



# HAE

Creating **Awareness, Recognition** and Improving  
**Therapeutic Management** for Patients

## Faculty



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# Accreditation Information

## Target Audience

This educational activity is designed for primary care physicians and other healthcare practitioners that diagnose and provide care to patients with angioedema.

## Learning Objectives

Upon completion of this Continuing Education activity, the participant will be able to:

- Describe the pathophysiology of angioedema
- Describe the signs and symptoms of hereditary angioedema and other forms of angioedema that may be seen by the primary care practitioner
- Outline the differential diagnosis of angioedemas
- Discuss current and emerging treatment options for recurring angioedema, with special emphasis on hereditary angioedema

## Content Delivery and Learning Methodology

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## Pathophysiology Angioedema

With nearly 25% of the population experiencing urticaria and / or angioedema at some time during their life, primary care practitioners will frequently encounter patients with this complaint. Patients present with both angioedema and urticaria approximately 40% of the time, while angioedema alone is seen in approximately 20% of the cases. Urticaria alone is observed in the remaining 40%.<sup>1,2</sup> Other physical findings and clinical presentation are detailed in **Table 1**.

**Table 1.** Findings and presentation of angioedema<sup>2</sup>

	<b>ANGIOEDEMA</b>
<b>Tissue involved</b>	Subcutaneous tissue and deep dermis
<b>Site</b>	Extremities, face, abdomen, genitals
<b>Appearance</b>	Well-defined edematous swelling; non-pitting
<b>Pruritic</b>	No – may burn, tingle or feel taut
<b>Erythematous</b>	Possible; usually flesh colored
<b>Duration</b>	Resolves slowly

Classification of angioedema is typically defined by the pathophysiology: histamine-mediated or bradykinin-mediated. Complications range from discomfort to respiratory distress, possible airway obstruction and death. Appreciating the difference in clinical presentation between the types of angioedema as well as the pathophysiology for each is important in guiding the primary care physician's therapeutic decisions.

Histamine-mediated angioedema results when mast cells release histamine and other vasoactive mediators. Allergy, IgE-mediated mast cell degranulation, is typically the most common cause of angioedema, and the patient often presents with urticaria. Diagnosis of allergic angioedema may be made easier if an identifiable trigger can be temporally linked to the event. Common triggers are listed in **Table 2**.

**Table 2.** Common triggers of histamine-mediated angioedema<sup>3</sup>

<b>Medications</b>	<b>Foods</b>	<b>Other</b>
Sulfonamide antibiotics	Nuts	Venom
Beta-lactam antibiotics	Eggs	Latex
Narcotics	Shellfish	
Oral contraceptives	Soy	
Antihypertensives	Wheat	
Aspirin	Milk	
Radiocontrast dyes		



There are two variants of HAE defined by C1 INH function:

- Type I is a *quantitative defect* in the plasma inhibitor of the first component of the complement cascade, C1 INH. Approximately 85% of HAE patients suffer from this form.
- Type II is a *functional defect* in C1 INH, which affects the other 15% of patients diagnosed with HAE.

The deficiency in C1 INH leads to an increase in the activation of C1, with consumption of C2 and C4. It also causes excessive formation of the enzyme kallikrein that transforms various kininogens into kinins including the vasoactive nonapeptide bradykinin, which is a major cause of the angioedema (**Figure 1**).<sup>12</sup>

Clinical attacks are most often seen in three anatomical sites:

- cutaneous
- laryngeal
- abdominal

#### *Cutaneous angioedema*

Cutaneous attacks are common and temporarily disfiguring although not generally dangerous. While angioedema without urticaria is the hallmark of HAE, approximately one third of patients do develop a non-pruritic erythematous rash, erythematous mottling, or erythema marginatum at the start of an attack, sometimes accompanied by pain.<sup>9</sup> The extremities, face (typically lips, eyelids and tongue), and genitals are the most common sites affected. In all cases, swelling is highly variable and often not symmetrical.

#### *Laryngeal edema*

The most serious symptoms of HAE occur when edema obstructs the airway and larynx, which may lead to a compromised airway and death from suffocation.<sup>13</sup> Laryngeal attacks account for less than 1% of all angioedema episodes, with an increased risk in patients between the ages of 11 and 45 years of age, and although each laryngeal attack has the potential to become life-threatening, the majority resolve before complete airway obstruction occurs.<sup>14,15</sup> The majority of laryngeal events occur without warning with swelling developing over a period of hours, with a reported mean of seven hours.<sup>14,15</sup> The photos in **Figure 2** show a patient suffering from an attack; the series demonstrates that such attacks are progressive, incapacitating, and life-threatening. As such, the greatest mortal threat to patients with HAE is the spontaneous and unpredictable nature of laryngeal attacks.<sup>14</sup>



