Introduction

Angioedema is a relatively rare disease but when paired with urticaria, its incidence is around 25% over one’s lifetime. Men and women are generally affected equally and it most commonly presents in the 3\textsuperscript{rd} and 4\textsuperscript{th} decades of life (13). The disorder was first described by Milton in 1876 and described as an acute circumscribed edema of the skin by Quinke in 1882. Osler in 1888 postulated that angioedema was a defect in the nervous system and therefore coined the term angioneurotic edema. In 1963 Donaldson and Evans first identified C1-inhibitor deficiency as the culprit in hereditary and acquired forms of angioedema, giving us a better understanding of the disease process (4).

Angioedema can have devastating effects on the individual especially if airway insult occurs. Fortunately airway edema is not necessarily the most common presentation and if present often times is not severe enough to require intubation. In this article we will review the different types of angioedema, discuss acute and chronic management strategies, and finally discuss an algorithm of evidenced based medicine to triage these patients into appropriate treatment sites.

Mechanisms of Urticaria

1. **Immune Mediated:** Occurs when an antigen or allergen binds to a preformed IgE antibody on a mast cell that causes cross linking and degranulation. The most common antigens are penicillin or foods.
2. **Complement Mediated:** This most commonly occurs when antigen and antibody complexes form in the blood and the anaphylatoxins involved in complement lead to mast cell degranulation.
3. **Non-Immune Mediated:** Destabilization of the mast cell can occur in diseases such as “red man syndrome” when vancomycin is infused too quickly. Other medications that can cause this type of mast cell destabilization include contrast, NSAIDs, and alcohol.
4. **Autoimmune Mediated:** Circulating auto-antibodies can also lead to mast cell degranulation as in other autoimmune disorders.
As you can see with each of these mechanisms, mast cell degranulation is the key component to urticaria formation.

**Types of Angioedema**

As with urticaria, there are multiple types of angioedema that have been described. Allergic angioedema fits most closely with urticaria given the production of mast cell degranulation, but as you will see, other forms have completely different mechanisms. The most important thing to remember is that angioedema can lead to life threatening laryngeal swelling. Therefore in the acute setting appropriate triage and management is employed to quickly and safely treat patients. Only after the patient is stabilized is a proper history physical exam performed to identify the etiology.

Allergic Angioedema is the most common type seen. It occurs as a result of the classic histamine response where mast cell degranulation leads to increased vascular permeability and edema, bronchiolar constriction, skin rash, and increased mucous production. Classic triggers include food, medications, and insect bites/stings. Classic findings include cutaneous and laryngeal swelling, urticaria, wheezing, vomiting, diarrhea, and hypotension. Urticaria is almost always present, events rapidly progress, and an inciting event is often very easy to identify. Complement assays are normal in these reactions which can be helpful in identifying the type of angioedema as you will see later.

ACE inhibitor induced angioedema is not related to mast cells or the histamine response. Instead it is secondary to overproduction of bradykinin. Bradykinin is a potent endothelial vasodilator and has effects to increase vascular permeability and contract nonvascular smooth muscle. When ACE inhibitors are used they not only prevent breakdown of Angiotensin I to Angiotensin II, but they also prevent the breakdown of bradykinin into inactive peptides. Therefore bradykinin builds up and attacks can occur. Luckily this generally only occurs in about 0.1-0.2% of patients on ACE inhibitors. Airway and oropharyngeal edema is the most common presentation in contrast to other forms of angioedema. Therefore airway management is important. As in allergic angioedema, complement assays are normal.

Acquired angioedema is the most similar form to that of hereditary angioedema. These patients will have low levels of C1-INH but will not likely have a family history of angioedema. These patients often present in their 4th decade of life because the cause of the disease is secondarily mediated by disease that often do not present until the 4th decade of life. Patients with Type I acquired angioedema have lymphoproliferative disorders like myelodysplastic syndrome or monoclonal gammopathy of undetermined significance. Type II acquired angioedema is most commonly related to autoimmune disorders such as systemic lupus erythematosus. It is important to note that not only are C1-INH levels low, but all other complement levels are also low in this disorder including C4, C2, and C1q.

