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A CONSENSUS PARAMETER FOR THE EVALUATION AND MANAGEMENT OF ANGIOEDEMA IN THE EMERGENCY DEPARTMENT

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I. INTRODUCTION AND RATIONALE FOR DEVELOPMENT

A. Overview

Angioedema is a physical sign secondary to swelling of the subcutaneous or submucosal tissues, and is due to enhanced vascular permeability, which allows movement of fluid from the vascular space into the interstitial space. Angioedema is non-pitting, non-dependent and transient (lasting up to 7 days). It is critical to distinguish angioedema from edema, which is pitting, dependent and persistent. Angioedema may be life-threatening, depending in large part on its underlying cause and body location. Thus, the clinical approach to a patient presenting in the emergency department (ED) with angioedema should include a consideration of potential causes. This document is meant to provide the ED physician with a practical framework for classifying angioedema, and to outline management based on this classification.

Most ED visits for angioedema will involve allergic or idiopathic angioedema, with or without concomitant urticaria or evidence of anaphylaxis. These forms of angioedema are typically mediated by histamine, and their management is usually familiar to ED staff. The key challenge in the management of angioedema in the ED, however, is recognizing and treating potential non-histaminergic (bradykinin-mediated) angioedema. Unlike histamine-mediated angioedema, bradykinin-mediated angioedema is not associated with urticaria, does not respond to antihistamines or corticosteroids, and is poorly responsive to epinephrine. Bradykinin-mediated angioedema tends to be more severe, longer lasting, and much more likely to involve concurrent abdominal symptoms than histamine-mediated angioedema.

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B. Epidemiology

When angioedema develops, it often leads to an urgent (unscheduled) office or ED visit. Population-based data are lacking, but it is likely that patients with new-onset or recurring angioedema will go to the ED. Although anecdotal, this behavior fits that of pediatric patients with anaphylaxis; data suggest that roughly three-fourths of these children are managed in the ED.(1)

Few studies have examined the epidemiology of ED visits for angioedema. To date, all studies have relied on the International Classification of Diseases, 9th Edition, Clinical Modification (ICD9CM) code 995.1 to identify cases. Using this approach is limited, as the sensitivity and specificity of ICD9CM criteria to identify angioedema are currently unknown. Findings by Clark and colleagues, who demonstrated the low sensitivity and clinically relevant bias that comes from using ICD9CM anaphylaxis codes as the only source of case identification, further emphasize the need to overcome these methodological issues in order to generate more accurate epidemiologic data on angioedema.(2)

Based on data from the National Hospital Ambulatory Medical Care Survey (NHAMCS), there are as many as 80,000 to 112,000 ED visits for angioedema annually.(3, 4) The hospitalization rate for angioedema was 4.0 per 100,000 in 2005, making this condition the “dominant allergic disorder that results in hospitalization in the United States.” (5) About 18% of ED visits coded as angioedema result in hospitalization.(4) However, understanding the true epidemiology of angioedema is hampered by persistent confusion among clinicians about the case definition and, more specifically, the distinction between different groups of allergic reactions that might present to the ED including: 1) anaphylaxis with angioedema; 2) an isolated angioedema disorder or; 3) other related conditions such as chronic urticaria with angioedema. This consensus parameter focuses on the presentation of isolated angioedema disorders to the ED.

Angioedema disorders are the result of either bradykinin- or histamine- mediated responses. (6) Many different factors are associated with the bradykinin- mediated angioedema disorders, most notably hereditary conditions and specific types induced by medication. Up to 50% of hereditary angioedema (HAE) patients in the United States experiencing attacks have historically been reported to require an ED visit, with the majority of these patients requiring hospitalization.(4) A chart review conducted at five academic EDs revealed that 30% of adult ED patients with angioedema had angiotensin-converting enzyme (ACE) inhibitor-induced angioedema, with 18% of these being admitted to an observation unit, 12% being admitted to an inpatient unit and 11% being admitted to an intensive care unit (ICU).(7) Bluestein and colleagues also found that 30% of angioedema cases in the ED were induced by ACE-inhibitors, although they noted a lower admission rate of 14% in their community setting.(8) The possibility of medication-induced angioedema in children should also not be ignored. Although rare, in one study of 42 cases of pediatric angioedema, 7% (n=3) presented with upper airway obstruction and were taking either an ACE inhibitor or calcium channel blocker.(9)

C. Classification

It is difficult, if not sometimes impossible, to establish a precise cause of swelling in a patient presenting with angioedema in the ED. Therefore, it is recommended that patients be categorized using the following classification (Table 1): 1) anaphylaxis; 2) histaminergic angioedema without anaphylaxis (including both allergic and idiopathic angioedema); and 3) non-histaminergic angioedema (including both hereditary angioedema [HAE] and ACE inhibitor [ACEI]-induced angioedema). Because the pathophysiology of these groups is different, the clinical manifestations and optimal treatments also differ. Unlike histamine-mediated angioedema, bradykinin-mediated angioedema does not respond to antihistamines or corticosteroids and is only poorly responsive to epinephrine. Bradykinin-mediated angioedema tends to be more severe, longer-lasting, and much more likely to involve the abdominal viscera than histamine-mediated angioedema.(10) Bradykinin-mediated angioedema also frequently involves the upper airway, with a significant risk of death due to asphyxiation.(11) Figure 1 illustrates the general approach to classifying and managing angioedema in the ED. Details of the evaluation and management are expounded below.

D. Rationale for Development of a Parameter for ED Angioedema Management

The growing body of evidence describing the underlying mechanisms resulting in angioedema presenting to the ED provides the foundation necessary to care for these patients. Likewise, with the recent development and availability of novel pharmaceutical agents to treat bradykinin-mediated angioedema, it has become paramount that ED physicians be able to distinguish between histamine-mediated and bradykinin-mediated etiologies.

E. The practice parameter developmental process

In the following sections, we discuss recommendations for the evaluation, management and follow-up of the angioedema patient presenting to the ED. These recommendations were developed collaboratively among a group of allergists and emergency medicine physicians with expertise in this area. This consensus parameter was developed following a rigorous process to maximize use of available evidence.

The workgroup included experts in the specialties of Emergency Medicine and Allergy and Immunology. The Chairs, Joseph Moellman, M.D. and Jonathan Bernstein, MD, invited workgroup members to participate in the parameter development. The charge to the workgroup was to use a systematic literature review, in conjunction with consensus expert opinion and workgroup-identified supplementary documents to develop practice parameters that provide a comprehensive approach for an assessment and management of angioedema in the Emergency Department. A search of the medical literature was performed for a variety of terms that were considered to be relevant to this practice parameter. Literature searches were performed on PubMed, Google Scholar, and the Cochrane Database of Systematic Reviews. All reference types were included in the results. References identified as being relevant were searched for relevant references, and those references also were searched for relevant references. In addition, members of the workgroup were asked for references that may have been missed by this initial search. Published clinical studies were rated by category of evidence and utilized to establish the strength of the recommendations.

Each individual element of the recommendations was derived by an allergist-emergency physician team pair. Elements were then combined into a parameter during an in-person conference. The approach taken was to generate a practical, evidence-based tool that could be used by emergency medicine physicians to guide their practice. The consensus parameter includes an executive summary of recommendations. Each recommendation is supported by a discussion of the literature. Lastly, participants identified areas where lack of evidence suggests a role for future research, as well as possible barriers to implementation of the parameter. The parameter was appraised by external reviewers identified by the workgroup as experts in the field of Emergency Medicine and Allergy and Immunology. Based on this process this parameter represents an evidence-based, broadly accepted consensus document.

