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## Management of hereditary angioedema

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### Abstract

Hereditary angioedema is characterised by unpredictable, painful and potentially life-threatening oedema. Recently, some C1 inhibitors have been approved for self-administration and/or routine prevention, enabling patients to be proactive in managing their disease and reducing the burden of illness. This article discusses the effect of these advances from a specialist nurse's perspective.

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HEREDITARY ANGIOEDEMA (HAE) is a rare autosomal dominant condition occurring in approximately one in 10,000-50,000 people in Europe (Bork *et al* 2000, Cicardi and Agostoni 1996). The most common types of HAE (type I and type II) are caused by either a low level or functional deficiency of the C1 inhibitor. This is a key protein involved in the regulation of multiple biochemical pathways, acting as an inhibitor in the complement and contact systems

and also playing a minor role in the activation of the coagulation and fibrinolysis pathways (Donaldson and Evans 1963, Caliezi *et al* 2000, Davis 2006, Craig *et al* 2009, Zuraw *et al* 2010). HAE is characterised by recurrent episodes or 'attacks' of localised subcutaneous or submucosal oedema that may affect any part of the body (Gompels *et al* 2005, Longhurst *et al* 2010, Cicardi *et al* 2012). Typically, attacks of HAE affect the extremities, face (Figure 1), gastrointestinal tract, upper respiratory tract, oropharynx and genitalia, and can be painful, disabling and even life-threatening in cases involving the tongue, soft palate or larynx (Gompels *et al* 2005, Bernstein and Qazi 2010, Cicardi *et al* 2012).

HAE episodes can be precipitated by minor surgery and trauma, infection, stress, anxiety and certain medications such as angiotensin-converting enzyme (ACE) inhibitors, although many occur without an apparent trigger (Gompels *et al* 2005, Longhurst *et al* 2010, Lumry *et al* 2010). HAE attacks are not triggered by an allergic reaction and therefore do not respond to treatment with antihistamines or glucocorticoids (Cugno *et al* 2003, Bowen *et al* 2010). Oedema is likely to be mediated by bradykinin as a consequence of C1 inhibitor deficiency (Cugno *et al* 2003, Gompels *et al* 2005, Zuraw 2008); therefore, management of patients with HAE focuses on restoring this deficiency and preventing the accumulation of bradykinin. The aim of this article is to discuss some of the recent advances in the management of HAE, while highlighting the essential role of nurse specialists in caring for and supporting patients with this condition.

### Burden of illness

HAE is associated with a significant burden of illness, which is compounded by the unpredictable

nature of attacks (Longhurst *et al* 2010, Lumry *et al* 2010). The burden of illness is not consistent between individuals because the effects of HAE differ depending on the location, frequency and severity of episodes (Gompels *et al* 2005, Longhurst *et al* 2010, Lumry *et al* 2010, Cicardi *et al* 2012). While some untreated patients with HAE may experience an attack every seven to 14 days, others may experience them rarely (Zuraw 2008).

Abdominal attacks are reputedly the most distressing aspect of the disease, and can be extremely painful and disabling (Bork *et al* 2005). In addition, misdiagnosis can result in hospitalisation and unnecessary surgery (Agostoni and Cicardi 1992, Gompels *et al* 2005). Patients with HAE are also frequently afraid of upper airway oedema, which can lead to asphyxiation and even death (Bork *et al* 2003, Longhurst *et al* 2010, Lumry *et al* 2010). Although laryngeal oedema is relatively infrequent, it is associated with a mortality rate of up to 40% (Bork *et al* 2000) and can occur at any age without an apparent trigger (Bork *et al* 2000, 2003).

In addition to the physical symptoms directly associated with an episode of HAE, the after effects may affect patient wellbeing. Patients may experience fatigue, decreased productivity and depression, which can result in days away from school or work, further contributing to reduced quality of life (Longhurst *et al* 2010, Lumry *et al* 2010). The frequent need for medical intervention has socio-economic implications for patients, their families, the healthcare system and wider society (Bygum *et al* 2009, Longhurst *et al* 2010, Lumry *et al* 2010).

