Position Paper on Hereditary Angioedema

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This is a revised version of the original ASCIA Position Paper on Hereditary Angioedema (HAE) developed by the ASCIA HAE Working Party in 2010:

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ABBREVIATIONS USED IN DOCUMENT

ACE	angiotensin converting enzyme
ASCIA	Australasian Society of Clinical Immunology and Allergy
C1 INH	C 1 inhibitor
ED	emergency department
HAE	hereditary angioedema
HRT	hormone replacement therapy
IRT	individual replacement therapy
OCP	oral contraceptive pill
PBS	Pharmaceutical Benefits Scheme
PID	primary immunodeficiency
TA	tranexamic acid
TGA	Therapeutic Goods Administration
SAS	Special Access Scheme

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1.0 INTRODUCTION

1.1 Definition

Hereditary angioedema (HAE) is a rare autosomal dominant disorder that has been described in 3 forms; types 1, 2 and 3. Types 1 and 2 result from deficiency in functional C1 inhibitor (C1 INH), either from low absolute levels or production of a dysfunctional protein. Type 3 is outside the scope of this document but will be referred to briefly in Section 4.0. 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 sometimes 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 [2]. Attacks may be preceded by a prodrome of tingling, or a non-itchy rash (erythema marginatum [3]) anywhere on the body. Affected patients also have higher than expected rates of autoimmune disease [4, 5].

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” [6]. The superceded term *angioneurotic edema* (a synonym for *angioedema*) is derived from Heinrich Quincke’s original explanation that swelling arose from increased vascular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 [7]. The autosomal dominant nature of this disorder was described by William Osler, who reported the disorder in each of five family generations [8]. 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 [9]. While investigating the properties of a newly discovered protein shown to inhibit C1 complement, Donaldson reported low

circulating levels of this protein in patients with HAE [10] [11]. 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) [12].

1.3 Epidemiology

Estimates of prevalence of HAE range from 1/10,000 to 1/150,000 individuals [13, 14]. There are no known ethnic or gender differences, with the exception of HAE Type 3 [15].

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 [16]. 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 of cases. If the currently quoted number of cases in other populations holds for Australia, then up to 480 cases could be expected to exist.

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 X11a). 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 CI 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, sometimes related to mutations of the active site of the protein.

3.0 CLINICAL PRESENTATION

HAE is suspected when a patient presents with angioedema without urticaria, that is unpredictable in its onset, but frequently follows a trigger such as trauma, and is associated with recurrent abdominal pain and upper airway swelling.

3.1 The Attack

HAE is characterised by episodic swelling of subcutaneous tissues, gut and upper respiratory tract [17]. Clinical episodes may occur frequently or may be years apart [18]. 50% of patients experience their first manifestation of the disease before the age of 10 [17].

HAE attacks in any one individual 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 [2, 19].

3.2 Manifestations

Abdominal pain, frequently accompanied by nausea, vomiting, dehydration, 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 [18 20].

Cutaneous angioedema, a non-pitting, non-pruritic swelling, usually affects the face, limbs or genitals. [18]

Oropharyngeal swelling is a much less frequent manifestation. 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 [18]. Historical data suggest that mortality from laryngeal swelling was 30% prior to the introduction of effective prophylaxis [2].

3.3 Other features

Urticaria is **not** a feature of HAE or other kinin-related forms of angioedema [21]. Although a family history is usual, about 25% of newly diagnosed patients report no known affected family members [22]. In these patients a de novo mutation is presumed [23]. 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 [4 25].

3.4 Trigger Factors

Recognised exacerbating factors include stress, infection, injury, dental and other surgery [2], oestrogens [26 27] (oral contraceptives, hormone replacement therapy and pregnancy) and angiotensin converting enzyme inhibitors [28]. 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 (eg IgE-mediated food or drug allergy)
• Drug induced histamine dependent angioedema (eg NSAID intolerance)
Suspect mast cell dependent when
• Angioedema coexists with urticaria or other features of anaphylaxis
• Obvious trigger (i.e. 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 [10]

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 a number of circumstances individuals 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 [29].

Chinniah and Katelaris [30] 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. 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.

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 individuals from acute attacks during interventions are based on uncontrolled studies and are aimed at increasing temporarily the plasma C1INH levels.

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 [31] and episodes have been triggered by the administration of local anaesthetics [21]. 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. C 1 INH concentrate or icatibant should be readily available.
- For any procedure requiring intubation, or for tooth extraction, C 1 INH concentrate 1-6 hours before the procedure with further doses readily available.

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 [17]. Occasionally episodes occur in the first year of life (7%) [18] and another 35% present in the second decade. The diagnosis, however, is usually not made until the second or third decade of life [18,32]. Studies have documented an average delay to diagnosis of 13 to 21 years despite improvements in screening and general awareness of HAE [2, 33, 34].

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 in adults.

There is an inverse correlation between age at onset and severity of disease. In a cohort of 209 patients, the 64 individuals 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 [18].

