving (e.g. preventing asphyxiation), and can avert unnecessary abdominal surgery and investigations. In 1976, Frank et al.^[47] reported the mean lag period from symptom onset to diagnosis of the disease to be 21 years. Three decades later, this duration was still unacceptably long and varied between 13^[61] and 21 years.^[60]

A diagnostic algorithm is summarized in figure 3. Indications for C1-inhibitor deficiency testing comprise recurrent angioedema or abdominal pain in the absence of associated urticaria. Although most patients with HAE report a family history of angioedema, up to one-quarter have a *de novo* *SERPING1* mutation.^[62] The differential diagnosis of pediatric angioedema has been covered in detail elsewhere and includes infections, IgE-mediated allergies (particularly food), and adverse drug reactions.^[63-65] The serum C4 level is an extremely reliable and cost-effective screening test for *SERPING1* deficiency as

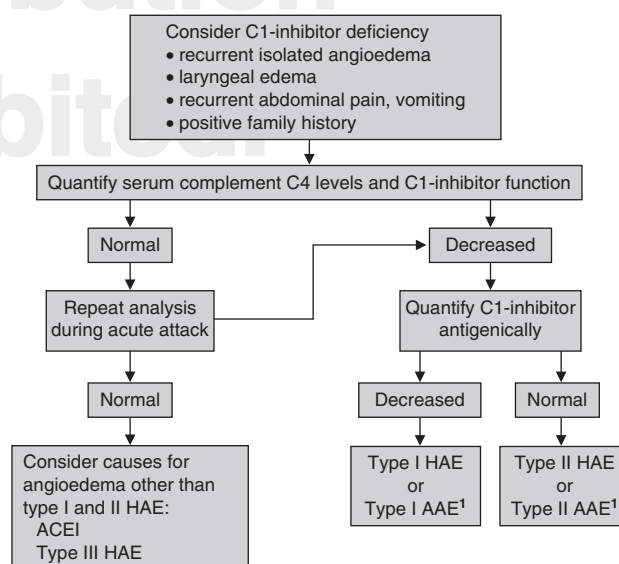


Fig. 3. Diagnostic algorithm. ¹ Differentiation between hereditary angioedema (HAE) and acquired angioedema (AAE) rests on familial history and analysis of serum complement C1q, which is normal in HAE and decreased in AAE. ACEI = angiotensin-converting enzyme inhibitor.

Table I. Complement profiles in hereditary angioedema (HAE) and acquired angioedema (AAE)

Disease	C1-inhibitor level		Complement		Anti-C1-inhibitor antibody
	antigenic	functional	C4	C1q	
HAE					
Type I	↓	↓	↓	No	–
Type II	No (↑)	↓	↓	No	–
Type III	No	No	No	No	–
AAE					
Type I	↓	↓	↓	↓	–
Type II	No (↓)	↓	↓	↓	+

No indicates normal; **No (↑)** indicates normal or increased; **No (↓)** indicates normal or decreased; ↓ indicates a decrease; – indicates negative; + indicates positive.

virtually all untreated patients with hereditary C1-inhibitor deficiency have persistently low antigenic levels of C4 (5–30% of the mean normal value of 10–30 mg/dL); levels <50% of normal would be expected with heterozygous deficiency.^[48,66,67] However, it has been demonstrated that the predictive value of serum C4 levels is not absolute and that, in very rare cases (1–2%), patients can have normal C4 titers.^[67–69] In addition, C4 levels have been demonstrated to be an unreliable indicator in very young children (<1 year of age), as the reference range is extended downwards with respect to adult normal values.^[70,71] Up to half of normal neonates have reduced antigenic and functional C1-inhibitor titers.^[72,73] However, as early infancy is a likely age for the first manifestations of HAE, physicians dealing with newborns to HAE-affected parents should suspect an underlying C1-inhibitor deficiency.

