Management of angioedema in the ER

Paul Keith MD MSc FRCPC
McMaster University
June 3, 2012
I have the following financial relationship to disclose:
Consultant for: Allergy Therapeutics, GSK, Merck, CSL Behring, Shire
Grant/Research support from: Allergy Therapeutics, GSK, Merck, Shire
Honoraria from: GSK, Merck, Nycomed, CSL Behring

-AND-

I will discuss off label use and investigational use in my presentation.
True or False?

1. ACE inhibitors cause angioedema due to a drug allergy
2. Epinephrine is best given subcutaneously if a patient is having anaphylaxis.
3. Itching is common in patients with swelling due to hereditary angioedema
Objectives

• To discuss the differential diagnosis of angioedema from an ER perspective
• To discuss the diagnostic tests used to distinguish the different causes of angioedema
• To review practical management strategies and new treatments for angioedema in the ER
Differential diagnosis:

- IgE dependent angioedema and anaphylaxis
- Chronic urticaria and angioedema
- Hereditary angioedema
- allergic to milk, peanut, soy
- asthmatic
- first month at high school
- possible cross-contamination with dairy on french fries
- confusion with asthma

Sabrina Shannon
1990 - 2003
Urticaria
Urticaria due to peanut allergy
Asthma

Common causes of anaphylaxis:

- **Food**: peanuts, tree nuts, shellfish, milk, eggs, fish, soy, sesame seeds, wheat

- **Stinging and biting insects**: bees, wasps, yellow jackets, hornets, fire ants

- **Medications**: penicillin, sulfa antibiotics, allopurinol, muscle relaxants, certain surgery fluids

- **Latex**

- **Exercise**

In some cases, the cause is unknown (**idiopathic anaphylaxis**).
Hypersensitivity Type I

Type I (Immediate)

occurs when

IgE on Mast Cells/Basophils

is crosslinked by

Antigen
to induce release of

Histamine and other Inflammatory Mediators

that may manifest

Locally

Systemically

Asthma or Allergic Rhinitis

Anaphylaxis
IgE-dependent Release of Inflammatory Mediators

Immediate Release
Granule contents:
Histamine, TNF-\(\alpha\), Proteases, Heparin

Over Minutes
Lipid mediators:
Prostaglandins, Leukotrienes

Over Hours
Cytokine production:
Specifically TNF-\(\alpha\), IL-4, IL-13

Cell recruitment

Sneezing
Nasal congestion
Itchy, runny nose
Watery eyes
Wheezing
Bronchoconstriction
Hypersensitivity Type I

Pharmacological Intervention: Summary

- Anti-histamines – H1 and H2
- Epinephrine
- Steroids
- New therapies: antileukotrienes, anti-IgE
Intraoperative anaphylactoid reactions
- prevalence of bradycardia with histamine release
- lack of skin findings
- clinically relevant histamine disturbance:
  - Ringer’s 8%
  - Haemaccel 26% (4 life threatening)
  - H1 + H2 antagonists 2% (p<0.0001)

Lorenz et al. Lancet 1994;343:933
Mouse model of anaphylaxis

Mouse model of anaphylaxis

Anaphylaxis management

MANAGEMENT OF COMORBIDITIES
- asthma
- other pulmonary disease
- cardiovascular disease
- mastocytosis/clonal mast cell disorder
- other

ALLERGEN AVOIDANCE

IMMUNOMODULATION
- allergen-specific
  - desensitization to β-lactam antibiotics, NSAIDs, chemotherapies, drugs, other
  - immunotherapy with insect venom

ASSESSMENT OF CONCURRENT MEDICATIONS
- β-adrenergic blockers
- ACE inhibitors
- other

• allergen non-specific
  - prednisone
Epinephrine Auto-Injectors

EpiPen® Jr. (green)
- 0.15 mg (0.3cc of 1:2000)
- Patients: 15-30 kg

EpiPen® (yellow)
- 0.30 mg (0.3cc of 1:1000)
- Patients: >30 kg

Consult with allergist for children <15 kg.

www.epipen.ca
Twinject

Twinject®

1\textsuperscript{st} dose:
auto-injector

2\textsuperscript{nd} dose:
manual syringe

0.15 mg and 0.30 mg
T = thigh, A = upper arm
Subcutaneous epinephrine

![Graph showing blood pressure and heart rate over time](image1)

![Graph showing plasma epinephrine concentration over time](image2)
Intramuscular epinephrine
Chronic “idiopathic” urticaria
Chronic urticaria management

- H1 antagonists – non-sedating, quadruple dose for rhinitis, divide total dose into twice daily
- H2 antagonists if lightheaded or heartburn
- Steroids only for severe exacerbations

- Allergist assessment – consider hydroxychloroquine, cyclosporine, anti-IgE
Hereditary angiodema (HAE)
Open = remission
Solid = attacks

Nussberger J et al. NEJM 2002;347:621
C1 Inhibitor Deficiency

\[
\text{HAE patients} \quad \text{Healthy subjects}
\]

\[\text{C1 Inhibitor (g/l)}\]

\[\text{p < 0.0001}\]

What is HAE?

- Autosomal Dominant Inherited Disease (Type I)
- 75% have a family history of HAE
- Deficiency of/or poorly functional C1-INH
- Presents with recurrent abdominal pain, upper airway swellings and skin swelling
- Swelling is gradual in onset and persists 2-5 days
- Abdominal pain can be very severe with obstruction
- It is not associated with urticaria
- The single best test in North America is C4
What is HAE? - Phenotypes

1. **HAE type I** - Approx 85% of patients; inadequate amounts of C1-INH

2. **HAE type II** - Approx 15% of patients; inactive C1-INH generated

3. **HAE type III** - Estrogen associated angioedema
Genetics of HAE I

- Heterozygous condition
  - Autosomal dominant
  - Occurs equally in both sexes
- 238 C1-INH gene mutations are known
- New mutations: ~ 25%
- No correlation between type of C1-INH mutation and frequency of attacks

Angioedema Pathways

Angioedema Caused by HAE
- Factor XII
- C1INH
- XIIa
- C1INH
- Prekallikrein
- High-molecular-weight kininogen
- Endothelial cell prolylcarboxypeptidase
- Kallikrein
- High-molecular-weight kininogen
- C1INH
- Bradykinin

Angioedema Caused by an Allergic Response
- Antigen
- Mast cell
- Release: histamine and other inflammatory mediators
- Edema

