



HAE

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

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The following series of posters and audio will provide you an overview of available accredited CE content. While at the booth, you will have the opportunity to register to receive the self-study materials on Angioedema in the Emergency Department.

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Accreditation Information

Target Audience

This educational activity is designed for emergency department 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 in comparison to the pathophysiology of urticaria
- List the various classifications of angioedema and their identifying characteristics
- Discuss how the etiology of angioedema will impact treatment choices and how new and emerging therapies may improve clinical outcomes in life-threatening angioedemas

Content Delivery and Learning Methodology

This Educational Activity is delivered as an enduring material. In order to obtain the maximum of 2 continuing education credit hours for this self-directed learning activity, the participant must read the educational content and then complete the Learning Assessment questions, obtaining a score of 70% or better. The Learning Assessment, the Evaluation and Request for Credit Form must be completed, printed and sent to:

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Educational Activity Dates

This educational activity is valid for credit beginning October 3, 2009 and will terminate October 3, 2010.

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Dr. Namita Kedia reports that she has no affiliations with commercial interests to disclose.

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Foreword

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In most emergency departments in the US, the presentation of patients with episodes of angioedema is all too common. The primary complicating factor in managing the patient appropriately is the varying etiologies associated with angioedema. The challenge to the busy emergency medicine practitioner is to quickly determine the pathology of the swelling and then to provide the most appropriate course of therapy. While antihistamines may offer relief to some patients, they may be entirely ineffective in other patients depending upon the cause of the swelling episode.

In spite of increased educational efforts directed towards improving the recognition of the array of etiologies of angioedema, there remains a significant gap in the practice behaviors of most emergency medicine practitioners. While the fundamentals of treating life-threatening angioedema in the emergency department are the same regardless of the etiology, the emergency department physician needs a greater awareness of the subtypes of angioedema to reach an accurate diagnosis, institute effective treatment and refer the patient to an allergist/immunologist for chronic prophylactic therapy.

One rare but potentially fatal cause of unexplained angioedema is Hereditary Angioedema (HAE). HAE is a genetic disorder that affects anywhere from 1 in 10,000 to 1 in 50,000 worldwide. Secondary to its acute and recurrent nature, patients with HAE present more often than expected to the emergency department and are often overlooked. The clinical presentation of angioedema encompasses many different etiologies, and many with HAE have never been correctly diagnosed or properly worked-up for the cause of their swelling episodes making the emergency department the first and only place they ever seek treatment. Because of this, it is important that the emergency medicine physician, as the first-line health care provider - and frequently the *only* physician some HAE patients will see - maintain a high level of suspicion that angioedema unresponsive to conventional therapies may be HAE. By taking a thorough history and physical, the emergency medicine physician has an opportunity to diagnose and treat a potentially fatal, chronic condition that is often misdiagnosed and can be mentally, physically, economically and socially disabling to patients.

Angioedema in the Emergency Department

While seen less frequent than urticaria, angioedema is often confused with urticaria and yet can be much more serious. Traditional anti-allergy therapies used to treat urticaria may prove ineffective, especially with angioedema mediated by bradykinin. Appreciating the differences between urticaria and angioedema, and between allergic angioedema and nonallergic angioedema is critical in the differential diagnosis of angioedema in the emergency department (ED).

Angioedema is a condition that can be caused by a number of different disorders. With the widespread use of ACE inhibitors it is likely that most emergency physicians will encounter patients with ACE-induced angioedema in their practice. Additionally, hereditary angioedema is a relatively rare autosomal dominant disorder that may go undiagnosed for years despite significant morbidity and even mortality. This paper will review the various etiologies of angioedema and methods of treatment.

Although angioedema is sometimes confused with urticaria, urticaria involves the upper papillary dermis with sparse perivascular infiltrate of neutrophils, eosinophils, monocytes and T-lymphocytes. In contrast, angioedema involves the skin as well as the deeper dermis and subcutaneous tissue with minimal infiltrate. Further, angioedema may be quite painful, but is not associated with itching. In both instances, however, local vasodilation and increased vascular permeability results in the observed swelling. In severe cases, ED physicians will see patients presenting with pending airway obstruction or painful abdominal symptoms and are very familiar with the traditional treatments for mast-cell mediated (allergic) types of angioedema. However, clinicians are less familiar with angioedema caused by non-IgE (nonallergic), bradykinin-mediated pathways. While angioedema caused by histamine release will respond to antihistamines and corticosteroids, bradykinin mediated inflammation will not. Thus, in the ED the need for immediate urgent therapies may be evident, but the actual cause – and the appropriate treatment – is not. Differentiating between the two mechanisms of angioedema becomes a critical step in diagnosis if the appropriate life-saving treatment is to be administered.