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 [15, 35]. 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 [35]. In comparison, severe laryngeal swelling in adults usually develops over 8 to 12 hours [27].

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 [36].

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 yr) [3]. 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.

In general however, symptoms in children 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. [32]

4.0 DIAGNOSIS

When there is a suspicion of the diagnosis of HAE, patients must be screened and if the diagnosis is confirmed, family members should 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 [21].

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 CI 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 C 1 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 [13].

A reduced serum C4 and C1 INH protein level should be followed up by measurement of serum C1q. 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 [37]. 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) [15 38, 39]. 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 for the diagnosis of Type 3 HAE. Now that genetic testing is available, prenatal diagnosis may be possible.

6.0 MANAGEMENT

Currently in Australia there are several treatment options for severe acute episodes of angioedema, although these are somewhat limited by cost.

Icatibant (Firazyr®) is now listed on the Pharmaceutical Benefits Scheme (PBS) for emergency treatment of acute angioedema in patients with known HAE, and can in suitable circumstances be self-administered at home.

Purified C1 INH (Berinert®, Cinryze®) is available for intravenous use in the hospital setting or possibly at home for severe attacks and is preferable for use in pregnancy and children and can also be used for short-term prophylaxis prior to procedures. It is not currently (2012) funded by the Commonwealth.

The only options for long term prophylaxis are **danazol** and **tranexamic acid**, which are limited, respectively, by side effects/intolerance and relative lack of efficacy.

Section 6 describes the current practices in terms of management of acute episodes and long term prophylaxis.

Sections 7 and 8 detail specific therapies and recommendations for optimal management.

6.1 Treatment of acute episodes of angioedema

Acute angioedema in patients with HAE does not respond to antihistamines, corticosteroids or adrenaline. Minor peripheral episodes are usually not treated and settle after a few days.

Historically, fresh frozen plasma has been used as a treatment modality for C1 INH replacement but with access to more specific treatment it has been superseded. It carries the risk of blood borne infection, worsening the severity of the attack because of the inclusion of other biologically active molecules and the risk of reaction to it, as a blood product [40]. It should be considered as a last resort and is probably preferable to no treatment in emergency cases where no alternatives are available [40].

The current treatments for acute episodes of HAE are replacement purified C1 INH (Berinert, Cinryze) or the bradykinin antagonist icatibant (Firazyr). Both are safe, well-tolerated and effective for moderate to severe episodes of angioedema in any location. C1 INH 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. Icatibant is administered subcutaneously and is suited to self-administration in out of hospital settings or administration in hospital. Treatment options are not determined by the location, severity or duration of angioedema.

***Cutaneous angioedema**:* Episodes of peripheral or truncal angioedema causing only mild or moderate discomfort and little or no disability may not require treatment. Symptomatic treatment with analgesics (paracetamol, NSAID, opiates) can be used. Early in the course of the episode or during a prodrome, the increase or introduction of danazol or the increase, introduction or addition (to danazol) of tranexamic acid may reduce or shorten the episode, however there is no good quality evidence for these approaches.

Some episodes of peripheral angioedema may be severe and cause pain and significant disability. Oedema of the face or genitalia may cause major discomfort and functional impairment. Treatment with icatibant or C1 INH may be warranted in these cases to reduce the severity and shorten the duration of the attack.

***Abdominal pain**:* Some minor episodes of gastrointestinal angioedema resolve with rest and simple analgesia. Episodes causing severe abdominal pain, distention and vomiting may require treatment in hospital with opiate analgesia and fluid replacement. Abdominal attacks which cause significant discomfort and disability warrant treatment with icatibant; 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 is also an option but currently may be limited by cost. C1 INH is the treatment of choice for significant episodes of abdominal angioedema in pregnancy and childhood.

***Laryngeal/airway oedema**:* Airway angioedema in HAE is dangerous and fatalities are well known. 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. Symptoms that suggest laryngeal oedema are the sensation of a lump or fullness in the throat, voice change, dysphagia and of course stridor in a

patient with known HAE. Indirect laryngoscopy is desirable for confirmation but 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 an absolute indication for icatibant or C1 INH concentrate. Treatment should commence at home if possible, by self-administration of subcutaneous icatibant or intravenous 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 further dose. 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 in a timely manner.

6.2 Short term prophylaxis

Short term prophylaxis is required to prepare patients for elective dental and surgical procedures involving the head and neck area.

For minor dental and medical procedures danazol is the preferred prophylaxis, 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 short-term prophylaxis 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. Tranexamic acid is less effective than danazol and is not preferred for prophylaxis but could be introduced where danazol is contraindicated or unacceptable (for dosing see section 6.3.4). 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.

For higher-risk procedures such as extensive dental work, head and neck surgery or any procedure requiring intubation, prophylactic C1 INH is used for prevention of angioedema (box 2). C1 INH concentrate can be used at short notice for urgent procedures. If C1 INH concentrate is unavailable then danazol prophylaxis should be used and the procedure undertaken with great caution and with emergency facilities immediately available.

