Hereditary Angioedema (HAE) Position Paper

This is an updated version (2020) of the original ASCIA Position Paper on Hereditary Angioedema (HAE) developed by the ASCIA HAE Working Party in 2010 and revised in 2012 and 2017. ASCIA HAE Working Party members are listed on the ASCIA website: www.allergy.org.au/members/committees#wp

This document has been compiled as a Position Paper for ASCIA and has not been formulated as a formal Guideline. This document aims to provide:

- Background education on various aspects of HAE.
- Treatment algorithms for the Australian and New Zealand environments.
- Statements regarding the Global Guidelines on HAE to which ASCIA is a signatory.

There are two parts to this ASCIA HAE Position Paper:

- **Part 1 provides an overview of HAE**, with background education on classification, definitions, pathogenesis, clinical presentation and diagnosis, which is unchanged from the 2017 revision.
- **Part 2 provides a guide to HAE management** including recent developments in treatments available in Australia and New Zealand, and a new ASCIA HAE Management Plan to provide for patients.

ABBREVIATIONS USED IN DOCUMENT

ACE	angiotensin converting enzyme
ASCIA	Australasian Society of Clinical Immunology and Allergy
C1-INH	C1 inhibitor
EAACI	European Academy of Allergy and Clinical Immunology
ED	emergency department
GA^{2}LEN	Global Allergy and Asthma European Network
HAE	hereditary angioedema
HRT	hormone replacement therapy
IV	intravenous
LTP	long term prophylaxis
NBA	National Blood Authority
OCP	oral contraceptive pill
PBS	Pharmaceutical Benefits Scheme
PID	primary immunodeficiency
TA	tranexamic acid
TGA	Therapeutic Goods Administration
SC	subcutaneous
SAS	Special Access Scheme
STP	short term prophylaxis
WAO	World Allergy Organisation

PART 1: AN OVERVIEW OF HAE

1.0 INTRODUCTION

1.1 Classification and definitions

Angioedema may result from mast cell activation with release of histamine and other mediators (histamine-mediated) or it can be mediated by bradykinin. Bradykinin-mediated angioedema may be the result of an acquired or hereditary abnormality, the latter due to a deficiency/defect of C1 inhibitor (C1-INH). Three forms of HAE have been defined:

1. **HAE due to C1-INH deficiency (type 1 HAE)** - patients with this condition have low antigenic and functional C1-INH levels.
2. **HAE due to C1-INH dysfunction (type 2 HAE)** - normal (or elevated) antigenic but low functional C1-INH levels define this condition.
3. **HAE with normal C1-INH antigenic and functional levels (type 3 HAE)** - this is a very rare condition where symptoms are very similar to HAE types 1 and 2. A subset of type 3 HAE patients have mutations in factor XII but there are other yet to be defined genetic abnormalities. This subtype will not be discussed in this document.

Acquired C1-INH deficiency (AAE) may cause angioedema in adults and must be distinguished from HAE (section 4.3).

1.2 Historical facts

The first description of HAE has been attributed to Robert Graves, who in 1843 described a patient with "a tumor rising on the forehead in the space of half an hour" and then later "sometimes the lips, inside of the mouth, palate, and uvula are attacked giving rise to a very considerable inconvenience" (Graves, 1843 as cited in Major, R.H.,(ed), 1955). The term *angioneurotic edema* (a synonym for *angioedema*) is derived from Heinrich Quincke's original explanation that swelling arose from increased vascular permeability that could affect not only the face and larynx, but also the gastrointestinal tract (Quincke,1882). The autosomal dominant nature of this disorder was described by William Osler, who reported the disorder in each of five family generations (Osler, 1888). The biological basis for this disorder remained unclear until 1962, when Landerman suggested that HAE might result from dysregulation in kinin generation and that there might be an inherited defect in an inhibitor to a permeability factor such as kallikrein (Landerman et al, 1962). While investigating the properties of a newly discovered protein shown to inhibit complement factor 1, Donaldson reported low circulating levels of this protein in patients with HAE (Donaldson & Evans, 1963; Donaldson & Evans, 1969). Further studies by Rosen found that 85% of patients with HAE had low circulating levels of C1-INH (Type 1 HAE), with the remainder producing a dysfunctional inhibitor (Type 2) (Rosen et al, 1965).

1.3 Epidemiology

Estimates of prevalence of HAE range from 1/10,000 to 1/150,000 patients (Naeko et al, 2001; Frank et al, 2000.) There are no known ethnic or sex differences in HAE types 1 and 2 (unlike HAE Type 3) (Bork et al, 2000).

1.3.1 HAE in Australia

No formal epidemiological research into this condition has been conducted in Australia. ASCIA established a Primary Immunodeficiency (PID) Register in 1994 with the aim of collecting and analysing data on all patients with PID in Australasia to facilitate diagnosis, treatment, research, education and quality assurance for patients with PID. HAE is defined by the World Health Organisation (WHO) as a PID. However, these patients are not prone to increased infection risk. Results from the database were first published in 1997 (Baumgart et al, 1997). At that time complement deficiencies accounted for 7.4% of PID cases in the Australian register, with HAE being the most common, accounting for 6.4% of cases,

giving a national rate of 0.18/100,000 in the general population. Currently, there are 66 HAE patients registered in the database (representing 5% of all PID registrations in database), which is undoubtedly affected by under-reporting. If the currently quoted number of cases in other populations holds for Australia, then up to 480 cases could be expected to exist. The patient support organisation HAE Australasia has more than 100 registered members with HAE in their database.

1.3.2 HAE in New Zealand

Currently, there are 54 patients known to have received C1-INH in New Zealand in the years 2015 to 2019. Of these patients, 51 have been diagnosed with HAE by a Clinical Immunologist (the remainder have acquired angioedema) and 75% of the patients with HAE have been recruited to the HAE in Aotearoa National Audit. These patients have been characterised in terms of HAE type age, gender, location, ethnicity, attack frequency, treatment and its impact on quality of life. Diagnostic delay in New Zealand for patients without a family history was a mean of 13.7 years.

2.0 PATHOGENESIS

C1-INH is a serine protease inhibitor whose major activity is inhibition of a number of complement proteases (C1r, C1s and mannose binding lectin associated-serine protease <MASP>) and contact system proteases (plasma kallikrein and coagulation factor XIIa). During attacks of HAE, these plasma proteolytic cascades are activated and several vasoactive substances are released. Studies have shown that bradykinin is the predominant mediator of enhanced vascular permeability. Bradykinin is generated by activation of the contact system and binds to its cognate receptor (the bradykinin B2 receptor) on vascular endothelial cells. It is the primary mediator of swelling in HAE. It is important for normal homeostasis, normal immune responses, inflammation, vascular tone and vascular permeability. Angioedema is primarily mediated through the B2 bradykinin receptor causing increased permeability.

In HAE Type 1 there is low C1-INH protein level and function. This pattern represents 85% of all cases of HAE. Typically, the C1-INH level is 5-30% of normal levels even though only one allele is affected. There is both decreased protein production and increased catabolism of the protein in these cases.

In HAE Type 2 there is normal C1-INH protein level but impaired C1-INH function, usually caused by mutations of the active site of the protein.

3.0 CLINICAL PRESENTATION

Summary

In the absence of adequate levels of C1-INH, subcutaneous and submucosal oedema result from the uninhibited action of vasoactive mediators, of which bradykinin is considered the most important. HAE is characterised by recurrent oedema of the limbs, trunk, face and genitals without urticaria, typically taking 24 hours to peak and resolving over 48-72 hours. Importantly it is neither itchy nor pitting. Visceral swelling of the gastrointestinal tract may result in abdominal pain, vomiting and hypotension. The most serious manifestation is laryngeal swelling, which was reported in older cohort studies to result in fatal asphyxiation in up to a third of patients (Quincke, 1882). Attacks may be preceded by a prodrome of tingling, or a non-itchy rash (erythema marginatum - Osler, 1888) anywhere on the body. Affected patients also have higher than expected rates of autoimmune disease (Landerman et al,1962; Donaldson, Evans, 1963).

3.1 The acute attack

HAE is characterised by episodic swelling of subcutaneous tissues, gut and upper respiratory tract (Bork et al 2006). Clinical episodes may occur frequently or may be years apart (Agostoni at el 2004). Fifty

percent of patients experience their first manifestation of the disease before the age of 10 (Bork et al 2006).

HAE attacks in any one patient follow a typical but not invariable pattern. There may be prodromal symptoms such as fatigue, flu-like symptoms, indigestion, tingling, and sometimes, a non-urticarial, non-pruritic macular serpiginous erythema (erythema marginatum) preceding the onset of swelling. This is most often observed on the chest and may not be adjacent to the area of swelling. The swelling usually worsens gradually over 24 hours and may last three to four days or longer and may spread to other sites, thereby prolonging the episode. It does not respond to antihistamines, corticosteroids or adrenaline (Quincke, 1882; Gompels et al, 2005).

3.2 Manifestations

Abdominal pain, frequently accompanied by nausea, vomiting, abdominal distention, dehydratin, diarrhoea or constipation, is the most frequent clinical manifestation of HAE. Acute attacks may mimic surgical emergencies and result in unnecessary appendectomy or exploratory laparotomy (Agostoni at el 2004; Bowen et al, 2008).

Cutaneous angioedema, a non-pitting, non-pruritic swelling, usually affects the face, limbs or genitals. (Agostoni at el 2004).

Upper airway swelling is a much less frequent manifestation and may affect the oropharynx (tongue, soft palate) or the larynx. Laryngeal swelling can cause death from asphyxiation. Even though it accounts for fewer than 1% of episodes, more than 50% of patients report at least one occurrence of laryngeal angioedema at some stage in life (Agostoni at el 2004). Historical data suggest that mortality from laryngeal swelling was 30% prior to the introduction of effective treatment (Quincke, 1882).

3.3 Other features

Urticaria is **not** a feature of HAE or other kinin-related forms of angioedema (Frank 2008). Erythema marginatum may mimic urticaria but it is flat and not pruritic. Although a family history is usual, about 25% of newly diagnosed patients report no known affected family members (Davis 2008). In these patients a de novo mutation is presumed (Winnewisser et al, 1997). Members of the same kindred (with presumably the same genetic variant) may differ greatly in their expression of the disease (age of onset and frequency, severity and location of manifestations) [24]. There is an increased frequency of autoimmune disorders in patients with HAE, such as glomerulonephritis, systemic lupus erythematosis (SLE), thyroiditis and inflammatory bowel disease (Landerman et al, 1962; Frank 1979).

3.4 Trigger factors

Recognised exacerbating factors include stress, infection, injury, dental and other surgery (Quincke, 1882), oestrogens such as oestrogen-oral contraceptives, hormone replacement therapy and pregnancy, (Bork et al, 2003; Agostini et al 1999) and angiotensin converting enzyme inhibitors (Postnikoff, Pritzker, 1979). Often no precipitating factor can be discerned.