The last form of angioedema is called chronic idiopathic angioedema. This is basically a wastebasket term for all types of angioedema that cannot be characterized into one of the other forms. Urticaria is often present in these patients and laryngeal attacks are very rare. Complement levels are completely normal as well.

As you can see there are many forms of angioedema and each is treated differently based on the underlying mechanism of disease. After the patient is acutely managed and stabilized, history and physical exam becomes very important in defining the cause of the illness. Below is a list of important questions that must be answered to arrive at a proper diagnosis.
Symptom Duration?
Previous Events?
Other Rheumatologic/Autoimmune disorders?
Rashes present?
Is pruritis present?
Is there any family history of a similar attack?
What are the complement levels?

Differential Diagnosis

Above we have discussed the different types of angioedema but we must keep in mind that several infectious etiologies can mimic angioedema. Epiglottitis is the first disease that comes to mind because it can lead to aggressive supraglottic and laryngeal swelling. It occurs at a rate of 1:100000 in the United States but rates are much higher in countries that do not regularly perform vaccinations. Because of vaccinations staphylococcus and streptococcus represent the most common pathogens and hemophilus influenza is rarely seen (6). Patients generally present complaining of sore throat, muffled voice, dysphagia, and often times a recent URI. On exam they will appear quite toxic with fever, inspiratory stridor, tachycardia, drooling, and potentially sitting in the classic tripod position. Progression can be quite rapid and respiratory distress can occur. Acute management of the airway and supportive care with intravenous antibiotics and fluids are used to appropriately treat these patients. A high index of suspicion is needed to differentiate this disease process from angioedema.

The second disease that can mimic angioedema is Ludwig’s Angina. First described by Ludwig, “of a certain type of inflammation of the throat, which despite the most skillful treatment is almost always fatal” (8), angina is defined as, “to strangle.” In Ludwig’s Angina submandibular space swelling becomes so bad that the tongue is literally pushed posteriorly leading to airway obstruction or strangling. The reason for this posterior displacement of the tongue is due to two structures that limit spread of infection into the rest of the neck, the myelohyoid muscle and the hyoid bone. Because swelling cannot enter the rest of the neck, it festers in the submandibular space and often becomes suppurative. Infections of the submandibular space are dental in origin in 80-90% of cases (16). Mortality used to be 50% but with better airway management techniques, this has significantly dropped to around 8%. Infections are most commonly polymicrobial with staphylococcus, streptococcus and bacteroides species predominating. One study showed that there was a higher incidence of acute airway management in patients who had staphylococcus and black pigmented bacteroides species isolated (14). Patients with neutropenia, diabetes, and other immunocompromised states are predisposed. Treatment is again with acute airway management as needed, as well as intravenous antibiotics and supportive care.

With regards to acute airway management, nearly all patients with Ludwig’s angina in the past required tracheotomy as a means of airway management. Over the past 20 years, many advances in airway management beyond straightforward intubation have developed including the glide scope, fiberoptic intubation, and retrograde intubation techniques. In a study by Wolfe et al. (17), it was shown that the airway was managed with advanced airway techniques in 19/29 patients (65%) leading to intubation, without the use of tracheotomy. They concluded that tracheotomy is a now a last resort situation and that advanced airway intubation techniques should be attempted first in all situations.
Hereditary Angioedema (HAE)

Now that we have discussed the differential on angioedema, we will focus on HAE because several breakthroughs in management have become available recently. HAE represents 15,000-30,000 ED visits per year with an incidence of about 1:50,000 patients. Unlike acquired angioedema where patients often present in their 3rd and 4th decades, HAE patients often present in their 2nd decade and commonly go years with symptoms before a definitive diagnosis is made (2). One of the most frustrating and debilitating attributes of the disease is that patients will often have frequent recurrent attacks on average occurring every 45.3 days (18). This makes life very difficult for patients and can often lead to excessive anxiety about when the next attack will occur.

In terms of genetics this disorder is inherited as autosomal dominant. The mutation is on chromosome 11 and over 200 different mutations have been identified. It is important to note that just because a patient has no family history, this does not rule HAE out for them as a diagnosis. Spontaneous mutations can occur in approximately 20-25% of patients (2). There are two different types of HAE with Type I representing 85% of cases and Type II representing the other 15%. Type I patients exhibit decreased levels of circulating C1-INH in the bloodstream whereas Type II patients have normal levels of C1-INH in the blood but the function of those molecules are <30% of normal.