Recent advances have addressed the need to reduce the burden of illness associated with HAE and provide opportunities for increased patient

involvement in the management of the condition. These advances have included the availability of plasma-derived C1 inhibitor concentrates for home administration and the option for routine prevention in patients who experience severe and recurrent episodes of HAE.

## Management

Historically, management of HAE focused on treatment of acute attacks to enable patients to resume daily activities (Bowen *et al* 2008, 2010, Cicardi *et al* 2012), and current treatment guidelines highlight several therapies available for this approach (Craig *et al* 2012). First-line therapies include plasma-derived C1 inhibitor concentrates comprising the C1-esterase inhibitor, C1 inhibitor (human) and recombinant analogue of human C1 inhibitor conestat alfa (Electronic Medicines Compendium (EMC) 2011, 2012a, 2012b). Icatibant, a bradykinin B2 receptor antagonist, has been approved for treatment of acute HAE attacks (EMC 2013). Icatibant inhibits bradykinin from binding to B2 receptors thereby preventing oedema.

As outlined previously, one of the main challenges in managing HAE is the unpredictable nature of the condition and therefore the conventional treatment approach for acute HAE may be inadequate, especially in patients experiencing frequent attacks (Bowen *et al* 2010, Longhurst *et al* 2010, Cicardi *et al* 2012). However, recent advances have led to the availability of effective preventive measures that have been shown to reduce the frequency of HAE episodes (Bowen *et al* 2010, Longhurst *et al* 2010, Cicardi *et al* 2012, EMC 2012b), and therefore decrease the burden of illness.

HAE treatment guidelines have evolved to include two preventive approaches: pre-procedural prevention (short-term prophylaxis) and routine prevention (long-term prophylaxis) (Craig *et al* 2012). C1 inhibitor concentrate including plasma-derived C1 inhibitors and androgens are recommended for routine prevention in patients with confirmed type I or type II HAE to prevent episodes of angioedema (Craig *et al* 2012). However, it should be noted that not all of these treatment options are licensed for this use. Some treatments, for example attenuated androgens, are associated with multiple side effects and contraindications, which must be considered before initiating routine prevention and require regular monitoring (Bork *et al* 2008, Bowen *et al* 2010, Craig 2008, Lumry *et al* 2010, Craig *et al* 2012). Among the plasma-derived C1 inhibitor concentrates, only C1 inhibitor (human) is approved, for pre-procedural and routine prevention of HAE attacks (EMC 2012b).

**FIGURE 1**

**Hereditary angioedema involving the face**



In addition to routine prevention, the option to self-administer and participate in home care support programmes is becoming more available. Plasma-derived C1 inhibitor concentrates (C1-esterase inhibitor and C1 inhibitor (human)) and icatibant are approved for self-administration; human plasma-derived C1 inhibitor concentrates are also approved for home infusion following approval by the prescribing physician and receipt of training that can be provided by a specialist nurse (Longhurst *et al* 2010, EMC 2012a, 2012b, 2013).

### Role of the nurse

Input from specialist nurses is essential in providing adequate training for self-administration of treatment by patients and treatment at home, but also in conducting regular reviews to ensure maintenance of optimal therapy (Longhurst *et al* 2010, EMC 2012a, 2012b). The availability of these management approaches will assist patients in gaining improved control of their disease, enable timely treatment and reduce the need for emergency hospital treatment (Longhurst *et al* 2010, EMC 2012a, 2012b).

The specialist nurse has a key role in the care and management of patients with HAE, particularly in light of increased home-based care (Longhurst *et al* 2007). In addition to patient education, training and monitoring, nurses have an important role in patient management, working in partnership with physicians (Hussar 2009, Longhurst *et al* 2010). Many specialist HAE nurses are also involved in prescribing treatments, are a prominent point of contact in an emergency, and are key in addressing any queries or difficulties experienced by patients.