If C1-inhibitor deficiency is highly suspected, it is recommended to quantify serum C4 and C1-inhibitor functional activity (table I). If both parameters are decreased then the diagnosis is compatible with C1-inhibitor deficiency and it is recommended to repeat the analysis for confirmation. In neonates, it might be appropriate to perform a repeat analysis after the age of 1 year, particularly when the clinical suspicion is high but the C1-inhibitor activity is normal.^[73,74]

Further laboratory diagnosis depends on demonstrating a quantitative deficiency of C1-inhibitor antigen (type I HAE) in most kindreds, or antigenically-intact but dysfunctional protein (type II HAE) in some kindreds. If AAE is a diagnostic possibility, demonstration of low C1q levels differentiates acquired C1-inhibitor deficiency from the genetic variety (table I). Although the presence of C1-inhibitor autoantibodies is considered a hallmark of acquired C1-inhibitor deficiency,^[75–78] IgM anti-C1-inhibitor antibodies have been demonstrated in some patients with HAE.^[79,80]

Considering the tremendous allelic heterogeneity with almost all family-specific mutations,^[6–9] molecular genetic analysis is expensive and labor intensive. Consequently, genetic screening cannot be recommended for initial testing. However, if complement analysis yields equivocal results, genetic analysis can constitute an effective instrument to confirm clinical suspicion. It should, however, be kept in mind that genetic analysis fails to identify the causative C1-inhibitor gene (*SERPING1*) mutation in about 10–20% of cases.^[6,8,9] Alternatively, genetic screening might allow identification of mutation carriers long before clinical presentation, and contribute to correct management of acute and potentially life-threatening episodes.

5. Patient Information and Education, and Prevention

A patient information and education strategy for HAE is outlined elsewhere.^[44] In-depth information and individualized education on the nature, course, prognosis, and treatment should be provided to all patients and their caregivers. Particular emphasis should be given to early recognition of the prodrome and symptoms, as well as how to self-administer replacement therapy in the event of severe (life-threatening) bouts of angioedema. In this context, we supply all our HAE patients with one or two vials of C1-inhibitor concentrate to keep on hand for emergencies, as not all hospitals have it readily available.

Patients should also be encouraged to carry an ‘alert’ identification that summarizes essential knowledge and emergency procedures. This can prove to be extremely valuable in children who are unable to correctly describe their condition and can be a very useful aid for physicians who are unfamiliar with HAE.

Finally, it is extremely important to search the treatable and evitable aforementioned triggers of HAE bouts as identification, avoidance, and elimination of precipitating agents and events can avert potentially life-threatening attacks. A broad variety of environmental and emotional factors can elicit HAE attacks. In children, (minor) mechanical traumata probably constitute the major eliciting factor. For this reason, some authors recommend against direct contact sports.

6. Treatment

As outlined in table II, three distinct situations in the management of HAE are classically recognized: (i) emergency treatment of exacerbation; (ii) short-term prophylaxis; and

Table II. Treatment of hereditary angioedema (adapted from Zuraw.^[81] Copyright © 2008 Massachusetts Medical Society. All rights reserved)

Agent ^a	Posology		Comments
	adults	children	
Emergency treatment			
C1-inhibitor concentrate	500–1500 U	<10 y: 500 U; >10 y: 1000 U	Repeat infusion if symptoms persist >2 h ONLY if C1-inhibitor is unavailable
Tranexamic acid	4 × 1–2 g/day	4 × 1 g/day	
ε-Amino caproic acid	10 g/day split tid or qid	0.025–0.1 g/kg bid	
Fresh frozen plasma	2 U (1 U = 200 mL)	10 mL (0.05 U)/kg	
Short-term prophylaxis			
C1-inhibitor concentrate	500–1500 U	<10 y: 500 U; >10 y: 1000 U	Up to 24 h prior to procedure
17α-Alkylated androgens	Danazol 100–600 mg/day, stanozolol 1–5 mg/day	Danazol 2.5–10 mg/kg/day (max 300 mg)	For 5 days before and 2 days after procedure
Tranexamic acid	4 × 1 g/day	20–50 mg/kg split bid or tid	ONLY if C1-inhibitor is unavailable and androgens are contraindicated or inappropriate, up to 12 h prior to procedure
ε-Amino caproic acid	6–10 g/day split tid or qid	0.025–0.1 g/kg bid	
Fresh frozen plasma	2 U	10 mL (0.05 U)/kg	
Maintenance therapy			
17α-Alkylated androgens ^b	Danazol 50–200 mg qod or bid, stanozolol 1–5 mg qod or split bid Oxandrolone 2.5–5 mg/day	Danazol 25–200 mg/day (use lowest effective dose, try alternate day) Oxandrolone 0.1–0.25 mg/kg/day	Androgens rarely indicated in children Oxandrolone: in selected patients unable to be treated with other drugs
Tranexamic acid	Start: 1–2 g bid or tid; reduce to 0.5 mg qod or tid	20–50 mg/kg split bid or tid	
ε-Amino caproic acid	6–8 g/day split tid or qid	0.025–0.1 g/kg bid	
C1-inhibitor concentrate	500–1500 U	<10 y: 500 U; >10 y: 1000 U	

