SETTING  
Bristol Royal Hospital for Children

FOR STAFF  
All clinical staff

PATIENTS  
All children with suspected or confirmed hereditary angioedema (C1 esterase inhibitor deficiency).

GUIDANCE

Headings
Management of suspected/confirmed HAE patient in Emergency Department (ED), p2
Clinical signs and symptoms p4
The diagnosis of paediatric C1-INH deficiency (asymptomatic paediatric patient with positive family history of C1-INH-HAE), p6
The diagnosis of paediatric C1-INH-HAE (paediatric patient with angioedema of unknown aetiology positive/negative family history), p7
Management & follow up, p9

Background
- The prevalence of hereditary angioedema (HAE) ranges 1:10,000 – 1:150,000.
- Males and females are affected equally.
- HAE is characterized by recurrent episodes of swelling (angioedema), without urticaria or pruritus, which most often affect skin or mucosal tissues of upper respiratory and gastrointestinal tracts.
- Although the swelling is self-limited and resolves in 2-5 days without treatment, laryngeal involvement may cause fatal asphyxiation.
- The swelling results from excessive production of bradykinin, a potent vasodilatatory mediator and its vascular permeability-enhancing effects.
- C1-INH normally plays a role in limiting bradykinin production by inhibiting both kallikrein and active factor XII, so when C1-INH is deficient or dysfunctional, bradykinin production is relatively unchecked.
- C1INH deficiency or dysfunction results in low levels of C4 because the C1 complex normally cleaves C4 as part of classical complement pathway, and this is exaggerated if C1INH is deficient.
- The diagnosis of C1-INH-HAE is often delayed for years. The time between the onset of symptoms and diagnosis averages 8.5 years. Early onset of symptoms may predict a more severe course of disease.
- Most patients with HAE are otherwise healthy and should be encouraged to lead as normal a lifestyle as possible.
- There is no recommendation for specific activity avoidance.
• Patients with HAE do not respond to antihistamine and/or glucocorticoid therapy (see Fig 1 and Table 1 for the management of acute HAE episodes)

**Figure 1.** Management of the patient with suspected /confirmed HAE presenting to the Emergency Department (ED)

1. **HAE patient presents to ED**

2. **Treat as an Emergency** *if the swelling affects the face, neck, throat or abdomen.* *Early treatment of any attack (at any site) will produce a more rapid response*

3. Has the patient brought their own medication?

4. **YES or NO – Prompt Treatment**

   - **If C1-Inh** (20units/kg), then administer via slow IV infusion. Maximum dose 1000 iu.
   - **If Icatibant** (children >12kg), inject slowly over 30secs sub-cutaneously into the abdomen

5. **Patient Responding inside 2 hours**
   - May go home as soon as feels well enough (unless airway symptoms are present)

6. **Patient NOT Responding**
   - If patient has not noticed the start of improvement after 2 hours then reconsider diagnosis. Check C3, C4 and C1-Inhibitor level and function.
   - Contact on-call Immunologist via switchboard

   **SWELLINGS MAY TAKE UPTO 24 HOURS TO RESOLVE COMPLETELY**
**Genetics**

There are several types of HAE.

**Type I HAE** accounts for 85% of C1-INH-HAE and is characterized by reduced secretion of the C1-INH protein. Plasma protein (antigenic) and functional C1INH levels are **both low** and range from undetectable to less than 30% of normal in most patients, although levels can occasionally be between 30% and 50% of normal.

**Type II HAE** results from the presence of a dysfunctional C1-INH protein, which is present in normal or elevated amounts. This type of HAE is found in about 15% of affected families. C1INH **function is low, but protein levels are normal or elevated**. Protein levels may be elevated because the defective C1-INH is unable to form complexes with proteases, resulting in an increased plasma half-life.

- The inheritance of types I and II HAE is autosomal dominant, so the majority of affected patients have affected family members.
- However, ~25 % of cases result from de novo mutations, so a positive family history is not required for diagnosis.
- The gene for C1-INH is located on the long arm, chromosome 11. Nearly 300 pathogenic variants are reported.