**Figure 2.** Sequential Photos of a Laryngeal Attack  
From AMCP Dossier, p 21.

### *Abdominal Pain*

Angioedema of the gastrointestinal tract can lead to a variety of symptoms including pain (frequently excruciating), nausea, anorexia, vomiting, and diarrhea resulting from edema of the bowel wall.<sup>9,13</sup> Gastrointestinal attacks are experienced by a majority of patients with HAE, and can be the principal presentation in 25% of patients.<sup>16</sup> Abdominal pain, caused by swelling of the intestinal wall, is reported by 70-80% of patients with HAE, and may be spasmodic.<sup>9,11</sup> The abdomen is typically sensitive to palpation, usually without guarding, while ascites may occur as a result of fluid extravasation from the vasculature into the peritoneal cavity.<sup>13</sup> Gastrointestinal attacks of HAE typically subside within five days.<sup>9</sup>

The diagnosis of abdominal HAE can be difficult because many patients with HAE present with isolated abdominal pain that may be severe enough to mimic an acute surgical abdomen. In fact, before a diagnosis of HAE has been made, patients frequently undergo unnecessary appendectomy or exploratory laparotomy.<sup>16</sup> HAE episodes involving the gastrointestinal tract may remain undiagnosed for decades despite repeat visits to the emergency department (ED). At times, patients have been inappropriately referred for psychiatric assessment because the symptoms were considered psychosomatic.<sup>13</sup>

A third variant of HAE has been reported and given various names. Referred to as Type III, inherited angioedema with normal C1 INH, or estrogen-dependent HAE, patients closely resemble those with C1 INH deficiency. In initial reported cases, angioedema occurred exclusively in women during pregnancy or receiving exogenous estrogen therapy and presented with normal C1 INH levels (antigenic and functional) with normal C4 levels.<sup>11,13</sup> Subsequently, mutations in Factor XII have been described associated with the gene encoding of Factor XII that results in increased bradykinin production by kallikrein.<sup>17</sup> Since no commercial test is available for Factor XII mutations, distinguishing between inherited angioedema with normal C1 INH and idiopathic angioedema is difficult. The specific pathology of Type III HAE has yet to be elucidated.

**ACE inhibitor (ACEI)-induced angioedema** may be the result of an adverse drug reaction that is not IgE mediated. The incidence of ACEI-induced angioedema is 0.1% to 1% of patients taking ACE inhibitors and is most commonly seen with captopril and enalapril.<sup>18,19</sup> Since ACE degrades bradykinin into inactive metabolites, ACE inhibition causes increased levels of bradykinin and its active metabolite causing angioedema in susceptible patients.<sup>20</sup> ACEI-induced angioedema normally occurs within the first six weeks of initiating treatment, but may appear after years of ACEI use, thus obscuring its relationship with the drug. Use of ACEIs should be avoided in patients with HAE or acquired angioedema.<sup>11</sup>

**Acquired C1 inhibitor deficiency** may be associated with lymphoproliferative disorders, autoimmunity with antibodies directed against C1 INH, or occasionally with other neoplastic, infectious, or autoimmune diseases.<sup>11</sup> About 14% of patients with acquired angioedema have no other underlying disease.<sup>13</sup> Unlike those with HAE, acquired angioedema patients often present after the 4th decade of life, and do not have a family history of swelling.<sup>11</sup> Patients have almost undetectable serum levels and/or activity of C1 INH, C4, and C1q.<sup>11</sup> Low C1q is unique to acquired C1 INH deficiency.

**Idiopathic angioedema** is a diagnosis of exclusion meaning the angioedema is not attributable to HAE, acquired angioedema, allergic disorders or any known drug-induced or physical cause. The clinical presentation is similar to HAE, and while typically accompanied by pruritis, laryngeal edema is rare.<sup>13</sup> Patients with idiopathic angioedema have normal complement values but may still be unresponsive to antihistamines.<sup>11</sup>

**Table 3** summarizes the etiology of nonallergic angioedema. Note that all of the angioedemas described are bradykinin driven, with the exception of NSAID/ASA-induced angioedema.

**Table 3.** Etiology of nonallergic angioedema

ANGIOEDEMA				
Bradykinin Mediated			Histamine/Leukotriene Mediated	
HAE	ACEI	Acquired	Idiopathic	NSAID
Inherited C1 INH deficiency or inactivity	Nonallergic ADR; ↑ bradykinin	Lymphoproliferative disorders	Unknown	COX 1 inhibition ⇨ ↑ leukotrienes

## Therapeutic Options

### Treatment of HAE Angioedema

Angioedema without urticaria is the hallmark of HAE. Recurring angioedema in the absence of urticaria, unexplained abdominal pain, and/or the presence of erythema marginatum prior to swelling and a poor response to antihistamines, corticosteroids or epinephrine may each suggest HAE. If signs and symptoms are suggestive of HAE, serum C1 INH and C4 should be checked even in the absence of a positive family history. Approximately 25% of patients diagnosed with HAE have no family history, suggesting a new genetic mutation.<sup>4,20</sup>

Abdominal attacks can be extremely painful, causing substantial incapacity. A prospective evaluation of 153 patients suffering from abdominal attacks demonstrated a mean pain score of 8.4 on a 10-point scale with four women reporting that their pain was worse than giving birth.<sup>21</sup> Misdiagnosis of abdominal angioedema caused by HAE may result in unnecessary surgeries and procedures. Therefore, "...hereditary angioedema must be included in the differential diagnosis of intermittent, unexplained abdominal pain."<sup>22</sup>