Table 1. Classification of angioedema

Bradykinin Induced
• HAE type 1 (C1-INH deficiency),
• HAE type 2 (C1INH dysfunctional),
• HAE type 3 (HAE with normal C1INH),
• AAE (acquired C1INH deficiency),
• ACE-I induced
• Idiopathic bradykinin induced angioedema

Histamine Induced (Mast cell-dependent) – majority of cases
• Idiopathic histamine induced angioedema
• Allergic angioedema (e.g. IgE-mediated food or drug allergy)
• Drug induced histamine dependent angioedema (e.g. NSAID intolerance)
Suspect mast cell-dependent when:
• Angioedema coexists with urticaria or other features of anaphylaxis
• Obvious trigger (e.g. drug, food)
• Response to antihistamines (either for treatment or prevention)
Trial of antihistamines and corticosteroids is indicated until diagnosis is confirmed.

Table 2. Features distinguishing HAE from other forms of Angioedema (Bork et al, 2000)

Symptom/Sign	**HAE**	**Acquired**	**Allergic/IgE Mediated**
Angioedema	Yes	Yes	Yes
Urticaria	No	No	Usually
Age of onset (most frequent)	6-20	> 50	Anytime
Family history	Usually	No	Variable
Underlying disease	No	Yes	No
Location of swelling	All	All	Especially face, lips
Precipitation by trauma	Yes	Yes	No
Duration of swelling, hr	48-72	48-72	2-48
Response to treatment with adrenaline, antihistamine, corticosteroids.	No	No	Yes

3.5 Special circumstances

In some circumstances, patients with HAE require special measures to protect them from the risk of swelling.

3.5.1 Pregnancy

The published experience regarding the effect of pregnancy on HAE has yielded conflicting results. The most substantial study on clinical manifestations of HAE to date has been a case series of 30 patients by *Frank et al* looking at the clinical characteristics of HAE. In this series there were 10 patients in whom the effect of HAE on pregnancy was evaluated. Among the 10 women with a total of 25 pregnancies more than 80% of the pregnancies were associated with a decreased incidence of attacks in the second and third trimester. In the two patients who had an increase in the frequency of attacks at this time, the attacks were not related to the delivery.

Trauma is recognised as a frequent trigger for acute HAE attacks, so it is somewhat surprising that angioedema attacks are rare at the time of delivery despite the associated injury to the birth canal. However, it has been suggested that the physical trauma associated with normal labour can precipitate airway difficulties, presumably as a result of straining. Similarly, the same mechanism may result in mucosal swelling in the genital tract, for example vulval oedema (Chinniah, Katelaris, 2009; Bork, Barnstedt, 2001) have recently published the results of a retrospective study reviewing the outcomes of 16 pregnancies in seven HAE patients in Australia. In 15/16 pregnancies, women had greatly reduced or no attacks in the last two trimesters compared with attacks occurring in the first trimester. No woman experienced angioedema at time of delivery. During the post-partum period, four women experienced

increased frequency and severity of attacks when compared to the pre-pregnancy state (baseline). For two women, this impacted on their breast feeding routine due to the need for commencement of danazol, the only prophylactic therapy available at the time of the study. Since danazol has the theoretical potential for androgenic effects in breast-fed infants, infants were weaned off breast milk before initiation of treatment with danazol. **Please refer to box on page 11 regarding supply of danazol in Australia.**

3.5.2 Perioperative period

Surgical procedures may pose a special risk to patients with HAE and when possible, require planning and consultation between the immunologist, anaesthetist and surgical teams. Some procedures such as those involving laryngopharyngeal manipulation or instrumentation carry a much greater risk of triggering potentially life-threatening episodes. Postoperative complications such as sepsis increase the risk of attacks during this period.

Regimens to protect patients from acute attacks during interventions are based on uncontrolled studies and are aimed at increasing temporarily the plasma C1-INH levels (see 6.2).

3.5.3 Dental procedures

Triggering of attacks following dental work is unpredictable. Extensive dental work may be carried out without complication and conversely, minor work may occasionally precipitate an attack. Fatal laryngeal attacks have been documented following tooth extraction (Farkas et al, 2007) and episodes have been triggered by the administration of local anaesthetics (Frank, 2008). All patients undergoing any dental procedure should be warned of the risk of an acute attack in the 36 hours following the intervention and should have prompt access to emergency treatment such as C1-INH concentrate or icatibant whether or not they have received prophylaxis. Given the difficulties with exact predictions of the likelihood of an attack a management plan for dental interventions should include the following:

- If minor work is planned no prophylaxis is given but ready access to emergency treatment such as C1-INH concentrate or icatibant should be assured.
- More complex manipulations may be covered by the use of danazol 10mg/kg/day for 5 days before and 2 days after the event. C1-INH concentrate or icatibant should be readily available.
- For any procedure requiring intubation, or for tooth extraction, C1-INH concentrate 1-6 hours before the procedure with further doses readily available.

Evidence of efficacy of pre-procedural prophylaxis is shown in a study (Jurado-Palomo et al, 2013) which examined outcomes in 24 HAE patients undergoing dental procedures. Increasing danazol or pre-procedural C1-INH administration protected from swellings. Nine patients were given no prophylaxis and 3 of 9 had swelling post-dental procedure.

3.6 Paediatric presentations

When a child has a parent or other family member with diagnosed HAE, there is a strong clinical suspicion about the diagnosis if the child presents with recurrent abdominal pain or swelling. There is typically, difficulty and delay with diagnosis if no such family history exists.

3.6.1 Delayed diagnosis

More than 50% of those with HAE have their first attack before the age of 10 years, the mean age being 8 to 12 years (Bork et al, 2006). Occasionally episodes occur in the first year of life (7%) (Agostoni et al, 2004) and another 35% present in the second decade. The diagnosis, however, is usually not made until the second or third decade of life (Agostoni et al, 2004; Roche et al, 2005). Studies have documented an average delay to diagnosis of 13 to 21 years despite improvements in screening and general awareness of HAE (Quincke, 1882; Zingale et al, 2006; Bork et al, 2000).

3.6.2 Implications of paediatric presentation

Angioedema *with* urticaria is common in children and in most cases is associated with allergy or recent infection. Thus there may be a greater chance that the significance of **angioedema *without* urticaria** may be missed than occurs in adults.

There is an inverse correlation between age at onset and severity of disease. In a cohort of 209 patients, the 64 patients whose symptoms commenced under 5 years had an average of 31.4 episodes per year whilst the 68 patients who first developed symptoms aged over 15 years averaged 17.8 episodes a year, a statistically significant difference (Agostoni et al, 2004).

3.6.3 Special clinical features

It is important to recognise that although episodes of severe swelling are less common in children, they nevertheless can occur and may need acute intervention.

Laryngeal oedema, more frequently reported in patients in their mid-20's, is less common in children (Cicardi, Pappalardo, 2003; O'Bier et al, 2005). However, when it does occur, usually in the context of swelling of the face and neck progressing to involve the uvula, soft palate and larynx, the small calibre of the airways increases the risk of rapid onset of obstruction from relatively mild swelling. A nine year old boy reportedly died of asphyxia 20 minutes after onset of swelling (O'Bier et al, 2005). In comparison, severe laryngeal swelling in adults usually develops over 8 to 12 hours (Agostoni et al, 1999).

Epiglottic swelling has also been reported as an unusual manifestation in a 12 year old boy, diagnosed with HAE at age 7. No precipitating factors were identified but early recognition leading to intubation and treatment with ε-aminocaproic acid lead to rapid resolution and discharge without complications (Zuraw, Herschbach, 2000).

Children presenting with ***episodic abdominal pain*** can be a difficult diagnostic dilemma since such episodes are usually secondary to causes other than HAE. Isolated abdominal pain can sometimes be the first and only manifestation of HAE. In 43 of 153 (28.1%) patients in a recent series, abdominal pain preceded subcutaneous swelling by a mean interval of 8.4 years (range 1–33 years) (Osler, 1888). Manifestations can range from diffuse abdominal pain to episodes mimicking an acute surgical emergency with ileus and hypovolaemic shock. Vomiting and diarrhoea are also common. A rare complication of severe swelling is intussusception.

However, symptoms in children generally consist of ***recurrent episodes of soft tissue swelling*** involving the extremities, predominantly involving fingers and toes (45%), sometimes also involving subcutaneous angioedema of face, neck, genitals and trunk. These usually resolve spontaneously within 2 to 4 days. Mechanical trauma and infection are common precipitating factors (Roche et al, 2005).

4.0 DIAGNOSIS

When there is a suspicion of HAE diagnosis, patients must be screened. If the diagnosis is confirmed, family members must be screened as well.

4.1 Indications for testing

Testing for HAE should be carried out if there is a clinical suspicion in any age group. Testing should also be carried out if there is a positive family history.

Tests of C1-INH level, function and C4 may not be reliable in patients younger than one year of age and therefore testing performed in patients before the age of one year should be confirmed after the age of one year.

4.2 Testing for HAE

The tests available for screening and diagnosis of HAE include C4 (screening), C1-INH level and C1-INH functional assay. In an untreated patient a normal C4 level makes the diagnosis of HAE unlikely. Serum C4 levels are invariably low during attacks however in approximately 2% of cases, the serum C4 level is normal in between attacks (Frank, 2008).

In patients with isolated angioedema where clinical suspicion of HAE is low, screening with C4 levels may be adequate. If HAE is strongly suspected, serum C4 and serum C1-INH level and function should be measured. In general, C1-INH level and functional assay measurements are 50% below the normal range in HAE.

Results should be confirmed by repeat testing before making a definitive diagnosis of HAE since delay in processing or refrigeration can result in artifactually low results especially in the C1-INH functional assay.

4.3 Acquired C1 INH deficiency (AAE)

A detailed discussion of acquired forms of angioedema (AAE) is beyond the scope of this paper. AAE usually has its onset in middle age with those affected experiencing attacks similar to HAE. There is an absence of a family history. The attacks do not respond to antihistamines or corticosteroids. AAE results from increased destruction or metabolism of C1-INH.

Two types are described:

- **Type 1 AAE** typically occurs in association with B cell lymphoproliferative and rheumatologic disorders. Such patients have circulating anti-idiotypic antibodies to immunoglobulins on the surface of B cells. Complexes between these are formed with continuous activation of C1-INH which is consumed in this process and levels decline below normal as synthesis cannot keep up with consumption.
- **Type 2 AAE** is characterised by formation of autoantibodies directed against C1-INH. Binding of these to C1-INH results in inactivation of C1-INH (Bork et al, 2006).

A reduced serum C4 and C1-INH protein level should be followed up by measurement of serum C1q. Approximately 75% of patients with acquired C1-INH deficiency have reduced serum C1q whereas C1q level is normal in HAE.