**HAE with normal C1 inhibitor (type III).** The patients have normal complement studies, including C4, C1 inhibitor (C1-INH) protein level, and normal C1-INH function

- The incidence and prevalence of HAE with normal C1-INH is limited
- It is a rare disorder that usually presents in adulthood (after puberty)
- There are no accepted test(s) for establishing the diagnosis
- Females are affected more often and more severely
- Signs and symptoms similar to those of C1-INH-HAE
- Two subtypes of HAE with normal C1INH are recognized
  - HAE with normal C1-INH and a factor XII mutation (FXII-HAE)
  - HAE with normal C1-INH of unknown cause (U-HAE)
- Diagnosis:
  - Episodic angioedema affecting characteristic organs, without urticaria
  - Family history of angioedema and failure to respond to chronic, high-dose antihistamine therapy or the presence of a FXII (or possibly an angiopoietin-1 mutation) associated with the disease
  - Normal C4, normal C1-INH level and function
  - No medications that could cause angioedema, such as angiotensin-converting enzyme (ACE) inhibitors or nonsteroidal anti-inflammatory drugs (NSAIDs)
  - Treatment options for HAE with normal C1-INH are overall similar to those for C1-INH-HAE

**Acquired form of C1INH (C1-INH-HAE)** deficiency presents in older patients (i.e., age >40 years) without a family history of angioedema and is associated with underlying disorders or autoantibodies in most cases. C4 and C1-INH is low, C1q is low in 70% of cases. The patients should be screened for a haematological or lymphoproliferative disorder.
Clinical signs and symptoms

- The age at which attacks begin is variable.
- ~ 40% of patients experience their first attack before age 5, and 75%, by age 15.
- Repeated attacks in preadolescent children are uncommon, attack frequency usually increases after puberty.
- 42% to 58% of paediatric patients experience prodromal symptoms including erythema marginatum
- Angioedema attacks most often affect 3 anatomical locations:

  o The skin (cutaneous attacks, 91% of patients)
    - Common and temporarily disfiguring, although not generally dangerous
    - The extremities are most commonly affected in children
    - Swelling occurs in nondependent areas and is non-pitting
    - Often associated with pain and dysfunction
    - Angioedema builds over the first 24 hours, then gradually subsides over 48 to 72 hours, swelling may last up to 5 days
    - Some patients develop skin changes that are usually described as a serpentine, mottled, and/or "chicken-wire" pattern of erythematous discoloration
    - These findings can be mistaken for urticaria, but more closely resemble erythema marginatum

  o The gastrointestinal tract (gastrointestinal attacks, 73% of patients)
    - The symptoms result from bowel wall oedema
    - Present as varying degrees of gastrointestinal colic, nausea, vomiting, and/or diarrhoea
    - Experienced by majority of patients with HAE, and can be the principal presentation in one-quarter of patients
    - Can be challenging to diagnose
    - As many as one-third of patients with undiagnosed HAE may undergo unwarranted abdominal surgery
    - Most attacks are not associated with fever, peritoneal signs, or an elevated white blood cell count
    - Standard biochemical and haematological blood tests are often not helpful
    - Imaging is not routinely needed during the attack
    - However, if the cause of the patient's presentation is unclear, a computed tomography (CT) scan of the abdomen and pelvis or ultrasonography is useful in confirming the findings of gastrointestinal angioedema
    - The most common early finding is bowel wall oedema, although this may resolve rapidly

  o The upper airway (laryngeal/pharyngeal attacks, 48% of patients)
    - Laryngeal swelling can occur in isolation, or in association with swelling of lips, tongue, uvula, and soft palate
    - Usually first occurs between 11 - 45 years of age, with the mean age of 26
    - Laryngeal oedema occurs in approximately one-half of all patients over their lifetimes; however, only a few percent experience recurrent episodes
    - Laryngeal attacks accounted for < 1% of all angioedema episodes
    - Tooth extraction and oral surgery are common triggers
When to suspect HAE

- Recurrent episodes of angioedema without urticaria or pruritus, lasting 2-5 days (without treatment)
- Unexplained recurrent episodes of self-limited, colicky, abdominal pain (typically lasting 1-3 days) especially in patients who also have had cutaneous angioedema
- Unexplained laryngeal oedema (even a single episode)
- Angioedema episodes in the absence of angiotensin-converting enzyme (ACE) inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), or history to suggest an allergic cause
- A family history of angioedema
- Low C4 level in a patient with angioedema

Triggers and exacerbation factors:

- In children, most attacks occur without a clear trigger.
- Most common: mechanical trauma, dental work, mental stress & upper airway infection.
- Medication: oestrogen-containing medications, such as hormone replacement therapy & contraceptives, angiotensin-converting enzyme (ACE) inhibitors.
- Hormonal changes in women: puberty, pregnancy, perimenstrual or menstrual period.