#### *C1 inhibitor (C1 INH) concentrate*

Several studies have shown that human C1 INH concentrate is safe and effective for treatment of acute swelling in HAE patients. Initial double-blind, placebo-controlled studies showed C1 INH replacement was effective in treating acute abdominal or laryngeal attacks and increased serum C1 INH levels.<sup>23,24</sup> Of 640 HAE attacks in 57 patients, the median time to symptom relief was:

- 16 minutes for laryngeal attacks
- 28 minutes for facial attacks
- 31 minutes for peripheral attacks (hands and feet)<sup>25</sup>

A study evaluating the treatment of laryngeal edema in patients with HAE demonstrated that C1 INH concentrate was effective in 192 of 193 swelling attacks with symptoms starting to resolve within 30-60 minutes of injection. The first symptoms resolved in all patients were difficulty breathing and fear of asphyxiation.<sup>26</sup>

Limitations of human C1 INH include its dependency on human blood supply, potential for transmission of infectious agents, and the need for intravenous administration. Three companies are currently producing C1 INH for HAE. Two products, Cinryze™ and Berinert®, use human plasma collected in the US.<sup>27</sup> Cinryze™ (ViroPharma) is a nano-filtered human C1 INH and is the first FDA-approved C1 INH for use as prophylactic therapy for HAE in the United States. Berinert® (CSL Behring) is a pasteurized human C1 INH. In October of 2009, the FDA approved Berinert® to treat acute abdominal and facial swelling attacks associated with HAE in adults and adolescents.<sup>28</sup> The third is Rhucin® (Pharming), a novel recombinant human C1 INH secreted from transgenic rabbits following the introduction of a cloned human gene for C1 INH.<sup>27</sup> As a result, it is not dependent on the human plasma supply and has less theoretic risk of infection compared with human C1 INH concentrate. Rhucin® has a plasma half-life of three hours and is being studied for treatment of acute swelling attacks in HAE.<sup>8</sup>

## Other Potential Agents for Acute HAE Management

The most current evidence suggests bradykinin is the primary mediator of swelling in HAE. Two novel therapies based on that premise are under development, and are presented in **Table 4**.<sup>8,27,29</sup>

**Table 4.** Investigational products for the treatment of HAE

Generic Name	Company	Mechanism of Action	Administration
Ecallantide (DX-88)	Dyax Corp.	Binds and inhibits human kallikrein thus decreasing bradykinin generation	<ul style="list-style-type: none"><li>• subcutaneous</li><li>• use during acute HAE attacks</li></ul>
Icatibant	Jerini AG/Shire Deutschland	A synthetic bradykinin receptor-2 antagonist	<ul style="list-style-type: none"><li>• subcutaneous</li><li>• use during acute HAE attacks</li></ul>

## Chronic, Long-Term Prophylaxis

In the United States, no definitive guidelines have been published to recommend specific long-term prophylaxis in this potentially life threatening illness. Therapeutic options in HAE include attenuated androgens, antifibrinolytic agents, and C1 INH concentrate. All of these have potential adverse effects and the risks and benefits should be discussed prior to long-term prophylaxis.

### *Attenuated androgens (17- $\alpha$ alkylated androgens)*

Over the past 30 years, attenuated androgens (17- $\alpha$  alkylated androgens) have been widely used for long-term prophylaxis in HAE.<sup>11</sup> Studies done almost three decades ago demonstrated daily therapy with attenuated androgens decreased the number of swelling episodes in HAE patients.<sup>9</sup> Attenuated androgens most frequently used for HAE include danazol, stanozolol, and oxandrolone though the majority of studies have been done with danazol.<sup>9</sup> While treatment with danazol results in a marked increase in C1 INH and normalization of C4 levels, the clinical response is not seen for at least 48 hours making it a poor choice for acute management.<sup>9</sup> Most assume danazol increases hepatic C1 INH production.<sup>9</sup>

The dose of danazol needed for clinical response is variable with approximately 95% of patients responding to 600 mg a day, and over 50% of patients responding to 300 mg a day or less.<sup>10</sup> Patients will usually begin therapy with danazol at 400 to 600 mg QD for a month and taper down to the lowest effective dose.<sup>11</sup> The side effects of attenuated androgens limit its use in some patients, particularly children. Long-term side effects of impeded androgens including masculinization, weight gain, deepening of the voice, fatigue, menstrual irregularities, hemorrhagic cystitis, arterial hypertension, headache, alteration in libido, hair growth or loss, liver function abnormalities, increased risk of thrombosis, hepatic malignancy (hepatic adenoma and carcinoma), and unfavorable abnormalities in serum lipids.<sup>9,11</sup> Long-term use of danazol also has been associated with an increased risk of early atherosclerosis.<sup>30</sup> Periodic monitoring of serum HDL and LDL may assist in identifying atherosclerosis risk associated with androgens. Contraindications for attenuated androgens include pregnancy, lactation, childhood, and prostate cancer.

