Hereditary angioedema: an update on causes, manifestations and treatment

ABSTRACT

Hereditary angioedema is a rare genetic disorder caused by deficiency of C1 esterase inhibitor (C1-INH) and characterized by recurrent episodes of severe swelling that affect the limbs, face, intestinal tract and airway. Since laryngeal oedema can be life-threatening as a result of asphyxiation, correct diagnosis and management of hereditary angioedema is vital. Hereditary angioedema attacks are mediated by bradykinin, the production of which is regulated by C1-INH. Hereditary angioedema therapy relies on treatment of acute attacks, and short- and long-term prophylaxis. Acute treatment options include C1-INH concentrate, icatibant and ecallantide. Self-administration of treatment is recommended and is associated with increased quality of life of patients with hereditary angioedema. Advances in diagnosis and management have improved the outcomes and quality of life of patients with hereditary angioedema.

Classical hereditary angioedema is an autosomal dominant disorder characterized by recurrent episodes of subcutaneous or submucosal oedema lasting for 2–5 days and involving mostly the extremities, face, airway and gastrointestinal tract (Longhurst and Cicardi, 2012). This rare hereditary disease is caused by mutations in the SERPING1 gene, which result in deficient or dysfunctional C1 esterase inhibitor (C1-INH), leading to overproduction of bradykinin. Other types of hereditary angioedema are discussed below.

Bradykinin-mediated angioedema should not be confused with the more common histamine-mediated angioedema. Histamine-mediated angioedema may be accompanied by urticaria and pruritus, has a duration of 24–48 hours if untreated, and responds to treatment with corticosteroids and antihistamines (Busse and Smith, 2017). Most cases of histamine-mediated angioedema are spontaneous, without direct trigger and develop over several hours. A minority are caused by allergy, usually with obvious allergen trigger, and of rapid onset. If severe, this type of angioedema is associated with features of anaphylaxis, with bronchospasm, rapid upper airway obstruction or vasodilatation causing hypotension. In contrast, bradykinin-mediated angioedema is non-pitting, non-pruritic, with no urticarial wheals or bronchoconstriction, lasts up to 5 days, and is unresponsive to antihistamines and corticosteroids (Busse and Smith, 2017).

While histamine-mediated angioedema is caused by mast cell degranulation (immunoglobulin E-mediated or spontaneous) leading to the release of mediators including histamine, bradykinin-mediated angioedema occurs following activation of the contact system, which leads to excessive production of bradykinin. Because of differences in the pathophysiology and treatment of bradykinin-mediated and histamine-mediated angioedema, World Allergy Organization guidelines highlight the importance of accurate diagnosis to ensure appropriate treatment (Maurer et al, 2018). Additionally, several other dermatological diseases present with swelling that resembles angioedema, including acute contact dermatitis, dermatomyositis, hypothyroidism and subcutaneous emphysema (Andersen et al, 2016). To avoid delays in diagnosis and treatment, particularly in the emergency room, knowledge of the key differentiating features is essential to distinguish conditions that mimic angioedema from classic angioedema.

The exact incidence and prevalence of hereditary angioedema is unknown, but it is estimated to affect around 1 in 50 000 people worldwide (Cicardi et al, 2014). Diagnosis is often delayed, with a median of 1.4–8.5 years from onset of symptoms (Zanichelli et al, 2018). Delays in diagnosis are particularly alarming since undiagnosed patients are at a higher risk of mortality by asphyxiation following laryngeal oedema (Bork et al, 2012), because patients and physicians may not be aware of the life-threatening nature of hereditary angioedema attacks and the appropriate treatment. Misdiagnoses contribute to diagnostic delays and result in unnecessary treatments, which increase the risk of death. Increased awareness of hereditary angioedema, its symptoms, differential diagnoses and treatment is crucial among treating physicians to avoid such delays. Misdiagnoses and diagnostic delays were identified by patients as important negative factors impacting their quality of life (Zanichelli et al, 2018).

Hereditary angioedema attacks substantially impact patients' personal, social, professional and mental wellbeing. Attacks can prevent patients from walking, performing daily tasks, leaving the house, attending social or family events or work or school, participating in activities or sports, and travelling. In the long term, attacks hinder

Dr Hilary J Longhurst, Consultant, Department of Immunology, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge CB2 0QQ

Professor Konrad Bork, Univ.-Prof. Dr, Department of Dermatology, University Medical Center, Johannes Gutenberg University, Mainz, Germany

Correspondence to: Dr HJ Longhurst (hlonghurst@doctors.org.uk)

career and educational progress as a result of absenteeism, reduced productivity and lost opportunities (Lumry et al, 2010). Patients often live in constant fear of an attack with the possibility of asphyxiation, and experience high levels of anxiety and depression (Longhurst and Bygum, 2016). The burden of hereditary angioedema not only impacts patients' quality of life, but also affects family and caregivers (Longhurst and Bygum, 2016).

Types of hereditary angioedema

Swelling in hereditary angioedema is primarily caused by bradykinin, the production of which is mediated by the contact system (*Figure 1*). Contact system activation is initiated by negatively charged surfaces that activate factor XII (FXII). Activated FXII (FXIIa) converts prekallikrein into kallikrein, which then cleaves high molecular weight kininogen to produce bradykinin. Bradykinin causes vasodilatation and increases vascular permeability, leading to angioedema. The contact system is regulated by C1-INH, a major inhibitor of FXIIa and kallikrein (*Figure 1*) (Caccia et al, 2014). Insufficient plasma levels of functional C1-INH lead to an increase in the formation of bradykinin as a result of sustained activation of FXIIa and kallikrein (Caccia et al, 2014).