Epidemiology of HAE

- 1:10,000 – 1:150,000 with no racial or gender predilection
Hereditary angioedema

![Bar chart showing the number of patients by age at onset.](chart.png)
Case presentation

- 66 yo lady
- Recurrent abdominal pain and surgeries to lyse adhesions
- Severe throat swelling on holiday in Thailand requiring tracheotomy at age 50
- Chronic cough
- One to two times per month has attacks
Case presentation

- Triggering events:
  - dental procedure
  - minor trauma
  - no identifiable cause
- No problems during pregnancies
- Diagnosis of HAE made at 50 after tracheotomy

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1 ESTERASE INH</td>
<td>0.09</td>
<td>L 0.21-0.39 g/L</td>
</tr>
<tr>
<td>C3 COMPLEMENT</td>
<td>1.04</td>
<td>L 0.73-1.73 g/L</td>
</tr>
<tr>
<td>C4 COMPLEMENT</td>
<td>0.02</td>
<td>L 0.13-0.52 g/L</td>
</tr>
</tbody>
</table>
First noticed episodes of facial swelling
- While in Thailand, she developed upper airway angioedema requiring an emergent tracheotomy
- Diagnosed with HAE type I

First use of Icatibant in open label study. (see text on right)

1996
1997
2005
2007
May
Sept
Oct
Dec

↑ Danazol 100 mg od
↑ Danazol 200 mg od

Multiple episodes of throat or abdominal angioedema from May 2007 – Dec 2008 (10 in total).
- Shown (●) are episodes requiring an ER visit or hospital admission.
- She required C1 est Inh infusions 2000 PU for most of the visits.
- 2008:
  - Jan: Danazol 100 mg od
  - Feb: Danazol 200 mg od
  - Mar: Danazol 300 mg od

- 2009:
  - Dec: Danazol 400 mg od
  - Jan: Emergent repair of incisional ventral hernia
  - Feb: Danazol 200 mg od
  - Mar: Icatibant used for GI angioedema

- 2010:
  - Aug: Surgical correction of incisional hernias
  - Nov: Pre-op infusion of C1 Inh 3000 PU
C1 inhibitor level (normal 0.21-0.39 g/L)
C4 (normal 0.13-0.52 g/L)
## ER visits – 66 yo female

<table>
<thead>
<tr>
<th>Date</th>
<th>LOS</th>
<th>Location</th>
<th>Attending Doctor</th>
<th>Principal Diagnosis/Reason for Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Feb, 12</td>
<td>1</td>
<td>MO-ER</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 Dec, 11</td>
<td>1</td>
<td>ER-G</td>
<td></td>
<td>LT FLANK PAIN</td>
</tr>
<tr>
<td>10 Sep, 11</td>
<td>1</td>
<td>JO-EMR</td>
<td></td>
<td>ABDOMEN PAIN</td>
</tr>
<tr>
<td>17 Jul, 11</td>
<td>1</td>
<td>GO-VCC</td>
<td></td>
<td>SORE THROAT / EYE INFECTION?</td>
</tr>
<tr>
<td>23 Jun, 11</td>
<td>1</td>
<td>MO-ER</td>
<td></td>
<td>SORE THROAT</td>
</tr>
<tr>
<td>16 Mar, 11</td>
<td>1</td>
<td>ER-G</td>
<td></td>
<td>ANXIETY CHEST PAIN</td>
</tr>
<tr>
<td>20 Dec, 10</td>
<td>1</td>
<td>MO-ER</td>
<td></td>
<td>?DIRECT SURGERY</td>
</tr>
<tr>
<td>18 Dec, 10</td>
<td>1</td>
<td>MO-ER</td>
<td></td>
<td>CELLULITIS</td>
</tr>
<tr>
<td>06 Nov, 09</td>
<td>1</td>
<td>MO-ER</td>
<td></td>
<td>VOMITING/ABDOMINAL SWELLING</td>
</tr>
<tr>
<td>30 Aug, 09</td>
<td>1</td>
<td>MO-ER</td>
<td></td>
<td>?THROAT SWELLING</td>
</tr>
<tr>
<td>14 Apr, 09</td>
<td>1</td>
<td>MO-ER</td>
<td></td>
<td>ABD SWELLING</td>
</tr>
<tr>
<td>13 Apr, 09</td>
<td>1</td>
<td>MO-ER</td>
<td></td>
<td>NEEDING BLOOD CHECKED</td>
</tr>
<tr>
<td>22 Mar, 09</td>
<td>1</td>
<td>MO-ER</td>
<td></td>
<td>ABD SWELLING</td>
</tr>
<tr>
<td>22 Mar, 09</td>
<td>1</td>
<td>MO-ER</td>
<td></td>
<td>SWELLING</td>
</tr>
<tr>
<td>17 Mar, 09</td>
<td>1</td>
<td>MO-ER</td>
<td></td>
<td>ABD SWELLING</td>
</tr>
<tr>
<td>07 Feb, 09</td>
<td>1</td>
<td>MO-ER</td>
<td></td>
<td>ABD SWELLING</td>
</tr>
<tr>
<td>07 Feb, 09</td>
<td>1</td>
<td>MO-ER</td>
<td></td>
<td>ABD SWELLING</td>
</tr>
<tr>
<td>07 Feb, 09</td>
<td>1</td>
<td>MO-ER</td>
<td></td>
<td>ABD PAIN</td>
</tr>
<tr>
<td>07 Feb, 09</td>
<td>1</td>
<td>MO-ER</td>
<td></td>
<td>ABDOMINAL SWELLING</td>
</tr>
</tbody>
</table>
Admissions - 66 year old female