### *Antifibrinolytic agents*

Epsilon aminocaproic acid (EACA) is the only antifibrinolytic agent currently available in the United States and is primarily used to treat hyperfibrinolytic bleeding during cardiovascular and genitourinary surgery, dental bleeding in hemophilia A, traumatic hyphema, hereditary hemorrhagic telangiectasia and missed abortion. A double-blind, placebo-controlled study demonstrated the effectiveness of EACA in reducing the frequency of attacks, however EACA was less efficacious than androgens. Unlike attenuated androgens, antifibrinolytic agents have no impact on C4 or C1 inhibitor levels.<sup>31</sup> EACA has been shown to reduce attack frequency at a daily dose of 8-12 g in four divided doses.<sup>11</sup> A number of side effects have been associated with EACA including thrombosis, severe muscle toxicity, and muscular pain and weakness associated with myositis.<sup>9,11</sup> Contraindications include previous thrombosis, or a procoagulant state.<sup>9</sup> Despite these adverse effects, EACA may be preferred over androgens for use in children.<sup>11</sup>

### C1 INH concentrate

C1 INH has been used for both acute attacks and long-term prophylaxis of HAE. It represents the most physiologic treatment.<sup>32</sup> There have been reports of patients being treated with 500 to 1000 U once or twice weekly for over a year with marked reduction in acute attacks.<sup>33,34</sup> A recent study using 1000 U of nanofiltered human C1 inhibitor biweekly showed a statistically significant decrease in the frequency of attacks compared with placebo.<sup>35</sup> Limitations of C1 INH products include dependency on the human blood supply and the need for intravenous access, although the efficacy of subcutaneous administration is presently being investigated. The risk of blood-borne pathogen exposure is also a concern with long-term use of human C1 INH concentrate. In October 2008, Cinryze™ was FDA approved for use in angioedema prophylaxis in HAE patients.

### Short-Term Prophylaxis

Therapeutic intervention can be used prior to events that may precipitate attacks, such as dental procedures, endoscopy, endotracheal intubation, or other types of surgery.<sup>11</sup> Most agree fresh frozen plasma (FFP) is useful for short-term prophylaxis prior to procedures.<sup>36</sup> FFP given in two unit doses intravenously the night before or the day of surgery has been successful in preventing angioedematous attacks in patients with HAE. EACA is effective in reducing the frequency of attacks when administered several days prior to triggering events. The daily dose is usually 8-12 g in four equally divided doses.<sup>11</sup> Attenuated androgens are used from five days before to three days after the event; danazol has been administered at a dose of 10 mg/kg/day with a maximum of 600 mg a day.<sup>11</sup>

C1 INH is safe and effective for prophylaxis of acute attacks in adults, children, and pregnant women, but is not approved by the FDA for this use. The dose for short term prophylaxis is 500-1000 U given the night before or on the day of surgery.<sup>11,37</sup> **Table 5** summarizes.

**Table 5.** Short-term prophylaxis options for HAE patients

Medication	Suggested Dose	Frequency
C1 INH	500-1000 U	Administer the night before or on the day of surgery
Danazol	10 mg/kg/day with a maximum of 600 mg a day	5 days before to 3 days after the event
EACA	8-12 g in 4 equally divided doses	Administer several days prior to event
FFP	2 units intravenously	Administer the night before or the day of surgery

Due to the complexities and variables involved in HAE, consultation with an allergist/immunologist is wise prior to prescribing any medications for short-term prophylaxis in an HAE patient.

### Treatment of ACE Inhibitor-Induced Angioedema

When ACEI-induced angioedema is expected, the medication should be stopped immediately. If ACEI therapy is continued despite episodes of angioedema, episodes may become progressively more severe.<sup>38</sup> While there are currently no controlled studies to provide guidelines for therapy, acute treatment may include antihistamines, subcutaneous epinephrine, and intravenous steroids.<sup>39</sup>

Angiotensin receptor blockers (ARBs) do not cause elevated bradykinin levels and is generally thought to be as safe therapeutic option for patients who have had previous swelling with an ACEI.

### **Non-Steroidal Anti-Inflammatory Drug (NSAID) Induced Angioedema**

Patients who suffer from angioedema due to NSAIDs or aspirin will manifest swelling primarily in the peri-orbital areas and lips.<sup>6</sup> Most recently, since leukotrienes are believed to play a role in this pathway, treatment using leukotriene antagonists has been suggested.<sup>40</sup> For treatment, discontinue use of offending medications. It is important to be aware that there are many COX 1 inhibitors available without a prescription, including those used in combination products such as cold medicines. Further, some over-the-counter products for stomach upset and diarrhea include derivatives of aspirin such as bismuth subsalicylate and should be avoided.

### **Idiopathic Angioedema**

Emergency management would include supportive care, diphenhydramine, corticosteroids, and H2 blockers. High-dose, non-sedating antihistamines administered twice a day can be used for prophylaxis. Patients with idiopathic angioedema who are not responding to standard-dose antihistamine therapy may require a referral to an allergist/immunologist to fine-tune high-dose therapy.