Classification and Pathophysiology of Angioedema

Differentiating histamine-mediated angioedema from kinin-mediated angioedema can have a profound impact on patient morbidity and mortality every 1-2 weeks.

Allergic angioedema occurs within 1 to 2 hours of exposure to an allergen and is associated with urticaria and/or pruritis in up to 90% of the cases. When mast cells are exposed and sensitized to an allergen, degranulation takes place with the release of several mediators including histamine, tryptase, and chymase. Activation of mast cells also results in the transcription of proinflammatory cytokines including TNF- α , interleukins,

Table 1. Primary differentiating features between allergic and nonallergic forms of angioedema

Feature	ANGIOEDEMA	
	Nonallergic or Bradykinin Mediated	Allergic or Mast-cell Mediated
Onset	Hours	Minutes to hours
Urticaria	-	+
Pruritis	-	+
Pain and/or burning	May be present	-
Response to antihistamines	-	+
Response to corticosteroids	-	+

and leukotrienes. With re-exposure to the antigen, adjacent IgE receptors cross-link leading to activation of intracellular tyrosine kinase and protein kinase C that results in an increase in the concentration of intracellular calcium and the release of preformed mediators. Common allergens include drugs, insect venom and foods, such as nuts, shellfish, milk and eggs. Non-specific stimulation of mast cells resulting in angioedema may also occur after exposure to radiocontrast media or opioids. The lesser-known, nonallergic angioedemas are not mediated by IgE and most are the result of increased plasma and tissue concentrations of bradykinin.¹ Bradykinin, a potent vasodilatory peptide regulated by Factor XII and plasma kallikrein in the contact system, binds to B2 receptors on endothelial cells leading to vasodilation and increased microvessel permeability.² Edema is caused by plasma leakage from post-capillary venules due to bradykinin-induced changes.^{3,4} In addition, bradykinin causes tissue smooth muscle contraction which leads to pain and cramping (**Figure 1**).¹

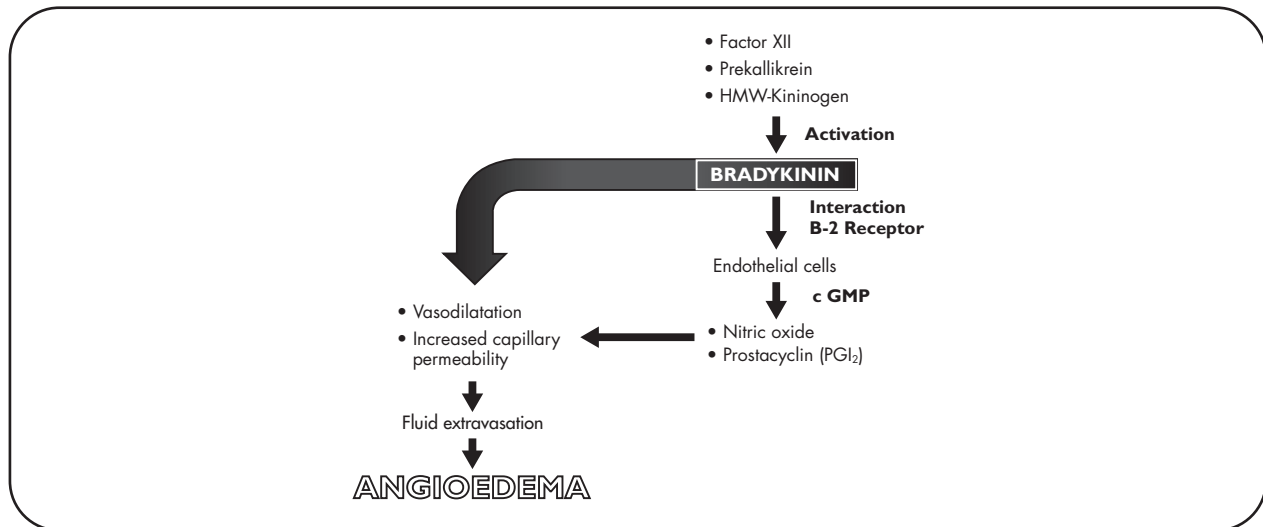


Figure 1. Bradykinin mediated angioedema

Nonallergic angioedema is commonly categorized into five different types:

- hereditary angioedema (HAE)
- ACE inhibitor (ACEI)-induced angioedema
- acquired C1 INH deficiency angioedema
- non-steroidal anti-inflammatory drug (NSAID) induced angioedema
- idiopathic angioedema

Hereditary angioedema (HAE) is a rare and potentially fatal genetic disorder involving a deficiency or dysfunction of C1 inhibitor (C1 INH).³ HAE is an autosomal dominant disease that occurs in approximately 1/10,000 to 1/50,000 individuals with no racial or gender predilection having been recognized.^{2,5,6} Symptoms usually present in early childhood, worsen at puberty and persist throughout life. The frequency of attacks is unpredictable ranging from every 3 days to very rare or not at all.⁶ Trauma (commonly dental procedures), stress, fever, and infection can be triggering factors, but many attacks occur without an identifiable stimulus.³ While the actual diagnosis of HAE is often made in the second or third decade of life, symptoms often begin earlier but mimic other disorders and are often misinterpreted.⁵ As the clinician who may first see an HAE patient, it becomes critical that the emergency medicine physician is able to distinguish between various presentations of angioedema.

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

- Type I is a quantitative defect in the 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 2**).⁷

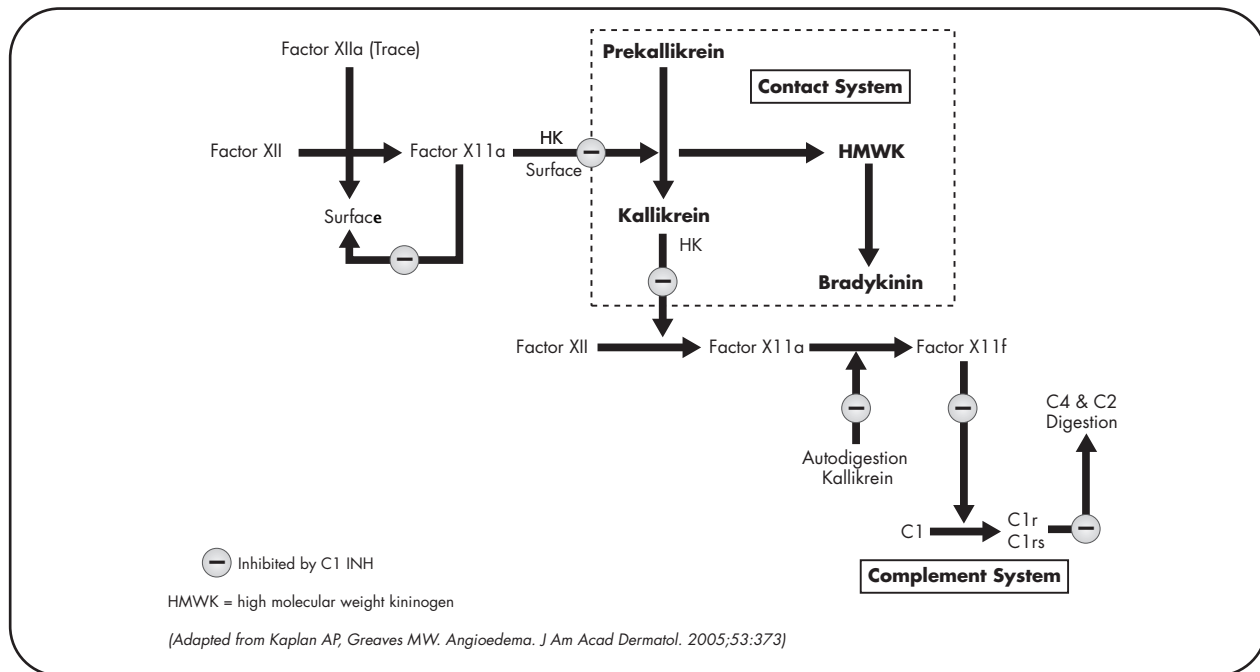


Figure 2. Schematic of plasma kinin-forming cascade

Clinical attacks are most often seen in three anatomical sites:

- extremities
- 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.³ The extremities, face, and genitals are the most common sites affected. The usual facial areas involved are the lips, eyelids, and tongue. Trauma during intercourse or parturition can result in genital edema. In all cases, swelling is highly variable and often not symmetrical. The cutaneous edema in HAE occurs in non-dependent areas and is non-pitting and minimally painful. Angioedema typically builds within the first 36 hours and then gradually subsides within 5 days, though the initial swelling may occur very rapidly.³