5.0 GENETIC DIAGNOSIS OF HAE

Three forms of HAE have been described. Mutations in the *SERPING1* gene that encode the C1-INH protein result in HAE Types 1 and 2 (OMIM 106100). Sequencing of multiple exons is required since the reported mutations are scattered throughout the gene (Bell et al, 2008).

The causative role of these mutations has allowed the categorisation of the disease into either a truncating deletional or non-sense mutation leading to a quantitative reduction in levels (Type 1) or missense mutations producing a dysfunctional protein (Type 2). The inheritance pattern is autosomal dominant. Haploinsufficiency of the C1-INH protein due to inadequate level of expression of C1-INH from the normal haplotype results in the disease. Medications such as attenuated androgens increase expression from the normal allele and reduce attack frequency.

HAE Type 3 is not caused by C1-INH deficiency and describes a rare form of angioedema mainly affecting females. Diagnosis requires a strong family history as the genetics are not well defined. A subset of patients have a mutation in the Factor XII gene (OMIM610618) (Cicardi et al, 2003; Deald, Bork, 2006; Prematta et al, 2008). Factor XII levels in HAE Type 3 are normal and affected females do not exhibit abnormal clotting.

Confirmation of the genetic basis for the diagnosis of HAE Type I has limited clinical utility but may be useful for confirming the status of young children who manifest normal or near-normal C1-INH levels when they come from affected families. Genetic testing may also be useful in clarifying the status of adults with less severe angioedema and borderline C1-INH as well as for re-evaluation of patients on androgenic therapy.

Genetic testing for confirmation of a diagnosis of HAE Type 2 has more clinical utility than for HAE Type I. The clinical laboratory assays of C1-INH function are less robust than the quantitative assays. Genetic testing may therefore be useful for distinguishing late onset acquired angioedema from HAE or when the laboratory tests for HAE have been inconclusive. Genetic testing is the only method to confirm the diagnosis of Type 3 HAE due to factor XII mutation. Genetic testing also enables prenatal diagnosis.

PART 2: HAE MANAGEMENT

1.0 AN OVERVIEW OF HAE MANAGEMENT

This section includes a short summary of management approaches, whilst section 3.0 includes detailed information for clinical immunologists/allergists specialising in management of HAE patients.

1.1 Global guidelines

ASCIA is a signatory to the GA^{2}LEN/EAACI/WAO Global Guidelines for the management of HAE (Maurer et al, 2018) and the general principles in the evidence-based Guidelines are in line with this document.

1.2 Quality of Life (QoL) assessment

As in other areas of medicine, quality of life for patients with HAE is being given the attention it deserves. There are complex issues to address, include the burden of living with a genetic disorder and the concern that the condition may be passed on to children. Other issues centre around the ever-present yet unpredictable threat of a painful, debilitating attack or a life-threatening swelling. This may impede educational and occupational progress. The availability of effective therapy for acute attacks that can be self-administered at home has made an enormous impact on the quality of life of HAE patients. The development of safe, effective prophylactic treatments holds the promise of being able to live attack-free and removing the ever-present fear of having an attack. QoL should be considered when discussing treatment options with HAE patients. Specific tools have been developed to assist in measuring QoL and these can be useful in following up the effect of treatment interventions.

1.3 Treatment strategies and home-based self management

There are three aspects to modern management for patients with HAE:

- Management of acute attacks.
- Administration of C1INH concentrate for short term prophylaxis (STP).
- Long term prophylaxis (LTP) for patients whose QoL is significantly impaired by the frequency and severity of attacks or by other factors related to the burden of HAE.

Home based therapy is now standard practice for management of HAE attacks. It is a particularly attractive option for the Australian population, particularly patients who live a distance from a hospital and those in regional, rural or remote areas. Many other patients with young families and busy lives welcome the possibility of self-management. Specialist Immunology centres offer training in the skills needed for HAE patients to undertake home management of their condition (see Appendices).

On demand therapy for acute attacks is now standard of care for HAE as it allows rapid access to treatment and autonomy over treatment decisions. Ideally, on-demand therapy is managed by, or in consultation with a clinical immunologist and patients will require regular follow up, monitoring of frequency of use and injection technique. With appropriate training, most patients with HAE can be taught to self-administer therapy for acute attacks:

- Icatibant (Firazyr®) is provided in a pre-filled syringe, administered by subcutaneous (SC) injection and is a very convenient and effective agent for on demand treatment.
- Berinert® IV C1-INH concentrate is given as an intravenous (IV) infusion, which is more complex to administer. However, some patients and support persons can be trained for home administration.

Until recently, LTP has been managed with older, oral agents with significant problems, lack of efficacy or side effects. For patients who qualify, Berinert® IV (C1-INH) twice weekly has been a very useful option, however some patients have difficulties with venous access and self-administration. Expanded choices for LTP, Berinert® SC and Takhzyro® (lanadelumab), are now available. Both recently registered products are delivered by subcutaneous (SC) injection, which will facilitate self-administration for most or all patients after appropriate training.

2.0 SUMMARY OF AVAILABLE HAE TREATMENT OPTIONS

In this section there is a summary of current management approaches in Australia and New Zealand, followed by a more detailed discussion of these approaches.

2.1 Australia

There are two specific treatment options for acute HAE attacks. For LTP there has been an increase in options. While treatment has been limited to danazol and tranexamic acid in the past, and to Berinert® IV twice weekly for a minority of patients, the registration of two new products, Berinert® SC and Takhzyro® (lanadelumab) will change management of HAE significantly.

Management of acute attacks

- **Firazyr®** (Icatibant, Takeda – formerly Shire) is listed on the Pharmaceutical Benefits Scheme (PBS) in Australia for emergency treatment of acute angioedema in patients aged two years and over with known HAE types 1 and 2. Icatibant is provided in 30mg/3ml syringes for SC injection and the majority of patients only require one dose per attack, although about 10% require a second dose. It is provided in a pre-filled syringe with allowance for two syringes (plus five repeats) to be dispensed. Provision of an authority script must be accompanied by education and training for self-injection, therefore reducing visits to the emergency department, ensuring prompt treatment of an attack and therefore faster resolution. A prescription must be accompanied by provision of an ASCIA HAE Management Plan. Treating acute attacks early is recommended for optimal response.
- **Berinert® IV** (purified C1-INH, CSL Behring**)** is available for IV use in the hospital setting or may be used by the patient at home after adequate training. Berinert® IV is funded by the NBA and is registered for use in patients with HAE types 1 and 2 for management of acute attacks in all age groups. The recommended dosing is 20U/Kg.
- **Cinryze®** (purified C-1INH, Takeda) is administered IV, is registered and available for treatment of acute attacks in patients over six years of age, but is not funded by the NBA in Australia.

Short term prophylaxis

Short term prophylaxis (STP) is required to prepare patients with HAE, for elective dental and surgical procedures involving the head and neck area, including intubation and any instrumentation. Generally, for STP treatment strategies are similar for children and adults. Berinert IV (provided for STP, funded by the NBA) is administered one to six hours before the procedure. Supplies of medication for treatment of acute attacks must be on hand post operatively. When Berinert® IV is unavailable, danazol, in increased doses for a few days before and after the procedure may be used.

Long term prophylaxis (LTP)

Danazol and **tranexamic acid** have historically been used for LTP, however use is limited by side effects and relative lack of efficacy, respectively. Danazol is currently a streamlined authority item for HAE and is available as 100mg and 200mg capsules in quantities of 100 capsules with up to five repeats. Low dose danazol (≤ 100mg/day) is efficacious in some patients and well tolerated, but carries long-term risks and requires ongoing monitoring.

Tranexamic acid is available on the PBS as a 500mg tablet and also in injectable form. The dose is 30-50mg/kg daily divided into two or three doses, which can result in up to ten large tablets per day.

Product supply update – danazol

Danazol (Azol) has been discontinued in Australia in January 2020 by the supplier (Mylan, formerly Alphapharm), as reported on the TGA website https://apps.tga.gov.au/Prod/msi/Search/Details/danazol
For more details go to www.allergy.org.au/about-ascia/info-updates/product-supply-update-danazol

Berinert® IV (CSL Behring)

Prophylaxis with **C1-INH concentrate (Berinert® IV)** became available under the national blood arrangements in 2015. The current indication is "as second line therapy for LTP for patients who experience the equivalent of eight or more acute HAE attacks per month". The recommended dose is 1,000 U IV twice weekly, although some patients require higher dosing to gain benefit. With appropriate training, many patients can learn to self-administer at home.

Berinert® SC (CSL Behring)

Clinical trial results provide good evidence that subcutaneous (SC) infusion of Berinert® SC twice weekly offers a superior treatment option, with improved ease of administration and efficacy over the Berinert® IV preparation. Two doses given twice weekly (40IU/Kg and 60IU/Kg) were studied in the COMPACT trial. The higher dose showed slight superiority over the lower dose, although both produced meaningful increase in C1-INH functional activity, a marked reduction in HAE attacks and reduced use of rescue medication compared to placebo.

Berinert® SC was registered in Australia in 2018 and will be funded by the NBA for LTP for patients experiencing eight or more attacks per month, with a starting dose of 40IU/Kg. If control of HAE attacks is not ideal after four to six weeks of therapy at this dose, there is provision for increasing the dose to 60IU/Kg after peer review of the case.

Takzhyro® (Lanadelumab, Takeda)

Lanadelumab is a fully human monoclonal IgG1 antibody that selectively binds and inhibits plasma kallikrein. In the pivotal phase three, 26 week clinical trial (HELP study), the percentage of patients who were attack free for the last 16 weeks of treatment was 77% in the group receiving 300 mg every two weeks, compared with only 3% of patients in the placebo group. Lanadelumab is registered for prophylaxis of HAE attacks in Australia but is not yet funded. The recommended dose is 300mg SC every two weeks.

2.2 New Zealand

Management of acute HAE attacks

- Icatibant is approved and funded for use in acute attacks of HAE down to two years of age.
- A Special Authority needs to be completed for this medication.
- Initial applications need to be completed by a clinical immunology/allergy specialist, but renewals can be done by other relevant clinicians, including general practitioners.
- For paediatric patients under a weight of 65 kgs equipment is available for weight adjusted dose administration.
- For patients who have not responded to icatibant, applications to New Zealand Blood Service (NZBS) can be made for on demand home treatment with IV C1-INH concentrate, once patients have been trained to do this.

Short and long-term prophylaxis

- For prophylaxis, Danazol is available and funded for HAE. **Please refer to box on page 11 regarding supply of danazol in Australia.**
- Stanazolol is also available but requires a "Named Patient Pharmaceutical Assessment" (NPPA) to Pharmac.
- Tranexamic acid is funded generically but used in paediatric patients and those with acquired C1-INH deficiency.
- For patients where C1-INH concentrate prophylaxis is required either short or long-term, an application to the NZBS needs to be made.