a Pregnancy: long-term 17α-alkylated androgens are contraindicated, particularly in the first two trimesters; tranexamic acid can be used with caution; C1-inhibitor replacement has been reported to be safe. Children: omit long-term use of 17α-alkylated androgens before Tanner V puberty stage.

b Minimal effective doses are recommended.

bid = twice daily; **qid** = four times daily; **qod** = every other day; **tid** = three times daily.

(iii) maintenance therapy. The management approach is similar for children and adults, but a treatment strategy must take into consideration age-related anatomical and physiological differences as well as age-dependent peculiarities of HAE such as smaller airways.

6.1 Therapy for Acute Angioedema

For all types of C1-inhibitor deficiency, exacerbation of angioedema is managed by supportive measures, with particular attention to maintaining a free airway. Notwithstanding early and accurate treatment, oropharyngeal and laryngeal angioedema may necessitate emergency intubation and/or tracheostomy, and such patients should be monitored closely in a hospital setting until the attack completely resolves. This is particularly relevant in children because of the smaller diameter

of their upper airways; relatively mild edema might cause substantial obstruction with ensuing suffocation.

Patients must also be hospitalized in the event of a severe non-resolving abdominal attack, particularly when other acute abdominal pathologies cannot be ruled out with certainty.^[37,82] Finally, patients should also be hospitalized when the attack is accompanied by obvious signs of hypovolemia. In such patients, volume replacement is mandatory to correct hypovolemic shock.

No evidence exists for the efficacy of epinephrine (adrenaline), H₁ and H₂ antihistamines, or corticosteroids in treating acute angioedema secondary to C1-inhibitor deficiency.^[11,47,60] Obviously, the treatment of choice for acute attacks of HAE is replacement therapy with a purified C1-inhibitor, which has been reported as highly efficacious, safe, and well tolerated in randomized controlled trials.^[45,83–90] In these studies, about

three-quarters of patients administered a C1-inhibitor improved within 30–60 minutes, and, compared with the 12% response with placebo, 95% of patients responded to C1-inhibitor therapy within 4 hours.^[45,85] Generally, 500–1500 U of C1-inhibitor concentrate is sufficient to stop severe attacks within 30–60 minutes. However, if symptoms persist at a high intensity after 2 hours of administration, a repeat dose of C1-inhibitor concentrate should be given and an alternative diagnosis considered. For a recent review on C1-inhibitor concentrate therapy, the reader is referred elsewhere.^[45] There are currently two C1-inhibitor concentrates available: Berinert® (CSL, Behring) and Cetor® (Sanquin, Viropharma). Berinert® is the more widely marketed, and at present the data available for this product are very favorable; postmarketing experience since 1985 indicates no transmission of infection.^[89] Plasma-derived C1-inhibitor has also been used favorably for self-administration at home, as an on-demand treatment for acute attacks or as a maintenance treatment.^[91,92] All patients with C1-inhibitor deficiency should be offered the opportunity for self-administration of C1-inhibitor concentrate at a therapeutic dose to treat a laryngeal emergency, as over half of the patients with HAE are at risk of developing life-threatening edema at some time.^[48,93] It is recommended that patients who require blood products receive vaccination against hepatitis B.