Complement studies

Complement testing

- C4 (the natural substrate for C1 esterase), C1NH protein (or "antigenic") levels, and C1-INH function are the critical diagnostic tests for patients with possible C1-INH-HAE.
- Confirmation of C1-INH-HAE requires low C4 plus decreased C1NH protein or function.
- Two sets of complement tests should be obtained, at least 1 month apart.
- Complement studies are normal in HAE associated with variants in factor XII (FXII-HAE), angiopeititin-1 (ANGPT1), and plasminogen, as well as HAE of unknown origin (U-HAE).
- C4 and C1NH protein levels are relatively reliable.
- In contrast, tests of C1-INH function are particularly prone to lab error and can be falsely low (chromogenic assay) or falsely normal (ELISA). They should be done with fresh or freshly frozen serum that has not been standing for > 4 hours.
- If C4 is normal and C1-INH function is low, the most likely explanation is laboratory error, and testing should be repeated.
- The normal range for C4 is extremely wide (from 10 to 40 mg/dL) and may be reported as a concentration, absolute level, or percentage of normal.
- A level below 50% of normal is strongly suggestive of C1-INH deficiency.
- If the C4 level is presented in mg without a percent:
  o 25 mg would be considered a normal level (100%),
  o levels <10 mg are strongly suggestive of C1INH deficiency (pathologic).
  o levels between 10 and 15 mg are possibly pathologic, and levels >15 mg are not pathologic.

Testing when there is “Low clinical suspicion”

- For episodes of angioedema that are not characteristic of HAE (eg, the attacks last 24 hours or less, angioedema is sometimes accompanied by hives, or the frequency of angioedema is reduced by antihistamines) or there is a potential medication or allergy that could be causing the angioedema.
- In such patients, C4 alone is an adequate screening test.
• If C4 is normal, HAE due to C1INH deficiency is unlikely, and other causes of angioedema should be considered.
• If C4 is low, then C1INH protein level and C1-INH function should be measured.

Testing when there is “High clinical suspicion”
• The patient develops recurrent episodes of angioedema without urticaria lasting 2-5 days (without treatment).
• A trial of high-dose antihistamines, if appropriate, did not prevent symptoms
• The patient is not taking ACE inhibitors or NSAIDs.

**Diagnosis** (Fig 2 and Fig 3)

**Figure 2.** The diagnosis of C1-INH deficiency in families with known C1-INH-HAE (International consensus of diagnosis of paediatric HAE, 2017)

Asymptomatic paediatric patient with positive family Hx of C1-INH-HAE

- **Neonate**
  - Umbilical cord blood
  - C1-INH functional & antigenic levels, C4
  - Repeat after 1 year of age

- **Infant**
  - Peripheral blood
  - C1-INH functional & antigenic levels, C4
  - Repeat after 1 year of age

If mutation detected in the family, and the test is available, then

Umbilical cord blood or peripheral blood DNA analysis

Until C1_INH-HAE diagnosis is ruled out on 2 separate testing with 2nd testing performed after 1 year of age, the patient should be considered to have inherited C1-INH deficiency.
Figure 3. The diagnosis of C1-INH-HAE in children with angioedema of unknown etiology (International consensus of diagnosis of paediatric HAE, 2017)

Paediatric patient with angioedema of unknown etiology

**positive/negative** family history

C1-INH functional & antigenic levels, C4

Positive screen*

Repeat testing in 3 months to confirm**

Negative screen

C1-INH-HAE excluded***

Screen first-degree relatives

Consider DNA analysis

*Positive screen: C1-INH functional level & C4 are low, accompanied by a low C1-INH antigenic level in HAE type I

**Repeat after 1 year of age

***Angioedema with acquired C1-INH deficiency is also excluded but HAE with normal C1-INH function, which is rare in children, is not ruled out

- HAE type I and type II
  - Suggestive clinical history and physical findings during episodes
  - Combined with consistent results from at least 2 sets of complement studies separated by ≥1 month
  - Family history of angioedema strongly supports the diagnosis, but it is not required, since approximately one-quarter of patients have de novo mutations.

- Genetic testing is not usually required to confirm the diagnosis

- The diagnosis of HAE associated with variants in factor XII (FXII-HAE), angiopoietin-1, or plasminogen based on
  - Suggestive clinical history and physical findings during episodes
  - Normal complement studies
  - Positive family history
  - Genetic studies confirm the diagnosis and is the only way to make a definitive diagnosis if the family history is negative

- HAE of unknown origin (U-HAE)
  - Requires a suggestive clinical history and physical findings during episodes
  - Normal complement studies
• Positive family history
  o Lack of effectiveness of a prolonged trial of high-dose non-sedating antihistamines.