EXECUTIVE SUMMARY

Angioedema can be classified as either bradykinin-mediated or histamine-mediated angioedema. Angioedema secondary to ACE inhibitors is a common side effect of this class of drugs and occurs when decreased metabolism of bradykinin leads to excess accumulation. Hereditary angioedema type I and type II are forms of angioedema due to a functionally abnormal C1-inhibitor (C1-INH) gene that results in the overproduction of bradykinin. Hereditary angioedema with normal C1-inhibitor function with or without a genetic defect has been well- described, but to date only indirect anecdotal evidence supports bradykinin as the mediator. Acquired C1 inhibitor deficiency clinically resembles HAE but the low C1-INH is from consumption of the protein due to an underlying lymphoproliferative disorder and/or an antibody directed against C1-INH resulting in the overproduction of bradykinin. Most idiopathic angioedema is thought to be histamine- mediated and is frequently responsive to H1-antagonists, epinephrine and corticosteroids; however, refractory cases may be secondary to bradykinin. In patients with idiopathic angioedema unresponsive to H1-antagonists, epinephrine and corticosteroids, without a family history of angioedema, in the absence of direct evidence for bradykinin as the primary mediator of swelling, it would be premature to recommend the use of therapies approved for HAE.

Different types of angioedema have various historical features that are helpful for determining the putative cause. The physical exam of the angioedema patient should focus initially on vital signs and proceed to a targeted, focused exam of the airway, integumentary and abdominal regions. There are no point-of-care or laboratory based tests available in the ED to provide immediate guidance on treatment to the emergency medicine physician. However, C4 and tryptase levels should be considered to assist in the diagnosis of HAE and angioedema associated with anaphylaxis, respectively. Results of these labs when drawn during an angioedema attack are particularly useful during follow-up with a primary care physician, allergist or angioedema specialist and on return of the patient to the ED.

All patients with head and neck angioedema with any lingual involvement, as well as those with upper airway complaints, may benefit from flexible fiberoptic laryngoscopy, if immediately available, to determine the extent of involvement of the base of the tongue and the larynx. This is necessary to determine the possible need for airway management and the appropriate disposition of the patient. Radiographic techniques for assessment of the airway in patients presenting with acute angioedema have limited utility, and the unavoidable delay

and reduced medical observation caused by these procedures may impose unnecessary risk. General monitoring of angioedema patients in the ED should be performed in a similar manner to the approach taken for patients with other respiratory or airway complaints, which includes close monitoring of oxygen saturation, cardiac status, and clinical signs and symptoms. Maneuvers such as supplemental oxygen, nasal trumpets and bag-valve mask ventilation may be useful temporizing measures for the angioedema patient with mild airway involvement, but are not a substitute for intubation if there is any concern about airway compromise. The decision to intubate or perform a more aggressive procedure should be based on the physician's assessment of the patient's prior history, airway anatomy, other co-morbidities and objective nasopharyngeal findings. When invasive airway management is indicated, maneuvers may involve the placement of an endotracheal tube, which requires patient sedation and analgesia to ameliorate significant discomfort. Once the decision to intubate is made, a rescue plan should be in place that involves having alternative airway devices available as rescue devices, as well as the means to perform a cricothyrotomy if necessary.

Treatment of angioedema depends on historical features of the patient and, if available, their preexisting diagnosis. If angioedema presents with signs of anaphylaxis (urticaria, asthma, hypotension) epinephrine is recommended. Standard treatment for histamine-mediated angioedema includes H1 and H2 antagonists and corticosteroids and may require epinephrine in life-threatening situations. While generally not effective for bradykinin-mediated angioedema, these treatments are not contraindicated and if a putative cause of angioedema is unknown, epinephrine followed by H1 antagonists and corticosteroids should be given. The only potential acute treatment currently readily available for the treatment of ACE-induced or other bradykinin-mediated angioedema in the ED is fresh frozen plasma, which has a risk of viral transmission, allergic reactions and volume overload, and a possibility of worsening symptoms in HAE. Several targeted therapies are now FDA approved in the United States for the treatment of acute HAE attacks. These novel therapies, including icatibant, ecallantide and C1-inhibitor concentrate, are effective for the treatment of HAE attacks and may have benefit in ACE-induced angioedema, but data are limited to support these treatments for non-HAE patients. There is a paucity of data to guide disposition decisions for hospitalization versus discharge home for angioedema patients. The Ishoo criteria provide one potential way for a physician to assess risk and admission decisions; however, these criteria have not yet been validated.

I. ANGIOEDEMA: DEFINITIONS

Summary Statement 1. Angioedema can be classified as either bradykinin-mediated or histamine-mediated angioedema.(LB)—Histamine-mediated angioedema is often associated with urticaria and with swelling episodes that typically resolve within 24 to 48 hours. Causes include drugs, foods, latex and insect stings. Bradykinin-mediated angioedema is not mediated by immunoglobulin IgE antibodies and is not associated with urticaria. Swelling attacks in bradykinin-mediated angioedema typically last 2–5 days and are characteristically unresponsive to antihistamines and/or corticosteroids. (6, 12–14)

Summary Statement 2. Angioedema secondary to ACE inhibitors is a common side effect of this class of drugs and occurs when decreased metabolism of bradykinin leads to excess accumulation. (LB)—Angioedema is a well-known side effect associated with use of ACE inhibitors. About 0.1% to 0.7% of patients treated with these agents are estimated to develop angioedema, characterized mostly by edema of the lips and tongue.(15, 16) African-Americans and patients on immunosuppressants tend to be at higher risk.(17) The rate of development of angioedema has been shown to be the highest during the first 30 days of initiation of ACE inhibitor therapy and thereafter declines in incidence. However, there is still an increased rate of ACE inhibitor angioedema even in patients taking ACE therapy for longer than one year (18). The treatment of choice is discontinuing all ACE inhibitors. Even after discontinuing the ACE inhibitor, patients may be at increased risk of a subsequent angioedema attack for many weeks. In patients who do not discontinue the ACE inhibitor, the average time to the next angioedema event is 10 months.(19) The mediator of angioedema is bradykinin.

It is notable that other drugs affecting the renin-angiotensin system such as angiotensin receptor blockers and renin antagonists have been shown to cause angioedema, but secondary to a different unknown mechanism. Other non-histamine-mediated drug reactions include angioedema associated with inhibition of cyclooxygenase leading to an accumulation of leukotriene mediators as seen with reactions to non-steroidal anti-inflammatory drugs (NSAIDs).(20) Patients with this condition usually manifest with urticaria and facial swelling upon exposure to the drug, but can present with swelling only. (20)

Summary Statement 3. Hereditary angioedema type I and type II are forms of angioedema due to a functionally abnormal C1-inhibitor (C1-INH) gene that results in the overproduction of bradykinin. (LB)—Hereditary angioedema is a rare form of angioedema that affects approximately 1:50,000 in the general population.(21) Angioedema of this type usually begins in childhood or young adulthood and may worsen at puberty.(21) Fifty percent of patients manifest recurrent episodes of swelling or abdominal pain by the age of 10.(22) The underlying cause is a mutation of the gene encoding the C1 inhibitor, which is inherited in an autosomal dominant pattern with relatively high penetrance. Two subtypes are recognized. Type I, which comprises 85% of cases, has low antigenic and functional C1 inhibitor levels. Patients with normal or high antigenic C1 inhibitor levels but abnormal C1 inhibitor function are referred to as Type II.(21, 23, 24) Type II HAE is caused by synthesis of a dysfunctional C1-INH protein.(23–25) HAE due to C1 inhibitor deficiency has been shown to be mediated by bradykinin.(26) Many patients experience prodromal symptoms prior to an attack. A prominent prodromal symptom is erythema marginatum. This is an erythematous serpentine but non-pruritic and non-raised rash that should not be confused with urticaria.(27)