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.⁸ Laryngeal swelling can occur in isolation or in association with cutaneous or abdominal symptoms, and the majority of laryngeal events occur without warning.¹⁰ In a survey of 221 patients with HAE, Bork and colleagues evaluated the long-term course of the disease in order to establish a specific pattern of swelling and found that 32% experienced an episode of facial swelling that extended to laryngeal edema at least once.⁹ Over the course of their lifetime, up to 50% of patients will experience laryngeal edema; however, only a small percentage experience recurrent episodes. 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.¹⁰ Laryngeal swelling usually develops over a period of hours, with a reported mean of seven hours.¹¹ Although each

laryngeal attack has the potential to become life-threatening, the majority resolve before complete airway obstruction occurs.¹¹ If undiagnosed, mortality from HAE can be as high as 30% to 40% with patients at risk of asphyxia even if they have no previous history of upper airway involvement.^{8,11} A study by Frank et al. noted a history of asphyxiation from airway swelling in 1/3 of untreated patients and asphyxiation rates as high as 50% have been reported.¹⁰⁻¹² Death from suffocation may result in as little as 20 minutes from onset of laryngeal edema, however the mean time from onset to maximum development of edema has been reported to be 8.3 hours.^{10,11} The photos in **Figure 3** show a patient suffering from an attack; the series demonstrates that such attacks are progressive, incapacitating, and life-threatening. Thus the greatest mortal threat to patients with HAE is the spontaneous and unpredictable nature of laryngeal attacks.¹⁰



Figure 3. 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.^{3,8} Gastrointestinal attacks are experienced by a majority of patients with HAE, and can be the principal presentation in 25% of patients.¹³ Abdominal pain, caused by swelling of the intestinal wall, is reported by 70–80% of patients with HAE.⁵ The pain can be severe and is often spasmodic rather than steady in nature.³ Pseudo-obstruction secondary to gastrointestinal wall edema has been described.¹⁴ 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.⁸ Gastrointestinal attacks of HAE typically subside within 5 days.³

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.¹³ HAE episodes involving the gastrointestinal tract may remain undiagnosed for decades despite repeat visits to the ED. At times, patients have been inappropriately referred for psychiatric assessment when the symptoms were considered psychosomatic.⁸

The diagnosis of HAE is often delayed, even by years, because of low awareness among clinicians and similarities to other disorders.⁵ The average time between symptom onset and diagnosis in 1977 was 22 years and the average delay still exceeded 10 years as recently as 2005.^{12,15}

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.^{5,16} Subsequently, mutations in Factor XII have been described associated with the gene encoding of factor XII that results in increased bradykinin production by kallikrein.¹⁷ 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 the result of an allergic mechanism. 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.^{18,19} Since ACE degrades bradykinin into inactive metabolites, ACE inhibition causes increased levels of bradykinin and its active metabolite causing angioedema in susceptible patients.²⁰ 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.⁵

Angiotensin receptor blockers (ARBs) do not cause elevated bradykinin levels; however, recent work has shown that angiotensin II type 2 receptor antagonists cause a threefold increase in bradykinin B2 receptor expression leading to increased bradykinin binding.²¹

In summary, swelling from ARBs has been described in patients both with and without ACEI-induced angioedema and may not be a wise therapeutic option for patients with a history of ACEI-induced angioedema.

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.⁵ About 14% of patients with acquired angioedema have no other underlying disease.⁸ Unlike those with HAE, acquired angioedema patients often present after the 4th decade of life, and do not have a family history of swelling.⁵ Patients have almost undetectable serum levels and/or activity of C1 INH, C4, and C1q.⁵ Low C1q is unique to acquired C1 INH deficiency.

Non-steroidal anti-inflammatory drug (NSAID) induced angioedema is typically accompanied by urticaria.⁶ Inhibition of the cyclooxygenase-1 (COX-1) enzyme is the likely mechanism and all COX-1 inhibiting NSAIDs need to be avoided in patients with this type of angioedema. Multiple reports have noted that NSAID-induced swelling occurs primarily on the face, causing peri-orbital angioedema.^{22,23}

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.⁸ Patients with idiopathic angioedema have normal complement values and but may still be unresponsive to antihistamines.⁵

Table 2 summarizes the etiology of nonallergic angioedema. Note that all of the angioedemas described are bradykinin driven, with the exception of NSAID-induced angioedema.