• Testing family members once the diagnosis of HAE has been made (Fig. 2)
  o In families with known C1-INH-HAE, first-degree relatives, whether symptomatic or asymptomatic, should be screened
  o C1-INH-HAE does not skip generations, although it can occasionally appear to do so if affected individuals are asymptomatic.

• Testing in infancy
  o Asymptomatic newborns or infants with a family history of C1-INH-HAE should be considered to have hereditary C1-INH deficiency until the diagnosis is ruled out.
  o Both C1-INH levels and function are difficult to interpret in children <1 year of age because C1-INH levels are normally 30 to 50% lower than adult levels, even in the absence of disease.
  o Complement levels are variable in this age group are influenced by birth weight & gestational age
  o C4 levels are frequently low and & not diagnostic for C1-INH-HAE
  o However, testing for C1-INH antigenic and functional levels are helpful to diagnose C1-INH-HAE. If normal, the HAE diagnosis is unlikely
  o If functional and/or antigenic C1-INH levels are low, repeat the testing after the age of 1.
  o Final diagnosis requires at least 2 matching HAE screening results with the second test performed after 1 year of age
  o Genetic testing is occasionally performed in infants <1 year if a definitive diagnosis is required and the disease-causing mutation in the family is known
  o In most cases, testing is simply postponed until the infant is older, and the diagnosis can be made using complement studies

• Testing if patient history suggestive of C1-INH-HAE but negative family history (Fig. 3)
  o Clinical suspicion of HAE-like symptoms at any age is an indication for screening regardless of the presence or absence of family history
  o If screening is suggestive of C1-INH-HAE, a second test should be performed to confirm the diagnosis
  o If C1-INH-HAE is suggested by testing, then all first-degree relatives in the ascending line should be screened. As with many AD disorders, 25% of cases may be a de novo mutation which may then be passed onto future descendants
  o SERPING1 gene sequencing may be helpful to confirm C1-INH-HAE in this setting
  o If screening is negative, angioedema with acquired C1-INH deficiency is also excluded, but HAE with normal C1-INH function, which is very rare in paediatric patients, is not ruled out.

• Differential diagnoses
  o A number of disorders share clinical or laboratory features of HAE
    • Allergic reactions and anaphylaxis
    • Idiopathic angioedema
    • Drug-induced angioedema
    • Allergic contact dermatitis
    • Autoimmune conditions
Management

1. Personalised patient care plan for emergency care
   a. All patients should have a plan for accessing treatment **rapidly**
   b. Immunology team should communicate with the hospitals nearest to the patient's home to ensure that acute therapies are available
   c. Patients should be provided with a form that summarizes treatments for acute episodes of angioedema – this should be reviewed regularly to adjust the dosing and adapting to the circumstances (e.g. starting/changing school)
   d. C1-INH-HAE patients should be offered home possession of C1-INH concentrate for emergency (2 vials)
   e. Teachers and responsible child care workers should be provided with detailed written information on the disease
   f. Alert devices, including identifying wrist or neck bands with emergency contact information, should be considered
   g. Every patient with C1-INH-HAE should be considered for home therapy & self/caregiver administration training

2. Treatment of acute attacks
   a. First-line therapies (table 1)
      i. Purified C1 inhibitor concentrate derived from human plasma (Berinert, Cinryze)
      ii. Recombinant human C1 inhibitor (Ruconest)
      iii. Icatibant (a synthetic bradykinin-B2-receptor antagonist)
   b. Second-line therapies
      i. If none of the first-line therapies is available, fresh frozen plasma (FFP) is recommended. Note that FFP occasionally has the paradoxical effect of making the angioedema acutely worse and the clinician must be prepared to intubate the patient if this happens.
   c. **Ineffective therapies** for acute attacks include glucocorticoids, antihistamines, androgens

3. Treatment of acute attacks at home (table 1)
   a. Early treatment of HAE attacks has been shown to result in improved efficacy.
   b. First-line therapies are likely to be effective if given in the first few hours of the angioedema attack (when the swelling is increasing).
   c. The clinician must consider each patient's situation, history of attacks, proximity to care, ability to self-administer medications, and preferences.
   d. Only parent/carer trained by immunology team should administer the first-line treatment to a child at home. Their competencies should be signed off before the initiation of the home therapy.