Summary Statement 4. Hereditary angioedema with normal C1 inhibitor function with or without a genetic defect has been well-described but to date only indirect anecdotal evidence supports bradykinin as the mediator. (C, LB) —Hereditary angioedema in patients with normal complement levels and normal C1-

inhibitor, but a well-defined family history of angioedema, is believed to be an autosomal dominant condition with low penetrance.(16, 28) Patients tend to present at a slightly older age compared to HAE due to C1-INH deficiency. It is reported more frequently in women and attacks are characteristically more common in the facial region, especially tongue swelling. When affected, men tend to have less severe and less frequent attacks. Taking estrogen- containing therapies increases attack frequency in most patients.(28, 29) A minority of these patients has a mutation in the gene encoding coagulation factor XII, but the underlying cause of angioedema is unknown.(16, 29) Bradykinin is presumed to be the mediator of swelling in these patients since most appear to respond to the same medications used to treat HAE with C1 inhibitor deficiency but not to H1-antagonists, corticosteroids and epinephrine.(16, 21)

Summary Statement 5. Acquired C1 inhibitor deficiency clinically resembles HAE but the low C1-INH is from consumption of the protein due to an underlying lymphoproliferative disorder and/or an antibody directed against C1-INH resulting in the overproduction of bradykinin.(B, LB)—Acquired angioedema with C1 inhibitor deficiency clinically resembles HAE due to C1 inhibitor deficiency but is not familial and tends to present in individuals over 40 years of age. Acquired C1 inhibitor deficiency results from excessive C1 inhibitor catabolism, which in approximately 15% of these cases is due to an underlying lymphoproliferative disorder and/or an autoantibody directed against C1-INH.(16, 30–32) The most common underlying disorders are lymphoreticular disorders (ranging from monoclonal gammopathy of unknown significance to lymphomas), but a variety of other malignancies and autoimmune disorders have been linked to the disease. In all cases, the mediator of swelling is bradykinin.

Summary Statement 6. Most idiopathic angioedema is thought to be histamine-mediated and is frequently responsive to H1-antagonists, epinephrine and corticosteroids; however, refractory cases may be secondary to bradykinin. In patients with idiopathic angioedema unresponsive to H1-antagonists, epinephrine and corticosteroids, without a family history of angioedema, in the absence of direct evidence for bradykinin as the primary mediator of swelling, it would be premature to recommend the use of therapies approved for HAE. (C)—Most patients with idiopathic angioedema are responsive to H1-antagonists, epinephrine and corticosteroids; however, there is a small group of patients with idiopathic angioedema who do not respond to H1-antagonists, and refractory cases may be secondary to bradykinin. There is limited and weak evidence that the mediator of swelling is bradykinin in this small subset of patients.

II. EVALUATION: HISTORY

Figure 1 summarizes how elements of the history and physical examination should help to establish the working diagnosis.

Summary Statement 7. Different types of angioedema have various historical features that are helpful for determining the putative cause.(B)—Table 2 summarizes the historical characteristics of different types of angioedema. Although these

characteristics do not directly distinguish one type of angioedema from another, they can help guide the emergency medicine physician toward the best possible treatment course.

III. EVALUATION: PHYSICAL EXAMINATION

Summary Statement 8. The physical exam of the angioedema patient should focus initially on vital signs and proceed to a targeted, focused exam of the airway, integumentary and abdominal regions. (D)

Vital signs: Although patients with either bradykinin- or histamine-mediated angioedema may have normal hemodynamic parameters, a number of patients may exhibit profound hypotension, tachycardia and respiratory failure secondary to fluid shifts and airway edema. Due to vasodilation and increased vascular permeability, both bradykinin- and histamine-mediated angioedema have the potential to cause hypovolemic shock due to the shift of fluids in various bodily compartments. More importantly, asphyxiation secondary to airway edema is the leading cause of death in such patients and thus it is essential to recognize subtle aspects of stridor and voice change in such patients immediately.(33)

Head and Neck: A focused, detailed oropharyngeal exam is essential in evaluating patients with either bradykinin- or histamine-mediated angioedema, specifically noting any edema in the lips, tongue, soft palate or posterior pharynx since many treatment algorithms are determined by the specific region of the oropharynx affected. In particular, any presence of stridor or hoarseness must be noted since further diagnostic tests may be necessary such as nasopharyngoscopy.(33)

Although oropharyngeal involvement can occur with either bradykinin- or histamine-mediated angioedema, it is more commonly seen in bradykinin-mediated angioedema. Over half of the patients with HAE have at least one episode of laryngeal edema during their lifetime. In the past, 30% of deaths in patients with HAE were due to laryngeal edema.(11, 34) In patients with ACE inhibitor induced angioedema, the head and neck is the site most commonly affected.

Integumentary: The characteristic physical exam finding in bradykinin-mediated angioedema is a firm, non-pruritic swelling resulting from the accumulation of fluid in the reticular dermis and subcutaneous or submucosal tissue. The lesions are sometimes tender to palpation and are non-pitting. Histamine- mediated angioedema involves the deeper dermis and tends to be more commonly associated with urticarial lesions that are discrete, pruritic erythematous papules in the epidermis that blanch with pressure. Both lesions arise from local vasodilatation and increased vascular permeability. Although it is uncommon to have urticarial lesions in bradykinin-mediated angioedema, some studies suggest that up to 50% of patients with histamine-mediated angioedema may present with both angioedema and urticarial lesions.(21, 35, 36) In HAE, the most common sites of edema include the arms, legs, hands and feet.(21)

Abdomen: Patients with bradykinin- or histamine-mediated angioedema may present with gastrointestinal symptoms. However, a patient presentation consistent with an “acute surgical abdomen” on exam, with severe tenderness, guarding and rebound tenderness due

to bowel wall edema is much more characteristic of HAE patients. Cases of unnecessary abdominal surgery have been documented in HAE patients.(21)

IV. EVALUATION: ANCILLARY TESTING

Summary Statement 9. There are no point-of-care or laboratory based tests available in the ED to provide immediate guidance on treatment to the emergency medicine physician. However, C4 and tryptase levels should be considered to assist in the diagnosis of HAE and angioedema associated with anaphylaxis, respectively. Results of these labs when drawn during an angioedema attack are particularly useful during follow-up with a primary care physician or angioedema specialist or upon return of the patient to the ED. (LB)—Almost all patients with HAE types I and II have a persistently low serum C4 level; C4 is an excellent screening tool for C1 inhibitor deficiency states.(13, 21, 37) C4 levels combined with C1 inhibitor level and C1 inhibitor function (<50% using the chromogenic assay or <68% using the quidel assay) can be used to differentiate between Type I and Type II HAE, and HAE that is not mediated by C1 inhibitor deficiency.(38) If C4 is normal during an attack in a patient not on androgens or C1-inhibitor replacement, proceeding to C1 inhibitor analysis is unnecessary.(13) Currently, the C4 test is not recommended for patients younger than one year because of its unreliability in this age group. C1 inhibitor and C4 concentrations increase to adult levels between 2 and 3 years of age.(39) The chromogenic functional C1 inhibitor assay appears to be superior to the ELISA-based (quidel) C1 inhibitor functional assay.(37)

Serum tryptase levels are sometimes considered in differentiating various causes of angioedema. Tryptase is normal in hereditary angioedema I and II and may be elevated in cases of anaphylaxis or other mast cell-mediated disorders manifesting with angioedema. An elevated tryptase level can be helpful in ruling out hereditary angioedema although a normal tryptase level provides no discriminatory information.