### Evidence for the use of plasma-derived C1 inhibitor concentrates

The role of plasma-derived C1 inhibitor concentrates for self-administration and routine prevention is supported by clinical data, and efficacy and safety have been demonstrated in one randomised, double-blind, placebo-controlled phase III study (Zuraw *et al* 2010). The use of plasma-derived C1 inhibitor concentrate (C1 inhibitor (human)) in the acute treatment of HAE and the prophylaxis of HAE was investigated in two separate studies. The first study included a 24-week study period where patients received either plasma-derived C1 inhibitor concentrate (C1 inhibitor (human) at 1,000 units/10mL) or placebo for the first 12 weeks and the opposite agent for the second 12-week period. In 22 patients (11 per group), the rate of HAE episodes decreased more than twofold with the administration of

plasma-derived C1 inhibitor concentrate compared to placebo (6.26 versus 12.73 attacks,  $P<0.001$ ). The administration of plasma-derived C1 inhibitor concentrate also decreased the severity ( $1.3\pm 0.85$  versus  $1.9\pm 0.36$  with placebo,  $P<0.001$ ) and duration ( $2.1\pm 1.13$  versus  $3.4\pm 1.39$  days with placebo,  $P=0.002$ ) of HAE episodes. In addition, patients experienced fewer days of swelling with plasma-derived C1 inhibitor concentrates ( $10.1\pm 10.73$  versus  $29.6\pm 16.9$  with placebo,  $P<0.001$ ) and required less rescue therapy ( $4.7\pm 8.66$  versus  $15.4\pm 8.41$  with placebo,  $P<0.001$ ).

Of the 24 patients in the prophylaxis study population, 21 experienced one or more adverse events, although only one patient had an adverse event, mild pruritus and rash, related to the administration of plasma-derived C1 inhibitor concentrate. An additional two patients experienced moderate adverse events, including light-headedness or fever, which were possibly related to plasma-derived C1 inhibitor concentrates. In the placebo group, one patient experienced severe chest discomfort and moderate cough. The same patient also experienced moderate erythema, which was possibly related to administration of the placebo (Zuraw *et al* 2010).

These data are supported by an open-label, single-arm, multicentre study involving 146 patients with HAE aged one year or more, with a history of laryngeal oedema or one or more episodes of HAE per month, who received 1,000 units of plasma-derived C1 inhibitor concentrate every three to seven days for routine prevention of HAE attacks (Zuraw and Kalfus 2012). Following routine prevention with plasma-derived C1 inhibitor concentrates, the median monthly rate of HAE attacks was reduced from 3.0 (interquartile range (IQR) 2-4) to 0.19 (IQR 0.00-0.64), where 88% ( $n=128$ ) of the patients experienced an average of one or fewer attacks per month and 35% ( $n=51$ ) did not report any attacks during the study. Zuraw and Kalfus (2012) reported that plasma-derived C1 inhibitor concentrate was well tolerated with no variation in efficacy despite the duration of treatment. These data demonstrate that routine prevention with plasma-derived C1 inhibitor concentrate is effective, has a good safety profile and the potential to reduce the burden of illness on the patient as a result of fewer disruptions to daily activities.

The efficacy and benefits of routine prevention in combination with self-administration of plasma-derived C1 inhibitor concentrate have also been demonstrated (Landmesser *et al* 2010). Of 243 patients who received plasma-derived C1 inhibitor concentrate at home, 42% of patients self-administered the medication while 16% and

23% of patients were administered the drug by a family member or home healthcare professional, respectively. The study concluded that home administration with plasma-derived C1 inhibitor concentrate is a viable option for patients using routine prophylaxis (Landmesser *et al* 2010). The benefits of self-administration and routine prevention have also been demonstrated in clinical practice (Boxes 1 and 2).