Table 2. Etiology of nonallergic angioedema

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

Differential Diagnosis of Angioedema in the Emergency Department

The mortality due to HAE and ACE inhibitor-induced angioedema is significant, and is usually attributed to the unavailability of appropriate emergency treatment, or mistaken use of inappropriate treatment.²⁴ A retrospective review indicated that asphyxiation occurred in up to 30% of untreated patients with HAE.³ Further, mortality attributed to undiagnosed HAE can be as high as 50%.^{10,11} Angioedema associated with urticaria is usually secondary to histamine release and appropriate treatment is well-established thus fatalities are rare.

Monitoring and supportive care of airway, breathing and circulation should be the first steps in treating a patient presenting with laryngeal, pharyngeal, or tongue edema. Prophylactic intubation in cases of laryngeal edema may be prudent as an early measure to maintain the airway and avoid tracheotomy.⁵ Abdominal attacks are often extremely painful and may be accompanied by vomiting and/or diarrhea. Spasmolytics and narcotics may be necessary for treatment of severe pain during acute abdominal attacks.^{3,5}

Table 3 describes some distinguishing characteristics between the histamine mediated, HAE and acquired forms of angioedema.²⁵

Table 3. Distinguishing features of variant forms of angioedema

Symptom/Sign	Bradykinin Mediated		Histamine Mediated
	HAE	Acquired	Allergic
Angioedema	Yes	Yes	Yes
Urticaria	No	No	Usually
Age of onset (most frequent)	6-20 years	> 50 years	Anytime
Family history	Usually	No	Variable
Underlying disease	No	Yes	No
Location of swelling	All	All	Especially face and lips
Precipitation by trauma	Yes	Yes	No
Duration of swelling, hr	48-72	48-72	2-48
Response to antihistamines, corticosteroids	No	No	Yes

Treatment

Treatment of Angioedema

Conventional emergency care of acute cases include the ABCs – airway management, breathing, and circulation – as well as monitoring of vital functions. Symptomatic treatment may include oxygen, IV fluids, diphenhydramine, H2 blockers, corticosteroids, and epinephrine. Physical imaging in the case of laryngeal or abdominal edema may also be warranted (**Figure 4**).¹ Family history and current patient medications should be obtained to aid in diagnosis. Physical examination may reveal edema associated with urticaria and may be described as itchy or painful.