C1-INH has many mechanisms of action but the main one involves inhibiting the conversion of kininogen into bradykinin by kallikrein. As discussed earlier bradykinin is a potent endothelial vasodilator and excess of the molecule leads to an angioedema attack. When C1-INH is deficient or non-functional, conversion kallikrein is not inhibited and therefore overproduction of bradykinin occurs.

Characteristics findings in patients having an angioedema attack are diffuse, non-pitting, non-pruritic edema. These patients will not have the urticaria that can be found in other type of angioedema and this can act as a differentiating factor. The site of involvement is also very different when compared to that of allergic or ACE inhibitor induced angioedema. The extremities (47%) and gastrointestinal tract (33%) are most commonly affected with oral cavity/larynx (6%) involvement being much less common (4). Despite this fact, 50% of patients will develop at least one laryngeal event in their lifetime and the mortality rate is 30% if left untreated (2). Extremity and facial involvement is often asymmetric.

The timing of a HAE event is important to understand. As discussed earlier most patients develop their first episode or attack in the 2nd decade of life but have a delay of 10-20 years in diagnosis (1,2). The reason for this delay is that initial attacks can be limited to the gastrointestinal tract or extremities and resolve on their own without incident. Gastrointestinal complaints can be as simplistic as nausea, vomiting and diarrhea and replicate viral illnesses that we all experience. In contrast to patients with allergic angioedema, the edema generally occurs over several hours instead of several minutes and if left untreated symptoms will resolve within 1-5 days. Treatment of an acute attack, however, can significantly decrease time to recovery as well as severity of the attack (4). Forty to eighty percent of patients will present with a preceding prodome of erythema marginatum (non-pruritic), fatigue and local discomfort (5,15).

Several triggers have been identified in HAE. Certainly infection and stress have been implicated in the development of an acute attack, but hormonal changes such as menstruation or the use of oral contraception have also been identified. Trauma or surgery, especially in the mouth, has been a source for concern due to the risk of oral cavity and laryngeal involvement. Any trauma to the upper
aerodigestive tract can lead to swelling and therefore prophylactic treatment is often instituted in patients with HAE undergoing any type of dental work (10).

The use of laboratory testing is not very helpful especially in the acute setting. Certainly a CBC can help identify a leukocytosis if infectious etiologies are suspected, but history will often lead to this diagnosis. Bradykinin levels have been studied in the past and have been shown to be more elevated in affected limbs compared to the contralateral side (10). This again speaks to the asymmetry of the disease process. Finally, complement levels (C1-INH, C4, C2, C1q) are important to help differentiate the type of angioedema present, however their use in the acute setting does not change management strategies.

**Diagnostic Criteria**

Patients must have at least one clinical and one laboratory criteria to be diagnosed with HAE (10).

1. **Clinical Criteria**
   - Recurrent angioedema that is non-pitting, non-pruritic, non-erythematous, and self limiting lasting >12 hours without urticaria.
   - Unexplained recurrent abdominal complaints of vomiting and diarrhea resolving within 24-72 hours.
   - Recurrent oral, pharyngeal or laryngeal edema
   - Documented family history of hereditary angioedema

2. **Laboratory Criteria**
   - Antigenic concentrations of C1-INH <50% normal on two occasions after 1st year of age.
   - Functional C1-INH <50% on chromogenic assay or <84% on ELISA testing on two occasions after 1st year of age
   - Mutation in C1-INH gene that modifies protein synthesis or function

**Medical Therapy of Angioedema**

HAE is mediated by elevated levels of bradykinin not histamine from mast cell degranulation. Therefore antihistamines, steroids, and epinephrine do not modify the disease state. The problem is that when patients arrive in the emergency setting acutely, unless the patient is well known to the hospital, the etiology of edema is not known and aggressive early treatment must be instituted. This means that patients are often treated with anti-allergic angioedema medications.