### Intravenous administration

In support of the clinical and practical evidence, routine prevention, self-administration and home care support programmes are also endorsed by management guidelines (Bowen *et al* 2010, Cicardi *et al* 2012) and the HAE international home therapy consensus (Longhurst *et al* 2010). The consensus document was developed by specialists in HAE following discussions with patients, nurses, physicians and other healthcare professionals, with the ultimate aim of 'improving the physical, psychological and economic wellbeing of those affected by HAE' (Longhurst *et al* 2010).

The HAE international home therapy consensus document (Longhurst *et al* 2010) recommends that every patient with HAE should be considered for home therapy and self-administration training for treatment and prevention of HAE attacks, preferably trained with a 'home therapy partner', such as a family member or friend, who can provide support and advice or administer the therapy if required. While the lack of a home

therapy partner does not exclude the possibility of self-administration, each patient has to be assessed individually and for some patients, the decision may be to self-administer the drug in a location where another responsible person can be called on for assistance if necessary.

The assessment of risks and benefits of home administration, procurement of informed consent and provision of a treatment plan, including an emergency plan, should be the responsibility of the physician, although training may be delegated to a trained specialist nurse (Longhurst *et al* 2010). The training programme for patients should ideally take place over several sessions, initially under medical supervision, with refresher training planned at regular intervals, for example at least once every 12 months (Longhurst *et al* 2010).

Both approved human plasma-derived C1 inhibitor concentrates (C1 inhibitor (human) and C1-esterase inhibitor (human)) require reconstitution before administration (EMC 2012a, 2012b). The recommended posology for the administration of these products is outlined in Table 1. Venepuncture for the intravenous administration of plasma-derived C1 inhibitor concentrates is recommended with a small (28 gauge) butterfly needle infusion set (Longhurst *et al* 2010). However, the necessity to administer plasma-derived C1 inhibitor concentrates via the intravenous route and consequently the need for intravenous cannulation at home may be viewed as a potential drawback of self-administration because of patient fears concerning the technique of self-injection, potential complications and practicalities of how to dispose of equipment at home. However, these issues can be overcome if the patient is supported during his or her first attempt at self-cannulation, taking confidence from having contact with a specialist nurse once at home to discuss any issues that may arise. This model has been demonstrated in the context of haemophilia management where home care programmes have been running successfully for the past 35 years (Bowen *et al* 2010, Longhurst *et al* 2010). Moreover, self-administration is reportedly associated with a lower incidence of cannulation failure and may help preserve veins more effectively compared to hospital-based care (Longhurst *et al* 2010).

In the UK, HAE specialist nurses provide individualised self-administration training programmes for patients and their families. This is supported by the Libertas Plus Home Care Service – a home delivery and self-administration training and support service provided by healthcare at home infusion nurses. These nurses provide:

## BOX 1

### Case study 1

#### Background

This case study concerns a 43-year-old patient with hereditary angioedema (HAE) and a history of disabling cutaneous oedema affecting the hands, feet, abdomen and larynx. In 2011, the patient attended the local emergency department 104 times for emergency treatment with C1 inhibitor (the patient cannot tolerate attenuated androgens), leading to considerable disruption to lifestyle and work. As a result, the patient experienced reduced quality of life, and increased levels of stress and anxiety, which may have contributed to triggering further attacks.

#### Management

In 2012, the patient was enrolled in the Libertas Plus Home Care Service – a dedicated patient service providing appropriate training and education for suitable patients, or their carers, to administer C1 inhibitor (human). The patient now self-infuses 1,000 units of C1 inhibitor twice a week.

#### Outcome

The patient has not needed to attend the emergency department since enrolling in the Libertas Plus Home Care Service and now manages all required prophylactic and on-demand treatment independently. This has allowed the patient to manage disease symptoms more effectively, with a reported reduction in stress and anxiety levels. The patient feels confident to travel abroad independently and no longer has to take time off work as a result of HAE-related problems, and has an improved quality of life.

