Managing Angioedema

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INTRODUCTION

Angioedema is defined by nonpitting, nondependent, transient edema affecting the skin and mucous membranes owing to accumulation of vasoactive substances (eg, bradykinin and histamine).[1-8] These vasoactive substances increase vascular permeability, leading to swelling of the deep dermal, submucosal, and subcutaneous tissues of the face, neck, lips, oropharynx, extremities, urogenital tract, and gastrointestinal tract.[1,9-12] Angioedema may be either hereditary (bradykinin mediated) or acquired (bradykinin or histamine mediated), and the type can affect its clinical presentation and treatment (Table 1).[1-7,10-16] Histamine-mediated angioedema is the most common form.[17-21] This is followed by medication-induced angioedema (most commonly with angiotensin-converting enzyme inhibitors [ACEI]), which develops in less than 0.7% of patients, and hereditary angioedema, which has an estimated prevalence of 1 in 50,000 persons.[1,2,4,5,8,12,20,22] Most patients with hereditary angioedema experience their first episode within the second decade of life, although it typically occurs between 4 and 26 years of age.[23-26] Although the underlying cause may be known in patients with a history of hereditary angioedema or suspected in those on an ACEI, in many cases, the underlying cause for angioedema may not be immediately apparent in the acute setting.

If left untreated, angioedema can result in significant morbidity and mortality, particularly when the larynx is involved, which may cause airway obstruction, with mortality rates ranging from 15% to 56%.[9,27,28] Therefore, early diagnosis and management are critical to improving patient outcomes. This report does not intend to be a comprehensive review of all aspects pertaining to angioedema but rather seeks to provide the key tenets of emergency management based on the current literature and years of practice.

ASSESSMENT

Begin by assessing the patient's airway, cardiovascular, and mental status, as asphyxiation is the most common cause of mortality.[1,14,29-31] Up to 15% of patients experience airway obstruction, which can progress rapidly.[1,4,6,16,30,31] More than half of patients with hereditary angioedema experience at least one episode of laryngeal edema, which accounts for more than 30% of deaths in these patients.[30,31] Evaluate for lip and tongue swelling, change in voice (eg, hoarseness and stridor), drooling, difficulty swallowing, shortness of breath, inability to lie flat, lightheadedness, pruritus, rash, and gastrointestinal symptoms (eg, pain, vomiting, and diarrhea).[3,4,14,24-26] Obtain a history of prior attacks of angioedema and treatments, medications, and family history. Ask about exposure to any trigger, which is common in those with hereditary angioedema and may include stress, medical procedures, trauma, infection, and medications (eg, hormone therapies, oral contraceptives, and opioids).[3,4,14,16,26,32] Patients may also develop prodromal symptoms including fatigue and rash.

Examination most commonly reveals swelling of the lips or face (Figure 1). A 2025 retrospective study of ACEI-induced angioedema found that lip and tongue swelling was most common in patients (87.5% and 43.6%, respectively).[33] Swelling of the tongue, floor of the mouth, and palate is concerning for airway involvement (Figure 2).[3,4,14,26,34] A study of 311 patients found several factors associated with the need for airway intervention: presentation within 4 hours of symptom onset; signs/symptoms including dysphagia, dysphonia, drooling, respiratory distress, and globus sensation; and involvement of the tongue, soft palate, vallecula, aryepiglottic folds, and true vocal cords.[34] A 2020 study found that rapid progression of symptoms within 6 hours of angioedema onset, anterior tongue swelling, voice changes, drooling, and dyspn2ea were associated with intubation in ACEI-

Table 1. Angioedema types.

Subtype	Condition	Cause	Features
Mast-cell/ histamine mediated	Allergy/anaphylaxis	IgE mediated with histamine release	Acute onset with exposure to allergen. Urticaria is common. Swelling, airway involvement, nausea/ vomiting may occur.
	Medication induced	IgE mediated with increased prostaglandin	Angioedema and bronchoconstriction, often with prior exposure to aspirin or NSAIDs. Urticaria is common.
Bradykinin mediated	Medication associated	Bradykinin overproduction or impaired degradation	Acute or delayed angioedema with ACEI (more common) or angiotensin II receptor blockers; Higher incidence in Black patients; 50% of cases present within the first week of treatment; 50% develop angioedema in months or years. Rarely caused by DPP-4 inhibitors, NEP inhibitors, thrombolytics, sirolimus, tacrolimus, and everolimus.
	HAE type I	Decreased C1-INH production	Onset in childhood; autosomal dominant inheritance. Presents with edema and abdominal pain.
	HAE type II	Dysfunctional C1-INH	Onset in childhood; autosomal dominant inheritance.
	HAE type III	Often estrogen-dependent with normal C1-INH activity, but there are other mutations	Affects women later in life; autosomal dominant inheritance but low penetrance.
	Acquired type I C1-INH deficiency	Consumption of C1-INH due to immune complexes	Onset>40 y; angioedema without urticaria with underlying lymphoreticular disorder.
	Acquired type II C1-INH deficiency	C1-INH autoantibodies	Onset>40 y; angioedema without urticaria with underlying lymphoreticular disorder.
	Chronic idiopathic	Unclear	Diagnosis of exclusion; rare;>3 attacks within 1 y.
	Gleich's syndrome	Unclear	Cutaneous angioedema and urticaria. Elevated eosinophil and IgM levels.