Laboratory testing is of little use to the ED evaluation and management of the patient with angioedema. Measurement of C4 and tryptase levels to discriminate between bradykinin- and histamine-mediated angioedema, respectively typically takes longer to process and provide results than the time-frame in which management decisions must be made in the ED. By the time testing is complete, it is known whether or not the patient has responded to H1-antagonists, corticosteroids and epinephrine, and thus the likely mechanism for the attack can be surmised. Laboratory testing at the time of an attack, however, can be useful for the long-term management of patients with angioedema. For example, in 2–4% of cases of HAE the C4 level is normal in between attacks but is low in virtually 100% during acute angioedema attacks, and in these patients subsequent measurements of the antigenic and functional C1 inhibitor level are helpful to evaluate for HAE Type I vs. Type II. (21, 37, 38)

Measuring the C4 level is an effective screening test to rule out HAE Type I and Type II, and initiating this in the ED will ensure the patient has results available during follow-up and subsequent ED visits.(21) It is not useful to screen with a CH50 or C3 complement level.(38) It is prudent to obtain a C4 level in a patient with angioedema when no obvious etiology is found, especially if the angioedema appears to be mediated by bradykinin.(39) It

is important that C4 is sent to the laboratory in a timely fashion, as degradation and artificially low C4 levels may be reported if there is a significant delay in transfer or poor handling.(37)

Summary Statement 10. All patients with head and neck angioedema with any lingual involvement, as well as those with upper airway complaints, may benefit from flexible fiberoptic laryngoscopy, if immediately available, to determine the extent of involvement of the base of the tongue and the larynx. This is necessary to determine the possible need for airway management and the appropriate disposition of the patient.(C)—In the perioral region and neck, angioedema can involve any number of mucosal sites from the lips to the larynx, and the involvement of these sites is random and can be noncontiguous.(33, 40–46) Angioedema of the upper aerodigestive tract can be life-threatening if it causes airway compromise that is not recognized and treated. A major question for emergency physicians is how and in who to evaluate the airway beyond what can be seen on physical examination.(33, 40–46) Current studies are of small sample size but suggest that any presentation of head and neck angioedema can have associated swelling of the larynx, base of the tongue or both. We recommend that those patients with involvement of the tongue, soft palate or floor of the mouth should have direct visualization, if immediately available, of the base of tongue and airway. Patients who do show involvement of these deeper structures may require airway intervention or at least close monitoring in an intensive care unit with repeat laryngoscopy depending on any changes in symptoms. Patients without involvement of these deeper structures may be medically treated, observed for a number of hours to document resolution of the swelling, and then discharged home.(33, 40–46). If nasopharyngoscopy is not immediately available to the emergency physician, then the clinical assessment should consider stridor, hoarseness, drooling and swelling as potential signs of airway involvement.

Summary Statement 11. Radiographic techniques for assessment of the airway in patients presenting with acute angioedema have limited utility, and the unavoidable delay and reduced medical observation caused by these procedures may impose unnecessary risk.(C)—There is very little in the medical literature regarding the use of neck x-rays or CT scans to help determine the extent of airway involvement in a patient presenting with acute angioedema. The use of radiography has most value in ruling out certain disease processes that may mimic angioedema, such as an abdominal CT scan in the patient with acute abdominal pain. The use of laryngeal ultrasonography may prove beneficial as a non-invasive tool to assess airway involvement, yet no studies to date have explored its feasibility or utility.

V. TREATMENT: ACUTE AIRWAY MANAGEMENT OF ANGIOEDEMA

Summary Statement 12. General monitoring of angioedema patients in the ED should be performed in a similar manner to the approach taken for patients with other respiratory or airway complaints, which includes close monitoring of oxygen saturation, cardiac status, and clinical signs and symptoms.(D)—The approach to monitoring patients with angioedema is similar to the course taken with other ED patients with either respiratory or airway complaints. All patients should be placed

on a pulse oximeter and a cardiac monitor. Pulse oximetry is useful to determine initial oxygenation during the primary assessment. Equally important, the physician can follow pulse oximetry to note trends with time and therapy. Unfortunately, pulse oximetry may be a late marker of airway issues and not be abnormal until there is significant upper airway edema, at which point the patient could already be in significant respiratory distress. In general, even if pulse oximetry is in the normal range for the patient, it should not be the primary factor in the decision to intubate if there is concern about significant upper airway compromise. Similarly, cardiac monitoring is helpful to determine if there are other causes of the patient's complaints, such as an arrhythmia or cardiac ischemia, or after potential cardiac-stimulatory medications (epinephrine) have been given. As with pulse oximetry, trends in cardiac monitoring may give an indication of whether the patient's situation is worsening or whether initial therapy is helping.

Capnography is a useful adjunct to monitor a patient's respiratory status, and is a more sensitive indicator of ventilation difficulties than pulse oximetry. However, similar to pulse oximetry, patients with pending upper airway obstruction often have normal capnography despite heading toward impending airway compromise. Capnography can be useful in two other scenarios associated with angioedema: 1) monitoring the adequacy of ventilation after intubation, and 2) monitoring the level of sedation associated with other medications that may have been used for diagnostic (benzodiazepines/ketamine to facilitate nasopharyngoscopy) or therapeutic (H1-antagonists in the initial management of undifferentiated upper airway difficulties) purposes.

Summary Statement 13. Maneuvers such as supplemental oxygen, nasal trumpets and bag-valve mask ventilation may be useful temporizing measures for the angioedema patient with mild airway involvement, but are not a substitute for intubation if there is any concern about airway compromise.(D)—Supplemental oxygen may be considered for patients with airway or respiratory complaints, and should be applied to those who are hypoxic. Nasopharyngeal airway devices (i.e. nasal trumpets) may act as temporizing measures and may assist with bag-valve mask ventilation. While bag-valve mask ventilation may temporarily be able to overcome the airway obstruction, as the disease progresses to significant laryngeal involvement, bag-valve mask ventilation will become very difficult. Non-invasive ventilation such as continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP) may act as a temporary measure to assist with ventilation in patients with hypercarbia. However, positive pressure ventilation does not aid in stenting open the airway for a prolonged period of time and is not definitive therapy.

Summary Statement 14. The decision to intubate or perform a more aggressive procedure should be based on the physician's assessment of the patient's prior history, airway anatomy, other co-morbidities and objective nasopharyngeal findings.(D)—The decision to intubate can be based on 2 broad approaches: 1) clinical gestalt and 2) objective evaluation. *Clinical gestalt* accounts for a patient's prior history, such as previous rapid progression to intubation, difficult airway anatomy, or concomitant comorbidities that may impact the need and ease of intubation such

as underlying cardiorespiratory disease. The *objective evaluation* combines physical examination with nasopharyngoscopy findings. Findings such as a change in the patient's voice, hoarseness, and stridor should raise the suspicion for significant airway involvement and the need for a definitive airway.(33) Further, examination of the oropharynx is also important to differentiate those with primarily lip and anterior tongue swelling from others. An objective evaluation may provide more specific information about where the edema is occurring or how extensive the progression.

Because of the importance of differentiating upper and lower airway involvement, in patients with throat or voice complaints it may be prudent to obtain direct visualization of lower airway structures. Visualizing epiglottic, aryepiglottic or laryngeal edema should raise concern for the need to secure the airway sooner than later. There are several methods to facilitate this evaluation, including an awake intubation or nasopharyngoscopy. Both of these approaches are discussed below. Tongue involvement should heighten one's suspicion of possible airway concerns, while pharyngeal or laryngeal involvement definitely warrant close monitoring and consideration of early invasive airway management.

Summary Statement 15. When invasive airway management is indicated, maneuvers may involve the placement of an endotracheal tube, which requires patient sedation and analgesia to ameliorate significant discomfort. Once the decision to intubate is made, a rescue plan should be in place that involves having alternative airway devices available as rescue devices, as well as the means to perform a cricothyrotomy if necessary.(C)

Choice of invasive maneuvers: Extraglottic and supraglottic devices have become common rescue devices for use in the prehospital setting, the operating room, and the emergency department. In many cases, they have also superseded endotracheal intubation as the primary method of choice for securing a patient's airway. However, they are not appropriate for patients with angioedema. Since a high proportion of patients with lingual and laryngeal involvement require intubation, there is a high likelihood that an extraglottic device will remain above the airway obstruction.(33). While some extraglottic devices allow for blind passage of an endotracheal tube through them, there is only a slim chance that a blindly passed tube will be able to thread between the edematous tissues present in angioedema. In fact, the trauma caused by the tube if it fails to pass may precipitate worsening symptoms. In patients with angioedema who require airway management, endotracheal intubation is the procedure of choice.