## **Clinical Pearls: Diagnosis and Management in the Primary Care Setting**

The following case presentations will describe patients who present to their primary care practitioner and the diagnostic process that is undergone to reach an accurate diagnosis of the etiology behind each swelling episode.

### **Case 1**

An 18-month-old WF child presents to your office with diffuse urticaria and pruritis minutes after being stung by an unidentified insect while playing in a field at a family picnic. She has also developed lip edema on the way to your office. No other systemic symptoms are noted. Parents note that they saw several fire ants in vicinity of play area. There was also a yellow-jacket wasp noted in the picnic area around the soda drinks.

**Medications:** multivitamin

**Past Medical History:** NC

**Social History:** 1 dog at home

**Family History:**

- Dad ⇒ HTN
- 6-year-old brother ⇒ eczema, dairy allergy

**Physical Exam:** Examination reveals a crying toddler in moderate distress.

- HEENT: mild lip angioedema
- Skin: diffuse urticaria
- Lungs: clear
- CVS: RRR

**Work up:** Serum RAST testing to yellow-jacket wasps, honey bee, white-faced hornet, paper wasp and fire ant are all <0.35kU/L.

### **Case 1 Assessment: Allergic angioedema**

History is paramount and must be elicited with insight and attention to detail. Based on time course of reaction and facts of history she is diagnosed with allergic angioedema.

Diagnostic testing is indicated in patients with a systemic reaction to stings, but not required if risk of future anaphylaxis is <10%. Skin testing is the preferred diagnostic method:

- Positive in 65-85% of patients who have a convincing history
- High sensitivity and proven safety

- Intradermal performed 0.001-1.0 mcg/ml
- Percutaneous performed < 1 mcg/ml
  - Initially for patients with very severe reactions

### Case 1: Management

Prevention is the most important component of management in these patients who should strive to avoid related exposures. In that regard, it should be noted that insect repellants provide no protection. Other practical suggestions may include:

- Avoid outdoor foods and drinks
- Keep living areas clean and free of food refuse or garbage
- Do not use lotions, perfumes, etc
- Do not wear wool, leather or suede
- Do not go out barefoot
- Wear clean, white, smooth-finished clothes

**Clinical Pearl:** Allergic angioedema is an antibody IgE-mediated process that has an immediate phase that is dependant on histamine release from mast cells.

Further, it is recommended that patients carry an epinephrine injector at all times.

Hymenoptera immunotherapy (IT) may be an option, and can follow any of the several recommended schedules:

- Maintenance injections are recommended every four weeks for one year, then every six weeks. Injection intervals have been increased to 2-3 months in some clinics
- Therapy is 98% effective in completely preventing systemic allergic reactions to stings when treatment includes mixed vespid venoms (300 mcg total dose)

Which of the following is true regarding allergic angioedema?

- A. It is mediated by bradykinin
- B. It is an autosomal-dominant condition
- C. It is usually responsive to anti-histamines and corticosteroids
- D. It is usually an autoimmune disease process

Which of the following is NOT a common trigger of allergic angioedema?

- A. Sulfonamide antibiotics
- B. Eggs
- C. Nuts
- D. Venom

### Case 2

A 49-year-old male with past medical history of hypercholesterolemia and hypertension was admitted to the hospital with chest pain and found to have an MI. During his hospitalization, angioedema of his lips was noted. The patient's right upper lip angioedema quickly progressed to right facial angioedema. He denied any respiratory distress, any wheezing, any urticaria, or any nausea, vomiting, or diarrhea. He denied any other swelling. The medications initiated upon admission included clopidogrel and metoprolol. His dose of ramipril was increased from 2.5 to 5 mg daily. The patient also reports about four episodes of minor lip angioedema during the past year. He reports no association with any food or changes in medications. The lip swelling resolved within 48 hours without medication. He has no other swelling in any other part of the body. He had no family history of recurrent angioedema.

**Medications:** prior to admission included aspirin 325 mg once daily; ramipril 2.5 mg once daily; and atorvastatin 40 mg once daily. He has no known drug allergies.

**Medical History:** as above

**Surgical History:** significant for an ACL repair in 2004

**Family History:** no significant history of atopy or any family history of recurrent swelling

**Physical Exam:** he is a well-developed, well-nourished man in no apparent distress. His blood pressure is 108/80, his heart rate is 60, and his respiratory rate is 18, and the rest of exam is normal.

**Case 2 Assessment: ACEI-induced angioedema**

Though ACE inhibitor angioedema happens most frequently during the first six weeks of therapy, this type of swelling can be seen many years after therapy has been initiated.

Which of the medications is most important to discontinue in order to decrease his risk for recurrent angioedema?

- A. Clopidogrel
- B. Atorvastatin
- C. Metoprolol
- D. Ramipril

**Case 2: Management**

The entire class of ACE inhibitors should be avoided in the future care of this patient. Recurrent intermittent swelling, though usually more mild, may appear for up to six to eight weeks after the offending ACEI has been discontinued.

**Clinical Pearl:** ACE inhibitor-induced angioedema is caused by a build up of bradykinin when normally functioning angiotensin converting enzyme is used by the body to help breakdown bradykinin.