<table>
<thead>
<tr>
<th>Date</th>
<th>LOS</th>
<th>Location</th>
<th>Attending Doctor</th>
<th>Principal Diagnosis/Reason for Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 Mar, 12</td>
<td>SCH</td>
<td></td>
<td></td>
<td>RECURRENT INCISIONAL HERNIA</td>
</tr>
<tr>
<td>11 Sep, 11</td>
<td>12</td>
<td>JI-6G1</td>
<td></td>
<td>GASTRIC ATTACK HEREDITARY ANGIO.</td>
</tr>
<tr>
<td>27 May, 10</td>
<td>7</td>
<td>G5</td>
<td></td>
<td>RECURRENT ABDOMINAL INCISION HERNIA</td>
</tr>
<tr>
<td>06 Nov, 09</td>
<td>4</td>
<td>MI-3Y</td>
<td></td>
<td>ABDO PAIN ? ANGIOEDEMA</td>
</tr>
<tr>
<td>15 Apr, 09</td>
<td>4</td>
<td>MI-4Z</td>
<td></td>
<td>CHRONIC SYMTOMATIC VENTRAL HERNIA</td>
</tr>
<tr>
<td>23 Mar, 09</td>
<td>5</td>
<td>MI-4Z</td>
<td></td>
<td>BOWEL OBSTRUCTION</td>
</tr>
<tr>
<td>07 Feb, 09</td>
<td>4</td>
<td>MI-4Z</td>
<td></td>
<td>? SBO</td>
</tr>
<tr>
<td>25 Dec, 08</td>
<td>5</td>
<td>MI-3Y</td>
<td></td>
<td>ANGIO EDEMA/QUERY BOWEL OBSTRUCTION</td>
</tr>
<tr>
<td>16 Mar, 08</td>
<td>1</td>
<td>MI-ER</td>
<td></td>
<td>HEREDITARY ANGIO EDEMA EXCERBATION</td>
</tr>
<tr>
<td>28 Oct, 07</td>
<td>10</td>
<td>MI-3X</td>
<td></td>
<td>HEREDITARY ANGIOEDEMA</td>
</tr>
<tr>
<td>23 Oct, 07</td>
<td>1</td>
<td>MI-3X</td>
<td></td>
<td>HEREDITARY ANGIO EDEMA</td>
</tr>
<tr>
<td>05 May, 07</td>
<td>1</td>
<td>MI-3Y</td>
<td></td>
<td>ACUTE ATTACK OF HEREDITARY ANGIOEDEMA</td>
</tr>
<tr>
<td>02 Sep, 06</td>
<td>1</td>
<td>MI-ER</td>
<td></td>
<td>A-TYPICAL CHEST PAIN-R.O. UNSTABLE A</td>
</tr>
<tr>
<td>30 Sep, 05</td>
<td>1</td>
<td>MI-3Y</td>
<td></td>
<td>ANGIO EDEMA</td>
</tr>
</tbody>
</table>
Toxins, injury, inflammation, ischemia, viral infections, etc.

Factor XIIa → Prekallikrein

C1-Inh → Kallikrein

HMW-Kininogen → Bradykinin

Kallikrein

ACE

ACE Inhibitors

des-8,9-Bradykinin inactive

Microvascular leakage, vasodilatation, pain
Dysregulation of Complement, Coagulation, and Contact Cascades in Hereditary Angioedema.

Common triggers of HAE attacks

- Trauma
- Menstruation
- Medications
- Infection
- Stress
- Allergic reaction

Angioedema attack
Recognizing Prodromal Symptoms as the First Signs of HAE Attacks

Prodromal symptoms experienced by some patients include one or more of the following:

- Erythema marginatum-like, nonpruritic rash
- Parasthesias (tingling, itching, tightness, or pain)
- Flu-like symptoms
- Headache
- Abdominal discomfort
- Urticaria
- Fatigue
- Malaise
- Irritability
- Mood changes
- Hyperactivity
- Thirst
- Nausea
HAE

patient with no swelling (patient with various facial swellings)
HAE
HAE

gastrointestinal swelling
HAE
HAE – erythema marginatum

Rash that preceeds or accompanies HAE attacks
HAE Attack Characteristics

Body location and intensity of 1085 attacks

Body location:
- Abdominal: 69%
- Peripheral: 22%
- Facial: 5%
- Laryngeal: 4%
- Other: 0.4%

Intensity of attack (patient-reported):
- Moderate: 59%
- Severe: 19%
- Mild: 21%
- Other: 0.5%

Craig et al. Allergy 2011 66 (12):1604-11
Time (%) That Patients Report Being Able to Predict an Acute HAE Attack Based on Prodromal Symptoms

- 50% Predict 75% of attacks
- 26% Predict 25% of attacks
- 9% Predict 50% of attacks
- 9% Unable to predict attacks
- 7% Predict 100% of attacks

• 40/46 patients report presence of prodromal symptoms

Proportion of any HAE and Angioedema (AE) Emergency Dept visits resulting in Hospitalisation

<table>
<thead>
<tr>
<th></th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAE</td>
<td>43.2%</td>
</tr>
<tr>
<td>AE</td>
<td>22%</td>
</tr>
</tbody>
</table>

Hospitalization n/100,000 discharge: 4.3 for HAE and 22 for AE.

Adapted from Zilberberg et al, Allergy Asthma Proc 2010 31: 511-519
HAE economic burden

• Largest cost component for the average HAE patient was ER costs – accounts for 48% total costs when treating acute attacks.

• ER visits and hospital stays account for 68% of all costs when dealing with a severe attack.

HAE vs Angioedema (AE) in the ER
Snapshot from the US

Proportion of Principal Diagnoses
of HAE and AE
US Emergency Department Visits

Proportion of any HAE and AE
Emergency Dept visits resulting
in Hospitalisation

Hospitalization n/100,000 d/c

HAE: 4.3
AE: 22

Adapted from Zilberberg et al, Allergy Asthma Proc 2010 31: 511-519
Treatment of HAE

Treatment plan based on three approaches:

• Acute Attack – on demand therapy of C1 inhibitor IV

• Long-term Prophylaxis
  – Attenuated androgens (mainly danazol)
  – Tranexamic acid, or,
  – C1-INH concentrate  IV twice weekly

• Short-term Prophylaxis
  – C1 inhibitor IV prior to surgery or delivery
# Treatment of Acute HAE Attacks

<table>
<thead>
<tr>
<th>Treatment recommendations during:</th>
<th>Cutaneous Swellings</th>
<th>Abdominal Attack</th>
<th>Laryngeal Attack*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other than face, neck</td>
<td>Face, neck</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wait and see</td>
<td>Optional</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><em>(spontaneous resolution)</em></td>
<td>Optional</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma-derived C1INH$^{1,2}$</td>
<td>Optional</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>ICU <em>(intubation$^3$, tracheotomy)</em></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**General measures for treatment of acute attacks:**

- **Treat as early as possible in an attack**
  1. Dosage of pdC1INH(intravenous): **20 units/kg**
  2. If first line drugs not available, consider solvent detergent treated plasma (SDP) or less safe frozen plasma. Some patients on anabolic androgens can abort attacks by doubling their dose at the first signs, or prodrome, of an attack.
  3. Intubation: consider **early** in progressive laryngeal oedema.