Box 1 - Minor dental and medical procedures

Short term prophylaxis with danazol:

- For those already on danazol - double the dose
- For those not on long-term prophylaxis - introduce danazol 600mg/day

(100-300mg in children)

For 5 days prior to procedure and 2 days afterwards:

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

Box 2 - Major dental procedures and intubation

Prophylaxis with C1 INH concentrate:

- 20U/kg Berinert® or 1,000U Cinryze® 1 to 6 hours prior to the procedure

6.3 Long term prophylaxis

6.3.1 General

Long term prophylaxis refers to the use of regular medication to prevent episodes of angioedema in those with confirmed HAE. The decision as to whether to institute long-term prophylaxis depends on individual factors such as the frequency of episodes, the severity and

location of previous episodes, the presence or absence of known triggers and their avoidability, and the balance of these factors against the acceptability, cost and potential morbidity of prophylactic agents.

Uniform criteria directing the use of prophylactic therapy have not been established. One expert consensus statement recommended consideration of prophylaxis if severe events occur more than once per month or if the patient is disabled for more than 5 days per month on average, or if there is a history of an airway compromising event [21]. However it should be noted that the pattern of angioedema is not consistent and laryngeal oedema can occur in those with a relatively benign history. Those who have had infrequent but severe attacks or dangerous laryngeal episodes should be considered for prophylaxis.

Antihistamines and oral corticosteroids do not prevent angioedema. There are no known alternatives to medication-based prophylaxis other than avoidance of triggers; for example, modification of the diet or environment has not been shown to reduce the frequency of episodes.

6.3.2 Avoidance of triggers

Avoidance of triggers is important for prevention of angioedema episodes. Angiotensin converting enzyme (ACE) inhibitors are contraindicated in HAE. Angiotensin receptor antagonists have also been shown to increase bradykinin levels [42] and should be avoided or used with caution. Oestrogen-containing oral contraceptives increase episodes in many patients but not all. The progesterone-only contraceptive pill may be associated with a reduced frequency of episodes [43] and is generally recommended for women with HAE.

6.3.3 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 individuals. 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 surprisingly high doses 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 [44].

Recommended dosage regimens vary. It is reasonable to commence with a moderate dose (for example 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). The maintenance dose required to suppress or substantially reduce angioedema varies between 100mg second daily and 800mg daily. The aim of treatment is to minimise the frequency and severity of angioedema episodes and not 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 (for example infection or stress) and may be advised to temporarily increase the dose of danazol.

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

Danazol is not recommended for long term prophylaxis in children but its long term use in children has been reported and in some cases the benefits outweigh the risks (see Paediatric section).

Danazol is currently a streamlined authority item for HAE in Australia. It is available as 100mg and 200mg capsules in quantities of 100 capsules with up to 5 repeats.

Other attenuated androgens such as stanozolol and oxandrolone have been used for HAE prophylaxis. Stanozolol was reported to be better tolerated than danazol in a retrospective survey [45] but is no longer available. Oxandrolone has a lower virilisation potential and may be preferable in children. It can be imported and used under the TGA SAS.

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

6.3.4 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 long term prophylaxis of angioedema in HAE but is less effective than attenuated androgens [46]. Epsilon-aminocaproic acid (EACA) is less effective than tranexamic acid and is no longer available.

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 2 or 3 doses (this can result in up to 10 large tablets per day). 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.

6.3.5 C1 INH concentrate prophylaxis

C1 INH concentrate has also been used for prophylaxis, where attenuated androgens and tranexamic acid have been unsuccessful or not tolerated and angioedema has been frequent and/or dangerous. In particular it has been used in pregnancy. The dose should be the minimum required to prevent angioedema but is usually 500-1,000U twice weekly. This could be self-administered at home, with appropriate protocols and patient training as well as safety measures and support. To date, C1 INH concentrate prophylaxis has seldom been used in Australia because of the lack of funding and the difficulties of home intravenous management although short-term prophylaxis during pregnancy is not uncommon.

6.3.6 Monitoring treatment

C1 INH replacement: C1 INH replacement therapy with C 1INH concentrate may have to be administered at any time on an emergency basis. Methods of production for C1 INH replacement therapy and the risk of blood borne pathogen transmission may differ among products. Both currently available products include a nanofiltration step to remove viral particles. However haemovigilance (bloodborne pathogen surveillance) and baseline biochemical analysis and viral studies (such as Hepatitis B, C and HIV screening) should be collected and stored at diagnosis and annually or biannually. The availability of recombinant preparations of C1 INH would overcome many of these issues.

Attenuated androgens and antifibrinolytics*:* Attenuated androgens and antifibrinolytics 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).

7.0 SPECIFIC THERAPIES

A number of specific therapies are now registered in Australia for management of HAE.

7.1 Berinert® (Human C1 INH concentrate)

Berinert® (distributed by CSL) was for many years the only available C1 INH product in Australia. Berinert is a highly purified, freeze-dried C1 INH derived from human plasma. It contains 500 units (U) of C1 INH per vial (50 U/mL). One unit is equal to the amount of C1 INH in 1mL of human plasma, which is equivalent to approximately 240 mg/L of plasma. It is a soluble single-chain glycoprotein containing 478 amino acid residues.