Of the following ACE inhibitors, which one can be used in this patient or in patients that suffer from HAE or Acquired C1 INH deficiency?

- A. Moexipril
- B. Fosinopril
- C. Lisopril
- D. Captopril
- E. None of the above. ACEI should be avoided in these patients.

### Case 3

A 12-year-old, adopted, African-American girl presents to the office complaining of recurrent abdominal pain. The patient has been given the diagnosis of inflammatory bowel disease by the emergency department. Her adopted parents note that in the last three or four years she has had multiple episodes of severe abdominal pain that have been associated with severe cramping, nausea, and diarrhea. Her pain was significant in the past such that she had an exploratory laparotomy, which did not reveal a cause for her pain. The pain normally last three to four days and then resolves. She has been hospitalized requiring IV fluids and narcotics to control the pain; however, she has never had associated fever or any leukocytosis. Her liver function in the past has been perfectly normal and she has not had any heme-positive stools. She has not had any constipation. Of note in the past year, she has had one episode of upper lip swelling and one episode of forearm swelling. She has seen the gastroenterologist and had both upper and lower endoscopies, which have been perfectly normal. CAT scan during the time of her previous abdominal pain revealed some thumb-printing of her small intestine with small intestinal wall swelling.

**Medications:** included polyethylene glycol 3350 although she has never complained of constipation

**Surgical History:** Notable for exploratory laparotomy and is otherwise negative

**Family History:** Unknown

**Physical Exam:** she is a well-developed, well-nourished girl who is resting comfortably. The rest of her physical exam was completely within normal limits.

**Laboratory Testing:** revealed a complement C4 of 1, a complement C1 of 2, within normal limits, a decrease in C1 inhibitor quantitative level, and a decrease in C1 inhibitor functional level.

#### Case 3 Assessment: HAE Type I

Recurring angioedema in the absence of urticaria, unexplained abdominal pain and a poor response to antihistamines, corticosteroids and epinephrine should suggest HAE or other bradykinin-mediated etiology. Because Type I HAE is a quantitative deficiency in C1 INH, and Type II HAE represents a defect in the function of circulating C1 INH, both quantity and functionality must be assessed. Expected laboratory results for each disorder are given in **Table 6**.

**Clinical Pearl:** HAE Type I is an autosomal dominant condition which is characterized by recurrent episodes of angioedema in response to low circulating total C1 INH total protein levels, therefore consuming classical complement factors C2/4.

**Table 6.** Laboratory results for HAE<sup>4</sup>

Type of Angioedema	Laboratory Results			
	C4 Level	Antigenic C1 INH Level	Functional C1 INH Level	C1q Level
Type I HAE	Decreased	Decreased	Decreased	Normal
Type II HAE	Decreased	Normal	Decreased	Normal
Type III HAE	Normal	Normal	Normal	Normal
Acquired C1 INH deficiency	Decreased	Decreased or normal	Decreased	Decreased

You suspect hereditary angioedema as the cause of your patient's swelling. Which of the following laboratory tests will confirm the diagnosis?

- A. C2, C4, CH50
- B. C1, C3, C4
- C. C4, C1 INH level and functional assay
- D. Laboratory studies will not be accurate during an acute attack

### Case 3: Management

She is started on C1 esterase inhibitor 1000 units IV push twice a week. Her abdominal pain ceased, and she no longer experiences persistent cramping and has no further peripheral swelling.

Which of the following is a recognized therapy for the management of HAE?

- A. Anabolic steroids
- B. C1 inhibitor concentrate
- C. Epinephrine
- D. Both A and B

### Case 4

A 20-year-old woman presents with a history of recurrent facial angioedema. She developed peri-orbital and lip swelling, which first occurred seven years ago. She has had nine episodes of recurrent lip and right eye swelling. She notes that since starting on tetracycline two months prior to her visit, she has not developed any recurrent swelling. She denies any history of shortness of breath, hypotension or urticaria. She notes the swelling resolves within 24 to 48 hours if untreated. Oral antihistamines or oral corticosteroids speeds the resolution of her swelling. She has no family history of recurrent angioedema and at no point has she had abdominal pain. There is no association with food.

**Medications:** include cetirizine 10 mg daily

**Surgical History:** noncontributory

**Physical Exam:** reveals a young woman who is well-developed and well-nourished in no apparent distress. Blood pressure is 120/80. Heart rate is 64. Respiratory rate is 12. Physical examination is within normal limits.

**Laboratory Testing:** Her labs revealed a normal C4 count; normal C1 INH quantitative level normal C1 INH functional level. Her CBC, ANA, latex IgE, total IgE, and sedimentation rate are all within normal limits.

**Clinical Pearl:** Idiopathic angioedema is a diagnosis of exclusion after allergic, ACEI-induced, HAE and acquired forms are ruled out. Often will involve pruritis and hives.

#### Case 4 Assessment: Idiopathic angioedema

She is currently diagnosed with chronic idiopathic angioedema, now without urticaria.

What distinguishes idiopathic angioedema from other forms of angioedema?

- A. It is usually not itchy
- B. Laryngeal symptoms are unusual
- C. It responds to C1inh concentrate
- D. It is diagnosed by skin-testing

What is the first step in the management of chronic idiopathic urticaria?