Hereditary angioedema with C1-INH deficiency

Two different types of hereditary angioedema caused by deficiency of functional C1-INH (HAE-C1-INH) have been identified. Both types result in similar phenotypic manifestations and both are inherited by an autosomal dominant mechanism (*Table 1*) (Longhurst and Bork 2006). Hereditary angioedema type I is the most common form of HAE-C1-INH (85% of cases) and is caused by deficient plasma levels of C1-INH. It is associated with various SERPING1 mutations, which result in impaired secretion of C1-INH protein. Hereditary angioedema type II is the less common form of HAE-C1-INH (15% of cases) and is characterized by normal plasma levels, but low functional activity levels, of C1-INH. In hereditary angioedema type II, mutations in SERPING1 result in the secretion of dysfunctional C1-INH protein. In both types, neither FXIIa nor kallikrein are subject to adequate inhibition, resulting in enhanced production of bradykinin and consequently increased vascular permeability.

Angioedema with C1-INH deficiency can also occur as a result of increased catabolism of C1-INH, primarily caused by an underlying lymphoproliferative disorder (Longhurst et al 2017a). This acquired angioedema with C1-INH deficiency (AAE-C1-INH) is not associated with genetic mutations (*Table 1*) and although clinically it resembles HAE-C1-INH, it is associated with later onset and there is no family history of angioedema (Longhurst et al, 2017a).

Hereditary angioedema with normal C1-INH

Hereditary angioedema with normal C1-INH (HAE-nC1-INH) is not a single type of hereditary angioedema, but includes patients with FXII, plasminogen and angiopoietin-1 gene mutations as well as cases with unknown causes (*Table 1*). The clinical features of HAE-nC1-INH are similar to those of HAE-C1-INH, but HAE-nC1-INH is less common and the mean age of onset of symptoms is later (Bork et al, 2009). Furthermore, diagnosis of HAE-nC1-INH is more difficult as plasma levels and function of C1-INH are normal, and routine laboratory tests that target other causes are not available,

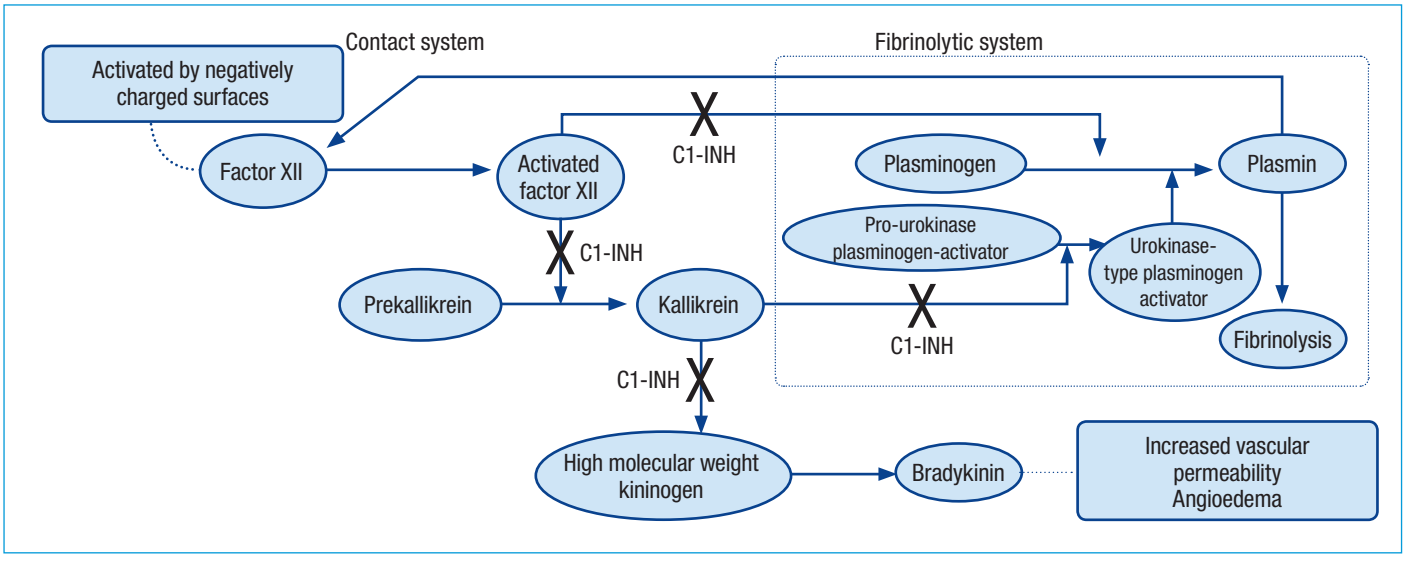

Figure 1. Pathway of contact system activation and interaction with fibrinolytic system. Contact system activation starts with the activation of factor XII. Activated factor XII converts plasma prekallikrein into plasma kallikrein. Kallikrein cleaves high molecular weight kininogen to produce bradykinin. Bradykinin causes vasodilatation and increases vascular permeability, leading to angioedema. The fibrinolytic system can also lead to bradykinin formation and vascular leakage via factor XII activation by plasmin. Kallikrein regulates the fibrinolytic system by cleaving pro-urokinase plasminogen activator into urokinase-type plasminogen activator, causing activation of plasminogen to plasmin. C1 inhibitor (C1-INH) regulates these pathways via inhibition (bold crosses).