Antihistamines do not alter bradykinin levels. Despite this fact many angioedema algorithms were developed and evaluated with antihistamines as a part of their treatment protocol. Therefore successful protocols indirectly show antihistamines to be effective. Despite the lack of evidence that antihistamines change the natural history of a HAE attack, one study by Grant et al. in 2007 (7) showed that patients with ACE inhibitor induced angioedema were extubated significantly earlier than those not treated with antihistamines. The reason this study is important for HAE attacks is because bradykinin elevation in these patients are similarly found in those with ACE inhibitor induced angioedema. More studies are needed to show direct causal relationship but for now use of antihistamines should be instituted since the adverse event risk is relatively low.

Androgens such as danazol, stanozolol and oxandrolone have been used in the acute and prophylactic setting for treatment of HAE for years. The mechanism of action is not well understood but
ultimately it has been shown to increase the amount of C1-INH and C4 in the bloodstream. The problem is that side effects are numerous including weight gain, acne, hypertension, virilization, hirsutism, coronary disease and hepatic neoplasms. Liver function assays must also be monitored. Up until recently these were first line treatment.

When androgens are contraindicated, antifibrinolytics are utilized. Common drugs are tranexamic acid and aminocaproic acid. The mechanism of action is again unknown in these patients especially because they have no affect on complement proteins, unlike the androgens. These drugs generally have a poor response and have significant side effects as well including: nausea, diarrhea, vertigo, cramps, orthostasis, fatigue and an increased incidence of thrombosis and tumors. This drug has been described as a teratogen, however, one study by Baker et al (3) showed no angioedema events and no teratogenicity with 6 pregnant women taking antifibrinolytics 1-2 times a week. This was a very small study but argues that antifibrinolytics can be used safely in pregnancy to prevent attacks.

Fresh frozen plasma (FFP) has been described in the past as a possible treatment option. The reason is that it contains C1-INH in high enough levels to prevent formation of bradykinin. The problem with FFP is that in addition to C1-INH, it also contains substrates that can prolong or exacerbate an acute attack of angioedema. Therefore it is recommended to only be used in the prophylactic setting when other medications are either not available or contraindicated.

**Novel Therapies**

Although the use of androgens and antifibrinolytics have been “adequate” for the treatment of HAE, Europe has been using Cinryze or purified C1-INH substrate for over 25 years. Recently this medication has become available in the United States and has really made a difference in the treatment of both acute attacks as well as in the chronic prophylactic treatment of patients with HAE. It’s mechanism of action is simply to increase circulating C1-INH to prevent formation of bradykinin. The problem is it is extremely expensive costing about $2500 per treatment vial. This amounts to $75,000 per month if used as daily prophylactic therapy. Therefore prophylactic therapy is limited to:

1. Patients with repeat attacks >2 per month and do not respond or cannot take androgens/antifibrinolytics
2. Patients who have had laryngeal attacks previously
3. Patients with severe anxiety about repeated attacks that prevent them from living normal lives.

Icatibant is another new therapy that is a bradykinin receptor 2 blocker. The drug acts to prevent bradykinin induced vasodilation and edema through competitive inhibition of the receptor which is constitutively expressed. In a randomized placebo controlled trial by Lumry et al. in 2011 (11), it was shown that patients treated with Icatibant has significantly faster times from onset to relief compared to placebo groups for patients with non-laryngeal symptoms. Because HAE patients rarely present with laryngeal symptoms only 8 patients in the study group were evaluated. In this group there was a trend towards improvement in symptoms for the Icatibant group, but again this was underpowered. Icatibant is approved in the United States for patients over 18 years old but the cost is $6800 for a single treatment.

Ecallantide is the second recombinant protein used in the acute treatment of HAE. It is produced in the yeast Pichia pastoris and directly inhibits plasma kallikrein from converting kininogen into
bradykinin. It was been shown to decrease length and severity of attacks and there is a small risk of anaphylaxis since it is produced in yeast. This anaphylaxis risk limits it use as a home administration tool unlike Icatibant. It is approved in the United States for those older than 16 years of age and costs about $10,000 per dose.

**Approaching the Acute Angioedema Patient**

Thus far we have talked a lot about the acute medical treatment of patients with angioedema understanding that the etiology is not often known until after the acute event. The important thing to note here, however, is that these patients need to be treated like a trauma patient with close attention to the ABC’s that will ultimately impact survival.