Administration of Berinert to patients with C1 INH deficiency replaces the missing or malfunctioning C1 INH protein resulting in relief from the symptoms of HAE. The product is administered intravenously and is immediately available in the plasma with a plasma concentration corresponding to the administered dose.

7.1.1 Berinert® - Studies of efficacy

A pivotal Phase III prospective, multinational, randomised, parallel-group, placebo-controlled, dose-finding, three-arm, double-blind clinical study (IMPACT-1) assessed the efficacy and safety of Berinert in 124 adult and paediatric subjects with C1 INH deficiency who were experiencing an acute moderate to severe attack of abdominal or facial HAE [41]. Subjects ranged in age from 6 to 72 years of age. The study objectives were to show that Berinert shortens the time to onset of relief of symptoms of an abdominal or facial attack compared to placebo and to compare the efficacy of two different doses of Berinert. Subjects were randomised to either receive a 10 U/kg body weight dose of Berinert (39 subjects), a 20 U/kg dose of Berinert (43 subjects), or placebo (42 subjects) by slow intravenous infusion (4 mL per minute) within 5 hours of onset of an attack.

Subjects treated with a 20 U/kg dose of Berinert experienced a highly significant reduction (p=0.0025) in the median time to onset of relief from symptoms of an HAE attack (30 minutes) as compared to placebo (90 minutes). The median time to complete resolution of HAE

symptoms was significantly shorter (p=0.0237) in the Berinert 20 U/kg group (4.9 hours) than in the placebo group (7.8 hours).

The study demonstrated that a 20 U/kg body weight dose of Berinert was significantly more efficacious than a 10 U/kg body weight dose of Berinert or placebo. Additionally, the 10 U/kg body weight dose of Berinert did not show a clinically significant difference compared to placebo.

7.1.2 Berinert® - Adverse effects

Berinert has been used for over 30 years in more than 400,000 treatments and has an excellent safety record. In the pivotal Phase III study, the most common adverse effects reported four hours post the 20U/Kg dose were nausea, dysgeusia, abdominal pain and headache; however, no serious adverse events were noted[41].

7.1.3 Berinert® - Present situation in Australia

Berinert is expensive ($AUD 1,700 per vial) and is usually funded through hospital budgets. National Blood Authority (NBA) funding has been applied for. It obtained an Orphan Drug Designation in October 2008. Supplies of C1 INH are usually kept either at one or more major hospitals in each state, or at CSL Biotherapies state branches, where there is 24-hour access (contact CSL Biotherapies Customer service – phone 1800 063 892 or email customerservice.plasmaproducts@csl.com.au).

Each state may have different arrangements and clinicians who treat HAE patients and families need to be familiar with local means of access to Berinert. Limited funding has usually restricted the use of C1 INH to life-threatening episodes such as laryngeal oedema, severe swelling in pregnancy, and perhaps abdominal attacks with obstruction that are not responding to conservative measures.

In January 2010 registration of the product was granted for the indication of “treatment of acute attacks in patients with HAE, recommended dose 20U/Kg body weight”. TGA SAS (category A or B) approval is no longer required.

Although rarely used in Australia, self-administration of C1 INH at home as “on demand” treatment, has been demonstrated to be feasible. Patients prone to frequent or dangerous

episodes should be considered as candidates. This facilitates the earliest use of the product which should more effectively terminate episodes. Extensive patient (and partner) training is essential and a second person should always be present during the infusion. Detailed protocols and nursing support are required. Consideration needs to be given to provision of supplies of C1 INH concentrate to patients who are travelling to remote or outlying areas, either for self-administration or for administration by available local medical personnel in an emergency.

For patients who live in remote areas, C1 INH concentrate should be kept at the local hospital or medical centre and local doctors should familiarise themselves with its use.

In some countries, Berinert is used as " individual replacement therapy" (IRT) where infusions are used regularly, usually twice per week. This is used in those patients who have very frequent, severe attacks and would otherwise present many times to emergency departments for acute management. IRT has been shown to improve the quality of life in HAE patients with severe attacks and to significantly reduce frequency of episodes.

7.2 Cinryze® (Human nanofiltered C1 INH concentrate)

Cinryze C1 INH concentrate is distributed internationally by ViroPharma, manufactured by Sanquin in the Netherlands and like Berinert is purified from human plasma. As such it was introduced in Europe in 1972 and was approved in 2008 by the FDA in USA for prophylaxis of HAE. It achieved orphan drug designation in Australia in 2010 "for the treatment, routine prevention and pre-procedure prevention of angioedema attacks in adults, adolescents, and children from 6 years of age with C1 INH deficiency".