3.0 DETAILED DISCUSSION OF MANAGEMENT STRATEGIES

3.1 Treatment of acute HAE attacks

Acute angioedema attacks in patients with HAE do not respond to antihistamines, corticosteroids or adrenaline. Any HAE attack is eligible for treatment at the patient's discretion. All oro-pharyngeal and laryngeal attacks must receive acute treatment early in the episode and the patient transported to hospital for close observation and further management as required.

The current treatments available in Australia and New Zealand for acute attacks of HAE are the bradykinin antagonist icatibant (Firazyr®) and purified C1-INH concentrate (Berinert® IV, Cinryze®). Both are safe, well-tolerated and effective treatments for all attacks of angioedema in any location. The choice of which product to use is not determined by the location, severity or duration of angioedema.

Icatibant is administered subcutaneously (SC) and is suited to self-administration in and out of hospital settings, or administration in hospital. Icatibant is supplied by pharmacies on an authority prescription, in a pre-filled syringe and patients or carers can be trained in home administration. Because of ready availability and relative ease of use, icatibant is generally preferred as the first line of treatment.

C1-INH concentrate is administered by IV injection and is therefore generally limited to use in a hospital or medical facility, although home or community use may be possible with appropriate training and facilities. There are several specific circumstances where C1-INH concentrate is the preferred option for acute attack management, including:

- Pregnancy and lactation.
- Children under two years of age.
- When icatibant is contraindicated or not tolerated.
- When icatibant is not effective.

Cutaneous angioedema:

- Episodes of very mild peripheral or truncal angioedema causing only mild or moderate discomfort and little or no disability may not require treatment. Symptomatic treatment can be used, however early treatment of mild angioedema may prevent progression to moderate or severe swelling.
- Peripheral angioedema may cause pain and significant disability, oedema of the face or genitalia may cause major discomfort and functional impairment and facial swelling can progress to involve the airway. Treatment with icatibant or C1-INH is warranted in these cases to reduce the severity and shorten the duration of the attack and prevent progression.

Abdominal pain:

- Some minor attacks of gastrointestinal angioedema resolve with rest and simple analgesia.
- Abdominal attacks that can cause significant discomfort and disability warrant treatment with icatibant or IV C-1INH, and early treatment may result in rapid resolution of discomfort, return to normal activities and avoid the need for hospitalisation. Treatment at home or in the community with C1-INH concentrate is also an option.
- C1-INH concentrate is the treatment of choice for attacks of abdominal angioedema in pregnancy, lactating women and early childhood.
- Attacks causing severe abdominal pain, distention and vomiting may require treatment in hospital with opiate analgesia and fluid replacement.

Laryngeal/airway oedema:

- Airway angioedema in HAE is dangerous and a medical emergency, and fatalities occur. Swelling can occur in the larynx or posterior pharynx. It should be noted that swelling of the tongue on its own

seldom affects respiration but patients with tongue swelling should be monitored in case of progression to the airway.

- Laryngeal swelling is not visible externally and may present as an isolated phenomenon in a patient who appears normal externally and even on examination of the oropharynx. Indirect laryngoscopy may be useful for confirmation but is not necessary in a patient with known HAE; direct laryngoscopy may aggravate swelling if traumatic.
- Symptoms of upper airway angioedema in a patient with known HAE are a medical emergency and are an absolute indication for immediate treatment with icatibant or C1-INH concentrate. Treatment should commence at home if possible, by self-administration of SC icatibant or IV C1-INH concentrate. Treatment should be administered urgently even if respiration does not seem to be threatened since oedema may sometimes progress rapidly and icatibant or C1-INH concentrate may take 30-60 minutes to begin to act. Lack of response after 60 minutes is an indication for a dose of C1-INH concentrate as either a second dose if C1-INH was initial treatment or a first dose if icatibant was the initial treatment. If treatment is commenced out of hospital or if home or community treatment is not available, urgent transfer to hospital by ambulance is indicated in all cases. Facilities and expertise for intubation should always be made available and because laryngeal oedema can make intubation difficult, tracheostomy or emergency cricothyrotomy may be required in extreme situations. These measures are seldom required when definitive treatment is given early in the attack.

3.2 Short-term prophylaxis

Short term prophylaxis (STP) is required to prepare patients for elective dental and surgical procedures involving the head and neck area including intubation and any instrumentation. STP treatment strategies are generally similar for children and adults:

- **High risk procedures -** C1-INH concentrate one to six hours before the procedure, and available for postoperative use if required. This is a funded indication for Berinert® IV in Australia. There are no studies on the prophylactic use of icatibant in this setting but because of its short half-life, it is not an ideal prophylactic agent.
- **Low risk procedures** – No pre-treatment is required, but IV C1-INH concentrate or icatibant should be available as rescue treatment.

If Berinert® IV is not accessible as STP for minor dental and medical procedures then danazol may be used, either by introduction in a patient not already on it, or by increasing the dose prior to the procedure (Box 1). Danazol can be used for STP in children since virilisation is only likely to occur with long-term treatment. Dental procedures should be undertaken in or near hospitals with facilities for emergency management and icatibant or C1-INH concentrate should be immediately available. It must be emphasised that attacks are not always predictable and do not always follow a consistent pattern, so patients and their doctors should not become complacent about the risk. Although the major focus of attention is on procedures on the head and neck area, because danazol prophylaxis is inexpensive and usually well-tolerated it can be used for other procedures.

Box 1 - Minor dental and medical procedures

Short term prophylaxis with danazol:

● For those already on danazol - double the dose.

● For those not on LTP - introduce danazol 600mg/day (100-300mg in children) for five days prior to procedure and two days afterwards.

● IV C1-INH concentrate or icatibant should be available in case of failure of prophylaxis.

Please refer to box on page 11 regarding supply of danazol in Australia.

Box 2 - Major dental procedures and intubation

Prophylaxis with C1-INH concentrate:

● 20IU/kg Berinert® IV (funded by NBA) or 1,000U Cinryze® one to six hours prior to the procedure

3.3 Long-term prophylaxis (LTP)

Recent advances in HAE management have provided the possibility of gaining complete control over HAE attacks and this is now the ideal treatment goal. Patient preference is an important determinant of choice of prophylaxis.

3.3.1 General

LTP refers to the use of regular medication to prevent HAE attacks. The decision to institute LTP depends on several factors, including:

- Impact on the patient's quality of life determined by the frequency of attacks.
- Severity and location of previous attacks.
- Presence or absence of known triggers and their ability to be modified.
- Accessibility to adequate medical support.
- The balance of these factors against the acceptability, cost and potential morbidity of prophylactic agents.

3.3.2 Avoidance of triggers

Avoidance of triggers is important for prevention of angioedema attacks:

- Angiotensin converting enzyme (ACE) inhibitors are contraindicated in HAE. Angiotensin receptor antagonists have also been shown to increase bradykinin levels (Bork et al, 2008) and should be avoided or used with caution.
- Oestrogen-containing oral contraceptives increase attacks in many patients but not all. The progesterone-only contraceptive pill may be associated with reduced attack frequency (Cicardi et al, 1997) and is generally recommended for women with HAE.

3.3.3 C1-INH concentrate prophylaxis

In Australia, funded supply of C1-INH concentrate for intravenous infusion (Berinert) for LTP under the national blood arrangements became available in December 2015. The current indication is "as second line therapy for LTP for patients who experience the equivalent of eight or more acute attacks per month".

The recommended dose is 1,000 U IV twice weekly although some patients require higher dosing to gain benefit. With appropriate training, many patients can learn to self-administer at home.

3.3.4. Berinert® SC (CSL Behring)

The results of an international, prospective, multicentre, randomised double blind, placebo-controlled phase 3 trial evaluating the efficacy and safety of Berinert® administered subcutaneously (the COMPACT trial) has been published recently (Longhurst et al, 2017). In the trial, patients with HAE types 1 or 2 who had experienced four or more attacks in a consecutive two month period within three months before screening were randomised to one of four treatment sequences in a cross over design. Two doses, 40IU/Kg or 60IU/Kg of Berinert® SC were used followed by placebo or vice versa.

The number of HAE attacks was the primary end point (Longhurst et al, 2017). Seventy nine of ninety patients randomised completed the study. Both doses reduced HAE attacks (mean difference with 40 IU

–2.42 attacks per month; 95% confidence interval [CI], –3.38 to –1.46; and mean difference with 60 IU, –3.51 attacks per month; 95% CI, –4.21 to –2.81; P<0.001 for both comparisons). Response rates were 76% (95% CI, 62 to 87) in the 40-IU group and 90% (95% CI, 77 to 96) in the 60-IU group. Adverse events were similar for the active and placebo arms.

In a long-term open label extension study (Craig et al, 2019),126 patients were treated for a mean of 1.5 yrs. For 40IU/Kg and 60IU/Kg median annualised attack rates were 1.3 and 1.0 respectively. Median rescue medication use was 0.2 and 0.0 times per year, respectively. Adverse events were similar in both treatment arms. Mean steady-state C1-INH functional activity increased with treatment to 66.6% +/- 34.9% with 60 IU/kg and 52.0% +/- 17.2% with 40 IU/kg at the end of study (Craig et al, 2019).

While the trial data showed that 60 IU/Kg was most efficacious and this is the recommended dose in the USA, many patients received excellent benefit from 40IU/Kg dose and only a minority had to step up to the higher dose to gain benefit.

Therefore we propose that it is acceptable to commence patients at 40 IU/Kg providing the physician has the ability to step up to the higher dose if attacks are not controlled after 2-3 weeks when steady state is reached. The ASCIA HAE Working Party has developed a mechanism for reviewing individual patient needs for accessing the higher dose.