When patients arrive in the emergency department with complaints of swelling or “angioedema”, a whiplash trigger of events is often instituted in a frenzied manner. This is because triage of patients with angioedema is not all that well understood. Luckily several reports in the otolaryngology literature have looked at characteristics which differentiate the need for aggressive versus non-aggressive treatment.

Ishoo et al. (9) performed a retrospective review of 80 patients treated for angioedema from 1985-1990. They categorized patients primarily on their site of involvement and correlated this to the level of care required to support patients through an acute attack. They developed an algorithm (9, shown below) for treatment based on anatomic site.

![Fig 2. Triage algorithm. Guide for management of angioedema based on anatomic site of presentation. DL/B, Direct laryngoscopy and bronchoscopy; H&N, head and neck.](image)
Patients were staged as:

I. Facial rash, facial edema, lip edema (31%)
II. Soft palate edema (5%)
III. Tongue edema (32%)
IV. Laryngeal edema (31%)

Patients with Stage I or Stage II disease were treated in either the outpatient setting or as an admission to the general floor and none of these patients required intubation. Those with tongue (III) or laryngeal (IV) involvement, however, were significantly more likely to be admitted to the ICU and significantly more likely to require intubation to control the airway. Tongue and laryngeal involvement required airway intervention in 7% and 24% of patients respectively. Acute airway management was required in 9.7% overall and was significantly more likely in patients with voice changes, hoarseness, dyspnea, and stridor (p<0.05). ICU admission was significantly more common in patients with ACE inhibitor use (p=0.05) and if patients presented with voice changes, hoarseness, dyspnea, or rash (p<0.05).

A similar study was performed by Al Khudari et al. (1) in 2011 in a prospective fashion. They evaluated 40 consecutive patients who were later found to have ACE inhibitor induced angioedema to help predict the need for acute airway management as well as the necessary level of care.

To be as consistent as possible, they developed the following algorithm to treat patients presenting to the ED with any form of angioedema.
After patients were initially evaluated they received twice daily assessments with only repeat fiberoptic laryngoscopy if their symptoms changed. Using this protocol patients were only extubated when they had a positive cuff leak test and had appropriate mental status to manage their airway. Extubation was also carried out over an exchange catheter.

Results of this study showed that the average age of patients was 62.9 and that 92.5% of patients were African American. Lisinopril was the offending agent in 87.5% of patients and the number of days that a patient had been taking an ACE inhibitor, on average, was 233 days. Presenting symptoms in the ED were dysphagia (44.7%), voice changes (42.1%), dyspnea (23.1%) and drooling in just 7.5% of patients. Patients were really either discharged from the ED (42.5%) or admitted to the ICU (50%) with only 1 patient being admitted to the general floor (7.5%).

Patients being admitted to the ICU were more likely to be older, present with dyspnea, have involvement of the floor of mouth, soft palate, aryepiglottic folds, or epiglottis or have multisite involvement. Patients were more likely to have airway edema if they had multiple sites involved (p=0.008) or have soft palate swelling (p=0.047). Patients were significantly less likely to have airway involvement if they had upper lip swelling (p=0.008). Intubation occurred in 15% of patients with only massive tongue edema and inability to close lips around tongue (p=0.008) and prolonged symptom duration from onset to resolution (p=0.008) predicting the need for intubation.

As you can see from both of these studies, patients can be appropriately triaged and treated according to symptoms severity, even to a point where they are discharged from the emergency
department. Although each patient needs to be evaluated on an individual basis, angioedema in general has a fairly predictable pattern of severity and therefore algorithms can be very helpful in acute management.

**Conclusion**

Angioedema is a rare disorder but with devastating consequences if not recognized and treated. Although there are many different types and etiologies, acute management is of the utmost importance with respect to the airway. Several algorithms have been reported to treat acute attacks and have been proven quite useful to triage patients appropriately. After the acute episode has resolved, a thorough history with complement testing is appropriate to determine if hereditary angioedema is the culprit. If so, patients need to be counseled regarding the risk of repeated attacks and medical therapies for acute treatment as well as prophylaxis should be evaluated to prevent future morbidity.

**References**