- ▶ Training for eligible patients who are starting self-administration of routine prevention therapy with C1 inhibitors (human).
- ▶ Ongoing intravenous injection training and support for eligible patients who are receiving routine prevention therapy with C1 inhibitors (human).

In some areas, access to C1 inhibitors for self-administration at home may be poor, for example where there is a lack of HAE specialists or where funds are restricted by local healthcare authorities. However, the recent availability of C1 inhibitors with a licence for self-administration, and home care training programmes should improve HAE management.

## Conclusion

HAE is a debilitating disease that not only affects the patient, but also his or her family, friends and the wider society. The approval of therapies for routine prevention of HAE attacks in patients who experience more than one severe episode per month (EMC 2012b), combined with the option to self-administer and availability of home care support programmes, are significant advances towards improving patient care. The ability to administer treatment at the earliest opportunity can reduce the frequency, severity and duration of an episode, decreasing the burden of illness by alleviating distress, reducing time off school or work, decreasing disruption to other daily activities, and reducing hospitalisation (Bygum *et al* 2009, Longhurst *et al* 2010). These benefits can minimise the effect of the

condition on patients' physical, social, emotional and economic wellbeing. In addition, self-administration enables patients to be proactive in managing their disease, which may also confer benefits in treatment adherence (Bygum *et al* 2009, Longhurst *et al* 2010).

The full benefits of self-administration and routine prevention rely on the administration of formal training and regular monitoring, all of which can be provided by specialist HAE nurses.

## BOX 2

### Case study 2

#### Background

This case study concerns a 48-year-old patient with poorly controlled hereditary angioedema (HAE) who, despite on-demand self-administration with a C1 inhibitor, experienced three to four HAE attacks per week, usually associated with abdominal pain, diarrhoea, vomiting and feeling faint. The patient also experienced two episodes of laryngeal oedema per month, and frequent limb and facial swellings. These attacks had a significant effect on the patient's professional life and resulted in frequent absences from work. The patient also reported a reduction in quality of life and feelings of hopelessness.

#### Management

Following assessment, the patient commenced prophylactic 1,500 units of C1 inhibitor twice a week.

#### Outcome

The patient is able to control disease symptoms more effectively, with a typical breakthrough attack occurring only every two to four weeks. Communication between the patient's employer and physician has allowed for special arrangements to be made whereby the patient is allowed time at work to administer the C1 inhibitor at the first signs of a breakthrough attack, contributing to a good attendance record at work. This has led to increased confidence, with the patient feeling hopeful about the future.

**TABLE 1**

### Recommended and approved posology for the administration of plasma-derived C1 inhibitors for the management of hereditary angioedema

Management approach	Drug and posology
	<b>C1 inhibitor (human) (for adults and adolescents)</b>
Treatment of acute hereditary angioedema attacks	1,000 units at the first sign of onset of an acute attack. A second dose of 1,000 units may be administered if the patient has not responded adequately after one hour. For patients experiencing severe attacks, in particular laryngeal attacks, or if initiation of treatment is delayed, the second dose can be provided sooner than one hour.
Pre-procedural prevention	1,000 units within 24 hours before a medical, dental or surgical procedure.
Routine prevention	1,000 units every three or four days is the recommended starting dose. However, the dose interval may need to be adjusted according to individual response. In addition, the continued need for regular prophylaxis should be reviewed on a regular basis.
	<b>C1-esterase inhibitor (human) (for adults and children)</b>
Treatment of acute hereditary angioedema attacks	20 units per kg body weight.
Pre-procedural and routine prevention	Not approved.

(Electronic Medicines Compendium 2012a, 2012b)

It is therefore essential that HAE nurses are aware of advances in management of the condition, to ensure they are equipped to offer support and guidance to both patients and physicians, with the ultimate aim of reducing the burden of HAE and improving quality of life for patients **NS**

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#### Conflict of interest

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