DPP-4, dipeptidyl peptidase; *HAE,* hereditary angioedema; *Ig*, immunoglobulin; *NEP,* neprilysin; *NSAID,* nonsteroidal anti-inflammatory drug.

induced angioedema, but isolated lip swelling was not.[35] Nonpitting edema may also occur in the head, neck, extremities, genitals, or abdomen; however, edema is typically noncontiguous.[1-7,10,11,36,37] Urticaria and pruritus may occur in those with histamine-mediated angioedema.[1,2,9-12,36] Whereas those with hereditary angioedema may develop erythema marginatum (eg, erythematous rings), urticaria and pruritus are uncommon in those with bradykinin-mediated angioedema.[29,38-40] Patients may present with evidence of peritonitis due to gastrointestinal involvement (more common with bradykinin-mediated angioedema), and those with histamine-mediated forms may have other organ involvement in anaphylaxis (eg, hypotension, wheezing, nausea, and vomiting) (Table 2).[4,29,38,41-43]

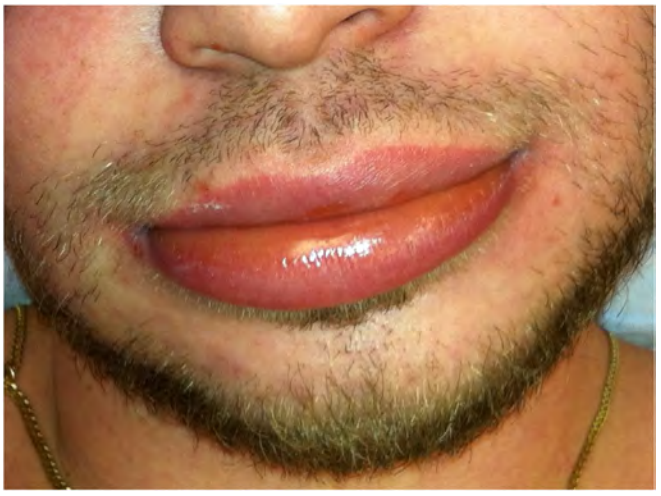

Figure 1. Angioedema affecting the lips. Obtained from https://commons.wikimedia.org/wiki/File:AngioedemaFra.JPG

Laboratory testing is not necessary for those with isolated angioedema in the emergency department (ED) to direct management.[1-6,10-14] In patients with swelling of the tongue, floor of the mouth, or soft palate on initial examination, we recommend flexible endoscopy to assess the degree of airway edema (Figure 3).[14,44] Although this requires topical anesthesia, this modality can visualize airway structures and allows for intubation if necessary.[44] Hyperangulated or standard geometry video laryngoscopy can be used with appropriate topical anesthesia to visualize the glottic structures if flexible endoscopy is not available.

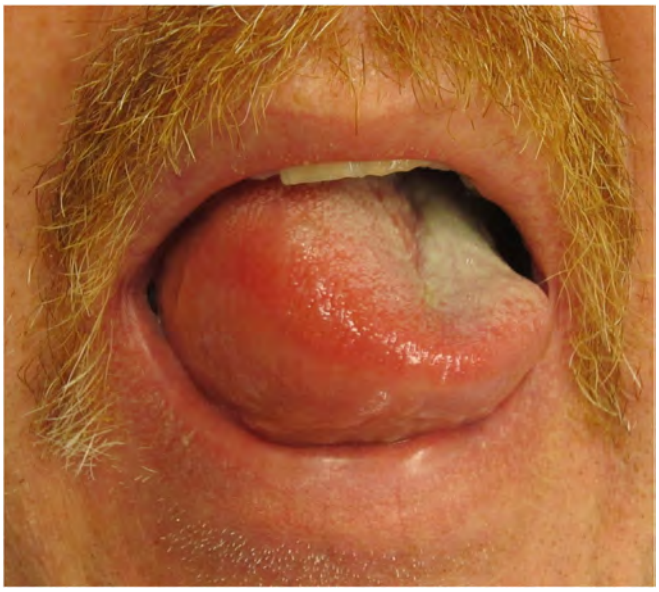

Figure 2. Angioedema affecting the tongue. Obtained from https://commons.wikimedia.org/wiki/File:Angioedema2013.JPG

Plain radiographs/computed tomography may reveal tongue, glottic, and airway swelling, but these are not recommended to assess airway integrity in patients with a concern for immediate airway obstruction.[45] The use of point-of-care ultrasound has also been described, in which the sonographer starts with the high-frequency linear transducer in the submandibular region, evaluating for airway edema as the probe is moved in the transverse orientation until the anterior base of the neck is reached.[46-48] Although further data are needed, this presents an alternate model to assess the airway for patients in whom flexible endoscopy is not possible.