Adapted from Bowen et al Allergy, Asthma & Clinical Immunology 2010; 6:24;
Includes products available in Canada only; * Laryngeal attacks is not a licensed indication in Canada
HAE Treatment Guidelines

The International Consensus Algorithm for HAE

1. C1-INH concentrate is the first-line therapy in severe attacks of HAE

2. Home care with C1-INH concentrate should be offered

3. C1-INH supply for personal use at home or with travel should be offered for self-administration

4. C1-INH prophylaxis for Danazol resistant patients should be considered

Toxins, injury, inflammation, ischemia, viral infections, etc.

- Factor XIIa
- C1-Inh
- HMW-Kininogen
- Prekallikrein
- Kallikrein
- (Aprotinin)
- DX-88
- ACE
- ACE Inhibitors

- Bradykinin
- des-8,9-Bradykinin (inactive)
- Icatibant

Microvascular leakage, vasodilatation, pain
What is Berinert®?

C1- Esterase Inhibitor, Human (C1-INH)

- Berinert® Vial (500 Units C1 INH)
- Diluent Vial (10 mL vial of sterile water for injection)
- Reconstitution: Mix2Vial™*

- dosing: 20 U/kg Body weight
- Administered by intravenous infusion at rate of 4 mL/min by push (ie. 70 kg gets 1500 PU or 3 vials over 7.5 minutes IV push)
- Room temperature storage (+2°C to +25°C)
- Shelf life: 30 months

* Registered trademark of West or one of its subsidiaries
# Integrated Safety System for Plasma Derived C1 inhibitor at CSL Behring

## 3 viral inactivation steps:
- **Pasteurization:** 10 hrs @ 60°C
- **Chromatography**
- **Nanofiltration**

### Selection of donation centers
- Exclusion of donors who pose risk
- Medical investigation of donors
- Serological testing of every donation
- 5-fold NAT/PCR testing of donations
- Inventory hold of source plasma with look-back procedure
- Computer monitoring of plasma selection

### Potential Contamination

### 1. Plasma Selection and Donation Control

### 2. Manufacturing Processes
- Removal and inactivation of potential contamination present
- Official certificate and release

### 3. Quality Control
- Internal quality control
- Reporting and evaluation of adverse drug reactions and performance of appropriate measures

### 4. Monitoring of Commercial Products
- Documentation of use

*Source: Property of CSL Behring*
C1 esterase inhibitor IV: Time to onset of symptom relief in all body locations (Primary Endpoint Result)

Median: 28 minutes (per-patient analysis)

C1 esterase inhibitor IV: Time to complete resolution of symptoms in all body locations (Secondary Endpoint Results)

Median: 15.5 hours (per-patient analysis)

Primary Outcome in the Trial of C1 Inhibitor Therapy for Acute Attacks of Angioedema


Circles = either subjects who received rescue therapy before 4 hours (competing events; 2 subjects in the placebo group received narcotic rescue at 15 and 146 minutes, respectively, and 1 subject in the C1 inhibitor group received open-label C1 inhibitor rescue at 110 minutes) or those who did not have an onset of unequivocal relief before 4 hours.
Major Events during the Prophylaxis Trial

1000 PU IV twice weekly for 12 weeks regardless of weight

Normalized Rate of Angioedema Attacks during the Prophylaxis Trial


1000 PU twice weekly for 12 weeks
Self-administration of intravenous C1-inhibitor therapy for hereditary angioedema and associated quality of life benefits

- 7/9 patients recruited and HRQoL assessed for 48 months
- Mean scores for both individual and combined components improved significantly
- No serious complications documented during follow-up
- Self-administration of C1-INH improved both physical and psychological parameters.

Icatibant – 10 amino acid peptide
Emergency Management of Hereditary Angioedema (HAE)

PATIENT IDENTIFICATION

Name: _____________________________
Date of Birth: _______________________
Health System #: ____________________

PROMPT TREATMENT REQUIED to PREVENT RAPID DETERIORATION

DIAGNOSIS

HAE is a rare potentially life threatening disease usually caused by C1-esterase inhibitor deficiency associated with tissue swelling (see description on back page of this wallet card).

PROMPT TREATMENT

PROMPT TRIAGE & ASSESSMENT:

To determine the severity of the swelling.

PROMPT TREATMENT:

Will rapidly initiate onset of relief of the angioedema in this patient and decrease morbidity.

AIRWAY OBSTRUCTION:

The risk of dying from airway obstruction if left untreated is significant. Consider early intubation in progressive laryngeal edema.

RECOMMENDED TREATMENT

C1-INH (IV): 20 U/Kg, 4mL/min

# of Vials: _____ of C1-INH 500 units (available at Blood Bank)

Other:

If above not available, consider: solvent detergent treated plasma (SDP) or less safe fresh frozen plasma (2 Units).

Angioedema attacks usually do not respond to treatment with glucocorticoids, antihistamines nor epinephrine.

This patient may require prophylaxis before surgery or dental procedures in order to prevent an angioedema attack.
Wallet Cards - Print

CLINICAL CHARACTERISTICS OF HAE

Recurrent non-pruritic edema of skin and submucosal tissue associated with pain, nausea, vomiting, diarrhea, and life-threatening airway swellings².

- Laryngeal / airway swelling:
  May result in asphyxiation
- Facial / neck swelling
- Abdominal attacks (abdominal pain, cramping, diarrhea, nausea / vomiting)
- Peripheral edema (other regions)

Supported by:
HAE Canada Inc (the Hereditary Angioedema Patient organization) (www.haeCanada.org)

HEALTHCARE TEAM

In case of Emergency, Contact my Physician:

MD/specialty: ____________________________
Hospital: ______________________________
  ______________________________

Other Clinic / Physicians

MD / specialty: __________________________
Hospital: ______________________________
  ______________________________

EMERGENCY CONTACTS

Please Contact:

Name: ________________________________
Relationship: _________________________
  ________________________________

Other Recommendations / comments:
_____________________________________
_____________________________________
_____________________________________
_____________________________________

_____________________________________

Physician signature

Date of Recommendation: / / ______ Day / Month / Year

References:
1. CHAN/RCAH WEBSITE FOR EMERGENCY TREATMENT
   www.haeCanada.com/files/TreatmentChart10602.pdf
2. CHAN/RCAH WEBSITE FOR PROPHYLAXIS
   www.haeCanada.com/files/ProphylaxisChart110602.pdf
Diagnosis Algorithm

Could It Be Hereditary Angioedema (HAE)?