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

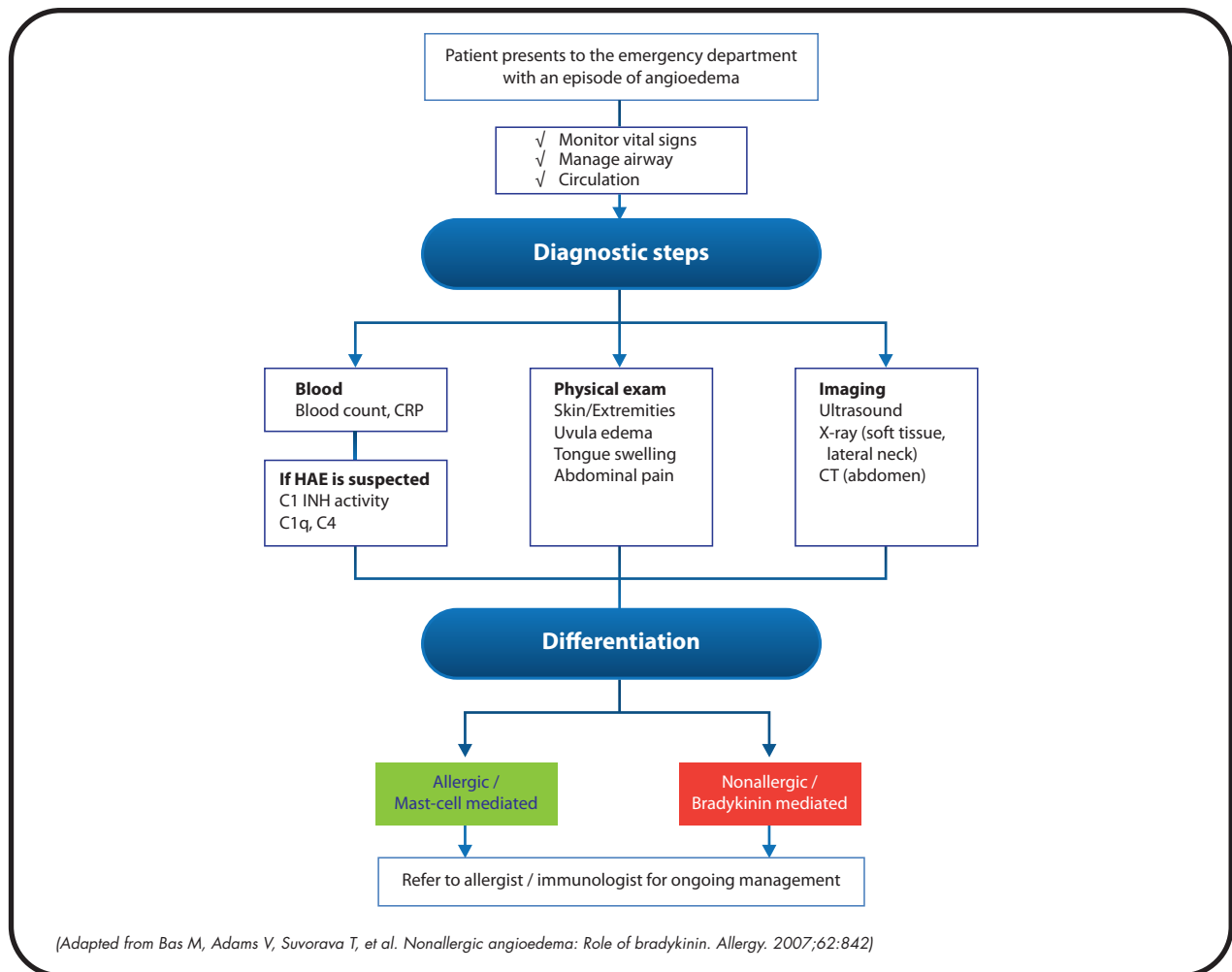


Figure 4. Suggested algorithm for the assessment of angioedema in emergency department

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.^{6,26}

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.²⁷ Misdiagnosis of abdominal angioedema caused by HAE may result in unnecessary surgeries and procedures. Therefore, "...angioedema must be included in the differential diagnosis of intermittent, unexplained abdominal pain."²⁸

C1 inhibitor (C1 INH) concentrate

Although not approved for acute treatment in the United States, international 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.^{29,30} 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)³¹

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.³² Limitations of human C1 INH include its dependency on human blood supply, potential for transmission of infectious agents, and the need for intravenous administration. C1 INH is not approved by the FDA for treatment of acute angioedema in patients with HAE.

Fresh frozen plasma (FFP)

The lack of availability of C1 INH in the US over the past several decades has made the treatment of acute swelling attacks unsatisfactory. FFP, which contains C1 INH, has been used for short-term prophylaxis and to rapidly decrease acute swelling particularly in cases of laryngeal involvement or severe abdominal pain. FFP is efficacious in most patients, and can be used in the absence of C1 INH; however, some have seen symptoms worsen when FFP is administered for swelling attacks in HAE.^{5,33} FFP is not virally inactivated, thus increasing the risk of transmitting infectious agents with its infusion. Urticaria, anaphylactic shock, and hemolysis have been reported with the use of FFP.⁵

Other Potential Agents for Acute HAE Management

Ecallantide is a potent recombinant protease inhibitor which can bind and inhibit human kallikrein, thus decreasing bradykinin generation.³³ Due to its short plasma half-life when administered subcutaneously, ecallantide is being studied only for acute HAE attacks.²

Icatibant is a synthetic bradykinin receptor-2 antagonist with a structure similar to bradykinin and is intended for subcutaneous use during acute swelling episodes.^{2,4,34}

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- α alkylated androgens)

Over the past 30 years, attenuated androgens (17- α alkylated androgens) have been widely used for long-term prophylaxis in HAE.⁵ Studies done almost 3 decades ago demonstrated daily therapy with attenuated androgens decreased the number of swelling episodes in HAE patients.³ Attenuated androgens most frequently used for HAE include danazol, stanazol, and oxandrolone though the majority of studies have been done with danazol.³ 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.³ Most assume danazol increases hepatic C1 INH production.³