3.3.5 Lanadelumab (Takzhyro®)

Lanadelumab is a fully human monoclonal IgG1 antibody that selectively binds and inhibits plasma kallikrein. Under normal physiological conditions C1-INH inhibits plasma kallikrein, but in HAE patients there is uncontrolled kallikrein activation resulting in cleavage of high molecular-weight kininogen (HMWK) and generation of bradykinin. Lanadelumab binds with high affinity to kallikrein, inhibiting its proteolytic activity and blocking the cleavage of HMWK. It has a longer half-life than C1-INH concentrate products with a mean elimination half-life of approximately 2 weeks. The HAE LTP (HELP) phase 3 study was a multicentre placebo -controlled trial of 125 HAE patients over 12 years of age evaluating the safety and efficacy of subcutaneous lanadelumab over 26 weeks (Banerji et al. JAMA 2018). Doses of 150mg every 4 weeks, 300mg every 4 weeks and 300mg every 2 weeks versus placebo were assessed and all doses showed significant superiority compared to placebo for the primary (HAE attacks over 26 weeks) and secondary (attacks requiring acute treatment, attacks of moderate-severe severity) endpoints. The percentage of patients who were attack-free for the last 16 weeks was 77% in the 300 mg every 2 weeks group, compared with only 3% of patients in the placebo group. Ad hoc analysis showed lanadelumab provided protection from attacks after the first dose of treatment. Antidrug antibodies were detected in 10 of 84 lanadelumab and 2 of 41 placebo treated patients. Two patients treated with lanadelumab 150 mg every 4 weeks developed antibodies that showed neutralizing properties *in vitro*, although 3 of the lanadelumab treated patients had pre-existing antibodies prior to drug exposure suggesting a risk for possible low-level false positive results due to an overly sensitive assay. Development of anti-drug antibodies did not appear to adversely affect the drug levels or clinical response

The most common (52%) adverse reactions associated with lanadelumab are injection site reactions such as injection site pain, erythema and bruising, of which the vast majority (>97%) are of mild intensity and with a median duration of 6 minutes. The only other treatment related adverse events which were more frequent in the treatment group in the phase 3 study were headaches (7.1% versus 2.4% with placebo) and upper respiratory tract infections in the 300mg every 2 week arm (37.0% versus 26.8 with placebo). There have been no deaths or serious treatment-related adverse events reported in the studies. (Wu. 2019)

Of note, as the aPTT coagulation test measures intrinsic coagulation through activation of plasma kallikrein, it increases but remains within the normal range in patients on lanadelumab. At therapeutic doses of lanadelumab used in prophylaxis for HAE there have been no bleeding or thrombotic events

reported. The long-term effects of kallikrein inhibition on cardiovascular events is currently unknown, although in the reported patients in the literature with a genetic deficiency of its precursor prekallikrein, there are no clear associated comorbidities. No data is available on the use of lanadelumab in pregnancy or breastfeeding. Although animal studies do not show evidence of developmental toxicity, in the absence of further data it is preferable to avoid lanadelumab in pregnancy. As it is a large protein molecule the amount in breast milk is likely to be low and it is considered acceptable to use if clinically indicated in breast feeding women.

Lanadelumab has been approved for long-term prophylaxis of HAE attacks in the USA, Canada and Europe. As it is a subcutaneous injection it is usually self-administered by the patient into the abdomen, thigh or upper arm after appropriate training. The recommended starting dose of lanadelumab approved elsewhere is 300mg every 2 weeks. (Reference FDA and EMA PI links) If the patient remains free of attacks with the two-weekly dose, the doctor can reduce the frequency to once every 4 weeks. Lanadelumab has been approved by the TGA for therapeutic use in Australia, but is not yet available on the pharmaceutical benefits schedule (PBS).

3.3.6 Attenuated androgens

Androgens increase hepatic synthesis of C1-INH protein from the remaining normal C1 gene. The response is dose-related but the dose required to suppress angioedema and/or normalise C4 and/or C1-INH levels varies widely between patients. Side effects (box 3) are also dose-related but again highly variable, with some patients unable to tolerate even low doses whereas others including females tolerate danazol for many years without apparent problems. In a recent survey, 79% of patients experienced adverse effects from danazol, but only 25% discontinued treatment because of these; the benefits were great with >90% reduction in episode frequency in >70% of patients, and a 95% reduction in the frequency of laryngeal episodes (Szeplaki et al, 2005).

Recommended dosage regimens vary. It is reasonable to commence with a modest dose (e.g. 100-200mg daily) and then increase or decrease on a monthly basis depending on the frequency of episodes until satisfactory control is reached (Budapest protocol). (Farkas et al, 2010). The maintenance dose required to suppress or substantially reduce angioedema varies between 100mg second daily and 800mg daily. However, for minimising long- term detrimental side effects, global guidelines suggest that a dose in excess of 200mg daily should not be used long term.

The aim of treatment is to minimise the frequency and severity of attacks rather than to normalise the biochemical parameters. Monitoring of patients on long-term danazol is essential (box 4). As in many chronic conditions patient autonomy is an issue and some patients vary the dosage without consultation depending on the activity of their condition, balanced against adverse effects. Non-adherence to regular dosage is often associated with breakthrough episodes. Conversely some patients experience prodromal symptoms or recognise trigger exposures (e.g. infection or stress) and may be advised to temporarily increase the dose of danazol at these times.

Danazol often causes amenorrhoea and may inhibit ovulation but cannot be relied upon to prevent pregnancy. Patients receiving danazol must be counselled to use contraception. The oestrogen-containing oral contraceptive pill is contraindicated. Danazol must not be taken during pregnancy because of the risk of virilisation of the foetus and should be ceased if pregnancy is planned. The safety of danazol during breastfeeding has not been established and it is usually avoided.

Danazol is not recommended for LTP in children but its long term use in children has been reported and in some cases the benefits outweigh the risks.

Please refer to box on page 11 regarding supply of danazol in Australia.

Box 3 - Potential side-effects of androgenic drugs e.g. danazol

● General: headaches, nausea, fatigue, constipation, myalgias or muscle cramps, weight gain

● Virilisation in females: hirsutism, acne, voice changes, decreased breast size, altered libido, menstrual irregularities, clitoromegaly

● Hepatic: abnormal liver enzymes, hepatic necrosis, cholestasis, adenoma, adenocarcinoma

● Metabolic: hypertension, dyslipidaemia (but not hypercholesterolaemia)[1], atherogenesis, polycythaemia, hyperglycaemia

Box 4 - Monitoring on long-term danazol

● 6 monthly- BP, Hb, glucose, lipids, liver enzymes, CK

● 12 monthly- alpha-fetoprotein, hepatic ultrasound

Please refer to box on page 11 regarding supply of danazol in Australia.

3.3.7 Antifibrinolytic agents

Antifibrinolytic drugs act by inhibiting plasmin which may partially inhibit the bradykinin pathway. They have no effect on C1-INH or C4 levels.

The only currently available antifibrinolytic drug is tranexamic acid (Cyklokapron). It has some benefit for LTP of angioedema in HAE but is less effective than attenuated androgens (Farkas et al, 2002).

Side effects include minor GI upsets, myalgia/CK elevation and a theoretical risk of thrombosis; it is contraindicated in the presence of thrombophilia or situations of increased thrombotic risk. There is little experience with tranexamic acid in pregnancy so it is rated category B1, but it is not contraindicated during breastfeeding. It may have a place in the management of prepubertal children when attenuated androgens are contraindicated; it is considered reasonably safe in children greater than 2 years of age.

3.3.8 Oral kallikrein inhibitors

Small-molecule orally bioavailable kallikrein inhibitors are currently in development but not yet available in Australia or elsewhere. Australian centres have participated in clinical trials. The drug most advanced in development is BCX7353 (Biocryst), with phase 2 trials published (Aygören-Pürsün et al, 2018) and phase 3 trials recently completed. Reported results show a 44% mean reduction in angioedema attack rates at the 150mg daily dose, however 50% of subjects experienced a >70% reduction in attacks and 23% a reduction of >90%, with good tolerance and no serious adverse events. Several other oral kallikrein inhibitors are at earlier stages of development. Oral kallikrein inhibitors are rapidly absorbed and may also be effective in treatment of acute attacks (Aygören-Pürsün et al, 2018).

3.3.9 Monitoring treatment

C1-INH replacement: C1-INH products being blood products, require haemovigilance (bloodborne pathogen surveillance) and baseline biochemical analysis and viral studies (such as Hepatitis B, C and HIV screening) should be checked at diagnosis before the use of product.

Attenuated androgens: Attenuated androgens may predispose patients to atherogenesis and liver disorders. Serum lipid profile should be obtained before androgen administration. Liver function studies, including alanine aminotransferase, total bilirubin, alkaline phosphatase, creatine kinase, lactic dehydrogenase, blood urea nitrogen, creatinine, complete and differential blood cell count, and urinalysis

should be performed at diagnosis. Blood pressure should be monitored. Abdominal liver and spleen ultrasonography can be considered before continuous androgen administration and performed every year if receiving regular androgen therapy and annually even after ceasing treatment if treated for more than 10 years (box 4).

3.3.10 Special circumstances

Travel

When a patient with HAE wishes to travel, it is advisable to have:

- Medical identification jewellery as well as an updated ASCIA HAE Management Plan and consultant's letter, translated into the relevant language if needed.
- Prescriptions for adequate supplies of danazol, if used.
- For those patients using C1-INH concentrate for funded indications, applications for temporary overseas supply of C1-INH concentrate is to be conducted in accordance with NBA temporary overseas supply policy
- Icatibant, at least two syringes, with a letter for customs/airport controls, for the management of acute attacks is ideal although one must investigate the legality of carrying certain medications if unregistered in the destination country.

Pregnancy and delivery

Danazol needs to be ceased prior to conception. Tranexamic acid may be used with caution if frequent attacks occur. C1-INH concentrate on demand, or at scheduled regular intervals if frequent attacks are occurring is now considered optimal therapy in the pregnant woman with HAE. There is no data on the use of icatibant in pregnancy. C1-INH concentrate must be available in the delivery room/suite in the event of triggering of oedema at parturition but routine prophylaxis with C1-INH is not usually recommended. C1INH concentrate is advisable for any complicated deliveries and for caesarean section.

Please refer to box on page 11 regarding supply of danazol in Australia.

4.0 HAE IN CHILDREN

The approach to HAE management in children is, in general, similar to adults with some exceptions:

- Episodes of severe swelling can occur, but are much less frequent than in adults.
- Episodic abdominal pain and peripheral soft tissue swellings are typical symptoms.
- Mechanical trauma and infections are common precipitants. However, children with HAE are usually able to participate in normal sporting activities without difficulty and these should not routinely be avoided.

On demand therapy for acute attacks (icatibant or C1-INH concentrate) and STP (C1-INH concentrate) for dental and surgical procedures involving the head and neck, including intubation, should be used as described above. The usual dose of C1-INH is 20U/kg, often with modification to align with the nearest whole vial.

Icatibant is approved for acute treatment of children over 2 years of age and the recommended dosing schedule is shown below.

Paediatric dosing of icatibant according to PI (2 to 17yrs)

Body Weight (kg)	Dose (Injection Volume)
12 to 25	10mg (1ml)
26 to 40	15mg (1.5ml)
41 to 50	20mg (2ml)
51 to 65	25mg (2.5ml)
>65	30mg (3ml)

In practice, children over 50Kg will receive 30mg (3ml) dose.

An escalation of attack frequency and severity can occur in adolescence. This may necessitate commencement of LTP, which is only occasionally required in pre-pubescent children. In summary:

- Tranexamic acid (30-50mg/kg/day in 2 to 3 divided doses) is generally well tolerated and may be effective as first line LTP.
- Danazol is not recommended in children, especially females, due to side effects (box 3), including virilisation.
- Twice weekly C1-INH (20 units/kg) is very effective but has the disadvantage of intravenous administration. Carers can be trained to administer at home.