Table 1. Types of hereditary angioedema

	Gene	Phenotype	Description
HAE with C1-INH deficiency	*SERPING1*	HAE-C1-INH type I	■ 85% of patients ■ Autosomal dominant disorder ■ Low C1-INH and C4 level and C1-INH function ■ Bradykinin mediated (contact system)
	SERPING1	HAE-C1-INH type II	■ 15% of patients ■ Autosomal dominant disorder ■ Normal C1-INH level, low C4 level and C1-INH function ■ Bradykinin mediated (contact system)
AAE with C1-INH deficiency	No genetic mutation	AAE-C1-INH	■ Associated with underlying autoimmune and lymphoproliferative diseases ■ Low C1-INH, C1q and C4 level and C1-INH function and high titre C1-INH antibodies ■ Bradykinin mediated (contact system)
HAE with normal C1-INH	*FXII*	HAE-FXII	■ Up to 30% of patients with HAE-nC1-INH ■ Autosomal dominant disorder ■ Normal C1-INH and C4 level and C1-INH function ■ Bradykinin mediated (contact system)
	Plasminogen	HAE-PLG	■ Autosomal dominant disorder ■ Normal C1-INH and C4 level and C1-INH function ■ Bradykinin mediated (fibrinolytic system)
	ANGIOPOIETIN-1	HAE-ANGTP1	■ Normal C1-INH and C4 level and C1-INH function ■ Bradykinin mediated (vascular system)
	Unknown	HAE-unknown	■ Undefined ■ Presumed bradykinin mediated

AAE = acquired angioedema; C1-INH = C1 inhibitor; HAE = hereditary angioedema

so diagnosis relies on genetic testing (Henao et al, 2016). Evidence suggests that HAE-nC1-INH is also mediated by increased production of bradykinin (Bork et al, 2009).

HAE-nC1-INH can be caused by mutations in the FXII gene (HAE-FXII) (Bork et al, 2009; Bork, 2010). In women, clinical symptoms, characterized by skin (mainly facial) and tongue swellings, often begin or are exacerbated after taking oral contraceptives, hormonal replacement therapy or during pregnancy, suggesting an important role of oestrogens in the disease (Bork et al, 2009; Bork, 2010). In contrast to HAE-C1-INH, clinical symptoms in HAE-FXII generally start in adulthood (Bork et al, 2009). Men are rarely affected, except in the presence of external cofactors, such as use of an angiotensin-converting enzyme (ACE) inhibitor (Bork, 2010). As with HAE-C1-INH, activation of the contact system and overproduction of bradykinin are involved in the pathophysiology of angioedema in HAE-FXII (Bork et al, 2009).

Two further gene mutations have been identified in patients with HAE-nC1-INH, resulting in hereditary angioedema with mutation in the plasminogen gene (HAE-PLG) (Bork et al, 2018) or hereditary angioedema with mutation in the angiopoietin-1 gene (HAE-ANGPT1) (Bafunno et al, 2018). HAE-PLG is an autosomal dominant trait and is characterized by high incidence of tongue swellings, which can lead to asphyxiation (Bork et al, 2018). HAE-PLG appears to be mediated by bradykinin, but overproduction of bradykinin is thought to be related to increased activation of the fibrinolytic system (Bork et al, 2018). This results in increased plasmin production and, since plasmin can activate the contact system, increased production of bradykinin and angioedema formation (*Figure 1*). Angiopoietin-1 regulates vascular permeability, protecting the vasculature from plasma leakage induced by bradykinin. Mutations in the angiopoietin-1 gene are associated with increased vascular permeability and angioedema (Bafunno et al, 2018), and in HAE-ANGPT1 the interaction of the angiopoietin-1 protein with its membrane receptor tunica interna endothelial cell kinase is impaired. This vascular variant thus increases susceptibility to normal levels of bradykinin. Therefore, although angioedema in HAE-ANGPT1 is bradykinin mediated, angiopoietin-1 is related to the vasculature rather than the contact system, representing a novel pathophysiological mechanism of hereditary angioedema attacks (Bafunno et al, 2018). In many HAE-nC1-INH cases, functional mutations in other genes remain unknown.

Clinical characteristics of hereditary angioedema

Hereditary angioedema manifests as recurrent episodes of localized oedema in the subcutaneous tissues of the extremities, face, trunk or genitalia, or submucosal tissues of the gastrointestinal and upper respiratory tract (*Table 2*). Subcutaneous oedema is non-pitting, non-pruritic, with no urticaria or wheals and usually resolves within 2–5 days. While abdominal attacks can cause excruciating pain, as a result of bowel obstruction or visceral oedema, and often lead to unnecessary surgeries, laryngeal attacks are life-threatening and may result in asphyxiation (Bork

Table 2. Distinguishing factors for hereditary angioedema *vs* other forms of recurrent angioedema