If a C1-inhibitor is not available, other therapies might include synthetic antifibrinolytics (e.g. tranexamic acid and ϵ -amino caproic acid) and eventually fresh frozen plasma (FFP). However, except for FFP, these therapies might reduce the reaction duration but do not abort it. In addition, most data for these drugs are from uncontrolled studies or are anecdotal.^[94–97] Although the use of FFP remains highly controversial because it also contains contact system proteins that could eventually provide substrate for additional generation of bradykinin with worsening of the already life-threatening

condition, to the best of our knowledge this has not yet been reported. For the dose regimen of these therapies, the reader is referred to table II.

Attenuated androgens and antifibrinolytic drugs (detailed in section 6.3) do not become effective for several days and are therefore unsuitable to abort an ongoing established attack. Mild edematous attacks (e.g. edema at the extremities) usually subside spontaneously within a couple of days even without treatment. Doubling the dose of maintenance therapy for the duration of the attack often prevents its progression and reduces the resolution time.

Three new compounds are currently being investigated as potential therapies for HAE: the plasma kallikrein inhibitor ecallantide (DX88), the bradykinin receptor (Bk2R) antagonist icatibant, and a recombinant human C1-inhibitor (table III).

Ecallantide is a recombinant 60-amino acid peptide (~7 kDa) derived from a Kunitz domain^[98] structural backbone that is synthesized in *Pichia pastoris* and reversibly inhibits plasma kallikrein.^[99,100] Ecallantide does not strongly inhibit activated C1r or C1s and has only a low affinity for coagulation factors XIIa and XIa. This agent, which is usually kept frozen before administration, has a plasma half-life of approximately 70 minutes when administered intravenously and 2 hours when injected subcutaneously. Ecallantide has been evaluated for efficacy and safety in the series of four EDEMA (Evaluating DX88's Effects on Mitigating Angioedema) trials at different dose regimens.^[18,101] In these studies, intravenous and subcutaneous administration of ecallantide showed a favorable benefit-risk ratio.

Icatibant is a selective antagonist of Bk2R, a receptor that belongs to the seven-transmembrane-spanning receptor super family.^[24] The cardiovascular effects of bradykinin mediated through the Bk2R on endothelial cells have been summarized by Bas et al.^[24] Icatibant has been evaluated for safety and efficacy in the FAST (For Angioedema Subcutaneous

Table III. Emerging drugs for hereditary angioedema (adapted from Zuraw.^[81] Copyright © 2008 Massachusetts Medical Society. All rights reserved)

Drug	Origin	Indication	Dose	Mechanism(s)	Anticipated adverse effect(s)	Drug manufacturer
rhC1-inhibitor	Recombinant human (rh) protein (milk transgenic rabbits)	Acute bouts, short-term prophylaxis	50–100 U/kg IV	Inhibits plasma kallikrein, FXIIa and FXIa, C1s, C1r, MASP1-2, plasmin	Rare: anaphylaxis	Pharming
Ecallantide (DX88)	Recombinant bovine protein (<i>Pichia pastoris</i>)	Acute bouts	30 mg SC	Inhibits plasma kallikrein	Common: prolonged partial thromboplastin time Rare: drug antibodies, anaphylaxis	Dyax
Icatibant	Synthetic peptide	Acute bouts	30 mg SC	Bradykinin 2B antagonist	Local discomfort	Jerini

IV = intravenous; **MAASP** = mannose-binding lectin-associated serine protease; **SC** = subcutaneous.

Treatment) trials; results from these studies are summarized elsewhere. In both FAST-1 and -2, the efficacy of subcutaneous icatibant 30 mg in the treatment of laryngeal episodes of hereditary angioedema was generally consistent with that seen for abdominal and cutaneous episodes, with a median time to first symptom improvement of 0.6–1.0 hours. Subcutaneous icatibant was generally well tolerated in adult patients with hereditary angioedema in the FAST trials, with the most common adverse events being injection-site reactions that were generally of mild severity, transient in nature, and resolved spontaneously without treatment.^[18,101] Icatibant has orphan drug status in Australia, EU, Switzerland, and the US.