Please refer to box on page 11 regarding supply of danazol in Australia.

5.0 MANAGEMENT PLAN

A personalised ASCIA HAE Management Plan giving indications of what to treat, when to treat and how to treat HAE attacks should be produced for all patients. This may be accompanied by a letter from the specialist so it may be given to any treating physician unfamiliar with the patient and their condition. Ideally, a patient's local emergency department will have an alert system in place to fast track patients when they need to present there, outlining the proposed management plan for each presentation such as abdominal pain or laryngeal attacks. This plan includes type in fields and is available on the ASCIA website www.allergy.org.au/hp/papers/hereditary-angioedema

ascia
australasian society of clinical immunology and allergy
www.allergy.org.au

MANAGEMENT PLAN FOR Hereditary Angioedema (HAE)

Patient details

Name:

Date of birth:

Family/emergency contact name:

Work Ph:

Mobile Ph:

Plan prepared by:

Doctor:

Signed:

Date:

Contact Ph:

Additional information:

ACUTE HAE ATTACKS

Peripheral swelling
- If appropriate administer medication as described below.

Abdominal pain
- Administer medication as described below.
- Seek urgent hospital treatment if symptoms worsen or last longer than 24 hours.

ADDITIONAL HOSPITAL TREATMENT:
- Opiate analgesia.
- IV fluid rehydration.
- Give dose of C1-INH (Berinert®) IV if inadequate response after 1 hour.
- Consider other causes of abdominal pain if no response to specific treatment.

Airway swelling (tongue or throat swelling, difficulty breathing, talking, swallowing).

Phone ambulance - 000 (AU) or 111 (NZ)
- Seek urgent hospital treatment.
- Administer medication as described below.

ADDITIONAL HOSPITAL TREATMENT:
- Prepare for emergency intubation or cricothyrotomy.
- Give dose of C1-INH (Berinert®) IV if inadequate response after 1 hour.

MEDICATION DOSES FOR ACUTE TREATMENT

Medication	Adults and Children >50Kg	Children
Icatibant (Firazyr®)[1, 2]	30mg/3ml syringe subcutaneous (SC)	12-25Kg 10mg (1ml) 26-40Kg 15 mg(1.5ml) 41-50Kg 20mg (2ml) subcutaneous (SC)
C1-INH (Berinert®)	20 U/Kg IV	20 U/Kg IV

SHORT TERM PROPHYLAXIS

For invasive medical, dental procedures, intubation or oropharyngeal instrumentation:
- Administer C1-INH (Berinert®) IV 20 U/Kg, 1-6 hours before procedure
- Have further doses of acute treatment (Firazyr® or Berinert®) available.

LONG TERM PROPHYLAXIS

Medication and dose: ☐ Not applicable

☐ C1-INH (Berinert®) IV: _____

☐ C1-INH (Berinert®) SC: _____

☐ Danazol: _____

☐ Tranexamic acid: _____

NOTES:
1. Adrenaline, antihistamines and corticosteroids are not effective for HAE attacks.
2. Use patient's own supply either at home or at hospital.
3. Products cited in this plan are TGA and Pharmac registered hence this information is specific for HAE treatment in Australia and New Zealand.
4. Please refer patient for immunology review after hospital presentation.

6.0 USE OF QUALITY OF LIFE (QoL) AND ACTIVITY MEASURES

Clinical assessment should include regular assessment of the frequency and severity of attacks as well as impact on QoL. Reduction of attack frequency and normalisation of health-related QoL should be the goal of care. Generic quality of life tools such as the SF36 are convenient and are frequently used in HAE patients.

HAE attack specific patient reported outcome measure the HAE-PRO, an 18-item questionnaire provides an assessment of the HAE attack experience including symptoms, impacts, treatment requirements, healthcare resource use and loss of productivity caused by HAE attacks.

HAE specific tools, the HAE-QoL from Spain, and the HAEA-Qol from the United States, are still undergoing validation.

The angioedema specific QoL assessment tool, AE-QoL has been validated for both histaminergic and bradykinin mediated angioedema, including HAE, but is not specific for HAE. In summary:

- AE-QoL has the convenience of being brief, has a four week recall period and is able to be completed in one clinic visit.
- AE-QoL consists of 17 items, addressing four dimensions: functioning, fatigue/mood, fears/shame and food.
- AE-QoL shows a total score value and four domain score values that vary from 0 to 100 after a linear transformation of raw values. Higher score values indicate a lower HRQoL.
- AE-QoL is also sensitive to change, with a minimal clinical important difference of six points.

There are no outcome measures yet validated in children.

References: Weller et al, 2012; Weller et al, 2016; Prior et al, 2012; Busse et al, 2019; Bonner et al 2015.

7.0 HIGH COST TREATMENT AND CLINICAL GOVERNANCE

ASCIA supports the responsible use of medication and acknowledges that the newer, prophylactic treatments becoming available for HAE, while most effective, are very high cost and supply needs to be carefully managed. This is particularly so for blood-derived products. To date, there has been a deficiency of data collection regarding usage and review processes, both of which are desirable for responsible use of resources, thus the following protocol will be instituted as Berinert® SC becomes available for LTP in selected patients. This form includes type in fields and is available on the ASCIA website www.allergy.org.au/hp/papers/hereditary-angioedema

This Hereditary Angioedema (HAE) case peer review form has been developed by the ASCIA HAE Working Party in 2020, to request prophylaxis dose increases using a new treatment option - Berinert® SC. This form should be used in conjunction with the updated 2020 versions of the ASCIA HAE Position Paper and Management Plan, which include information about new treatment options.
For further information about HAE go to www.allergy.org.au/hp/papers/hereditary-angioedema

REQUEST FOR PROPHYLAXIS DOSE INCREASE (BERINERT® SC)

Date: _____

Centre: _____

Form completed by: _____

ASCIA HAE working party member to review case: _____

Patient Initials: _____

Patient DOB: _____

Patient Age: _____

Diagnosis - HAE type: _____

Current status: List attack frequency/severity/AEQoL or other measures: _____

Current therapy and doses: _____

_____

Questions/discussion points:

1. _____
2. _____
3. _____

Summary of discussion (for completion by requesting physician after teleconference)

- Starting dose of Berinert® SC will be 40IU/Kg twice weekly.

- Prior to prescription of Berinert® SC prophylaxis the patient will acknowledge that there is an undertaking for regular, approximately six monthly reviews with the prescribing specialist. This will be necessary for continuation of supply.

- Patients will be reviewed within four to six weeks of a new prescription.

- If control on 40IU/Kg is not optimal, there is capacity for an increase in dose to a maximum of 60IU/Kg twice weekly upon a peer review process involving discussions between the prescribing specialist and at least one member of the ASCIA HAE Working Party.

- The case review form shown on this page is provided for documenting this review and will be retained by ASCIA for record-keeping. Use of one of the various assessment tools discussed above is encouraged for this process.

8.0 MANAGEMENT OF HAE WITH NORMAL C1-INH AND IDIOPATHIC NON-HISTAMINERGIC ANGIOEDEMA

Patients may be diagnosed with hereditary angioedema with normal C1-INH when they have isolated angioedema with a positive family history and normal levels of C4 and C1-INH, no history of use of ACE-inhibitors or other drugs suspected to cause bradykinin-mediated angioedema and no response to antihistamines, steroids, or adrenaline. If there is no family history the appropriate diagnosis is idiopathic non-histaminergic angioedema (Magerl et al, 2017).

The clinical features differ in some ways from those of classic HAE: the swelling episodes are more likely to commence in adult life; the symptoms are less frequent and they usually affect the skin, tongue, lips and abdomen more than other areas; the symptoms are more common in women; exogenous oestrogen is a risk factor; prodromes are rare and erythema marginatum does not occur; haemorrhages have been observed in some patients in the areas of swelling after a day or two.

A number of cases have been associated with a genetic mutation in exon 9 of the gene for coagulation factor XII. In other cases genetic changes have been reported in the angiopoietin 1 gene and in the plasminogen gene. The defect remains undefined in other cases. (Zuraw. 2018) There are no routine laboratory tests to confirm the diagnosis of HAE with normal C1-INH (Magerl et al, 2017).

In these rare conditions there are no randomised controlled trials to guide treatment. Evidence from case series suggests that icatibant and C1-INH concentrate may be effective as on-demand treatment to terminate acute attacks. In reports of short-term prophylaxis prior to a surgical procedure or parturition, C1-INH concentrate is usually reported to be successful although there is little data about exacerbation of swelling by the procedure (and therefore whether the C1-INH concentrate actually prevented any threatened harm). Finally, LTP is also used although patients with HAE with normal C1-INH have longer disease-free periods.

Tranexamic acid, in contrast to its feeble activity in HAE with C1-INH deficiency, has been reported to markedly reduce attack rates by some investigators but not all. Bork and colleagues (Bork et al 2017) have reported that treatment with progesterone only-contraceptives (oral or implanted) results in near complete freedom from symptoms in affected women with HAE with factor XII gene abnormalities. Positive reports of long-term use of C1-INH concentrate or danazol in a few patients have also been reported. In aspects of treatment, the drugs do not appear to work as reliably or as promptly as in classic HAE (Magerl et al, 2017).

Please refer to box on page 11 regarding supply of danazol in Australia.