7.2.1 Cinryze® - Studies of efficacy

A single publication (Zuraw 2010) reported 2 randomised trials of Cinryze for the treatment and prophylaxis of hereditary angioedema. In the treatment trial, 68 HAE subjects were randomised to receive Cinryze or placebo within 4 hours of the onset of an episode of moderate to severe nonlaryngeal oedema (laryngeal episodes were treated with open-label Cinryze). Although entry criteria allowed for children down to the age of 6, the majority of

subjects were adults. Unlike the Berinert IMPACT-1 trial, a fixed dose of 1,000U of C1 INH was used in all subjects. There was a statistically significant reduction in time to onset of relief in the treatment group (2h) compared with placebo group (>4h, P=0.02) but the proportion of subjects achieving unequivocal relief within 4 hours was still only 60% (42% in the placebo group, P=0.06). 64% of subjects treated with Cinryze required a second dose of the drug at 60 minutes because of inadequate improvement compared with 80% of those treated with placebo. Interestingly in the open-label extension phase of the trial the rate of response to treatment within 4 hours was 93%; the authors commented on psychological factors affecting perception of pain in abdominal attacks.

Cinryze (1,000U twice weekly) was compared with placebo for long-term prophylaxis of angioedema attacks. Episodes were reduced by 50% and were 32% less severe and 38% shorter in duration. Overall swelling days were reduced by 66%. The use of additional Cinryze for episodes was reduced by 70%. These reductions persisted for beyond a year of treatment. In an open label study Cinryze was administered prior to 91 different medical, surgical and dental procedures with no angioedema attacks reported within 72h of the procedure in 98% of cases.

Children were included in the acute treatment trial (22, age range 2-17), long-term prophylaxis trial (23 subjects, age range 3-17 years) and the open-label short term prophylaxis study (40 subjects). In each case the results were comparable with adult subjects with no adverse effects.

7.2.2 Cinryze® - Adverse effects

Adverse reactions in clinical trials and in clinical use have been mild, including nonspecific rash, dizziness and headaches. There is a theoretical risk of thrombosis at high dosage but this has not been observed in HAE patients. Cinryze is a blood product and there is a theoretical risk of transmission of blood-borne pathogens, however the manufacturing process includes 3 viral inactivation/removal steps including nanofiltration at 15nm, smaller than any known viral particles. There is no contraindication to use in children, or in pregnancy or lactation.

7.2.3 Use of Cinryze®

Cinryze is indicated for treatment, pre-procedure prophylaxis and long-term prophylaxis of angioedema in adult and paediatric HAE patients. Recommended treatment dose for an acute episode is 1,000U (2 vials) for adults or children, with provision for a second 1,000U dose after 60 minutes if response inadequate. The dose for short-term prophylaxis prior to procedures is 1,000U between 1 and 24h prior to the procedure, with a second dose held in reserve. Dosage for long-term prophylaxis is 1,000U twice weekly in adults and children. Cinryze is supplied as a freeze-dried powder with solvent for reconstitution and can be stored for up to 2 years at room temperature (<25°C).

7.3 Future uses of C1 INH concentrate

Besides administration of C1 INH concentrate to treat acute severe attacks of HAE in hospital, “on demand” or individual replacement therapy (IRT) is an attractive option for patients. This involves individuals having prompt access to the product for administration at the earliest sign of an attack. Ideally, patients or family members would be trained to administer this at home.

A recent study [50] of self-administration of C1 INH concentrate has demonstrated significant improvement in quality of life by both physical and psychological parameters with no serious complications arising from home administration.

Long-term prophylactic therapy with regular scheduled doses of C1 INH concentrate is another option for those with contraindications to other drug therapy who have frequent HAE attacks, but continues to be limited by the high cost of the product.

7.4 Icatibant (Firazyr®)

Bradykinin is thought to be the final mediator of vascular permeability that causes local tissue oedema in HAE. Its effects are mediated by binding to the constitutive bradykinin 2 receptor (B2R) on vascular endothelial cells. Icatibant is a synthetic peptidomimetic B2R antagonist with high specificity suitable for human subcutaneous administration.

Several studies have examined the efficacy of icatibant in the acute management of angioedema episodes. An initial uncontrolled pilot study reported that the mean time to relief of symptoms after treatment with Icatibant was significantly reduced from 42 hours in historical controls to 1.16 hours. Subcutaneous treatment was well tolerated and relieved symptoms more quickly than intravenous injection [51].

Three double-blinded placebo-controlled trials were subsequently carried out; the first two, FAST 1 and 2, were reported in a single publication [5].

The FAST-1 trial compared subcutaneous injection of icatibant with placebo in 57 subjects presenting acutely with superficial cutaneous or abdominal angioedema episodes. The primary outcome measure was the time to onset of a 30% symptom improvement, but unfortunately the results for the combined group did not meet statistical significance. This result was due to the placebo arm having a higher use of rescue medication including C1 INH, an effective therapy. This would have increased the overall perceived effectiveness of the placebo arm. Subgroup analysis indicated significantly faster time to relief of cutaneous swelling and cutaneous pain in the icatibant group, and a significant difference was seen between the groups at the 4-hour post-treatment time point.