- A. Montelukast
- B. Avoid outdoor activity
- C. H1/H2 antagonists
- D. Trial of NSAIDs

#### Case 4: Management

She will be continued on cetirizine 10 mg once daily. If angioedema recurs, a blood test to evaluate Factor XII abnormality would be considered.

### A Closer Look: The Social and Economic Burden of HAE

HAE has a significant personal and economic impact on patients due to its chronicity and recurrent and unpredictable nature of acute attacks. The disease has a significant mortality and morbidity burden, with the mortality rate reportedly as high as 33%, primarily due to upper airway obstruction.<sup>40</sup> HAE can have a devastating impact on a patient's quality of life as the frequency and severity of attacks increase or worsen. Extremity and facial attacks can also be disabling. In the case of extremity attacks, the loss of manual dexterity or ambulation can be problematic. The disfigurement of facial attacks may cause significant social stigma. Abdominal attacks can be extremely painful, causing substantial incapacity. A prospective evaluation of 153 patients suffering from abdominal attacks demonstrated a mean pain score of 8.4 on a 10-point scale with four women reported that their pain was worse than childbirth.<sup>41</sup> Vomiting occurred in 73% of patients and 16 of 169 attacks required medical attention over a period of 24 months.

Patients with HAE require substantially more healthcare resources than patients without the disease, including drug therapy, physician visits and ER visits, and hospitalizations. Analyses of a European registry of 1,168 patients found a total of 1,333 hospitalizations per year attributable to HAE (approximately 1.2 hospitalizations/patient/year). Of these patients, 10% had four or more hospitalizations in the past year.<sup>42</sup> A separate, US-based, patient survey reported that patients averaged 4.7 ER visits per year; this rate far exceeds the national average of 39.6 ER visits per 100 persons (0.396 visits per person per year) in 2005.<sup>43,44</sup> Therefore, HAE may account for 15,000 to 30,000 ER visits annually in the US.<sup>40</sup> Hereditary angioedema patients also have a greater likelihood of costly invasive procedures, such as emergency tracheotomy or intubation for laryngeal attacks.<sup>45</sup>

The risk of unnecessary surgery or treatment is an additional concern, especially in undiagnosed HAE. Approximately one-third of patients with abdominal attacks undergo unnecessary surgery.<sup>11</sup> In a chart review of 22 patients diagnosed with HAE, at least three had numerous surgical procedures including appendectomies, laparotomies, and endoscopies/colonoscopies for diagnosis or attempted treatment.<sup>46</sup> Approximately 25% of patients with laryngeal attacks have been inappropriately treated for anaphylaxis in the ED, delaying appropriate treatment and potentially worsening outcomes.<sup>43</sup>

The Burden of Illness Study was a web-based survey of 457 HAE patients (345 women, 112 men). The survey reviewed attack characterization; acute attack treatment; chronic disease management; and financial, physical, and emotional burden of disease management. Disease-specific questions included: treatment patterns and providers; side-effects and burden of androgen therapy; and the impact of the disease on quality of life.<sup>47</sup> This study found that HAE has a pervasive and detrimental impact on its sufferers, with 94% of participants experiencing attacks in past year (mean 26.9 attacks/year). The typical acute attack lasted more than 2.5 days (60 hours).<sup>48</sup> Monetized cost averaged \$45,000/year/patient, including physician visits, missed work days, reduced productivity, hospital stays, tests, and procedures, chronic therapy, and patient co-pays. Direct medical costs for a patient suffering from severe attacks is an estimated \$71,000 annually.<sup>48</sup> The total cost of managing acute HAE attacks exceeded \$24,460 per patient per year, with 81% borne by payers. Disease severity defined by acute attacks was associated with increasing costs of both acute and chronic treatment.<sup>48</sup>

The random nature of HAE attacks has a significant impact on quality of life.<sup>49</sup> The Burden of Illness Study demonstrated a substantial psychological and financial burden of HAE, with non-monetized costs including long-term side effects from anabolic steroids (current standard of care), missed school, missed educational and career opportunities, and decreased overall mental and physical health.<sup>50</sup> Most respondents (69%) reported they had not been able to consider certain jobs as a result of their condition, and 100% reported that HAE limited them from advancing in school.

As a result of an acute attack, more than half of patients with HAE missed at least one day of work (51% of full- or part-time workers), one day of school (44% of students), and one day of leisure activities (59% of survey respondents).<sup>50</sup> In addition, 69% of patients reported that their disease affected the ability to consider certain jobs and 58% reported that it affected career advancement.<sup>50</sup> Nearly half (42.5%) of patients studied had scores indicative of clinical depression, when evaluated with a standardized screening instrument. In comparison to normal populations, HAE patients scored significantly ( $P < 0.0001$ ) higher on the HDI-SF depression assessment tool and demonstrated significant ( $P < 0.0001$ ) decreases in all the physical and mental components of the SF-12 Health Survey.<sup>50</sup>

