PAEDIATRIC ACUTE CARE GUIDELINE	
Hereditary Angioedema (HAE)	
Scope (Staff):	All Emergency Department Clinicians
Scope (Area):	Emergency Department

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Hereditary Angioedema (HAE)

- Hereditary Angioedema (C1-esterase inhibitor deficiency) is a rare autosomal dominant disorder due to absolute (Type I - majority of cases) or functional (Type II) deficiency of C1-esterase inhibitor (C1-INH)

Background

- Airway swelling, including laryngeal oedema, can be life-threatening
- Oedema in HAE is non-pitting, and is not associated with urticaria, itching, or redness
- Family history of HAE is absent in about 25% of newly-diagnosed cases

General

- The diagnosis of HAE is usually delayed, typically to the 2nd or 3rd decade of life, although 50-75% of patients have their first attack by the age of 12 years
- Although attacks in children are usually not as frequent and/or severe as in adults, life-threatening laryngeal oedema can occur at any age
- Attacks may be precipitated by injury, including local trauma, dental or other surgery, infection, psychological stress, drugs, menstruation, vigorous exercise and certain foods
- Attacks may evolve rapidly, or progress slowly over 24 hours, and may last 3-4 days or more although are usually self limiting
- They can be variable in their severity

Assessment

- HAE is suspected when a patient presents with:
  - angioedema without urticaria or pruritis
  - that is unpredictable in its onset
  - but frequently follows a trigger
  - and is associated with recurrent abdominal pain and upper airway swelling
- HAE is characterised by episodic swelling of subcutaneous tissues, gut and the upper respiratory tract which can each be involved on their own or in combination
  - **Oropharyngeal and airway swelling:** (including laryngeal oedema) can be life-threatening
  - **Abdominal pain and vomiting:** most frequent manifestation is colicky abdominal pain
  - **Cutaneous angioedema:** non-pitting and non-pruritic, affecting the face, limbs especially the fingers and toes, and genitals

History

- A family history of HAE is usually present (absent in 25%)
- A trigger factor (stress, infection, injury) may be present, but not always
- Prodromal symptoms such as fatigue, flu-like symptoms, indigestion, tingling, or a rash (erythema marginatum) may precede the onset of swelling

Examination

- General appearance and observations
- Look for airway swelling: tongue, fauces, soft palate, uvula
- Assess for laryngeal oedema: stridor, hoarseness, altered voice (ask caregivers)
- Assess hydration, and perform an abdominal examination
- Assess and document facial and limb swelling
- Confirm the absence of redness and itching, which would raise differential diagnoses other than HAE

Investigations

- In the non-acute setting, screening for HAE may be considered, in consultation with an Immunologist: serum C4 level
- Add a serum C1-INH and C1 functional assay if HAE is strongly suspected

Differential diagnoses

- Anaphylaxis
- Urticaria
- Allergic reactions (local or systemic)
- Skin / soft tissue infection (cellulitis)

- Oedema (e.g. due to hypoalbuminaemia)

Management

- Treatment of acute attacks depends on severity and site of involvement
- Allergy therapies such as adrenaline, antihistamines, and steroids are generally unhelpful
- The Immunologist on-call can be contacted via PMH switchboard to discuss the management
- Intravenous infusion of C1-INH (Berinert®) 20 units/kg is indicated for airway involvement

Resuscitation

Severe symptoms with airway swelling:

- Call for Senior ED Doctor
- Give intravenous C1-INH (Berinert®) 20 units/kg over 10 mins
- Prepare for emergency intubation or cricothyrotomy
- Consider FFP only if C1-INH is definitely not available

Initial management

- Refer to the Australasian Society of Clinical Immunology and Allergy: ASCIA HAE Action Plan
- Consult the Immunologist on-call in all cases

Further management

Additional useful information, for in-hospital management of children with HAE attack:

Facial and Airway Swelling: • Upper airway involvement usually begins slowly, but cases of progression within 20 minutes have been reported • If there is any suspicion of upper airway involvement (including tongue swelling, throat swelling, difficulty with breathing, swallowing or talking - hoarse voice), give C1-INH promptly • PICU admission for close monitoring may be required
Abdominal Pain and Vomiting: • While simple analgesics including NSAIDs can be useful, moderate to severe abdominal pain, vomiting or abdominal distension requires C1-INH administration • Admission for observation is usually necessary • Symptoms generally improve within 30 to 90 minutes • If symptoms worsen or last longer than 2 hours after the initial infusion, give a 2nd dose of C1-INH, consider opiate analgesia and IV fluids, and consider alternative diagnoses
Limb Involvement: • Mild swelling of limbs usually does not require any specific treatment and will usually resolve within 3 days, admission is usually not necessary • Severe facial, genital or peripheral swelling, causing significant discomfort, requires administration of C1-INH and admission for observation

Medications

C1-INH (C1-esterase Inhibitor, Berinert® or Cinryze®): • Berinert®: Each vial contains 500 Units (powder reconstitutes to 10mL) • Dose is 20 Units/kg, IV infusion, given over 10 mins • At PMH ED, Berinert is located in the Medication Room fridge in ED • Administration and Monitoring: as per product insert (or refer to MIMS online)
Currently Not Available at PMH: • Cinryze®: Each vial contains 1000 Units (powder reconstitutes to 10mL). Dose is 500 units, IV infusion • Icatibant (Firazyr®) is a bradykinin antagonist used for emergency treatment of acute angioedema in adults with known HAE. There is no experience of the use of icatibant in children and it is therefore not recommended in children.
Other Medications which may be used (in consultation with Immunologist): • Danazol (10mg/kg per day in 2-4 divided doses, up to 200mg TDS) - androgenic side effects • Tranexamic Acid (25mg/kg BD or TDS to max 4g/day) - procoagulant, risk of clotting (caution if family history of thrombophilia) • Fresh Frozen Plasma (FFP) - not to be used if C1-INH is available - complement activation and risk of antibodies

Admission criteria

- Most patients with an HAE attack should be admitted for observation - ward or PICU depending on the severity
- All patients with upper airway oedema should be admitted to PICU for close observation
- If in doubt, discuss with the on-call Immunologist

Referrals and follow-up

- Patients should be followed up by an Immunologist to discuss:
  - Long-term prophylaxis
  - Patients with recurrent life-threatening episodes or frequent attacks may be considered for prophylaxis with Danazol or Tranexamic acid
  - Prophylaxis for elective surgical or dental procedures
- An Immunologist should be consulted in advance, if there are any planned dental manipulations or elective surgical procedures (especially involving the head and neck area), even if these are considered minor. Prior treatment (for up to 5 days beforehand) may be indicated (Danazol or C1-INH).

Health information (for carers)

- Locate a Specialist: ASCIA Website List of Practitioners

Tags

ACE inhibitor, allergy, anaphylaxis, angioedema, edema, oedema, swelling, tongue

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File Path:			
Document Owner:	Dr Meredith Borland HoD, PMH Emergency Department		
Reviewer / Team:	Kids Health WA Guidelines Team		
Date First Issued:	21 August, 2013	Version:	
Last Reviewed:	17 March, 2014	Review Date:	23 February, 2015
Approved by:	Dr Meredith Borland	Date:	17 March, 2014
Endorsed by:	Medical Advisory Committee	Date:	17 March, 2014
Standards Applicable:	NSQHS Standards: 		
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