The third product under investigation is a recombinant human C1-inhibitor (rhC1-inhibitor). For this product, the human *SERPINE1* gene was cloned and introduced in rabbits under the regulatory control of a bovine α S1 casein promoter.^[102] This stimulated the lactating transgenic rabbits to produce rhC1-inhibitor in their milk at levels up to 12 g/L. Because the rabbit-synthesized rhC1-inhibitor is glycosylated differently from the human counterpart, it has a considerably shorter half-life.^[103] The half-life at 100 U/kg, which is the recommended dose to treat acute HAE bouts, is approximately 3 hours.^[102] For an efficacy and safety analysis of rhC1-inhibitor replacement therapy the reader is referred elsewhere.^[104]

6.2 Short-Term Prophylaxis

Short-term prophylactic treatment to prevent attacks of HAE is recommended in all patients with planned exposure to a situation likely to trigger angioedema, such as a significant dental procedure, invasive medical procedures, and surgery (intubation). Although children might require short-term prophylaxis less frequently,^[44,105,106] we recommend short-term prophylaxis in all patients who will undergo major procedures in the head and neck region or will need intubation.

Consensus guidelines recommend that HAE attacks can be prevented by C1-inhibitor replacement therapy 500–1500 U up to 24 hours before intervention. When C1-inhibitor replacement is not available, it is recommended to temporarily increase C1-inhibitor levels through treatment with 17 α -alkylated androgens for 5 days before and after the provoking event (see table II). Synthetic antifibrinolytics are less recommended for short-term prophylaxis, as these drugs do not become effective for several days. If a patient has to undergo an emergency medical or surgical procedure and a C1-inhibitor is not available and administration of androgens is not possible, FFP can be administered at 10 mL (0.05 U)/kg in children or 400 mL (2 U) in adults 1–12 hours before the event.^[107]

6.3 Maintenance Therapy

Maintenance therapy for HAE should be considered if a patient experiences more than one severe event per month, is disabled for more than 5 days per month, or has suffered from airway compromise.^[74] Because severe or life-threatening attacks are less common during childhood, maintenance therapy is rarely required in children.^[49]

Attenuated androgens constitute the mainstay of maintenance therapy in HAE. Several androgens such as testosterone, methyltestosterone,^[108] fluoxymesterone, and oxymetholone^[109] were early therapeutic agents for HAE, but have been replaced by more attenuated 17 α -alkylated androgens such as danazol and stanozolol that were also observed to have a therapeutic benefit.^[110–117] Biochemical evidence in support of 17 α -alkylated androgen therapy includes the partial correction of C1-inhibitor concentrations and reversal of the secondary depression in C4 serum levels.^[110,118] However, it is certainly not mandatory to achieve correction of these proteins for therapeutic success. Usually, 50% of normal C1-inhibitor function is sufficient to obtain clinical success, and it is rare to observe clinical remission without an increase in C1-inhibitor activity.^[110] The minimal effective maintenance dosage of danazol is patient dependent, and varies considerably between 50–200 mg every other day up to twice daily in adults, and 25–200 mg every other day in children (for a review on different long-term protocols with 17 α -alkylated androgens see Bowen et al.^[74]). Stanozolol, another synthetic attenuated androgen, which is inferior to danazol in efficacy but has less masculinizing potential, is generally recommended at a dosage of up to 5 mg every other day up to twice daily in adults (see table II). Long-term use of danazol and stanozolol can cause several dose-dependent adverse effects such as masculinization in women and children (acne, hirsutism, weight gain, deepening of voice), delayed menarche, irregular menstruation, behavioral changes (aggression or depression), and hypertension. It is wise to restrict the use of androgens in children who cannot be treated with other drugs. Furthermore, it is recommended to use the lowest effective maintenance dosage in alternate-day or intermittent-dosage regimens (i.e. dosages repeated at 3-day intervals) whenever possible, particularly in children.