9. ORDERING PROCESS FOR C1-ESTERASE INHIBITOR FUNDED BY THE NBA

CSL Behring BERINERT® Order Form

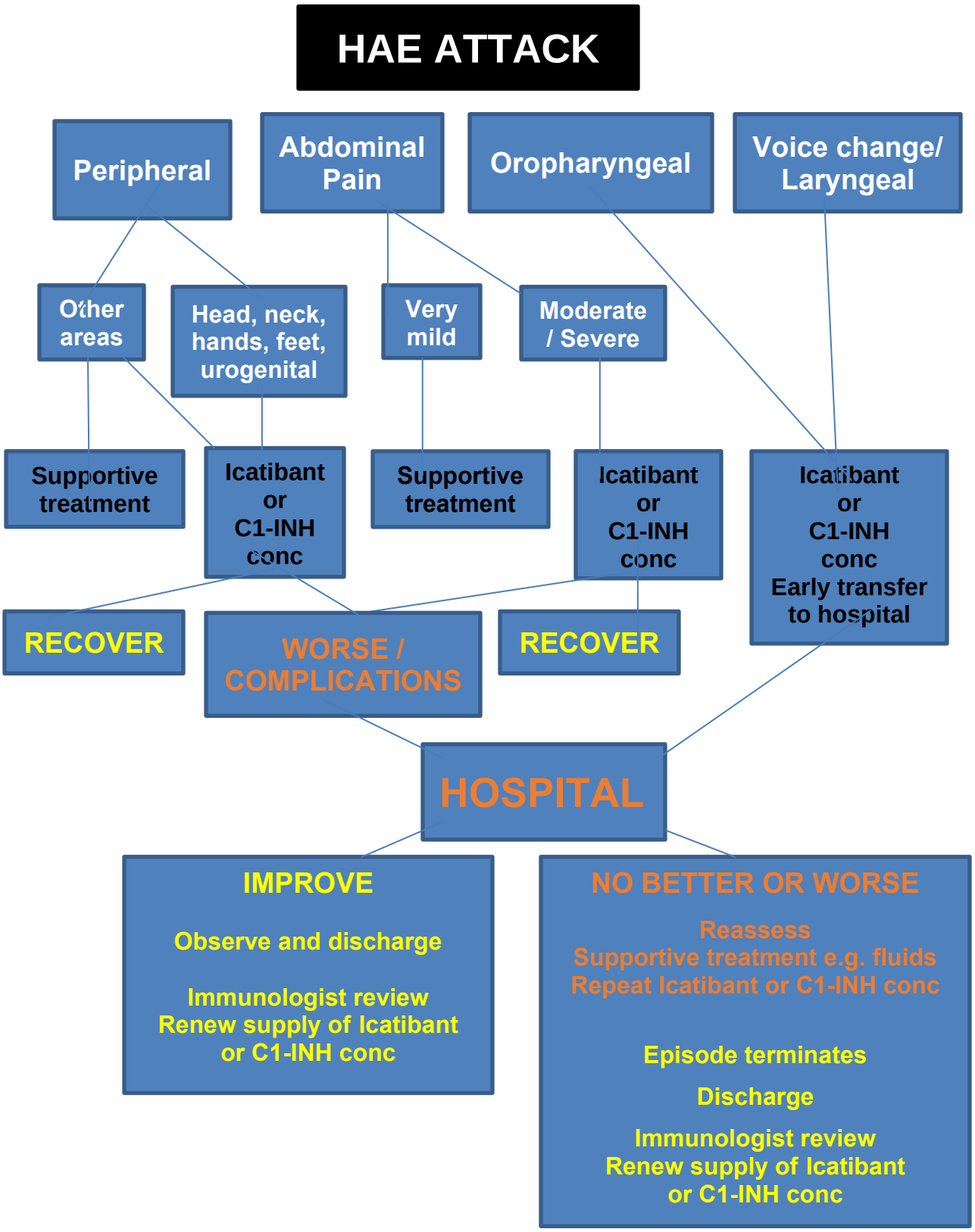
Please send to CSL Behring Customer Service (Email: customerservice@cslbehring.com.au or Fax: 03 9246 5342). For URGENT/AFTERHOURS request call 1800 063 892 after form has been emailed/faxed. Supply of C1-esterase inhibitor (Berinert) funded under the national blood arrangements requires mandatory completion of all fields of this Order Form. For further information on funded indications: www.blood.gov.au/plasma-and-recombinant-product-procurement

Order details			
Order date:	/ /		
BERINERT® IV 500IU	Product number: A5532	Number of 500IU vials ordered:	
*BERINERT® IV 1500IU (*from July 2020)	Product number: G3787	Number of 1500IU vials ordered:	
BERINERT® SC 2000IU	Product number: G3788	Number of 2000 IU vials ordered:	
BERINERT® SC 3000IU	Product number: G3789	Number of 3000IU vials ordered:	
Delivery details			
Hospital /Entity name:			
Contact details:	Name:	Phone:	
	Email:		
Delivery address details: *(Department,Street no. name, suburb, state, postcode)*			
Order Type:	Routine (delivery > 48 hours)	Urgent (delivery within 48 hours)	
Required delivery date:	/ /	Deliver by close of business (please tick)	
Special delivery instructions (if required):	Specify time : (for time sensitive arrangements)	Other instructions	
Special instructions:	*Products are supplied under the Deed between CSL Behring and the National Blood Authority for the following indications for Type I or II hereditary angioedema:* • *treatment of acute attacks* • *pre-procedural (short term) prophylaxis for high risk procedures such as dental work, head or neck surgery, or surgery requiring intubation* • *second line as routine (long term) prophylaxis for patients who experience the equivalent of eight or more acute attacks per month.* *Authorisation of this order confirms that the product is being ordered for the indications funded by the NBA and is in accordance with the Australasian Society of Clinical Immunology and Allergy (ASCIA) clinical guidance for funded access.*		
Authorisation details			
Authorised by (name):	Signature:	Date: / /	
Name of Clinic/Hospital:			

10.0 APPENDICES

10.1 Home therapy training programs should include the key areas listed below.
• When to use concentrate
• Dose of concentrate
• Supply and storage of concentrate and equipment
• Aseptic techniques
• Preparation of equipment for administration of concentrate
• Product checking procedure (e.g. dosage, expiry date)
• Demonstration of the correct technique for reconstitution of solution
• Cannulation with butterfly
• Blood sampling pre-infusion
• Administration of injection/management of infusion
• Management of adverse reactions
• Disposal of equipment
• Documentary evidence of the patient's training and competence
• Receiving and monitoring infusion logs and other relevant documentation for monitoring appropriate use and technique and keeping the specialist nurse/consultant immunologist informed of any relevant issues regarding care and treatment
• Investigating any adverse reactions/events and taking appropriate action
• Compliance with clinic visits
• Performing an annual review of the patient's competence to administer injection/infusion
• Liaising with the patient, their GP, clinical immunologist, pharmacist and other relevant care providers.

10.2 ASCIA Algorithm for modern management of HAE in Australia



11. REFERENCES

Agostoni, A., Aygoren-Pursun, E., Binkley, K.E., Blanch, A., Bork, K., Bouillet, L., … Zingale, L. (2004). Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. *Journal of Allergy and Clinical Immunology*,114 (3 Suppl), S51-131.

Agostoni, A., Cicardi, M., Cugno, M., Zingale, L.C., Gioffre, D., & Nussberger, J. (1999). Angioedema due to angiotensin-converting enzyme inhibitors. *Immunopharmacology*, 44 (1-2), 21–25.

Agostoni, A. & Cicardi, M., (1992). Hereditary and acquired C1-inhibitor deficiency: biological and clinical characteristics in 235 patients. *Medicine (Baltimore*); 71(4), 206-215.

Aygören-Pürsün E, Bygum A, Grivcheva-Panovska V, Magerl M, Graff J, Steiner UC, Fain O, Huissoon A, Kinaciyan T, Farkas H, Lleonart R, Longhurst HJ, Rae W, Triggiani M, Aberer W, Cancian M, Zanichelli A, Smith WB, Baeza ML, Du-Thanh A, Gompels M, Gonzalez-Quevedo T, Greve J, Guilarte M, Katelaris C, Dobo S, Cornpropst M, Clemons D, Fang L, Collis P, Sheridan W, Maurer M, Cicardi M. (2018) Oral Plasma Kallikrein Inhibitor for Prophylaxis in Hereditary Angioedema. N Engl J Med. Jul 26;379(4):352-362.

Baumgart, K.W., Britton, W.J., Kemp, A., French, M., & Robertson D. (1997). The spectrum of primary immunodeficiency disorders in Australia. *Journal of Allergy and Clinical Immunology*, 100(3), 415-423.

Bell, C.G., Kwan, E., Nolan, R.C., Baumgart, K.W. (2008). First molecular confirmation of an Australian case of type III hereditary angioedema. *Pathology*, 40(1), 82-83.

Bernstein, J.A., Levy, R., Wasserman, A. Bewtra, A., Hurewitz, D., Obtulowicz, K., … Craig, T.J., (2008). Treatment of Acute Abdominal and Facial Attacks of Hereditary Angioedema (HAE) with Human C1-Esterase Inhibitor (C1-INH): Results of a Global, Multicenter, Randomized, Placebo-controlled, Phase II /III Study (I.M.P.A.C.T.1). *Journal of Allergy and Clinical Immunology*, 121(3), 795.

Bonner N, Abetz-Webb L., Renault L., Caballero T., Longhurst H., Maurer M., Christiansen S., Zuraw B. (2015) Icatibant Outcome Survey (IOS) International Executive Committee and the Hereditary Angioedema Association (HAEA) Medical Advisory Board Health Qual Life Outcomes. 13: 92.

Bork, K., Barnstedt, S., Koch, P., & Traupe, H. (2000). Hereditary angioedema with normal C1-inhibitor activity in women. *Lancet*, 356 (9225), 213-217.

Bork, K., & Barnstedt, S. (2001). Treatment of 193 episodes of laryngeal oedema with C1-INH concentrate in patients with hereditary angioedema. *Archives of Internal Medicine*, 161(5), 714-718.

Bork, K., Bygum, A., & Hardt, J. (2008). Benefits and risks of danazol in hereditary angioedema: a long-term survey of 118 patients. *Annals Allergy Asthma Immunology*, 100(2), 153-161.

Bork, K., Frank, J., Grundt, B., Schlattmann, P., Nussberger, J., & Kreuz, W. (2007). Treatment of acute edema attacks in hereditary angioedema with a bradykinin receptor-2 antagonist (Icatibant). *Journal of Allergy and Clinical Immunology,* 119(6),1497-1503.

Bork, K., Hardt, J., Schicketanz, K.H., Ressel, N. (2003). Clinical Studies of Sudden Upper Airway Obstruction in Patients with Hereditary Angioedema Due to C1 Esterase Inhibitor Deficiency. *Archives of Internal Medicine*, 163(10), 1229–1235.

Bork, K., Meng, G., Staubach, P., & Hardt, J. (2006) Hereditary Angioedema: new findings concerning symptoms, affected organs, and course. *American Journal of Medicine*, 119(3), 267-274.

Bork, K., Siedlecki, K., Bosch, S., Schopf, R.E., & Kreuz, W. (2000). Asphyxiation by laryngeal edema in patients with hereditary angioedema. *Mayo Clinical Procedures*, 75(4), 349-354.

Bork, K., Staubach, P., Eckardt, A.J., & Hardt, J. (2006). Symptoms, course, and complications of abdominal attacks in hereditary angioedema due to C1 inhibitor deficiency. *American Journal of Gastroenterology*, 101(3), 619-627.

Bork K, Wulff K, Witzke G, Hardt J. (2017) Treatment for hereditary angioedema with normal C1-INH and specific mutations in the F12 gene (HAE-FXII). *Allergy* 2017; 72: 320-324.

Bouillet, L., Longhurst, H., Boccon-Gibod, I., Bork, K., Bucher, C. Bygum, A. … Cicardi, M. (2008). Disease expression in women with hereditary angioedema. *American Journal of Obstetrics and Gynecology* 2008; 199(5), 484.e1-.e4.

Bowen, T., Cicardi, M., Bork, K., Zuraw, B., Frank, M., Ritchie, B., …. Zhi, Y.X. (2008). Hereditary angioedema: a current state-of-the-art review, VII: Canadian Hungarian 2007 International Consensus Algorithm for the Diagnosis, Therapy and Management of Hereditary Angioedema. *Annals of Allergy, Asthma & Immunology* 100, S30-S40.