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.⁴ Patients will usually begin therapy with danazol at 400 to 600 mg QD for a month and taper down to the lowest effective dose.⁵ 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.^{3,5,23} Long-term use of danazol also has been associated with an increased risk of early atherosclerosis.³⁵ 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.³⁶ EACA has been shown to reduce attack frequency at a daily dose of 8-12 g in 4 divided doses.⁵ A number of side effects have been associated with EACA including thrombosis, severe muscle toxicity, and muscular pain and weakness associated with myositis.^{3,5} Contraindications include previous thrombosis, or a procoagulant state.³ Despite these adverse effects, EACA may be preferred over androgens for use in children.⁵

C1 INH concentrate

C1 INH has been used for both acute attacks and long-term prophylaxis of HAE. It represents the most physiologic treatment.¹² 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.^{37,38} 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.³⁹ 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.⁵ Most agree FFP is useful for short-term prophylaxis prior to procedures.⁴⁰ 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 4 equally divided doses.⁵ Attenuated androgens are used from 5 days before to 3 days after the event; danazol has been administered at a dose of 10 mg/kg/day with a maximum of 600 mg a day.⁵ C1 INH is safe and effective for prophylaxis of acute attacks in adults, children, and pregnant women. The dose for short term prophylaxis is 500-1000 U given the night before or on the day of surgery.^{5,41}

Treatment of ACE Inhibitor-Induced Angioedema

While there is no specific treatment for this type of angioedema, emergency management would include supportive care and with special precautions taken to closely monitor for airway compromise.⁴² Systemic antihistamines and corticosteroids are minimally effective and are recommended as second-line therapy.

Currently the most common exogenous cause of angioedema seen in the ED, patients should be closely monitored and considered for admission and continued observation as relapses following apparent recovery are common. ACE inhibitor therapy should be discontinued and treatment resumed with another class of drugs.

Treatment of Acquired C1 INH Deficiency Angioedema

Often the result of a lymphoproliferative disorder, treatment of acute exacerbations would include supportive care and close monitoring for airway compromise. Pharmacotherapy in these patients would follow the recommendations for acute episodes of HAE with C1 INH concentrate or, if not available, FFP. In the presence of C1 INH antibodies, C1 INH concentrate may need to be supplemented with tranexamic acid.^{3,43} Patients should be closely monitored in the ED and should be considered for admission and continued observation. Identification and treatment of the underlying disorder should be pursued and has been associated with a decrease in related acute angioedema episodes therefore patient should be referred to the appropriate specialist for follow-up.

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.²³ Most recently, since leukotrienes are believed to play a role in this pathway, treatment using leukotriene antagonists has been suggested.⁴⁵ Discontinue use of offending medications.

Idiopathic Angioedema

Emergency management would include supportive care, diphenhydramine, corticosteroids, and H2 blockers. Consider the addition of epinephrine if angioedema is rapidly advancing.

A Closer Look at HAE: Social and Economic Burden

HAE has a significant personal and economic impact on patients due to its chronicity and unpredictable, recurrent 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.⁴⁵ 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 and, 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. Patients with HAE require substantially more healthcare resources than patients without the disease, including drug therapy, physician visits, ED 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 4 or more hospitalizations in the past year.⁴⁷ A separate, US-based, patient survey reported that patients averaged 4.7 ED visits per year; this rate far exceeds the national average of 39.6 ED visits per 100 persons (0.396 visits/person/year) in 2005.⁴⁸ Therefore, HAE may account for 15,000 to 30,000 ED visits annually in the US.⁴⁵ HAE patients also have a greater likelihood of costly invasive procedures, such as emergency tracheotomy or intubation for laryngeal attacks.¹⁵

The risk of unnecessary surgery or treatment is an additional concern, especially in undiagnosed HAE. Approximately 1/3 of patients with abdominal attacks undergo unnecessary surgery.⁵ 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.⁴⁹ Approximately 25% of patients with laryngeal attacks have been inappropriately treated for anaphylaxis in the ED, delaying appropriate treatment and potentially worsening outcomes.⁴⁷

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.⁵⁰ This study found that HAE has a pervasive and detrimental impact on its sufferers, with 94% of participants experiencing attacks in the past year (mean 26.9 attacks/year). The typical acute attack lasted more than 2.5 days (60 hours).⁵¹ 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.⁵¹ The total cost of managing acute HAE attacks exceeded \$24,460/patient/year, with 81% borne by payers. Disease severity, defined as acute attacks, was associated with increasing costs of both acute and chronic treatment.⁵¹ The random nature of HAE attacks has a significant impact on quality of life.⁵² 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.⁵³ Sixty-nine percent 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 1 day of work (51% of full- or part-time workers), 1 day of school (44% of students), and 1 day of leisure activities (59% of survey respondents).⁵³ In addition, 69% of patients reported that their disease affected the ability to consider certain jobs and 58% reported that it affected career advancement.⁵³ 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.⁵³

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.²⁷ 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 at 45.9% and severe asthma patients at 28%. HAE patients had marked impairment in productivity in all WPAI categories including 45% impairment in overall activity.⁵³

Conclusions and Take Away Points

When a patient presents to the ED with angioedema the first steps to follow in patient care are to assess and stabilize the patient's airway, breathing, and circulation.