Induction agents: If a patient is not predicted to have a difficult airway and laryngoscopy is to be performed, standard induction and paralytic agents should be chosen. Etomidate is frequently used in the ED management of patients requiring intubation at a dose of 0.3 mg/kg IV. Etomidate is widely available, has a rapid onset time, and is appropriate for use in patients with angioedema. If available, ketamine may be a preferable agent. Induction doses of ketamine, typically 1.5 mg/kg IV, do not preserve airway reflexes. However, lower doses, typically below 1mg/kg, may preserve a patient's abilities to maintain his or her own airway and be appropriate for awake intubation. Midazolam is slower in onset but can serve as an induction agent when etomidate and ketamine are not available.

Paralytics: Paralytics should be used with caution in patients with angioedema. Once given, the patient will be unable to respire on his or her own and the full responsibility of maintaining oxygenation and ventilation falls on the provider. If the provider is unable to intubate and the angioedema prevents effective bag-valve mask ventilation, a cricothyrotomy may be required. Succinylcholine is the most commonly used paralytic agent for intubation in the ED, having rapid onset at a dose of 1.5mg/kg IV. Succinylcholine is contraindicated in the presence of burns, denervating diseases, crush injuries, myopathies, and other risk factors for succinylcholine-induced hyperkalemia. If these comorbidities are present, non-depolarizing neuromuscular blocking agents such as rocuronium (1.0 mg/kg) and vecuronium (0.01 mg/kg) are appropriate alternatives.

Intubation methods: The decision of how best to intubate a patient with angioedema should be made based upon the patient's prior history of disease severity and any direct airway visualization.(47) If the patient has difficult airway predictors, a history of having a difficult airway, or angioedema so severe that the airway cannot be directly visualized, rapid sequence intubation with paralysis should not be attempted. Awake intubation using either video laryngoscopy or fiberoptic nasotracheal intubation should be performed. This allows for airway management without the removal of a patient's airway reflexes until the endotracheal tube has passed through the vocal cords.

For awake intubation, local anesthesia should first be used, including atomized or topical nasal vasoconstrictors and anesthetic agents, followed by a drying agent such as glycopyrrolate (0.4–0.8 mg IV) to decrease saliva secretion and facilitate visualization. After sedation, the intubation can be performed. Nasotracheal intubation should never be performed blindly in the patient with angioedema as airway distortion makes passage of the endotracheal tube extremely unlikely and localized trauma may induce further swelling. However, a fiberoptic nasopharyngeal scope or bronchoscope, if available, may be used to directly visualize passage of the tube. The endotracheal tube should be pre-loaded onto the scope and then the scope passed through the nose. Similarly, video laryngoscopy can be used in patients who are only partially sedated. Additional sedation and a paralytic agent can be administered as soon as the airway is secured.

In patients without a difficult airway, video laryngoscopy still allows for better intubating conditions than direct laryngoscopy, resulting in faster times to intubation and an improved first-pass success rate. A direct laryngoscope may be used with awake laryngoscopy, if needed, or may be used to intubate the patient directly via rapid sequence with both a full-dose induction agent and a paralytic if a difficult airway is not predicted.

Patients with angioedema may have such severe edema that passage of an endotracheal tube through the glottis is impossible, even with advanced fiberoptic or video techniques. In these cases, a cricothyrotomy will be required. In those patients in whom this is anticipated to be a possibility, the location of the cricothyroid membrane should be marked prior to any airway intervention being attempted and, ideally, local anesthetic pre-injected with the cricothyrotomy kit opened as a "double setup" in case it is needed emergently.

VII. ACUTE PHARMACOLOGIC TREATMENT OF ANGIOEDEMA

Summary Statement 16. Treatment of angioedema depends on historical features of the patient and, if available, their preexisting diagnosis.(C) If angioedema presents with signs of anaphylaxis, epinephrine is recommended. Standard treatment for histamine-mediated angioedema includes H1 and H2 antagonists and corticosteroids and may require epinephrine in life-threatening situations.(A) While generally not effective for bradykinin-mediated angioedema, these treatments are not contraindicated and if the putative cause of angioedema is unknown, epinephrine followed by H1 antagonists and corticosteroids should be given.(C)—If the cause of angioedema is not apparent, initial standard of care treatment of angioedema should include epinephrine, H1and H2 antagonists and oral corticosteroids. If the patient manifests other organ system involvement (wheezing, shortness of breath, chest tightness), urticaria, or drop in blood pressure consistent with anaphylaxis, epinephrine should be administered. Epinephrine and oxygen are the most important therapeutic agents administered in anaphylaxis. Although there are no direct data to demonstrate that antihistamines mitigate any noncutaneous symptoms, theoretical benefit is possible. (48) Appropriate volume replacement either with colloid or crystalloids is essential for patients who are clinically unstable or refractory to initial therapy.

Epinephrine is the drug of first choice for life-threatening histamine-mediated angioedema, in particular when there is airway swelling or hypotension.(48) It is not contraindicated in bradykinin-mediated angioedema but may have minimal benefit for severe upper airway swelling until other drugs and intubation are available. Epinephrine is not indicated for non-life-threatening angioedema not involving the airway. Epinephrine (0.01 mg/kg of a 1:1000 solution to a maximum of 0.5 mg) is best given intramuscularly for rapid absorption; intravenous administration should be avoided except in an emergency or code-type resuscitation. Duration of action is short so repeat dosing may be required if symptoms persist or return. Adverse effects are short- lived and include increased heart rate, tremor and anxiety. Use should not be withheld if indicated despite heart disease or other cardiovascular diseases.

H1 antagonists are the treatment of choice to suppress histamine-mediated angioedema, although they have no benefit in bradykinin-mediated angioedema.(10) Because H1 antagonists are well-tolerated with minimal adverse effects, other than sedation, they should be administered in the absence of a clear history of HAE or ACE inhibitor-induced angioedema. In older adults, side effects can include delirium, urinary retention, constipation and effects on ocular pressure. For time-critical therapy IV diphenhydramine is the preferred agent. Doses vary by specific agents. The benefit is limited in anaphylaxis and in airway swelling; H1 antagonists should never be used in place of epinephrine for these two emergencies. Low dose or non-sedating agents are preferred if time is not critical. H2 blockers, added to H1 antagonists, may be considered to prevent hypotension and urticaria associated with pruritus secondary to histamine. There is limited data to support the use of H2-blockers for allergic emergencies associated with angioedema in the acute setting.(48, 49)

Corticosteroids are effective for histamine-mediated angioedema.(48) They have little to no benefit in bradykinin-mediated angioedema. Their action depends on suppression and activation of many proteins and peptides and onset can take hours to days. They should not be used as a substitute for epinephrine for this reason. Adverse effects limit long-term use, but for acute therapy the adverse effects are considered acceptable. Dosing is specific to the agent. For IV therapy, 60 to 120 mg of methylprednisolone is commonly used, but randomized studies in angioedema are lacking. In those with allergy to other corticosteroids, dexamethasone is the preferred agent.