	C1-INH deficiency			Normal C1-INH		Mast cell mediator
	HAE-C1-INH type I	HAE-C1-INH type II	Acquired angioedema-C1-INH	HAE-FXII, HAE-ANGTP1, HAE-PLG, HAE-unknown	ACE inhibitor-induced angioedema	Angioedema with urticaria
Development and medical history	Family history (most patients) Onset of clinical symptoms in first or second decade No history of urticaria Abdominal colics	Family history (most patients) Onset of clinical symptoms in first or second decade No history of urticaria Abdominal colics	No family history Onset of clinical symptoms after fourth decade No history of urticaria Associated with underlying lymphoproliferative diseases	Family history (most patients) Onset of clinical symptoms in adulthood No history of urticaria	No family history No history of urticaria Onset of clinical symptoms usually after fourth decade	Usually no family history History of urticaria and sometimes anaphylaxis Normally no abdominal pain
Triggering factors	Trauma (50%), especially dental Emotional stress Co-existing illnesses Oestrogens ACE inhibitors Often no obvious trigger	Trauma (50%), especially dental Emotional stress Co-existing illnesses Often no obvious trigger	No obvious trigger	Oestrogen-containing oral contraceptives, hormonal replacement therapy or pregnancy ACE inhibitors	ACE inhibitors	Exposure to allergens in a minority (associated with rapid symptom onset)
Prodromes	Erythema marginatum in 50% of cases	Erythema marginatum in 50% of cases	Usually no erythema marginatum	No erythema marginatum	None	None
Symptoms	Cutaneous angioedema Abdominal pain Laryngeal oedema 3–5 days duration	Cutaneous angioedema Abdominal pain Laryngeal oedema 3–5 days duration	Cutaneous angioedema Abdominal pain Laryngeal oedema 3–5 days duration May present with additional symptoms of the underlying diseases	Cutaneous angioedema (particularly facial) Tongue swelling Abdominal pain (fewer) Laryngeal oedema 3–5 days duration	Cutaneous angioedema (particularly face and tongue) 12–48-hour duration	Cutaneous angioedema Urticaria Abdominal pain (rare) Laryngeal oedema (rare) 24–48-hour duration
Laboratory markers	Low C1-INH plasma activity Low C1-INH plasma level Low C4 plasma level	Low C1-INH plasma activity Normal C1-INH plasma level Low C4 plasma level	Low C1-INH plasma activity Low C1-INH plasma level Low C4 plasma level Low C1q plasma level High titre anti-C1-INH antibodies (some patients)	Normal FXII/ANGPT1/PLG mutation (diagnose by genotyping)	Normal	Normal Mast cell tryptase may be elevated in presence of anaphylaxis (small minority)
Treatment	Acute attacks: emergency procedures if necessary, C1-INH concentrate, icatibant, ecallantide Prophylaxis: C1-INH concentrate, androgens, (tranexamic acid)	Acute attacks: emergency procedures if necessary, C1-INH concentrate, icatibant, ecallantide Prophylaxis: C1-INH concentrate androgens, (tranexamic acid)	Treatment of underlying disease C1-INH concentrate, icatibant, ecallantide, tranexamic acid, rituximab Prophylaxis: tranexamic acid	Acute attacks: emergency procedures if necessary, C1-INH concentrate, icatibant Prophylaxis: tranexamic acid, progestagens, androgens	Emergency procedures if necessary Immediate discontinuation of ACE inhibitors	Emergency procedures if necessary Adrenaline (in minority with rapid onset and suspicion of anaphylaxis) Corticosteroids Antihistamines

ACE = angiotensin-converting enzyme; ANGPT1 = angiopoietin-1; C1-INH = C1-inhibitor; FXII = factor XII; HAE = hereditary angioedema; PLG = plasminogen

et al, 2012; Henao et al, 2016). Hereditary angioedema attacks are often preceded by a prodrome, such as fatigue, malaise, mood changes, joint or muscle pain, nausea, thirst or erythema marginatum; the latter is absent in HAE-nC1-INH. Most attacks occur spontaneously, but several triggering factors have been identified, including local trauma, infectious diseases and emotional stress. The frequency of attacks varies greatly from patient to patient; some patients are generally asymptomatic and others have attacks every few days. The clinical symptoms of hereditary angioedema often manifest in the first decade of life, and generally before the end of the second decade (Bork et al, 2006).

Laryngeal oedema is associated with significant risk of asphyxiation, particularly in undiagnosed or misdiagnosed patients, and is the cause of hereditary angioedema-related fatalities (Bork et al, 2012). This is primarily a result of delays in diagnosis and ineffective drug treatment, so prompt and accurate diagnosis and management of laryngeal attacks is vital (Bork et al, 2012; Bernstein et al, 2017). Asphyxiation from mismanagement of laryngeal attacks has been frequently reported (Bork et al, 2000, 2012; Bork and Barnstedt, 2003). Laryngeal oedema typically occurs following oral trauma such as dental surgery, but can also occur spontaneously (Longhurst and Bork, 2006; Bork et al, 2012). Although on average a fatal laryngeal oedema episode lasts a few hours before asphyxiation, in some cases the fatal laryngeal attack lasted less than 20 minutes (Bork and Barnstedt, 2003; Bork et al, 2012).

Owing to the unpredictable nature of laryngeal attacks, and the possibility of rapid progression from minor to life-threatening symptoms (Bork et al, 2012), patients, relatives and treating physicians should be aware of the possibility of a laryngeal attack and how it should be managed. It is particularly important that effective drug therapy is given soon enough to take effect as onset of symptom relief occurs 15–60 minutes after drug administration (Bork et al, 2016; Longhurst et al, 2016). However, in cases of laryngeal oedema with a rapid course, ineffectiveness of drugs or restricted time, emergency measures such as intubation, cricothyrotomy or tracheotomy may be required. Emergency physicians should be able to differentiate between types of angioedema (*Table 2*) and be aware that hereditary angioedema patients do not respond to corticosteroids, antihistamines and adrenaline (Bernstein et al, 2017). Delayed treatment of an advanced laryngeal attack may lead to hypoxaemia with signs of irreversible brain damage including permanent blindness and tetraspasticity (Bork et al, 2017a).

Laboratory blood tests confirm the diagnosis of HAE-C1-INH. C1-INH activity and C1-INH concentration in plasma are used to differentiate between hereditary angioedema types I and II. Genetic testing is necessary to diagnose HAE-nC1-INH. None of these tests is likely to be available quickly enough during emergency assessment of an acute attack. D-dimers, which are widely available, have been reported to be elevated in acute hereditary angioedema attacks (Reshef et al, 2015), but they are non-specific and there are no formal analyses of sensitivity or specificity in this context. A shortened activated partial thromboplastin time, which is rapidly and widely available, may help to diagnose HAE-C1-INH and AAE-C1-INH when determination of C1-INH is not available (Bork and Witzke, 2016).