While the urgency of the situation is self-evident, the cause may not be and yet the cause will dictate the approach to treatment. The most common type of angioedema seen is histamine mediated and will respond to conventional therapies. However, bradykinin mediated events must be kept in mind, especially if the angioedema is progressive, and not responding to traditional treatment of antihistamines, corticosteroids, H2 blockers or epinephrine. If the angioedema does not respond, does not seem typical of histamine-induced angioedema or physical exam finds edema without urticaria, consider C1 INH concentrate if available or FFP, and consultation with an allergist. Patients with any signs or symptoms of airway edema, worsening attacks, or attacks not responding to the above-mentioned medications, should be admitted for inpatient observation.

HAE 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. Many times, clues to diagnosing HAE will be found in a patient history of repeated attacks or recent trauma. Family history may reveal a pattern of similar attacks. During the exam, inquire:

1. Have you had other unexplained swelling episodes?
2. Has anyone in your family experienced unexplained swelling episodes?

An affirmative response may indicate the need to change treatment strategies and contact an allergist/immunologist for ongoing management and follow-up.

When assessing any patient with angioedema, or patient with non-specific acute abdominal pain, a high level of suspicion for HAE should be maintained. Correct and timely diagnosis and treatment of HAE could be life saving and life changing for the HAE patient.

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CME Accreditation Documents

Angioedema in the Emergency Department

Authors

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CME Quiz

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

- Which of the following characteristic is NOT commonly seen with bradykinin-mediated angioedema?
 - Pain
 - Swelling
 - Itching
 - Difficulty breathing
- Intermittent angioedema, abdominal pain, and urticaria are features of which of the following disorders?
 - Hereditary angioedema
 - Acquired angioedema
 - Idiopathic angioedema
 - All of the above
- Which of the following treatments are generally ineffective in patients with bradykinin-mediated angioedema?
 - Aspirin
 - Epinephrine
 - Diphenhydramine
 - Prednisone
 - All of the above
- Which of the following is thought to be the major mediator of swelling in HAE?
 - Fibrin
 - C1 INH
 - Histamine
 - Bradykinin
- Symptoms frequently associated with HAE include all of the following EXCEPT:
 - Swelling of extremities
 - Post coital pelvic pain
 - Abdominal pain
 - Conjunctival edema
- Which of the following agents may sometimes be used to treat acute episodes of HAE?
 - Packed red blood cells
 - Fresh frozen plasma
 - Cryoprecipitate
 - Albumin
- Which of the following symptoms of HAE is associated with the highest mortality risk?
 - Swelling of the lips and eyelids
 - Laryngeal edema
 - Severe, unexplained abdominal pain
 - Vomiting and diarrhea
- Which of the following therapeutic options is indicated in the United States for chronic, long-term prophylaxis of HAE?
 - C1 inhibitor concentrate
 - Ecallantide
 - Fresh frozen plasma
 - Icatibant
- HAE and ACEI-induced angioedema share which of the following features?
 - Bradykinin is a likely mediator
 - Antihistamines are not effective
 - Laryngeal edema may be fatal
 - All the of the above
- According to the Burden of Illness study, what percentage of HAE patients experienced an acute attack over the course of 1 year?
 - Less than 25%
 - 50%
 - 75%
 - over 90%

(Please Print Legibly)

First Name _____ Last Name _____ Degree _____

Signature _____

Evaluation and Request for Credit Form

Angioedema in the Emergency Department

Authors

Adam J. Singer, MD; Namita Kedia, MD; Mark A. Davis-Lorton, MD and Doug Johnston, DO

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 in comparison to urticaria	4	3	2	1
• List the various classifications of angioedema and the characteristics	4	3	2	1
• Discuss how the etiology of angioedema will impact treatment choices	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?

Comments about this CE activity and suggestions for future activities:

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