If your patients answer “yes” to the first 7 questions and “no” to the last question, they may have C1-INH deficiency — not a GI problem or an allergic angioedema.

1. Has your patient had unexplained attacks of well-demarcated edema of the hands, feet, arms, legs, face, throat, genitals, or other part of the body?  
   - YES  
   - NO

2. Have these swelling attacks sometimes occurred on just one side of the body, for example, just the left hand or just the right foot?  
   - YES  
   - NO

3. Has the patient had unexplained attacks of abdominal pain?  
   - YES  
   - NO

4. Have these attacks of swelling or abdominal pain occurred more than once?  
   - YES  
   - NO

5. Has anyone in the patient’s family had similar episodes of swelling or abdominal pain? Or has anyone in the family “choked to death”?  
   - YES  
   - NO

6. Does the patient sometimes experience prodrome (such as fatigue, tingling, nausea, or flu-like symptoms) — minutes, hours, or days before an attack?  
   - YES  
   - NO

7. Have medications, such as antihistamines, epinephrine, or corticosteroids, provided little, if any, relief?  
   - YES  
   - NO

8. When these attacks have occurred, have the patient’s eyes been watery or itchy?  
   - YES  
   - NO

Confirm the diagnosis:

Low C4 during an attack adds further credence to the diagnosis of HAE. Not all laboratories are standardized to conduct assays of C1-INH proteins or C1-INH function, but a national HAE expert can help direct you.
Could It Be
Hereditary Angioedema (HAE)?

If your patients answer "yes" to the first 7 questions and "no" to the last question, they may have C1-INH deficiency — not a GI problem or an allergic angioedema.

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Has your patient had unexplained attacks of well-demarcated edema of the hands, feet, arms, legs, face, throat, genitals, or other part of the body?</td>
<td>☐</td>
</tr>
<tr>
<td>2.</td>
<td>☐</td>
</tr>
<tr>
<td>3. Has the patient had unexplained attacks of abdominal pain?</td>
<td>☐</td>
</tr>
<tr>
<td>4.</td>
<td>☐</td>
</tr>
<tr>
<td>5. Has anyone in the patient’s family had similar episodes of swelling or abdominal pain? Or has anyone in the family “choked to death”?</td>
<td>☐</td>
</tr>
<tr>
<td>6. Remember that 25% will have no family history</td>
<td>☐</td>
</tr>
<tr>
<td>7. Have medications, such as antihistamines, epinephrine, or corticosteroids, provided little, if any, relief?</td>
<td>☐</td>
</tr>
<tr>
<td>8.</td>
<td>☐</td>
</tr>
</tbody>
</table>

Confirm the diagnosis:
Low C4 during an attack adds further credence to the diagnosis of HAE. Not all laboratories are standardized to conduct assays of C1-INH proteins or C1-INH function, but a national HAE expert can help direct you.
Could it Be
Hereditary Angioedema (HAE)?

If your patients answer "yes" to the following questions, they may have C1-INH deficiency — not a GI problem or an allergic angioedema.

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Has the patient experienced unexplained attacks of well-demarcated edema (swelling) of the hands, feet, arms, legs, face, throat, genitals, tongue or other part of the body?</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Has the patient experienced unexplained attacks of abdominal pain?</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Can you confirm that the swelling is not itchy and is not associated with hives or urticaria.</td>
<td></td>
</tr>
</tbody>
</table>

Confirm the diagnosis: Low C4 during an attack makes it further likely the diagnosis is HAE Type I or II. Order a C4 test.

Your local contact is: Dr: __________________________
Tel: __________________________
AllaboutHAE.ca
Could It Be
Hereditary Angioedema (HAE)?

If your patients answer “yes” to the following questions, they may have C1-INH deficiency — not a GI problem or an allergic angioedema.

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Has the patient experienced unexplained attacks of well-demarcated edema (swelling) of the hands, feet, arms, legs, face, throat, genitals, tongue or other part of the body?</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Has the patient experienced unexplained attacks of abdominal pain?</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Can you confirm that the swelling is not itchy and is not associated with hives or urticaria.</td>
<td></td>
</tr>
</tbody>
</table>

Confirm the diagnosis: Low C4 during an attack makes it further likely the diagnosis is HAE Type I or II. Order a C4 test.
Summary

• HAE is a rare disorder with a large burden of disease
• Replacement treatment of CI inhibitor is available but requires intravenous administration
• Patients are under-recognized and under-treated
ACE inhibitor angioedema
## ACE inhibitor use in Canada

- Total volume of prescriptions dispensed from Canadian pharmacies for 1 year ending October 2010 (+ compared to year ending October 2009)

<table>
<thead>
<tr>
<th>#</th>
<th>Drug</th>
<th>Total Scripts</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Atorvastatin</td>
<td>15,768,000</td>
<td>+2.7%</td>
</tr>
<tr>
<td>2.</td>
<td>Levothyroxine</td>
<td>14,964,000</td>
<td>+5.1%</td>
</tr>
<tr>
<td>3.</td>
<td>Metformin</td>
<td>10,637,000</td>
<td>+8.4%</td>
</tr>
<tr>
<td>4.</td>
<td>Ramipril</td>
<td>9,349,000</td>
<td>-1.6%</td>
</tr>
<tr>
<td>47.</td>
<td>Perindopril</td>
<td>2,690,000</td>
<td>+17.3%</td>
</tr>
</tbody>
</table>

(IMS Brogan, Canadian Compuscript)
angiotensinogen → renin → angiotensin I → ACE → angiotensin II → AT1, AT2 receptors → bradykinin → B1, B2 receptors

ACE inhibitors

AT1 receptor antagonists

Prospective study of C1 esterase inhibitor in the treatment of 663 successive acute abdominal in 50 patients and 43 facial hereditary angioedema attacks in 16 patients.

The median time to onset of relief for all attacks was 19.8 minutes, with a median time to complete resolution of 11.0 h. The median time to onset of relief was 19.8 minutes for abdominal attacks and 28.2 minutes for facial attacks.