Treatment of hereditary angioedema

Since HAE-C1-INH is a genetic disease, a causal treatment is not currently viable. Therapeutic strategies focus on the reversal and/or prevention of attacks, reduction of morbidity and mortality, and improvement in quality of life. There are two approaches to treatment: on-demand treatment of acute attacks and prophylactic treatment, both short and long term (*Table 3*).

On-demand treatment

The World Allergy Organization strongly recommends early treatment of HAE-C1-INH attacks with C1-INH concentrate, icatibant or ecallantide; tranexamic acid or androgens are ineffective for acute attacks (Maurer et al, 2018) (*Table 3*). On-demand treatment is associated with shorter attack duration and reduced disease-related morbidity compared with no treatment (Bork et al, 2008a; Zanichelli et al, 2015). Since breakthrough attacks occur despite currently available prophylaxis, every patient is advised to have an action plan for treatment of acute attacks, ideally via self-administration (Maurer et al, 2018).

C1-INH concentrate, either plasma-derived or recombinant, replaces deficient or dysfunctional C1-INH protein, and thus regulates production of bradykinin through inhibition of the contact system. Both plasma-derived and recombinant C1-INH are effective and well tolerated for the treatment of acute attacks (Craig et al, 2009; Zuraw et al, 2010; Riedl et al, 2014). Currently, two plasma-derived C1-INH concentrates (Berinert, CSL Behring; Cinryze, Shire) and one recombinant C1-INH (Ruconest, Pharming) are available for on-demand treatment of hereditary angioedema attacks (*Table 3*).

While C1-INH concentrates for on-demand treatment require intravenous administration, two subcutaneous on-demand therapies are also available (*Table 3*). Icatibant (Firazyr, Shire) is a bradykinin B2 receptor inhibitor used for on-demand therapy of hereditary angioedema attacks (Lumry et al, 2011). Ecallantide (Kalbitor, Shire) is a kallikrein inhibitor, licensed only in the USA, shown to be effective for the treatment of acute attacks (Cicardi et al, 2010). Ecallantide requires health-care provider supervision because of the risk of anaphylactoid reactions, while the other treatments are available for patient or carer self-administration after training.

Prophylactic treatment

Short-term prophylaxis

Hereditary angioedema patients should receive short-term prophylaxis with C1-INH concentrate before

situations that may induce an attack, e.g. surgical and dental procedures, or invasive medical interventions (Maurer et al, 2018). C1-INH concentrate is an effective and well-tolerated treatment for short-term prophylaxis (Bork et al, 2011). However, since breakthrough attacks can still occur, access to on-demand treatment is essential (Longhurst and Zinser, 2017). The two plasma-derived C1-INH concentrates, Berinert and Cinryze, are licensed for short-term prophylaxis (*Table 3*).

Long-term prophylaxis

Long-term prophylaxis aims to reduce the frequency and severity of hereditary angioedema attacks. The need for long-term prophylaxis is decided on a patient-by-patient basis depending on factors such as the frequency, severity and location of attacks, comorbidities, and level of control with on-demand therapy (Longhurst and Zinser, 2017). Patients on long-term prophylaxis should be monitored regularly for efficacy and tolerability of treatment and on-demand therapy should be available to treat breakthrough attacks (Maurer et al, 2018).

Plasma-derived C1-INH concentrates are commonly used as prophylaxis for patients with hereditary angioedema (*Table 3*). Routine prophylaxis with intravenous plasma-derived C1-INH is well tolerated and effective (Zuraw et al, 2010). Until recently, Cinryze was the only plasma-derived formulation licensed for long-term prophylaxis. However, this requires intravenous administration, which may be a limiting factor in patients with poor venous access, and has limited efficacy (51% average attack reduction) (Zuraw et al, 2010). Studies have demonstrated the good safety profile and excellent efficacy of subcutaneous C1-INH (median 95% attack reduction) (Longhurst et al, 2017b) and subcutaneous administration is more convenient and easier for patients requiring long-term prophylaxis. Subcutaneous C1-INH, Haegarda (CSL Behring), is licensed in the USA for long-term prophylaxis.

Attenuated androgens have been used for long-term prophylaxis for a long time. Oral administration is an advantage, and their effectiveness is high (83% average attack reduction) (Bork et al, 2008b). However, a number of, often dose-dependent, side effects may occur during long-term treatment (Bork et al, 2008b) (*Table 3*). If attenuated androgens are given, the minimal effective dose should be used (maximum 100–200 mg/day danazol) (Maurer et al, 2018).

Tranexamic acid is not as effective as attenuated androgens, although it has fewer side effects (Maurer et al, 2018). However, since efficacy data are lacking and alternatives such as plasma-derived C1-INH are available, tranexamic acid, although commonly used in children, is not generally recommended for long-term prophylaxis (Maurer et al, 2018).

Treatments in late stage of development

The tolerability and efficacy of subcutaneous lanadelumab, a monoclonal antibody against plasma kallikrein for the prophylactic treatment of hereditary angioedema attacks, has been studied in a phase 3, multicentre, randomized, double-blind, placebo-controlled clinical trial involving 125 patients with hereditary angioedema type I or II (HELP study; NCT02586805) (Banerji et al, 2018).