Summary Statement 17. The only potential acute treatment readily available for the treatment of ACE-induced or other bradykinin-mediated angioedema in the ED is fresh frozen plasma, which has a risk of viral transmission, allergic reactions and volume overload, and a possibility of worsening symptoms in HAE.(B)—Fresh frozen plasma (FFP), which contains variable amounts of C1-INH, may be used for volume replacement in patients failing initial therapy. It tends to be readily available, inexpensive and is effective in most cases.(37) There is a possibility of a hypersensitivity reaction to FFP. Worsening of an HAE attack has been described when FFP is given, but this has not been documented in the literature for ACE-induced disease.(37) The worsening of an HAE attack is believed to be due to providing additional substrate that may potentially worsen attack symptoms.(37) This is primarily of concern only when the angioedema involves the airway.(37) However, other investigators have reported this phenomenon with FFP to be rare.(50)

Patients with a history of HAE may be taking anti-fibrinolytics and anabolic androgens for prophylaxis at the time of attack.(21, 37) Neither have an onset of action fast enough to be effective for treatment of an attack, although many patients will report taking “extra” androgen doses when an attack begins. (21, 37) Neither anti-fibrinolytics nor androgens will interfere with effectiveness of therapies for HAE.(21, 37) However, knowledge that anti-fibrinolytics and androgens may be prescribed to and used by this population helps identify these patients as possibly having HAE.(21, 37)

Analgesics and anti-emetics should be prescribed as needed to alleviate the pain and nausea frequently manifested by HAE patients presenting with an acute abdominal attack. In mild HAE attacks analgesics and anti-emetics may be all that is needed; however, use of targeted therapies may mitigate the need for narcotics and result in more rapid resolution of the pain.

Summary Statement 18. Several targeted therapies are now FDA approved in the United States for the treatment of acute HAE attacks.(A) These novel therapies, including icatibant, ecallantide and C1-inhibitor concentrate, are effective for the treatment of HAE attacks and may have benefit in ACE-induced angioedema, but data are limited to support these treatments for non-HAE patients.(C)—Bradykinin-mediated angioedema resulting from dysregulation of the kallikrein-bradykinin pathway is distinct from allergic or histamine-mediated angioedema.(21, 37) Because bradykinin-mediated angioedema is generally unresponsive to H1 antagonists, corticosteroids, and epinephrine, five medications targeted at the underlying pathophysiology have been developed: two purified C1-INH protein concentrates derived

from pooled donor plasma, a recombinant C1-INH protein product, a kallikrein inhibitor—ecallantide, and a bradykinin 2-receptor antagonist—icatibant. Of these, three are FDA approved for attacks of HAE: ecallantide, icatibant and one of the purified C1-INH protein concentrates. Table 3 summarizes these agents, their mechanism of action, dosing and side effects.

Human plasma-derived C1-INH concentrate (Berinert- CSL Behring, Marburg, GR) administration provides the native plasma protein with numerous physiologic inhibitory functions, including regulation of Factor XII and kallikrein activity thereby reducing bradykinin production in the setting of C1-INH deficiency. C1-INH protein concentrate is FDA-approved for the treatment of acute abdominal, facial, or laryngeal attacks of HAE in adult and adolescent patients, at a dose of 20 U/kg, given intravenously.(51) This dose is apparently appropriate in children even though it is off label in those patients below 12 years of age.(52, 53) Another plasma derived C1-inhibitor, Cinryze (Viropharma, Exton, PA, USA) can also be used off label for HAE attacks in the USA and is approved for the treatment of HAE in adults in the EU at 1000 units IV. Recombinant human C1-INH (Ruconest) replaces C1-INH protein activity. It is currently investigational in the United States, but is licensed in Europe for the treatment of HAE attacks in adults (See Table 3). (54)

Ecallantide (Kalbitor) is a highly specific plasma kallikrein inhibitor targeted at reducing kallikrein-mediated production of bradykinin. This product is FDA-approved for the treatment of acute HAE attacks in patients 16 years and older and is administered by 3 subcutaneous injections (each injection 1cc or 10 mg) for a total dose of 30mg.(55) Due to a risk of anaphylaxis, which was observed in approximately 3% of study participants, ecallantide should be administered under the direct supervision of a health care professional capable of treating hypersensitivity reactions.(37) Since the majority of the anaphylaxis reactions occurred within 1 hour of use, observation of the patient for at least 60 minutes or greater following use of ecallantide is recommended.

Icatibant (Firazyr) is a synthetic decapeptide and selective bradykinin-2 receptor antagonist that blocks the vascular effects of bradykinin. FDA-approved for physician- or patient-administered treatment of HAE attacks in adults 18 years and older, it is administered by single subcutaneous injection at a dose of 30 mg.(56) Pain and erythema at the injection site occurs in the majority (97%) of patients, but this side effect is considered relatively benign and temporary. As with ecallantide and C1-INH, a second, and rarely a third dose of icatibant may be necessary.

No randomized comparative studies of the targeted therapies have been conducted and both trial design and efficacy end points have differed among the studies. Differences also exist among agents with regard to safety concerns and route of administration. Clinical studies of HAE-specific agents have also demonstrated that a small subset of HAE attacks (~10%) require a second dose of medication due to a partial response or recurrence of symptoms.

Studies examining the efficacy of these agents in ACE-I and acquired angioedema are ongoing.(57–60) Their use in idiopathic angioedema refractory to histamine-targeted treatment has not been studied.

VIII. DISPOSITION

Summary Statement 19. There is a paucity of data to guide disposition decisions for hospitalization versus discharge home for angioedema patients. The Ishoo criteria provide one potential way for a physician to assess risk and admission decisions; however, these criteria have not yet been validated.(C)

Risk Stratification: Patient disposition for hospital admission or discharge home should be determined according to the severity of their airway involvement. The Ishoo classification includes principles that can be applied to various bradykinin-mediated angioedema disorders.(33) While this tool does assist the treating physician with information to aid in risk stratification, it was derived retrospectively, has yet to be validated, and requires the use of laryngoscopy to stage a patient (Table 4).

Patients in classification stages I and II with only face, lip or soft palate edema can often be managed as outpatients or admitted to an extended monitoring location (inpatient ward or observation unit). This is because patients at Ishoo stage I or II and patients with a normal appearing larynx on nasopharyngoscopy rarely progress to the need for airway intervention.(61) When the angioedema involves more than three physical sites from among lips, anterior tongue, floor of mouth, soft palate, base-of-tongue and larynx, there is increased risk of airway involvement and therefore outpatient management is not recommended.(43) Generally, all patients with respiratory distress or in need of an airway intervention should be admitted to an intensive care unit; Patients in Stages III and IV should be cared for in the intensive care unit.

Role of Observation Units: Patients with mild to moderate angioedema that are admitted to the inpatient ward can frequently be discharged home within 24 hours.(33) This opens the possibility of using ED-based observation units. Although not rigorously studied for use in angioedema, some centers have implemented angioedema protocols in ED-based observation units, and standardized diagnostic and therapeutic protocols with inclusion/exclusion criteria and disposition decision aids already exist (http://www.emergencykt.com/).

Consultation in the Emergency Department: Consultation with anotolaryngologist should be considered regarding decisions on airway management if time permits. Consultation with an allergist/immunologist for the treatment of ED patients with acute and/or recurrent angioedema is unlikely to change the emergent or acute therapeutic course and airway management. However, consultation may guide the emergency physician in obtaining useful laboratory testing during the time of an attack, and for ensuring that appropriate follow-up is arranged. Patients with HAE presenting with angioedema may have targeted therapy available, and consultation with their HAE specialist, which is most often an allergist/immunologist, could guide the use of targeted therapies.