( vs icatibant ?48 min and ecallantide ?165 min)

## Distinguishing Hereditary Angioedema (HAE) From Other Forms of Angioedema

<table>
<thead>
<tr>
<th></th>
<th>Hereditary Angioedema (C1-INH Deficiency)</th>
<th>Angioedema Associated With Chronic Urticaria</th>
<th>Angioedema Associated With ACE Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History</strong></td>
<td>• Usually positive familial history, though de novo mutation is possible</td>
<td>• Usually no familial history</td>
<td>• No familial history</td>
</tr>
<tr>
<td></td>
<td>• Usually manifests in the first, second, or third decade of life</td>
<td>• History of urticaria</td>
<td>• First manifestation usually after the fourth decade of life</td>
</tr>
<tr>
<td></td>
<td>• No history of urticaria</td>
<td>• Typically no abdominal pain</td>
<td>• Usually occurs shortly after initiation of ACE inhibitor therapy</td>
</tr>
<tr>
<td></td>
<td>• Spasmodic abdominal attacks/colic</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Increased incidence of autoimmune diseases</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Summary

Allergic angioedema: itch present with hives, precipitant usually identifiable, responds to antihistamine and steroid

Chronic urticaria: swelling only involves skin and lips, usually no abdominal pain, responds to antihistamine

HAE: no itch, usually family history, abdominal pain, don’t respond to typical treatment

ACE inhibitor: no itch, can occur at any time on an ACE inhibitor, may also have cough
True or False?

1. ACE inhibitors cause angioedema due to a drug allergy **FALSE**
2. Epinephrine is best given subcutaneously if a patient is having anaphylaxis. **FALSE**
3. Itching is common in patients with swelling due to hereditary angioedema **FALSE**
Management of angioedema in the ER

Paul Keith MD MSc FRCPC
McMaster University
June 3, 2012
“Seeing Beyond A Scratchy Throat”
Practical Management of Angioedema in the ER Department.

Paul Keith MD MSc FRCPC
McMaster University

Toronto, 27 March 2012
Thank you
True or False?

Sam is 5 years old and weighs 22 kg. The correct epinephrine autoinjector for him is the Senior strength 0.3 cc.  **FALSE**

Epinephrine is best given subcutaneously if a patient is having anaphylaxis.  **FALSE**

After one removes the safety cap on an autoinjector you should not cover the hole with your thumb.  **TRUE**
Comprehensive care centres initiative
Centres Currently Treating HAE

Dr Hebert

Drs Rivard & Boursiquot
Dr Laramée

Dr Yang

SMH Group:
Drs Binkley, Sussman, Betschel & Vadas

Drs Keith & Waserman

Drs Moote & Mazza

Dr Kim
Hereditary angioedema
C1 Inhibitor Deficiency

C1 Inhibitor (g/l)

HAE patients

Healthy subjects

p<0.0001

Food– and exercise-induced anaphylaxis: importance of history in diagnosis

David N. Perkins, BSc, MD and Paul K. Keith, MD, MSc, FRCPC

Annals of Allergy, Asthma, & Immunology 2002;89:15-23
HAE & HRQoL

- 457 patients responded:
  - Mean age at diagnosis - 22 years
  - Mean number of attacks experienced per year: 26.9
  - Majority of attacks moderate, ¼ severe
  - Mean duration of attacks approx 60 hours

- HAE patients report significant decrements in all aspects of HRQoL

<table>
<thead>
<tr>
<th>Mean Score ± SD</th>
<th>HAE Population</th>
<th>Normative Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Functioning</td>
<td>50.0 ±11.4</td>
<td>50.0 ±10.0</td>
</tr>
<tr>
<td>Role Physical</td>
<td>45.1 ±9.8</td>
<td>45.0 ±9.8</td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>41.0 ±12.7</td>
<td>40.5 ±10.9</td>
</tr>
<tr>
<td>General Health</td>
<td>43.1 ±10.0</td>
<td>42.9 ±10.7</td>
</tr>
<tr>
<td>Vitality</td>
<td>50.0 ±10.0</td>
<td>50.0 ±10.0</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>50.0 ±9.8</td>
<td>42.5 ±9.8</td>
</tr>
<tr>
<td>Role Emotional</td>
<td>50.0 ±10.0</td>
<td>43.7 ±9.9</td>
</tr>
<tr>
<td>Mental Health</td>
<td>50.0 ±10.0</td>
<td>49.6 ±10.1</td>
</tr>
<tr>
<td>Physical Component Summary</td>
<td>49.4 ±10.2</td>
<td>42.6 ±9.8</td>
</tr>
<tr>
<td>Mental Component Summary</td>
<td>49.4 ±10.1</td>
<td>49.4 ±9.8</td>
</tr>
</tbody>
</table>

Lumry WR et al; Allergy Asthma Proc 2010; 31:407–414
HAE & Depression Scores

- Depression scores (HDI-SF survey) - HAE patients demonstrated higher scores than the population norms
  - Worsens with increased severity of attacks
  - Approx 19% of respondents taking psychotropic or antidepressant medication

![Graph showing depression scores](image)

Adapted Lumry WR et al; Allergy Asthma Proc 2010; 31:407–414
HAE & Productivity

- 50.6% of all patients (full/part-time workers) missed at least 1 day of work due to attack

- HAE patients report a mean of 33.6% overall work impairment

- Work and activity impairment suffered by HAE patients comparable patients with severe asthma and Crohn’s disease.

Adapted from Lumry WR et al; Allergy Asthma Proc 2010; 31:407–414
Missed Opportunities due to HAE

- HAE impacted career advancement: 57.5% (n=263)
- Unable to consider certain jobs due to HAE: 69.1% (n=316)
- HAE impacted career choices: 63.0% (n=288)
- Did not go as far in school as desired due to HAE: 40.5% (n=185)
- HAE hindered educational attainment: 48.4% (n=221)
- HAE impacted educational choices: 54.5% (n=249)

Lumry WR et al; Allergy Asthma Proc 2010; 31:407–414
<table>
<thead>
<tr>
<th></th>
<th>Allergic</th>
<th>Pseudoallergic</th>
<th>Nonallergic</th>
<th>Idiopathic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Causes</td>
<td>Food, Latex drugs, Venom</td>
<td>ASA NSAIDs</td>
<td>C1 INH Bradykinin</td>
<td>Unclear</td>
</tr>
<tr>
<td>Mediators</td>
<td>Histamine, LT, cytokines</td>
<td>LT, Histamine, Cytokines?</td>
<td>Bradykinin</td>
<td>Varies, unclear</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihistamine</td>
<td>++++</td>
<td>++</td>
<td>-/+</td>
<td>+++</td>
</tr>
<tr>
<td>H2 blocker</td>
<td>++</td>
<td>+/-</td>
<td>-/+</td>
<td>+</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>++++</td>
<td>++++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>LT antagonists</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>++++</td>
<td>+++</td>
<td>-/+</td>
<td>+++</td>
</tr>
<tr>
<td>Immunomodulators</td>
<td>++</td>
<td>+</td>
<td>+/-</td>
<td>+++</td>
</tr>
<tr>
<td>DAB</td>
<td>NK</td>
<td>NK</td>
<td>NK</td>
<td>+/−</td>
</tr>
</tbody>
</table>

Table 1. Comparison of different types of angioedema: causes, mediators, and treatment.