Androgens can cause significant hepatotoxicity with liver function derangement, cholestatic jaundice, peliosis hepatis, and hepatocellular adenoma.^[113,115,119,120] Liver function tests should be performed every 6 months, and it is recommended to perform a baseline hepatic ultrasound that should be repeated every 1–2 years. Other adverse effects include polycythemia, and alteration of blood lipid levels and coagulation factors,^[121]

thus conferring an added risk for cardiovascular disease. Androgen treatment is also a risk factor for prostate adenocarcinoma. The safety profile of long-term stanozolol therapy has been re-evaluated recently.^[117] Apart from virilization with premature puberty, another important adverse effect that restricts the use of androgens in childhood is premature epiphyseal closure. During pregnancy, androgens are contraindicated because of the potential for masculinization of the fetus.

Oxandrolone is a synthetic anabolic corticosteroid with limited virilizing effect that has been used in a variety of pediatric conditions, including HAE. Administered at a daily dose of 0.1–0.25 mg/kg/day, oxandrolone treatment has been reported to result in clinical and biological improvement as maintenance therapy in patients with HAE.^[122] Synthetic antifibrinolytic agents (plasmin inhibitors) such as tranexamic acid and ϵ -amino caproic acid (which is about seven times less potent than tranexamic acid on a molar basis) are also used for maintenance therapy in HAE.^[123,124] Antifibrinolytic agents inhibit the activation of plasmin, and thus demonstrate a 'sparing' effect on C1-inhibitor consumption. Because of the virilizing effect of androgens, antifibrinolytic agents are considered the first choice in children (before Tanner V puberty stage) and pregnant women with HAE who require maintenance therapy.^[44] However, synthetic antifibrinolytics are less effective than androgens.^[17] The main adverse effects of tranexamic acid are nausea, diarrhea, myalgia, increased serum creatine phosphokinase and aldolase, and rhabdomyolysis. The finding of retina tumors in experimental animals after long-term use of tranexamic acid has limited its use in the US but not in Europe. The *British National Formulary* advocates that patients receiving long-term treatment with tranexamic acid should have regular eye examinations and regular liver function checks. Use of synthetic antifibrinolytic agents is contraindicated in active thromboembolic disease or procoagulant states.

C1-inhibitor replacement has also been advocated as maintenance therapy for HAE.^[17,74,91] Unfortunately, the short half-life, intravenous administration, and high cost preclude its regular use. Therefore, C1-inhibitor maintenance therapy is generally restricted to those cases where treatment with other agents is not effective, is contraindicated, or is not tolerated.

7. Conclusions

HAE is a hereditary disease characterized by recurrent subepithelial swelling of sudden onset due to the generation of highly potent vasodilator bradykinin. Three forms of HAE are currently recognized. Type I and type II HAE are rare auto-

somal dominant diseases due to mutations in the C1-inhibitor gene. Type III HAE (estrogen-dependent HAE) is characterized by normal C1-inhibitor activity.

The diagnosis of HAE is suggested by a positive family history, the absence of accompanying pruritus or urticaria, the presence of recurrent gastrointestinal attacks of colic, and episodes of laryngeal edema. For type I and type II HAE, diminished C4 concentrations are highly suggestive for the diagnosis. Further laboratory diagnosis involves demonstrating a deficiency of C1-inhibitor antigen (type I) in most kindreds, but some kindreds have an antigenically intact but dysfunctional protein (type II) and require a functional assay to establish the diagnosis. There are no particular laboratory findings in type III HAE.

Prophylactic administration of either 17 α -alkylated androgens or synthetic antifibrinolytic agents has proven useful in reducing the frequency or severity of attacks. Plasma-derived C1-inhibitor concentrate, recombinant C1-inhibitor, ecallantide and icatibant have been demonstrated efficacious in the treatment of acute bouts, whereas C1-inhibitor concentrate has also provided a significant benefit as long-term prophylaxis. However, these compounds are not licensed in all countries and not always readily available.

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