Boyle, R.J., Nikpour, M., & Tang, M.L. (2005). Hereditary angio-oedema in children: a management guideline. *Pediatric Allergy and Immunology*, 16(4), 288-294.

Brickman, C.M., Tsokos, G.C., Balow, J.E., Lawley, T.J., Santaella, M., Hammer, C.H., & Frank, M.M. (1986). Immunoregulatory diseases associated with hereditary angioedema: 1. Clinical manifestations of autoimmune disease. *Journal of Allergy and Clinical Immunology*, 77(5), 749–757.

Busse P.J., Christiansen S.C., Birmingham J.M., Overbey J.R., Banerji A., Otani I.M., et al. (2019). Development of a health-related quality of life instrument for patients with hereditary angioedema living in the United States. J Allergy Clin Immunol Pract. 7: pp. 1679-1683.

Bygum, A., Andersen, K.E., & Mikkelsen, C.S. (2009). Self-administration of intravenous C1-inhibitor therapy for hereditary angioedema and associated quality of life benefits. *European Journal of Dermatology*, 19(2),147-151.

Campbell, D.J., Krum, H., & Esler, M,D. (2005). Losartan increases bradykinin levels in hypertensive humans. *Circulation*, 111(3),315-320.

Chinniah, N., & Katelaris, C.H. (2009). Hereditary angioedema and pregnancy. *Australian and New Zealand Journal of Obstetrics and Gynaecology*, 49(1), 2-5.

Cicardi, M., Zingale, L., Pappalardo, E., Folcioni, A., & Agostoni, A. (2003). Autoantibodies and lymphoproliferative diseases in acquired C1-inhibitor deficiencies. *Medicine (Baltimore)* 82(4), 274–281.

Cicardi, M., Bergamaschini, L., Cugno, M., Hack, E., Agostoni, G., & Agostoni, A. (1991). Long-term treatment of hereditary angioedema with attenuated androgens: a survey of a 13-year experience. *Journal of Allergy and Clinical Immunology*, 87(4), 768-773.

Cicardi, M., Castelli, R., Zingale, L.C., & Agostini, A. (1997). Side effects of long-term prophylaxis with attenuated androgens in hereditary angioedema: comparison of treated and untreated patients. *Journal of Allergy and Clinical Immunology*, 99(2), 194-196.

Craig T, Zuraw B, Longhurst H, Cicardi M, Bork K, Grattan C, et al. (2019) Long-Term Outcomes with Subcutaneous C1-Inhibitor Replacement Therapy for Prevention of Hereditary Angioedema Attacks. The Journal of Allergy and Clinical Immunology in Practice, 7:1793–1802.

Davis, A.E. (2008). Hereditary angioedema: a current state-of-the-art review, III: mechanisms of hereditary angioedema. *Annals of Allergy Asthma and Immunology*, 100 (1 Suppl 2), S7-12.

Deald, G., & Bork, K. (2006). Missense mutations in the coagulation factor XII (Hageman factor) gene in hereditary angioedema with normal C1 inhibitor. *Biochemical and Biophysical Research Communications*, 343(4), 1286-1289.

Donaldson, V.H., & Evans, R.R. (1963) A biochemical abnormality in hereditary angioneurotic edema: absence of serum inhibitor of C' 1-esterase. *American Journal of Medicine*, 35, 37-44.

Donaldson, V.H., Rosen, F.S. (1964). Action of complement in hereditary angioedema: the role of C'1-esterase. *Journal of Clinical Investigation*, 4, 2204–2213.

Farkas, H., Harmat, G., Füst, G., Varga, L., & Visy, B. (2002). Clinical management of hereditary angio-oedema in children. *Pediatric Allergy and Immunology*. 13(3), 153-161.

Farkas, H., Varga, L., Szeplaki, G., Visy, B., Harmat, G., & Bowen, T. (2007). Management of hereditary angioedema in pediatric patients. *Pediatrics*, 120(3), e713-722.

Farkas H, Czaller I, Csuka D et al. (2010) The effect of long-term danazol prophylaxis on liver function in hereditary angioedema-a longitudinal study. Eur J Clin Pharmacol; 66:419-426)

Frank, M.M. (2000). Urticaria and angioedema in Goldman L, Bennett JC, (ed) *Cecil Textbook of Medicine.* 21 ed. Philadelphia, WB Saunders Co 1440-1445.

Frank, M.M. (1979). Effect of sex hormones on the complement-related clinical disorder of hereditary angioedema. *Arthritis and Rheumatism*, 22(11),1295–1299.

Frank, M.M., Gelfand, J.A., & Atkinson, J.P. (1976). Hereditary angioedema: the clinical syndrome and its management. *Annals of Internal Medicine,* 84()580-93.

Frank, M.M. (2008). Hereditary angioedema: a current state-of-the-art review, VI: novel therapies for hereditary angioedema. *Annals of Allergy Asthma and Immunology*, 100(1 Suppl 2), S23-29.

Frank, M.M. (2006). Hereditary angioedema: the clinical syndrome and its management in the United States. *Immunology and Allergy Clinics of North America*, 26, 653-668.

Gompels, M.M., Lock, R.J., Abinun, M., Bethune, C.A., Davies, G., Grattan, C., … Watters, D. (2005). C1 inhibitor deficiency: consensus document. *Clinical and Experimental Immunology*, 139, 379-394.

Graves, R. (1843). Clinical lectures on the practice of medicine, In: Major, R.H., editor. (1955). *Classic Descriptions of Disease*. 3rd Ed. Springfield, IL: Charles C. Thomas Pub Ltd, p. 623- 624.

Jurado-Palomo et al. (2013) Management of Dental-Oral Procedures in Patients with Hereditary Angioedema due to C1 Inhibitor Deficiency (*J Investig Allergol Clin Immunol*; Vol. 23(1): 1-6)

Landerman, N.S., Webster, M.E., Becker, E.L., & Ratcliffe, H.E. (1962). Hereditary angioneurotic edema. *Journal of Allergy*, 33, 330–341.

Longhurst, H.J. (2005). Emergency treatment of acute attacks in hereditary angioedema due to C1 inhibitor deficiency: what is the evidence? *International Journal of Clinical Practice*, 59, 594-599.

Longhurst H, Cicardi M, Craig T, Bork K, Grattan C, Baker J, et al. (2017). Prevention of Hereditary Angioedema Attacks with a Subcutaneous C1 Inhibitor. *N Engl J Med*. 376:1131–40.

Magerl M, Germenis AE, Maas C, Maurer M. (2017) Hereditary Angioedema with Normal C1 Inhibitor: Update on Evaluation and Treatment. *Immunol & Allergy Clin N America*; 3: 571-584.

Maurer, M., Magerl, M., Craig, T. (2018) The international WAO/EAACI guideline for the management of hereditary angioedema – the 2017 revision and update. World Allergy Organization Journal volume 11, Article number: 5 https://waojournal.biomedcentral.com/articles/10.1186/s40413-017-0180-1

Nzeako, U.C., Frigas, E., & Tremaine, W.J. (2001). Hereditary angioedema: a broad review for clinicians. *Archives of Internal Medicine*, 161, 2417-2429.

O'Bier, A., Muniz, A.E., & Foster, R.L. (2005). Hereditary angioedema presenting as epiglottitis. *Pediatric Emergency Care*, 21, 27-30.

Osler, W. (1988). Hereditary angio-neurotic oedema. *American Journal of Medical Science*, 95, 362–367.

Postnikoff, I.M. & Pritzker, K.P. (1979). Hereditary angioneurotic edema: an unusual case of maternal mortality. *Journal of Forensic Sciences*, 24, 473-478.

Prematta, M.J., Prematta, T., & Craig, T.J. (2008). Treatment of HAE with plasma-derived C1inhibitor. *Therapeutics & Clinical Risk Management,* 4, 1-8.

Prior N, Remor E, Gomez-Traseira C, Lopez-Serrano C, Cabanas R, Contreras J, et al. (2012) Development of a disease-specific quality of life questionnaire for adult patients with hereditary angioedema due to C1 inhibitor deficiency (HAE- QoL): Spanish multi-centre research project. *Health Qual Life Outcomes.* 10:82. doi:10.1186/1477-7525-10-82 57.

Quincke, H. (1882). Concerning the acute localized oedema of the skin. *Monatsh Prakt Dermatology,* 1, 129–31.

Roche, O., Blanch, A., Caballero, T., Sastre, N., Callejo, D., & Lopez-Trascasa, M. (2005). Hereditary angioedema due to C1 inhibitor deficiency: patient registry and approach to the prevalence in Spain. *Annals of Allergy, Asthma, & Immunology*, 94, 498-503.

Rosen, F.S., Pensky, J., Donaldson, V., & Charache, P. (1965). Hereditary angioneurotic edema: two genetic variants. *Science,* 148, 957–958.

Szeplaki, G., Varga, L., Kleiber, M., Karadi, I., Romics, L., Fust, G., & Farkas, H. (2005). Adverse effects of danazol prophylaxis on the lipid profiles of patients with hereditary angioedema. *Journal of Allergy and Clinical Immunology*, 115, 864-869.

Weller K, Groffik A, Magerl M, Tohme N, Martus P, Krause K, et al. (2012) Development and construct validation of the angioedema quality of life questionnaire. *Allergy* 67:1289–98. doi:10.1111/all.12007

Weller K, Magerl M, Peveling-Oberhag A, Martus P, Staubach P, Maurer M. (2016). The Angioedema Quality of Life Questionnaire (AE-QoL) - assessment of sensitivity to change and minimal clinically important difference. *Allergy*, 71:1203–9

Winnewisser, J., Rossi, M., Späth, P., Bürgi, H. (1997). Type I hereditary angio-oedema. Variability of clinical presentation and course within two large kindreds. *Journal of Internal Medicine*, 24.

Wu MA. Lanadelumab for the treatment of hereditary angioedema. (2019). *Expert Opin Biol Ther.* 19:1233–45.

Zingale, L.C., Beltrami, L., Zanichelli, A., Maggioni L, Pappalardo E, Cicardi B, & Cicardi M. (2006). Angioedema without urticaria: a large clinical survey. *Canadian Medical Association Journal*, 175, 1065-1070.

Zuraw, B.L. & Herschbach, J., (2000). Detection of C1 inhibitor mutations in patients with hereditary angioedema. *Journal of Allergy Clinical Immunology*, 105, 541-546.

Zuraw, B.L. (2008). Clinical practice. Hereditary angioedema. *New England Journal of Medicine*, 359, 1027-1036.

Zuraw BL. (2018) Hereditary angioedema with normal C1 inhibitor: Four types and counting. J Allergy Clin Immunol. Mar;141(3):884-5.