LT: leukotrienes, DAB: Drugs Affecting Bradykinin (metabolism), e.g. C1 INH supplement (Cinryze, Berinert-P, Rheucin), Kallikrein inhibitor (Ecallantide, Kalbitor), and Bradykinin receptor antagonist (icatibant, Firzyre)
Fig 1. Pathways for production of prostaglandins and leukotriene from mobilized arachidonic acid. 5 HPETE, 5 Hydroperoxyeicosatetraenoic acid; FLAP, five lipoxygenase activating factor; LT, leukotrienes; PG, prostaglandin
Fig 2. Bradykinin production and metabolism. ACE: angiotensin-converting enzyme, CPN: Carboxypeptidase-N, APP: aminopeptidase P, DPP₄: Dipeptidyl peptidase IV; NEP: Neutral endopeptidase
FIG 2. Regional differences in EpiPen prescriptions per 1000 persons.
Role of vitamin D? : Vitamin D level and season

Figure 1

Hollams EM et al. ERJ Express. May 12, 2011
Vitamin D supplementation in children 5 to 18 yo may prevent asthma exacerbations.

## Wallet Cards - Print

### Emergency Management of Hereditary Angioedema (HAE)

#### Patient Identification
- **Name:**
- **Date of Birth:**
- **Health System #:**

#### Diagnosis
HAE is a rare potentially life-threatening disease usually caused by C1-esterase inhibitor deficiency associated with tissue swelling (see description on back page of this wallet card).

#### Prompt Treatment
**Prompt Triage & Assessment:**
To determine the severity of the swelling.

**Prompt Treatment:**
- Will rapidly initiate onset of relief of the angioedema in this patient and decrease swelling.
- **Airway Obstruction:**
The risk of dying from airway obstruction if left untreated is significant. Consider early intubation in progressive angioedema.

#### Recommended Treatment
- **CT-1081 (IV):** 20 mg/kg, 4ml/min, preferably given by infusion pump (if available) or 0.55 mg/kg of C1-esterase (available in oral form, 4 tablets of 0.14 mg each).
- **Other:**

#### Gestion à l’urgence de : ANGICÉDEMÉ HERÉITAIRE (AH)

#### Identification du patient
- **Nom:**
- **Date de naissance:**
- **# Ass. médicale:**

#### Traitement immédiat d’angioédmé
- **Triage et évaluation rapides:**
  - Pour éviter la perte de connaissance.

#### Traitement rapide
- **Premiers soins**
  - Prendre en charge rapidement les symptômes, dû à ce patient, et faire une réduction de la médication.

#### Voies respiratoires
- Le risque de décès en raison d’une obstruction des voies respiratoires est réel, si le traitement n’est pas apporté. Consulter une information notée dans le cadre d’un ordre légal éventuel.

### Clinical Characteristics of HAE
- Recurrent non-pruritic edema of skin and subcutaneous tissue associated with pain, nausea, vomiting, diarrhea, and life-threatening airway swelling.
  - Lingual/tongue swelling: May result in aspiration.
  - Facial / neck swelling.
  - Abdominal attacks (abdominal pain, cramping, diarrhea, nausea / vomiting).
  - Peripheral edema (other regions)

### Healthcare Team
- **In case of Emergency, Contact My Physician:**
  - **MD/specialty:**
  - **Hospital:**
  - **Other Clinic / Physicians:**
  - **MD / specialty:**
  - **Hospital:**

### Emergency Contacts
- **Please Contact:**
  - **Name:**
  - **Relationship:**

### Emergency Contacts
- **Other Recommendations / comments:**

### References
- [1. Emergency Card Website for Emergency Treatment](http://www.haerh.com/En/RecommendationChart/HAERevised2.pdf)
- [2. HAE/EAH Recommendations](http://www.haerh.com/En/RecommendationChart/HAERevised2.pdf)

###呈現在clinique de l’AH

- **En cas d’urgence, mon médecin traitant est:**
  - **MD/specialty:**
  - **Hospital:**

### Contact - Équipe de Soins
- **Autre médecin/chirurgien:**
  - **MD / spécialité:**
  - **Hospital / clinique:**

### Contact en cas d’urgence
- **Veuillez contacter:**
  - **Nom:**
  - **Relation:**
  - **Autres recommandations / commentaires:**

### Traite de la recommandation
- **Date de la recommandation:**
  - **Jour / Mois / Année**
Emergency Management of Hereditary Angioedema (HAE)

PATIENT IDENTIFICATION

Name: ___________________________
Date of Birth: ______________________
Health System #: ___________________________

PROMPT TREATMENT REQUIRED to PREVENT RAPID DETERIORATION

Supported by the Canadian Hereditary Angioedema Network (CHAEN) / Réseau Canadien d’Angioédème Heréditaire (RCAH) (www.haecanada.com)

DIAGNOSIS

HAE is a rare potentially life threatening disease usually caused by C1-esterase inhibitor deficiency associated with tissue swelling (see description on back page of this wallet card).

PROMPT TRIAGE & ASSESSMENT:

To determine the severity of the swelling.

PROMPT TREATMENT:

Will rapidly initiate onset of relief of the angioedema in this patient and decrease morbidity.

AIRWAY OBSTRUCTION:

The risk of dying from airway obstruction if left untreated is significant¹. Consider early intubation in progressive laryngeal edema².

RECOMMENDED TREATMENT

C1-INH (IV): 20 U/Kg, 4mL/min
# of Vials: ____ of C1-INH 500 units (available at Blood Bank)
Other:

If above not available, consider: solvent detergent treated plasma (SDP) or less safe fresh frozen plasma³ (2 Units).

Angioedema attacks usually do not respond to treatment with glucocorticoids, antihistamines nor epinephrine⁴.