4. Short-term prophylaxis
   a. The most common indications are medical or dental procedures, anticipated stressful events and for travel to remote areas or countries where access to health care is limited
   b. C1 inhibitor concentrate (Berinert or Cinryze) (for high-risk procedures) or tranexamic acid can be used (Table 2)
5. Long term prophylaxis
   a. Tranexamic acid is considered to be first choice in paediatrics
      o well tolerated but less effective compared with C1 inhibitor concentrate & androgens
      o start at the lowest dose & increase as needed to suppress events
   b. C1 inhibitor concentrate (Cinryze) can be used for severe, recurrent attacks of HAE where acute treatment is inadequate, or when oral prophylaxis is inadequate or not tolerated (Table 2).
   c. Long term attenuated androgen (AA) therapy is usually effective but can have significant adverse effects. It should be avoided in growing children (premature closure of growth plate).
      o after Tanner Stage V, AA may be used trying to achieve the minimum effective dose
      o Danazol has been used effectively in paediatrics at doses of 2.5 to 5 mg/kg/ day (200 mg daily should not be exceeded).
      o treatment should start at 2.5 mg/kg/day and increase slowly every 2 weeks until symptom suppression or the maximum tolerated or maximum recommended dose is reached.
      o AA administration requires careful safety monitoring
### Table 1. Treatment of acute episodes of hereditary angioedema (HAE) in children

<table>
<thead>
<tr>
<th>Medication</th>
<th>Age</th>
<th>Dosing</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1 inhibitor concentrate (plasma-derived)</td>
<td>Any age</td>
<td>20 units/kg, Maximum dose 1000 iu</td>
<td>Do not shake solution because protein will denature</td>
</tr>
<tr>
<td>(Berinert, Berinert P)</td>
<td></td>
<td>Symptoms usually stabilize in 30 minutes.</td>
<td>Side effects unusual &amp; frequency not known (fever, headache can occur)</td>
</tr>
<tr>
<td>Given IV</td>
<td></td>
<td>Second dose uncommonly needed but may be given</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 minutes to 2 hours after first.</td>
<td></td>
</tr>
<tr>
<td>C1 inhibitor concentrate (plasma-derived)</td>
<td>2-11 years old (10-25 kg)</td>
<td>500 units for 1 dose (may be repeated after 60min if needed)</td>
<td>Do not shake solution because protein will denature</td>
</tr>
<tr>
<td>(Cinryze)</td>
<td></td>
<td>1000 units for 1 dose (may be repeated after 60 min if needed)</td>
<td></td>
</tr>
<tr>
<td>Given IV</td>
<td>2-11 years old (≥ 26 kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12-17 years old</td>
<td>1000 units for 1 dose (may be repeated after 60 min or sooner if needed)</td>
<td></td>
</tr>
<tr>
<td>Recombinant C1 inhibitor Conestat alfa (Ruconest, Rhucin)</td>
<td>&gt;12 years (&lt;84 kg)</td>
<td>50 units/kg</td>
<td>Common: headache</td>
</tr>
<tr>
<td></td>
<td>&gt;12 years (&gt;84 kg)</td>
<td>4200 units (2 vials)</td>
<td>Uncommon: nausea, vomiting, urticarial, paraesthesia, vertigo, throat irritation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Second dose rarely needed</td>
<td></td>
</tr>
<tr>
<td>Bradykinin B₂ receptor antagonist Icatibant (Firazyr)</td>
<td>12 kg to 25 kg</td>
<td>10 mg (1.0 ml)</td>
<td>Injection site reactions (usually mild)</td>
</tr>
<tr>
<td>Given by subcutaneous injection</td>
<td>26 kg to 40 kg</td>
<td>15 mg (1.5 ml)</td>
<td>NB. In clinical trial, not more than 1 injection per HAE attack administered</td>
</tr>
<tr>
<td>(approved for self-administration at home)</td>
<td>41 kg to 50 kg</td>
<td>20 mg (2.0 ml)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>51 kg to 65 kg</td>
<td>25 mg (2.5 ml)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;65 kg</td>
<td>30 mg (3.0 ml)</td>
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</tr>
<tr>
<td>Antifibrinolytics:</td>
<td>Any age</td>
<td>15-25mg/kg 2-3 times a day</td>
<td>Well tolerated in most patients</td>
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<tr>
<td>Tranexamic acid PO</td>
<td></td>
<td>(max per dose 1.5g)</td>
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<tr>
<td></td>
<td></td>
<td>Given for 48 hours</td>
<td></td>
</tr>
<tr>
<td>Fresh Frozen Plasma (FFP)</td>
<td>Any age</td>
<td>Consult paediatric haematologist</td>
<td>Common: nausea, pruritus, rash</td>
</tr>
<tr>
<td>NB. No controlled trials performed</td>
<td></td>
<td></td>
<td>Rare: allergic reactions, bronchospasm, cardiorespiratory collapse, fever</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Very rare: arrhythmia, hypertension, thromboembolism</td>
</tr>
</tbody>
</table>