The FAST-2 trial compared subcutaneous icatibant with oral tranexamic acid using a double-blind double-dummy design. In this trial the median time to onset, 30% improvement, and almost complete symptom relief was significantly better in the icatibant group (0.8, 2 and 10 hours) than in the tranexamic acid group (7.9, 12 and 51 hours). No serious adverse events occurred.

FAST-3 was a further placebo-controlled randomised double-blind trial in 88 subjects with HAE presenting with acute episodes affecting the abdomen, periphery or airway. The primary endpoint of 50% reduction in symptom scores was significantly different between active treatment (2h) and placebo (19.8h), again without significant adverse events. The time to initial symptom relief was 0.8h versus 3.5h.

The parameters of efficacy of icatibant (time to effect, degree of effect, adverse effects) were broadly similar to those of C1 INH products although direct comparisons have not yet been made. Icatibant has the advantage of the lack of blood-product-associated risks and costs. The

possibility of subcutaneous administration will facilitate rapid use in emergency situations, and potentially allow home use and self-administration by patients.

The effectiveness of icatibant in the treatment of HAE demonstrates the importance of the bradykinin pathway in the production of angioedema in HAE. There is additional potential for this agent to treat angioedema caused by acquired C1 INH deficiency and ACE-inhibitors.

Icatibant (distributed in Australia by Shire) was registered in Australia in 2010 and as of 1 August 2012 has been funded by the PBS, as an authority item. It can be supplied to patients via community pharmacies.

Patients may hold their own icatibant supply (a pack of two syringes) either for self-administration or for administration by a trained companion or a medical professional at a clinic or hospital. It is suitable for storage at room temperature and may be taken when travelling.

7.5 Ecallantide (Kalbitor®)

Plasma kallikrein plays a major role in the contact (kallikrein-kinin) cascade producing bradykinin. Bradykinin is a vasodilator, which increases vascular permeability, activates inflammation and produces pain and swelling associated with HAE.

Ecallantide is a potent and specific inhibitor of plasma kallikrein. It is given via the subcutaneous route and is a non plasma-derived therapy.

Because it bypasses the C1 INH pathway, it shows potential in treating not just HAE but also the acquired forms of angioedema (AAE) that can occur secondary to blood malignancies or autoimmune disease.

Ecallantide has been the subject of 4 clinical trials including 2 randomised controlled trials. In general results have been positive, with rapid reduction in oedema and minimal adverse effects. Response times were similar to icatibant and C1 INH.

Ecallantide was approved by the FDA in the US for the treatment of acute attacks of angioedema in adults. It is not yet available in Australia.

8.0 MANAGEMENT RECOMMENDATIONS FOR AUSTRALIA

8.1 General advice

An individualised care plan giving indications of what to treat, when to treat and how to treat episodes 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 individual and the 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. The optimal approach will include a lower threshold for therapy than is currently used.

Individuals must be counselled about avoiding and managing triggers, for example:

- OCP - In general, progesterone-only pills, such as levonorgestrol, are preferred.
- ACE inhibitors - Use of alternative antihypertensive agents is strongly recommended.
- Increase dose of danazol as prophylaxis during infections and times of acute stress or trauma.
- Stress management techniques, if stress is an identified factor in an individual.
- Avoid prolonged pressure, for example, when using tools.

8.2 Special circumstances

8.2.1 Travel

When an individual with HAE wishes to travel, it is advisable to have:

- A MedicAlert bracelet as well as an updated ASCIA Action Plan for HAE and consultant's letter, translated into the relevant language if needed.
- Prescriptions for adequate supplies of prophylactic medication, if used.
- Supply of C1 INH concentrate or icatibant (when available) with a letter for customs/airport controls, for the management of acute events is ideal although one must investigate the legality of carrying certain medications if unregistered in the destination country.

8.2.2 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, as individual replacement therapy (IRT), 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 partuition.

8.3 Acute attacks

If acute episodes are occurring frequently or if there has been a laryngeal episode, prophylactic therapy must be considered.

8.3.1 Peripheral swellings

- Minor: No treatment.
- Severe: Hands and feet where there is loss of function/work/school loss – C 1 INH concentrate or icatibant (when available).
- Alternatively, self-administer C1 INH concentrate or icatibant at early stages to abort episode (IRT).

8.3.2 Oropharyngeal/facial attacks

Treat early with C1 INH concentrate or icatibant.

8.3.3 Abdominal attacks

Treat early with C1 INH concentrate or icatibant. May still require analgesics and IV fluids.

8.3.4 Laryngeal attacks

Treat early with C1 INH concentrate or icatibant. May be an indication for long term prophylaxis. May be an indication for IRT strategies.

8.4 Short term prophylaxis

Generally, for short term prophylaxis, treatment strategies are similar for children and adults. Short term use of danazol in children is safe. There is no experience of the use of icatibant in children.

Surgery and dental procedures

High risk procedures

- C1 INH concentrate 1-6 hrs before and available for postoperative use.
- There are no studies on the prophylactic use of icatibant in this setting.