HAE also has significant implications on daily functioning and work-life. During an acute attack, patients may miss work due to incapacitating pain or discomfort, or due to the inability to perform work activities (e.g., inability to type due to edema in the hands). More than 90% of patients with abdominal attacks require bed rest for 24 to 50 hours per attack, preventing them from work as well as activities of daily living.<sup>41</sup> The productivity impairment suffered by HAE patients is similar to that of patients with other severe chronic diseases. The Work Productivity and Activity Impairment (WPAI) assessment showed overall work impairment at 33.6%, which is between the range of WPAI measurements reported for Crohn's disease patients (45.9%) and severe asthma patients (28%). Hereditary angioedema patients had marked impairment in productivity in all WPAI categories including 45% impairment in overall activity.<sup>50</sup>

Hereditary angioedema provides a series of challenges to the clinician. One of the greatest of these is the unpredictable frequency and severity of acute attacks combined with a lack of FDA-approved therapeutic options. Patients must live with frequent disruptions in social activity and work/education. The risk of life-threatening laryngeal edema may cause ongoing anxiety and reluctance to travel.<sup>11</sup> With the arrival of new therapeutic options for acute management and prophylaxis combined with a deeper understanding of the pathophysiology of this potentially life-threatening disorder, the quality of life for patients suffering from HAE is likely to improve.

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## Angioedema in the Primary Care Setting

Mark A. Davis-Lorton, MD; Doug Johnston, DO; Maz Rezvani, MD

### CME Quiz

Please indicate your response by circling the letter of the most appropriate answer for each question.

#### Case 1

- Which of the following is true regarding allergic angioedema?
  - It is mediated by bradykinin
  - It is an autosomal-dominant condition
  - It is usually responsive to anti-histamines and corticosteroids
  - It is usually an autoimmune disease process
- Which of the following is NOT a common trigger of allergic angioedema?
  - Sulfonamide antibiotics
  - Eggs
  - Nuts
  - Venom
  - All of the above are considered common triggers

#### Case 2

- Which of the medications is most important to stop to decrease this patient's risk for recurrent angioedema?
  - Clopidogrel
  - Atorvastatin
  - Metoprolol
  - Ramipril
- Of the following ACE inhibitors, which one can be used in this patient or in patients that suffer from HAE or Acquired C1 INH deficiency?
  - Moexipril
  - Fosinopril
  - Lisopril
  - Captopril
  - None of the above. ACEI should be avoided in these patients.

#### Case 3

- You suspect hereditary angioedema as the cause of your patient's swelling. Which of the follow the laboratory tests will confirm the diagnosis?
  - C2, C4, CH50
  - C1, C3, C4,
  - C4, C1 INH level and functional assay
  - Laboratory studies will not be accurate during an acute attack
- Which of the following is a recognized therapy for the management of HAE?
  - Anabolic steroids
  - C1 inhibitor concentrate
  - Epinephrine
  - Both A and B

#### Case 4

- What distinguishes idiopathic angioedema from other forms of angioedema?
  - It is usually not itchy
  - Laryngeal symptoms are unusual
  - It responds to C1 INH concentrate
  - It is diagnosed by skin-testing
- What is the first step in the management of chronic idiopathic urticaria?
  - Montelukast
  - Avoid outdoor activity
  - H1/H2 antagonists
  - Trial of NSAIDs
- According to the Burden of Illness study, what percentage of patients experienced an acute attack over the course of 1 year?
  - Less than 25%
  - 50%
  - 75%
  - Over 90%
- Which of the following statements is true about HAE?
  - Approximately one-third of HAE sufferers undergo unnecessary surgeries due to misdiagnosis of abdominal attacks
  - Mortality rate can be as high as 33% due to upper airway obstruction
  - Common sites for HAE angioedema are the skin, the abdomen and the face and neck
  - C1 INH can be used for chronic, long-term prophylaxis
  - All of the above are true

(Please Print Legibly)

First Name \_\_\_\_\_ Last Name \_\_\_\_\_ Degree \_\_\_\_\_

Signature \_\_\_\_\_

# Evaluation and Request for Credit Form

## Angioedema in the Primary Care Setting

Mark A. Davis-Lorton, MD; Doug Johnston, DO; Maz Rezvani, MD

By circling your choice, please evaluate the effectiveness of this CE Activity

	Excellent			Poor
Overall quality of the activity	4	3	2	1
Overall quality of learning materials including handouts	4	3	2	1
Effectiveness of the learning activities	4	3	2	1
Activity provided fair balance of information	4	3	2	1
Content free of commercial bias (Please comment below)	4	3	2	1
Educational objectives achieved:				
• Describe the pathophysiology of angioedema	4	3	2	1
• Describe the signs and symptoms of hereditary angioedema and other forms of angioedema that may be seen by the primary care practitioner	4	3	2	1
• Outline the differential diagnosis of angioedemas	4	3	2	1
• Discuss current and emerging treatment options for recurring angioedema, with special emphasis on hereditary angioedema	4	3	2	1
Level of content appropriate for the target audience	4	3	2	1
Information provided will improve professional effectiveness	4	3	2	1

How will this activity facilitate change in your practice?

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Comments about this CE activity and suggestions for future activities:

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