Follow-up: A well-formulated plan with which the treating clinician is comfortable and follow- up to an appropriate care provider can allow patients with mild to moderate angioedema to be discharged home and avoid an unnecessary hospital admission. Results from testing performed in the ED, in particular C4 and tryptase levels, usually require greater than 24 hours for processing, and therefore should be evaluated during the follow-up visit. Patients with HAE should have follow-up with a specialist familiar with their disease, who can be involved in their care.(52) In addition, when it is a patient's first episode of angioedema, the attack is unresponsive to H1 antagonists and corticosteroids, and the patient carries a family history of angioedema, it is important to arrange follow-up with an HAE specialist which is usually an Allergist/Immunologist, as the patient may have HAE. This will ensure the patient is educated on HAE triggers, including medications such as estrogens and ACE-inhibitors, and on procedures including both surgery and invasive dental work.(30) Moreover, when the patient is in the care of an HAE specialist it is more likely he or she will have an individualized emergency action plan in place to treat angioedema, which involves targeted treatments, including home treatment options that may reduce the need for potential future ED visits.(53, 54) Patients with HAE may present to an ED with their emergency plan and their medications. As many EDs /hospitals have specific policies regarding the administration of these "brown bagged" therapies, it is beneficial to have this policy addressed in advance. When developing an emergency plan, an ED near the patient's home should be identified. However, such an arrangement may not always be feasible when patients travel or are not near their home.

Discharge instructions: When discharged from the ED, patients should have ready access to at least one specific modality to treat recurrent symptoms. In the case of HAE, this may include a targeted on-demand therapy.(52) For all other patients, and for suspected HAE where no targeted therapy is available for self-administration, they should be discharged with an epinephrine auto-injector kit until seen by an angioedema specialist who can confirm their diagnosis and the need for specific therapy. Many HAE patients prescribed pdC1-INH or ecallantide are required to have epinephrine on hand in the event of an allergic reaction to these agents. The patient and family members or friends should receive training for self-administration of targeted therapies in case the patient can't self-administer during an attack. For patients with known HAE who have on-demand targeted therapy available to them already, refresher training on self-administration of their rescue medication may be needed. The patient should be told to return to the ED, their specialist, or their primary care provider if symptoms persist or worsen.(52) Patients with ACE-inhibitor-induced angioedema should be told to discontinue their ACE-inhibitor. An alternative anti-hypertensive agent should be discussed with the patient's primary care physician, if possible. Otherwise, the emergency physician should consider starting a substitute agent until primary care follow-up can be established. Although, a modest risk of recurrent angioedema may exist in patients with ACE-I angioedema switched to a calcium channel blocker or an angiotensin receptor blocker (ARB), most patients can safely use these agents without recurrent angioedema.(62, 63)

Follow-up: A well-formulated plan with follow-up to an appropriate provider can avoid an admission for the patient with mild to moderate angioedema whom the treating clinician is

comfortable discharging home. Testing performed in the ED, particularly C4 levels, can be evaluated during the follow-up visit. HAE patients should have a specialist familiar with the disease involved in their care.(64) When it is a patient's first episode of angioedema, the attack is unresponsive to H1 antagonists and corticosteroids, and the patient carries a family history of attacks, it is important to arrange follow-up with an allergist/immunologist or HAE specialist. This will ensure the patient is educated on HAE triggers, including medications such as estrogens and ACE-inhibitors, and both surgery and dental work.(38) Moreover, when the patient is in the care of an HAE specialist it is more likely he or she will have targeted treatment available, including home treatment options that should reduce the need for ED visits.(65, 66) Patients with HAE will often present to ED with an emergency action plan and specific therapy prescribed by their treating physician for home use or to take to an ED for administration in the event of emergency. It is encouraged that ED/ hospitals change policies if necessary to allow the administration of these ‘“brown bagged” therapies as directed in emergent situations.

Discharge instructions: When discharged from the ED, patients should have ready access to at least one specific modality to treat recurrent symptoms. In the case of HAE, this should include a targeted on-demand therapy.(64) For all others, and for suspected HAE where no targeted therapy is available for self-administration, they should be discharged with epinephrine until seen by an angioedema specialist who can confirm their diagnosis and appropriate therapeutic intervention. HAE patients on C1-INH or ecallantide are required to have epinephrine on hand in the event of an allergic reaction to these agents. The patient and any available friends or family should receive training for self-administration of targeted therapies. For patients with known HAE who have on-demand targeted therapy available to them already, refresher training on self-administration of their rescue medication may be needed. Most HAE specialists advocate for self-therapy to help ensure early treatment leading to shorter duration and less severe attacks, which may result in a reduction in absenteeism and morbidity and even potential mortality. The patient should be told to return to the ED, their specialist or their primary care provider if symptoms persist or worsen despite therapy.(64) Emphasis should be placed on the necessity for patients with upper airway swelling to self-treat without delay and present to the ED for observation since not all cases respond to therapy. Patients with ACE-inhibitor-induced angioedema should be told to discontinue their ACE-inhibitor. An alternative agent should be discussed with the patient's primary care physician, if possible. Otherwise, follow-up with a primary care physician to start a new anti-hypertensive or starting a substitute agent at the discretion of the emergency physician should be performed.

REMAINING CONTROVERSIES

As the parameter was developed, several areas were identified that required further investigation, including:

1. The use of novel pharmaceutical agents (C1-INH, kallikrein inhibitor or bradykinin receptor antagonist) in patients with ACE-inhibitor-induced or HAE with normal C1-INH.

2. The use of novel pharmaceutical agents (C1-INH, kallikrein inhibitor or bradykinin receptor antagonist) in patients whose poor response to conventional therapy suggests they have non-HAE non-histamine mediated angioedema which could be bradykinin mediated.
3. A validated clinical decision algorithm to identify patients who require nasopharyngoscopy.
4. The use of other modalities to assess the airway in patients with angioedema of the head and neck due to the potential unavailability of nasopharyngosopy.
5. A point of care or laboratory based test that can be used to rapidly differentiate bradykinin-mediated angioedema from other forms of angioedema.
6. Comparative-effectiveness studies to guide disposition decision-making and follow-up.
7. Head to head comparisons of available therapies to determine the most effective intervention for emergency care of the patient with ACE-induced angioedema or HAE

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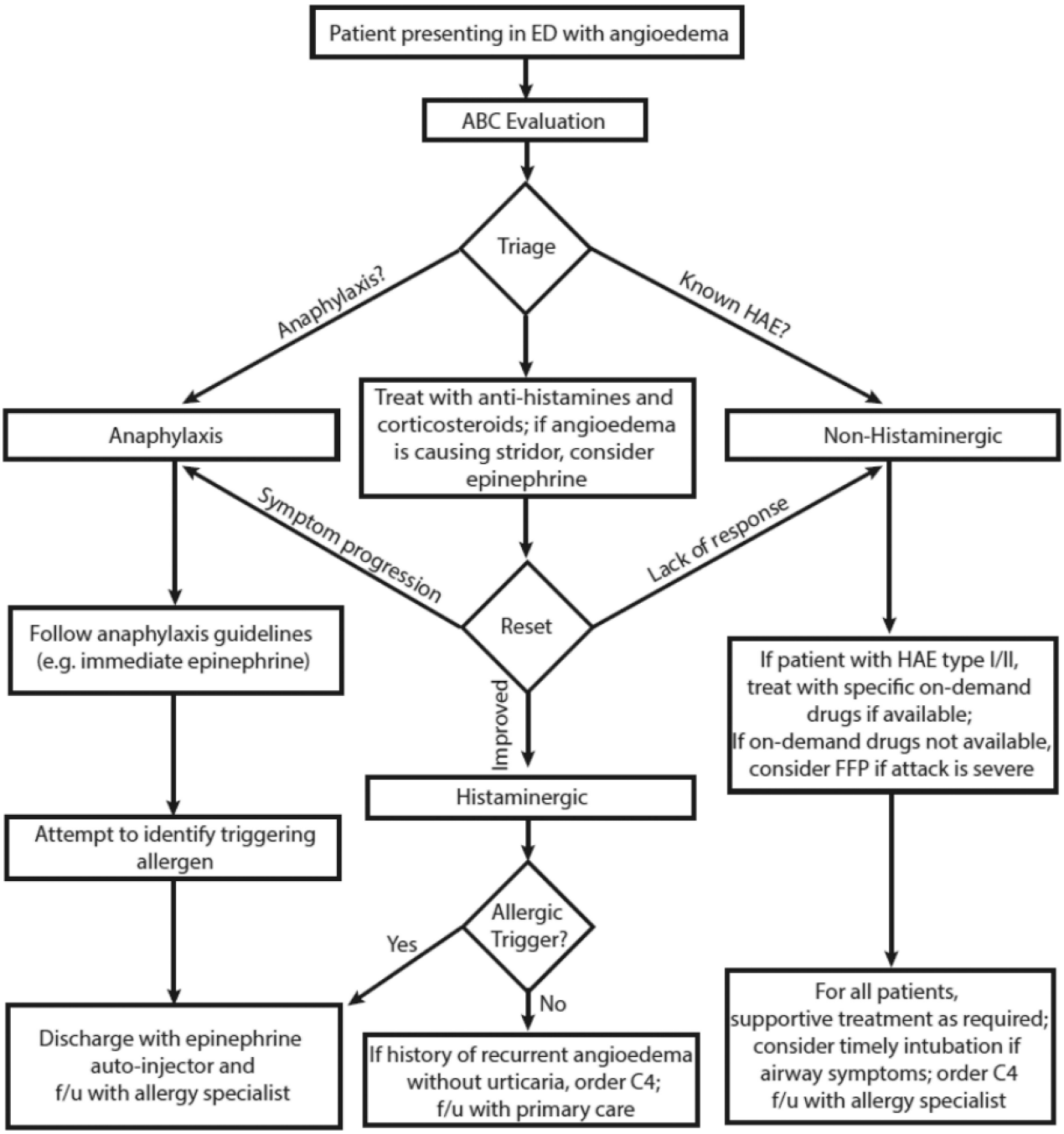