Low risk procedures

- No treatment, but have C1 INH concentrate or icatibant available as rescue treatment. (There is no data on the use of icatibant in children).

  or

- Short term danazol for 5 days before and 2 days after with rescue medication on hand. (If already on danazol, double dose for same period).

8.5 Long term prophylaxis

The common options for long term prophylaxis have been discussed in the document. When to institute long term prophylactic therapy requires input from the individual patient and treating Immunologist. Any patient experiencing laryngeal episodes must consider this option as should those with severe episodes, more than five times per month. Patients living in rural or remote regions may opt for prophylaxis earlier than city patients because of the lack of readily available services.

With the availability of C1 INH concentrate, regular, scheduled injections/infusions of these products is another option. The major drawback is the expense of such an approach and it is difficult to justify in those who experience very infrequent attacks. On demand IRT is a much better option in this instance. However, in special circumstances, such as in pregnancy, when frequent attacks are being experienced and where there are no real alternatives, scheduled regular doses of C1 INH concentrate remain an option. Because of its short half life icatibant is not suitable for use in this manner.

8.6 On demand individual replacement therapy (IRT)

While this has not been practice in Australia to date, this is a desirable method of management for patients with HAE as it gives them autonomy over a lifelong condition and access to early and thus more effective treatment. It is particularly attractive for patients living in rural or remote regions or for those who travel frequently. Both C1 INH concentrate and icatibant can be used in this manner with suitable training in technique. Icatibant is particularly suitable for administration in the general practice setting.

This form of treatment must be done in consultation with an Immunologist and patients will require regular follow up, monitoring of frequency of use and injection technique.