This patient may require prophylaxis before surgery or dental procedures in order to prevent an angioedema attack¹.
Wallet Cards - Print

CLINICAL CHARACTERISTICS OF HAE

Recurrent non-pruritic edema of skin and submucosal tissue associated with pain, nausea, vomiting, diarrhea, and life-threatening airway swellings².

- Laryngeal / airway swelling: May result in asphyxiation
- Facial / neck swelling
- Abdominal attacks (abdominal pain, cramping, diarrhea, nausea / vomiting)
- Peripheral edema (other regions)

HEALTHCARE TEAM

In case of Emergency, Contact my Physician:

MD/specialty: ________________________
Hospital: ____________________________
☎ ________________________________

Other Clinic / Physicians

MD / specialty: ________________________
Hospital: ____________________________
☎ ________________________________

EMERGENCY CONTACTS

Please Contact:

Name: _____________________________
Relationship: _______________________
☎ ________________________________

Other Recommendations / comments:

______________________________
______________________________
______________________________
______________________________

Physician signature

Date of Recommendation: / / Day / Month / Year

Supported by:
HAE Canada Inc (the Hereditary Angioedema Patient organization) (www.haecanada.org)

References:
1. CHABN/RCAH WEBSITE FOR EMERGENCY TREATMENT
www.haecanada.com/files/TreatmentChart110602.pdf
2. CHABN/RCAH WEBSITE FOR PROPHYLAXIS
www.haecanada.com/files/ProphylaxisChart110602.pdf
Could It Be
Hereditary Angioedema (HAE)?

If your patients answer “yes” to the first 7 questions and “no” to the last question, they may have C1-INH deficiency — not a GI problem or an allergic angioedema.

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Has your patient had unexplained attacks of well-demarcated edema of the hands, feet, arms, legs, face, throat, genitals, or other part of the body?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>2</td>
<td>Have these swelling attacks sometimes occurred on just one side of the body, for example, just the left hand or just the right foot?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>3</td>
<td>Has the patient had unexplained attacks of abdominal pain?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>4</td>
<td>Have these attacks of swelling or abdominal pain occurred more than once?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>5</td>
<td>Has anyone in the patient’s family had similar episodes of swelling or abdominal pain? Or has anyone in the family “choked to death”?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>6</td>
<td>Does the patient sometimes experience prodrome (such as fatigue, tingling, nausea, or flu-like symptoms) — minutes, hours, or days before an attack?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>7</td>
<td>Have medications, such as antihistamines, epinephrine, or corticosteroids, provided little, if any, relief?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>8</td>
<td>When these attacks have occurred, have the patient’s eyes been watery or itchy?</td>
<td>YES</td>
<td>NO</td>
</tr>
</tbody>
</table>

Confirm the diagnosis:
Low C4 during an attack adds further credence to the diagnosis of HAE. Not all laboratories are standardized to conduct assays of C1-INH proteins or C1-INH function, but a national HAE expert can help direct you.
Could It Be

Hereditary Angioedema (HAE)?

If your patients answer "yes" to the first 7 questions and "no" to the last question, they may have C1-INH deficiency — not a GI problem or an allergic angioedema.

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Has your patient had unexplained attacks of well-demarcated edema of the hands, feet, arms, legs, face, throat, genitals, or other part of the body?</td>
<td>![ ]</td>
</tr>
<tr>
<td>2</td>
<td>![ ]</td>
<td>![ ]</td>
</tr>
<tr>
<td>3</td>
<td>Has the patient had unexplained attacks of abdominal pain?</td>
<td>![ ]</td>
</tr>
<tr>
<td>4</td>
<td>![ ]</td>
<td>![ ]</td>
</tr>
<tr>
<td>5</td>
<td>Has anyone in the patient’s family had similar episodes of swelling or abdominal pain? Or has anyone in the family “choked to death”?</td>
<td>![ ]</td>
</tr>
<tr>
<td>6</td>
<td>Remember that 25% will have no family history</td>
<td>![ ]</td>
</tr>
<tr>
<td>7</td>
<td>Have medications, such as antihistamines, epinephrine, or corticosteroids, provided little, if any, relief?</td>
<td>![ ]</td>
</tr>
<tr>
<td>8</td>
<td>![ ]</td>
<td>![ ]</td>
</tr>
</tbody>
</table>

Confirm the diagnosis:

Low C4 during an attack adds further credence to the diagnosis of HAE. Not all laboratories are standardized to conduct assays of C1-INH proteins or C1-INH function, but a national HAE expert can help direct you.
If your patients answer “yes” to the first 7 questions and “no” to the last question, they may have C1-INH deficiency — not a GI problem or an allergic angioedema.

<table>
<thead>
<tr>
<th>Question</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has your patient had unexplained attacks of well-demarcated edema of the hands, feet, arms, legs, face, throat, genitals, or other part of the body?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have these swelling attacks sometimes occurred on just one side of the body, for example, just the left hand or just the right foot?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has the patient had unexplained attacks of abdominal pain?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have these attacks of swelling or abdominal pain occurred more than once?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has anyone in the patient’s family had similar episodes of swelling or abdominal pain? Or has anyone in the family “choked to death”?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the patient sometimes experience prodrome (such as fatigue, tingling, nausea, or flu-like symptoms) — minutes, hours, or days before an attack?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have medications, such as antihistamines, epinephrine, or corticosteroids, provided little, if any, relief?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>When these attacks have occurred, have the patient’s eyes been watery or itchy?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
AllaboutHAE.ca
If your patients answer "yes" to the first 7 questions and "no" to the last question, they may have C1-INH deficiency — not a GI problem or an allergic angioedema.

<table>
<thead>
<tr>
<th>Question</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Has your patient had unexplained attacks of well-demarcated edema of the hands, feet, arms, legs, face, throat, genitals, or other part of the body?</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>2 Have these swelling attacks sometimes occurred on just one side of the body, for example, just the left hand or just the right foot?</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>3 Has the patient had unexplained attacks of abdominal pain?</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>4 Have these attacks of swelling or abdominal pain occurred more than once?</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>5 Has anyone in the patient's family had similar episodes of swelling or abdominal pain? Or has anyone in the family &quot;choked to death&quot;?</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>6 Does the patient sometimes experience prodrome (such as fatigue, tingling, nausea, or flu-like symptoms) — minutes, hours, or days before an attack?</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>7 Have medications, such as antihistamines, epinephrine, or corticosteroids, provided little, if any, relief?</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>8 When these attacks have occurred, have the patient's eyes been watery or itchy?</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>