Table 3. Summary of treatments for hereditary angioedema

Drug	Indication	Administration	Potential adverse events
Plasma-derived C1-INH (Berinert, Haegarda, CSL Behring)	Self-administration, acute and prophylaxis	Intravenous, subcutaneous (only USA)	Very rare: anaphylaxis* Theoretical: transmission of infectious agent* Uncommon: injection site reactions, hypersensitivity, nasopharyngitis, dizziness†
Plasma-derived C1-INH (Cinryze, Shire)	Self-administration, acute and prophylaxis	Intravenous	Very rare: anaphylaxis Theoretical: transmission of infectious agent
Recombinant human C1-INH (Ruconest, Pharming)	Acute	Intravenous	Uncommon: anaphylaxis (in rabbit allergy)
Ecallantide (Kalbitor, Shire)	Acute (only USA)	Subcutaneous	Common: prolonged partial thromboplastin time, anaphylactoid reactions Uncommon: development of antidrug antibodies
Icatibant (Firazyr, Shire)	Self-administration, acute	Subcutaneous	Common: local swelling, pain, pruritus at injection site
Tranexamic acid	Prophylaxis	Oral, intravenous	Common: nausea, vertigo, diarrhoea, postural hypotension, fatigue, muscle cramps with increased muscle enzymes Rare: thrombosis
Attenuated androgens (danazol and oxandrolone)	Prophylaxis	Oral	Common: weight gain, virilisation, acne, altered libido, muscle pains and cramps, headaches, depression, fatigue, nausea, constipation, menstrual abnormalities, increase in liver enzymes, hypertension, and alterations in lipid profile Uncommon: decreased growth rate in children, masculinization of the female fetus, cholestatic jaundice, peliosis hepatis and hepatocellular adenoma

** intravenous administration; † subcutaneous administration.*

Treatment with lanadelumab significantly reduced the mean attack rate compared with placebo (0.26–0.53 *vs* 1.97 investigator-confirmed attacks/month respectively) during the 26-week treatment period. An open-label extension study will evaluate the long-term tolerability and efficacy of lanadelumab for the prevention of hereditary angioedema attacks (Riedl et al, 2017).

An oral plasma kallikrein inhibitor, BCX7353, is currently in development. Part 1 of a phase 2, dose-ranging, placebo-controlled study evaluating the efficacy, tolerability, pharmacokinetics and pharmacodynamics of BCX7353 for the prevention of hereditary angioedema attacks found that daily doses of oral BCX7353 125 mg or more significantly reduced the rate of hereditary angioedema attacks compared with placebo, with the greatest reduction seen with a daily dose of 125 mg (74%, $P<0.001$) (Aygören-Pürsün et al, 2018). Gastrointestinal adverse events were the most commonly reported adverse events, occurring in 29%, 50% and 44% of those treated with 125 mg, 250 mg and 350 mg BCX7353 respectively.

Hereditary angioedema with normal C1-INH

Increased bradykinin production mediates both HAE-C1-INH and HAE-nC1-INH, thus treatments available for HAE-C1-INH, particularly C1-INH concentrate and icatibant, are effective for different types of HAE-nC1-INH (Bork et al, 2017b, 2018; Bafunno et al, 2018).

Home therapy and self-administration

Since early treatment of hereditary angioedema attacks is critical, the World Allergy Organization recommends that patients have access to on-demand therapy and are taught to self-administer (Maurer et al, 2018). Self-administration training includes a home therapy partner, who usually provides support and may also be trained to administer the therapy (Maurer et al, 2018). Receiving treatment in a medical facility usually results in delays in treatment initiation, the necessity of travelling during an attack and sometimes even inappropriate treatment. In the case of laryngeal oedema, delays in treatment may be fatal (Longhurst et al, 2010). The therapy can be safely administered by the patient at home and reduces the duration and frequency of hereditary angioedema attacks (Longhurst et al, 2010). Self-administration is also more convenient and improves patients' quality of life and independence (Longhurst et al, 2010). The ability to administer treatment quickly whenever and wherever required reduces patients' fear of attacks, and allows them to regain control of their lives, and resume normal working and personal lives, including having the freedom to travel (Bygum et al, 2009). Self-administration also leads to fewer health-care visits and hospitalisations, as well as reduced time off work (Bygum et al, 2009).

The intravenous C1-INH concentrates Berinert, Cinryze and Ruconest are licensed for self-administration in children, adolescents and adults, and the subcutaneous C1-INH Haegarda is approved for self-administration in adolescents and adults. Icatibant (Firazyr) is licensed for self-administration in adults and by a caregiver for children.

KEY POINTS

- Hereditary angioedema is a rare autosomal dominant disorder caused by C1 esterase inhibitor (C1-INH) deficiency.
- Hereditary angioedema is characterized by recurrent episodes of swelling without urticaria, which involve the face, limbs, airway or intestinal tract.
- Deficiencies in C1-INH plasma level or function lead to increased production of bradykinin, which mediates vascular permeability, thus causing angioedema.
- Laryngeal oedema is potentially life-threatening as a result of asphyxiation and requires immediate treatment.
- Hereditary angioedema therapy aims to avoid fatalities and to reduce the frequency and severity of angioedema attacks by means of on-demand and prophylactic treatment.

Conclusions

Hereditary angioedema is characterized by swelling attacks that can be excruciating and potentially fatal. Prompt and accurate diagnosis is essential as patients with hereditary angioedema do not respond to drugs typically prescribed for histaminergic-mediated angioedema. Delays in diagnosis can be fatal, particularly in the case of laryngeal oedema.

Several treatment options are available, including C1-INH concentrate and icatibant, licensed for home administration, and ecallantide, available in the USA for health-care provider administration. Access to specialist care and effective treatment in the past 10 years has improved the quality of life and reduced the mortality rate in patients with hereditary angioedema. **BJHM**

Medical writing assistance was provided by Anna Mestres-Missé of Meridian HealthComms Ltd (Plumley, UK), funded by CSL Behring.
Conflict of interest: Dr HJ Longhurst has participated in research funded by, received educational and research grants from, received educational support and/or personal fees for consultancy and speaker's services from the following companies: Adverum, BioCryst, CSL Behring, Pharming, Shire; Professor K Bork has received speaker fees from CSL Behring and Shire.