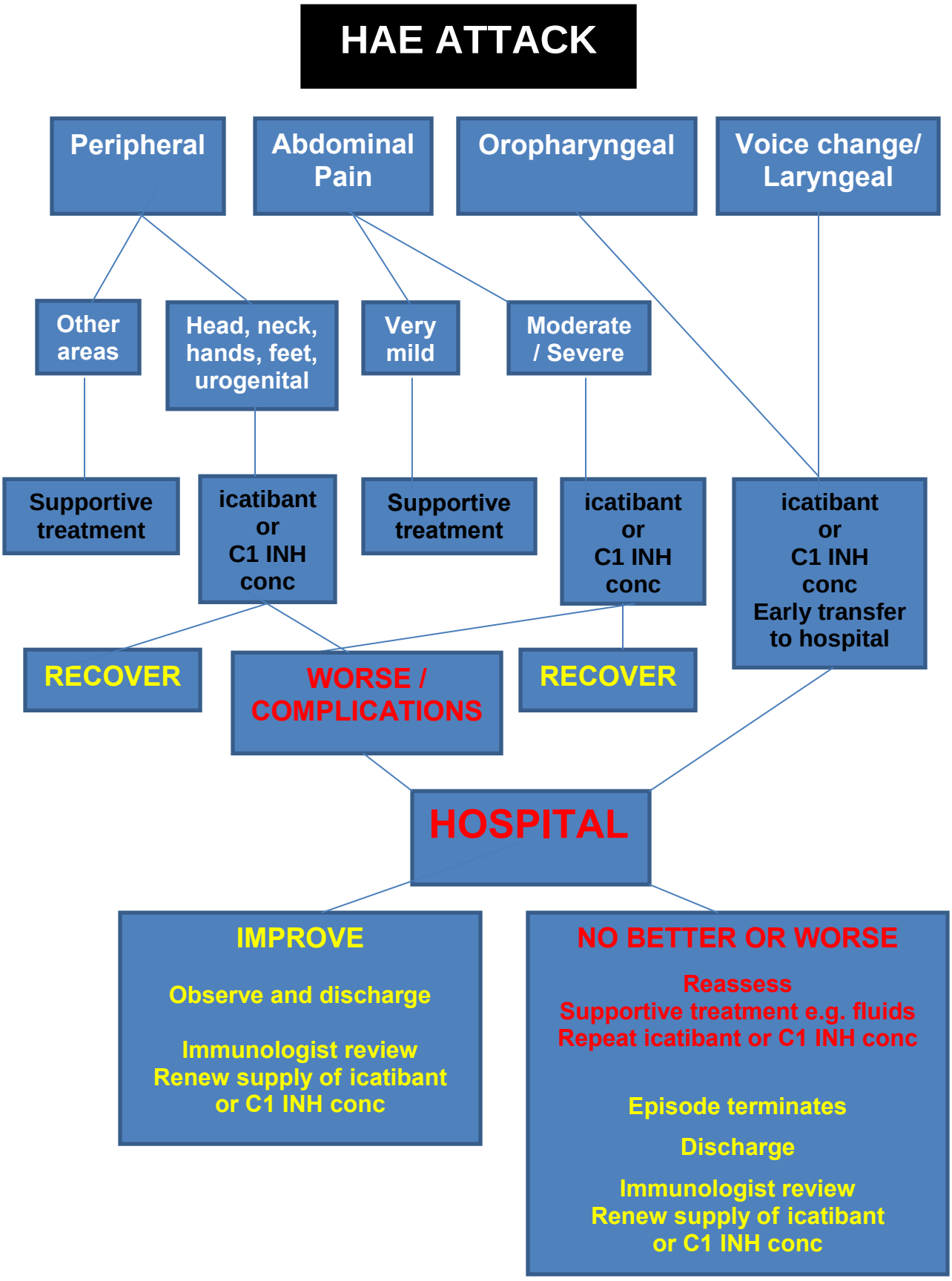
8.7 Quality of life (QOL) issues

Very little attention has been given to QOL issues in patients with HAE in Australia. While most have had access to C1 INH concentrate for acute, severe episodes or for short term prophylaxis, patients do tolerate a great deal of discomfort with many episodes for which C1 INH concentrate is not usually given. Danazol and TA are commonly used for long-term prophylaxis but this has been problematic in some patients with unacceptable side effects or lack of efficacy. The advent of wider availability of two products suitable for treatment of acute episodes and short term prophylaxis will no doubt improve the QOL of our patient population with this condition.

8.8 Home based therapy

Home based therapy has rarely been used in Australia but it is a very attractive option for our patient population, particularly those in rural and remote areas. Many other patients with young families and busy lives would welcome the possibility of self-management if it were available. In this regard, icatibant offers an attractive option as it is given by subcutaneous injection so training is relatively simple. C1 INH concentrate use in home-based therapy will require careful training and monitoring. Specialist Immunology centres could offer this as part of long term care of patients with HAE (see Appendix).

8.9 Algorithm for modern management of HAE in Australia



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10.0 APPENDIX – HOME CARE PROGRAM

Recent Canadian and UK consensus documents on the management of HAE have recommended the option of home therapy for HAE patients. This choice should be made available to all HAE patients including children and those who suffer from infrequent attacks, as 50–75% have a life-threatening attack at some time and it is not possible to predict which episodes will deteriorate quickly [52]. It provides a quick, convenient and probably safe method of dealing with acute attacks of angioedema. This is particularly valuable where access to emergency care is likely to be difficult through reasons of resource or geography. A UK audit has shown that home possession could reduce the number of avoidable adverse effects (evidence level 2) and enriches QOL [50]. In order to be effective a referral to specialist HAE centres, good local links to accident and emergency, and a care management plan are essential.

Below are assessment guidelines (Table 3) and a training program (Table 4).

There is also a requirement to maintain competence in the administration of home infusions and a number of important safety considerations.

There has to be provision of refrigeration facilities for the storage of the product. Fortunately, the product retains efficacy for many months under less than optimal storage conditions e.g. 6 months at 25^{o}C (evidence level 4).

Home therapy programs with intravenous immunoglobulin have demonstrated that it is possible to train patients, with an ‘infusion partner’, to manage infusions and adverse events safely at home.

Because C1 INH concentrate is likely to be required when the patient is unwell, 24 hour emergency treatment at the local hospital must remain an option. Patients and carers should be encouraged to use this option where appropriate.

A number of patients may not wish to, be able to or fail to achieve, the self-directed administration of C1 INH concentrate. An alternative in these cases is to have a supply of

concentrate held by the patient for his/her use under the supervision of a medical practitioner or other trained healthcare provider. This may involve the general practitioner or a local emergency department.

There is evidence that self-possession reduces the time patients spend awaiting infusions (evidence level 2). Any such programme should be accompanied by appropriate information to be carried with the patient and advice as to strategies for resupply of concentrate.

Table 3. Assessment guidelines for home infusion of C1 INH concentrate

Criteria to assess the suitability of an individual for entry into home infusion program:
• Proven C1 inhibitor deficiency
• Requiring infusions at least every 3 months (so that infusion skills can be maintained)
• The patient/parent must be motivated to comply with the home therapy program and all its implications - written consent from patient/parent confirming this must be obtained before the program is commenced
• The patient/parent must have a partner willing to attend the home therapy program who will be present when therapy is required
• The patient/parent must have access to a telephone when administering therapy
• The patient/parent must have good venous access
• The patient must agree to call for an ambulance if self-cannulation is unsuccessful when concentrate is required
• In most circumstances home therapy is not employed in children

Table 4. Home therapy training program

Home therapy training programs should include the following key areas:

• 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, i.e. dosage; expiry date
• Demonstration of the correct technique for reconstitution of solution
• Cannulation with butterfly
• Blood sampling preinfusion
• Administration of injection/management of infusion
• Management of adverse reactions
• Training in the use of autoinjecting adrenaline devices (for treatment of possible anaphylaxis from infusion and NOT for an acute attack)
• Disposal of equipment
• Documentary evidence of the individual'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 individual's competence to administer injection/infusion
• Liaising with the individual, their G.P, consultant immunologist, pharmacist and other relevant care providers.

The Australasian Society of Clinical Immunology and Allergy (ASCIA) is the peak professional body of Clinical Immunology and Allergy Specialists in Australia and New Zealand.

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