**NB.** Kallikrein inhibitor Ecallantide (Kalbitor) approved >12 years in US only
### Table 2. Short and long-term prophylaxis of hereditary angioedema (HAE) in children

<table>
<thead>
<tr>
<th>Medication</th>
<th>Age</th>
<th>Dosing (short-term prophylaxis)</th>
<th>Dosing (long-term prophylaxis)</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antifibrinolytics: Tranexamic acid PO</td>
<td>Any age</td>
<td>15-25mg/kg 2-3 times a day (max.per dose 1.5g)</td>
<td>15-25mg/kg 2-3 times a day (max.per dose 1.5g)</td>
<td>Well tolerated in most patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Should be started 5 days before planned procedures eg, dental work &amp; continued 2 days afterwards</td>
<td>Use lowest effective maintenance dose, consider alternate day or x2 weekly regimens</td>
<td>Occasionally can cause diarrhoea</td>
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<td></td>
<td></td>
<td>Less effective compared with androgens and C1 inhibitor concentrate</td>
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<td></td>
<td></td>
<td></td>
<td>Avoid in patients with history of thrombosis or thromboembolic disease or risk factor for thrombosis</td>
</tr>
<tr>
<td>C1 inhibitor concentrate (plasma-derived) (Berinert, Berinert P) Given IV</td>
<td>Any age</td>
<td>15-30 units/kg (max per dose 1000 units) for 1 dose</td>
<td>N/A</td>
<td>See table 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>To be administered less than 6 hours before procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C1 inhibitor concentrate (plasma-derived) (Cinryze) Given IV</td>
<td>2-11 years (10-25kg)</td>
<td>500 units for 1 dose to be administered up to 24 hours before procedure</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1000 units for 1 dose to be administered up to 24 hours before procedure</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1000 units for 1 dose to be administered up to 24 hours before procedure</td>
<td>500 units every 3-4 days, dose &amp; dosing intervals can be adjusted as per response</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1000 units every 3-4 days, interval between doses to be adjusted according to response</td>
<td>1000 units every 3-4 days, interval between doses to be adjusted according to response</td>
<td></td>
</tr>
</tbody>
</table>

**NB**: So far, no randomized controlled trials (RCTs) of prophylactic treatment restricted to the paediatric population have been conducted.
Follow up

- Requires baseline liver function test and hepatitis virology.
- Annual review if asymptomatic.
- 3-6 monthly follow up for the patients on long-term prophylaxis or if clinically indicated
- The efficacy of C1-INH therapy should be assessed clinically by sufficient reduction of attacks.
- Monitoring C4 or C1INH antigenic levels is not recommended routinely.
- If the patients on tranexamic acid (high doses) long-term prophylaxis:
  - consider 6-12 monthly monitoring of urinalysis, renal and liver function tests, creatinine kinase
  - annual ophthalmological examination
  - if there is a personal or family history of thromboembolic disease, a thrombophilia screen should be performed before commencing treatment

Prognosis

- The prognosis for the patients with HAE is variable.
- The frequency of attacks can be dramatically reduced by therapy.
- Despite effective treatments, deaths secondary to laryngeal attacks still occur, and can be as high as 13 percent.

Support groups and leaflets:

- [http://www.haeuk.org/](http://www.haeuk.org/)
- [http://www.piduk.org/usefulcontactsandlinks/professionalorganisations](http://www.piduk.org/usefulcontactsandlinks/professionalorganisations)

References:

| AUTHORISING BODY | Children’s Clinical Effectiveness Committee  
|                  | Paediatric Medical Clinical Governance |
| QUERIES          | (Monday-Friday 9am-5pm): contact ID registrar bleep 3997 or ID Consultant on service via switchboard |