Andersen MF, Longhurst HJ, Rasmussen ER, Bygum A. How not to be misled by disorders mimicking angioedema: a review of pseudoangioedema. Int Arch Allergy Immunol. 2016;169(3):163–170. https://doi.org/10.1159/000445835

Aygören-Pürsün E, Bygum A, Grivcheva-Panovska V et al. Oral plasma kallikrein inhibitor for prophylaxis in hereditary angioedema. N Engl J Med. 2018 Jul 26;379(4):352–362. https://doi.org/10.1056/NEJMoa1716995

Bafunno V, Firinu D, D'Apolito M et al. Mutation of the angiopoietin-1 gene (ANGPT1) associates with a new type of hereditary angioedema. J Allergy Clin Immunol. 2018 Mar;141(3):1009–1017. https://doi.org/10.1016/j.jaci.2017.05.020

Banerji A, Riedl MA, Bernstein JA et al; HELP Investigators. Effect of lanadelumab compared with placebo on prevention of hereditary angioedema attacks. JAMA. 2018 Nov 27;320(20):2108–2121. https://doi.org/10.1001/jama.2018.16773

Bernstein JA, Cremonesi P, Hoffmann TK, Hollingsworth J. Angioedema in the emergency department: a practical guide to differential diagnosis and management. Int J Emerg Med. 2017 Dec;10(1):15. https://doi.org/10.1186/s12245-017-0141-z

Bork K. Diagnosis and treatment of hereditary angioedema with normal C1 inhibitor. Allergy Asthma Clin Immunol. 2010 Dec;6(1):15. https://doi.org/10.1186/1710-1492-6-15