Figure 1. Algorithmic Approach to the Management of Angioedema in the ED

Employing a simple classification scheme for angioedema can help in developing an efficient and effective approach to assessing and managing patients presenting with angioedema. The first step in managing any patient in the emergency department is to sufficiently manage the airway and breathing, as well as to support circulatory function if necessary. Once the patient is stabilized a focused history and physical should be obtained to separate bradykinin-mediated (ACE-induced, HAE) from histamine-mediated. Subsequent distinctions between the underlying causes of angioedema can then be made to ensure

appropriate longitudinal management and follow-up care. If the patient is on an ACE inhibitor, stop medication and provide airway management support. If the patient has a known history of hereditary angioedema, treat according to HAE guidelines using one of the recommended “on demand” therapies (Table 2).(37) If the patient has signs of anaphylaxis (i.e., hypotension, vomiting, vasculature instability), administer epinephrine and treat according to anaphylaxis guidelines.(48)

Table 1

Classification of angioedema

High level classification	Disease	Pathogenesis	Prevalence	Salient features	Risk of mortality
Anaphylaxis	Anaphylaxis	IgE-mediated with mast cell degranulation	Common	Preceded by exposure to relevant allergen (especially foods, stinging insects, and drugs); rapid development of symptoms, often including pruritic urticaria with the angioedema. Multi-system involvement, possibly including lower respiratory, circulatory or gastrointestinal systems	Yes
Histaminergic angioedema without anaphylaxis	Allergic angioedema	IgE-mediated with mast cell degranulation	Common	Preceded by exposure to relevant allergen (especially foods, stinging insects, and drugs); rapid development of symptoms, often including pruritic urticaria with the angioedema	Variable
	Idiopathic angioedema	Probably mast cell degranulation	Common	Recurrent swelling usually but not always associated with pruritic urticaria	Very low
	Drug-induced	Probably mast cell	Common	Often associated with exposure to aspirin/NSAIDs or drugs that cause non-specific mast cell degranulation	Variable
Non-histaminergic angioedema	HAE due to C1-INH deficiency	C1-INH deficiency with bradykinin generation	Rare	Recurrent angioedema or abdominal pain without urticaria; may be associated with prodrome; symptoms usually begins before age 20 years; often positive family history with autosomal dominant inheritance	Yes
	HAE with normal C1-INH	Unknown, possibly with bradykinin generation	Rare	Recurrent angioedema without urticaria; often involves face and tongue; predominantly affects women; inherited in autosomal dominant pattern with low penetrance	Yes
	Acquired C1- INH deficiency	C1-INH deficiency with bradykinin generation	Rare	Recurrent angioedema or abdominal pain without urticaria. Usually seen in individuals over the age of 40 years and often associated with an underlying disease, especially lymphoreticular disorder	Yes
	ACEI- induced	Prolonged half-life of bradykinin	Common	Should be suspected in any patient with angioedema who is taking an ACE inhibitor (or an ARB). African-Americans and patients on immunosuppressives are at significantly enhanced risk. Can occur at anytime, even years after starting the ACEI.	Variable
	Idiopathic	Unknown, Possibly bradykinin	Rare	Resembles histaminergic idiopathic angioedema except that patients are non-responsive to even high-dose antihistamines.	Unknown

Table 2

Historical Features of Patients Presenting with Different Causes of Angioedema

Characteristic	HAE	Acquired	ACE induced	Allergic	Idiopathic
Age of onset	2-13 yrs	Adult	Adult	Any age	Any age
Family history	75%	No	No	History of Atopy	No
Ethnicity	None	None	80% African-American	None	None
Gender predilection	No**	No	No	No	No
Location of attacks	Peripheral, abdominal, facial, laryngeal, genitourinary	Peripheral, abdominal, facial, laryngeal, genitourinary	Lips, tongue, facial	Lips, tongue, laryngeal	Lips, tongue, rarely laryngeal
Speed of attack onset	Gradual over a few hours*	Gradual over a few hours	Gradual over a few hours	Immediate within 1 hour	Variable
Duration of attacks	3-5 days Without treatment	3-5 days Without treatment	24-48 hours after drug discontinued	Several hours Without treatment	Several Hours Without treatment
Recurrent nature of attacks	Yes	Yes with or Without treatment	No if drug discontinued; attacks can persist for 4-6 weeks after drug discontinuation	Yes only if re-exposed to allergen avoided	Yes with or Without treatment
Associated with urticaria	No	No	No	Yes or No	Typically No but possible
Presents with abdominal pain	Yes	Yes	Usually not	No	No
Response to H1 antagonists and oral corticosteroids	No	No	No	Yes	Variable
Response to epinephrine	No	No	No	Yes	Variable

* can have a rapid onset in less than an hour

** for hereditary angioedema with normal complement with or without a genetic mutations Female>>Male.

Table 3

Targeted Therapies for Treatment of Acute Hereditary Angioedema Attacks

Medication	Trade Name	Dose	Route	Common Side Effects	Potential Serious Side Effects	Mechanism of Action
Plasma-derived C1-INH	Berinert Or Cinryze (off label in the USA)	20 units/kg OR 1000 units for Cinryze	IV	Dysgeusia	Hypersensitivity reactions Thrombosis Blood borne Infectious risk	C1-INH Protein replacement
Ecallantide	Kalbitor	30 mg	SQ	Headache Nausea Pyrexia Injection site reactions	Hypersensitivity reactions	Plasma-kallikrein inhibitor
Icatibant	Firazyr	30 mg	SQ	Injection reactions Pyrexia Increased transaminases Dizziness	None reported	Bradykinin 2-receptor antagonist
Recombinant C1-INH*	Ruconest	50 units/kg	IV	Sinusitis Rash Pruritis	Hypersensitivity reactions	C1-INH Protein replacement

* currently not FDA-approved but licensed in Europe.

Table 4

Ishoo Classification for Monitoring Severity of the Upper Airway

Stage	Clinical Findings	Disposition
I	Facial rash, facial edema, lip edema	Home or admission
II	Soft palate edema	Home or admission
III	Lingual edema	Intensive care unit
IV	Laryngeal edema	Intensive care unit