Bork K, Barnstedt SE. Laryngeal edema and death from asphyxiation

after tooth extraction in four patients with hereditary angioedema. J Am Dent Assoc. 2003 Aug;134(8):1088–1094. https://doi.org/10.14219/jada.archive.2003.0323
Bork K, Witzke G. Shortened activated partial thromboplastin time may help in diagnosing hereditary and acquired angioedema. Int Arch Allergy Immunol. 2016;170(2):101–107. https://doi.org/10.1159/000447695
Bork K, Siedlecki K, Bosch S, Schopf RE, Kreuz W. Asphyxiation by laryngeal edema in patients with hereditary angioedema. Mayo Clin Proc. 2000 Apr;75(4):349–354. https://doi.org/10.4065/75.4.349
Bork K, Meng G, Staubach P, Hardt J. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. Am J Med. 2006 Mar;119(3):267–274. https://doi.org/10.1016/j.amjmed.2005.09.064
Bork K, Staubach P, Hardt J. Treatment of skin swellings with C1-inhibitor concentrate in patients with hereditary angio-oedema. Allergy. 2008a Jun;63(6):751–757. https://doi.org/10.1111/j.1398-9995.2007.01577.x
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. 2008b Feb;100(2):153–161. https://doi.org/10.1016/S1081-1206(10)60424-3
Bork K, Wulff K, Hardt J, Witzke G, Staubach P. Hereditary angioedema caused by missense mutations in the factor XII gene: clinical features, trigger factors, and therapy. J Allergy Clin Immunol. 2009 Jul;124(1):129–134. https://doi.org/10.1016/j.jaci.2009.03.038
Bork K, Hardt J, Staubach-Renz P, Witzke G. Risk of laryngeal edema and facial swellings after tooth extraction in patients with hereditary angioedema with and without prophylaxis with C1 inhibitor concentrate: a retrospective study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2011 Jul;112(1):58–64. https://doi.org/10.1016/j.tripleo.2011.02.034
Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. J Allergy Clin Immunol. 2012 Sep;130(3):692–697. https://doi.org/10.1016/j.jaci.2012.05.055
Bork K, Bernstein JA, Machnig T, Craig TJ. Efficacy of different medical therapies for the treatment of acute laryngeal attacks of hereditary angioedema due to C1-esterase inhibitor deficiency. J Emerg Med. 2016 Apr;50(4):567-80.e1. https://doi.org/10.1016/j.jemermed.2015.11.008
Bork K, Brehler R, Witzke G, Boor S, Heineke W, Hardt J. Blindness, tetraspasticity, and other signs of irreversible brain damage in hereditary angioedema. Ann Allergy Asthma Immunol. 2017a Apr;118(4):520–521. https://doi.org/10.1016/j.anai.2017.01.027
Bork K, Wulff K, Witzke G, Hardt J. Treatment for hereditary angioedema with normal C1-INH and specific mutations in the F12 gene (HAE-FXII). Allergy. 2017b Feb;72(2):320–324. https://doi.org/10.1111/all.13076
Bork K, Wulff K, Steinmüller-Magin L, Braenne I, Staubach-Renz P, Witzke G, Hardt J. Hereditary angioedema with a mutation in the plasminogen gene. Allergy. 2018 Feb;73(2):442–450. https://doi.org/10.1111/all.13270
Busse PJ, Smith T. Histaminergic angioedema. Immunol Allergy Clin North Am. 2017 Aug;37(3):467–481. https://doi.org/10.1016/j.iac.2017.03.001
Bygum A, Andersen KE, Mikkelsen CS. Self-administration of intravenous C1-inhibitor therapy for hereditary angioedema and associated quality of life benefits. Eur J Dermatol. 2009 Mar-Apr;19(2):147–151. https://doi.org/10.1684/ejd.2008.0603
Caccia S, Suffritti C, Cicardi M. Pathophysiology of hereditary angioedema. Pediatr Allergy Immunol Pulmonol. 2014 Dec;27(4):159–163. https://doi.org/10.1089/ped.2014.0425
Cicardi M, Levy RJ, McNeil DL et al. Ecallantide for the treatment of acute attacks in hereditary angioedema. N Engl J Med. 2010 Aug 05;363(6):523–531. https://doi.org/10.1056/NEJMoa0905079
Cicardi M, Aberer W, Banerji A et al; HAWK under the patronage of EAACI (European Academy of Allergy and Clinical Immunology). Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group. Allergy. 2014 May;69(5):602–616. https://doi.org/10.1111/all.12380
Craig TJ, Levy RJ, Wasserman RL et al. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. J Allergy Clin Immunol. 2009 Oct;124(4):801–808. https://doi.org/10.1016/j.jaci.2009.07.017
Henao MP, Craig T, Kraschnewski J, Kelbel T. Diagnosis and screening of patients with hereditary angioedema in primary care. Ther Clin Risk Manag. 2016 May;12:701–711. https://doi.org/10.2147/TCRM.S86293
Longhurst HJ, Bork K. Hereditary angioedema: causes, manifestations and treatment. Br J Hosp Med. 2006 Dec;67(12):654–657. https://doi.org/10.12968/hmed.2006.67.12.22439
Longhurst H, Bygum A. The humanistic, societal, and pharmaco-economic burden of angioedema. Clin Rev Allergy Immunol. 2016 Oct;51(2):230–239. https://doi.org/10.1007/s12016-016-8575-2
Longhurst H, Cicardi M. Hereditary angio-oedema. Lancet. 2012 Feb;379(9814):474–481. https://doi.org/10.1016/S0140-6736(11)60935-5
Longhurst H, Zinser E. Prophylactic therapy for hereditary angioedema. Immunol Allergy Clin North Am. 2017 Aug;37(3):557–570. https://doi.org/10.1016/j.iac.2017.04.003
Longhurst HJ, Farkas H, Craig T et al. HAE international home therapy consensus document. Allergy Asthma Clin Immunol. 2010 Dec;6(1):22. https://doi.org/10.1186/1710-1492-6-22
Longhurst HJ, Aberer W, Bouillet L, Caballero T, Maurer M, Fabien V, Zanichelli A; IOS Study Group. The Icatibant Outcome Survey: treatment of laryngeal angioedema attacks. Eur J Emerg Med. 2016 Jun;23(3):224–227. https://doi.org/10.1097/MEJ.0000000000000292
Longhurst HJ, Zanichelli A, Caballero T et al; IOS Study Group. Comparing acquired angioedema with hereditary angioedema (types I/II): findings from the Icatibant Outcome Survey. Clin Exp Immunol. 2017a Apr;188(1):148–153. https://doi.org/10.1111/cei.12910
Longhurst H, Cicardi M, Craig T et al. COMPACT Investigators. Prevention of hereditary angioedema attacks with a subcutaneous C1 Inhibitor. N Engl J Med. 2017b Mar 23;376(12):1131–1140. https://doi.org/10.1056/NEJMoa1613627
Lumry WR, Castaldo AJ, Vernon MK, Blaustein MB, Wilson DA, Horn PT. The humanistic burden of hereditary angioedema: impact on health-related quality of life, productivity, and depression. Allergy Asthma Proc. 2010 Sep 01;31(5):407–414. https://doi.org/10.2500/aap.2010.31.3394
Lumry WR, Li HH, Levy RJ et al. Randomized placebo-controlled trial of the bradykinin B2 receptor antagonist icatibant for the treatment of acute attacks of hereditary angioedema: the FAST-3 trial. Ann Allergy Asthma Immunol. 2011 Dec;107(6):529–537.e2. https://doi.org/10.1016/j.anai.2011.08.015
Maurer M, Magerl M, Ansotegui I et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2017 revision and update. Allergy. 2018 Aug;73(8):1575–1596. https://doi.org/10.1111/all.13384
Reshef A, Zanichelli A, Longhurst H, Relan A, Hack CE. Elevated D-dimers in attacks of hereditary angioedema are not associated with increased thrombotic risk. Allergy. 2015 May;70(5):506–513. https://doi.org/10.1111/all.12587
Riedl MA, Bernstein JA, Li H et al. Recombinant human C1-esterase inhibitor relieves symptoms of hereditary angioedema attacks: phase 3, randomized, placebo-controlled trial. Ann Allergy Asthma Immunol. 2014 Feb;112(2):163-169.e1. doi: 10.1016/j.anai.2013.12.004
Riedl MA, Bernstein JA, Craig T et al. An open-label study to evaluate the long-term safety and efficacy of lanadelumab for prevention of attacks in hereditary angioedema: design of the HELP study extension. Clin Transl Allergy. 2017 Dec;7(1):36. https://doi.org/10.1186/s13601-017-0172-9
Zanichelli A, Mansi M, Azin GM et al. Efficacy of on-demand treatment in reducing morbidity in patients with hereditary angioedema due to C1 inhibitor deficiency. Allergy. 2015 Dec;70(12):1553–1558. https://doi.org/10.1111/all.12731
Zanichelli A, Magerl M, Longhurst HJ et al; IOS Study Group. Improvement in diagnostic delays over time in patients with hereditary angioedema: findings from the Icatibant Outcome Survey. Clin Transl Allergy. 2018 Dec;8(1):42. https://doi.org/10.1186/s13601-018-0229-4
Zuraw BL, Busse PJ, White M et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. N Engl J Med. 2010 Aug 05;363(6):513–522. https://doi.org/10.1056/NEJMoa0805538