MANAGEMENT

Airway

Obtain a definitive airway in patients with evidence of airway obstruction (eg, stridor, drooling, dyspnea, and marked edema in the larynx) (Figure 4).[1-3,14] Airway intervention is rarely needed in those with angioedema involving only the external face and lips.[42,43,49-54] For those with airway obstruction, inhaled epinephrine has been described in case reports and can be attempted while preparing for emergency intervention.[55] We recommend using an awake intubation strategy with flexible intubating endoscopy, if available. If this is not feasible, we recommend video laryngoscopy using the blade with which the clinician feels most comfortable. When intubating, avoid excessive physical manipulation, which can worsen airway edema. Literature suggests cricothyrotomy or tracheostomy is needed in up to 50% of patients with angioedema requiring an emergent airway intervention.[30,51,56,57] Thus, ED clinicians should use a "double set-up" approach, in which the clinician prepares for cricothyrotomy by having equipment available and the skin of the neck overlying the cricothyroid marked. A second airway provider is recommended if possible. Noninvasive positive pressure ventilation can be used to temporize the patient and for preoxygenation, but this is not a long-term solution and should not delay intubation. Supraglottic airway devices are not recommended, as they

Table 2. Comparison of features between bradykinin- and histamine-mediated angioedema.

Features	Bradykinin Mediated	Histamine Mediated
Onset	H	Min
Duration	48-72 h	12-24 h
Distribution	Asymmetric/focal; often involves tongue primarily	Symmetric/diffuse; more often involves lips and eyes
Skin findings	Atypical; hereditary angioedema may have erythema marginatum	Urticaria, pruritus, flushing in approximately 50%
Laryngeal edema	Possible and more severe	Less common but may occur
Other organ involvement	May involve bowel (pain, nausea, vomiting, and diarrhea) but usually does not involve other organs	May occur with anaphylaxis (hypotension, wheezing, nausea, vomiting, and diarrhea)
Abdominal pain	Possible	Less common
Therapy with epinephrine, antihistamines, and corticosteroids	Minimal or no response (<10% respond)	Effective (>90%)

These are generalized findings; in many situations, the clinician will not know the underlying form.

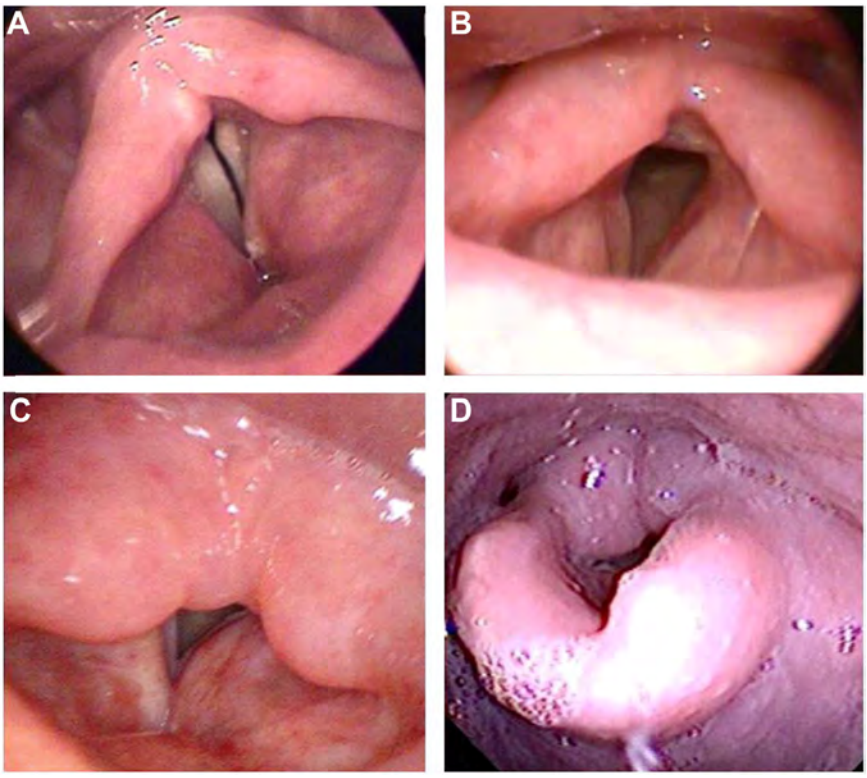

Figure 3. Laryngeal visualization. *A*, No edema. *B,* Mild edema. *C,* Moderate edema. *D,* Severe edema. Obtained and reused with permission from Bae JS, et al (Laryngeal edema after radiotherapy in patients with squamous cell carcinomas of the larynx and hypopharynx. *Oral Oncol*. 2012 Sep;48:853-858).

can be displaced with progressive swelling and may worsen the airway edema.[1,3,6,10,14,49,57]

Medications

Administer standard therapies for anaphylaxis including epinephrine, antihistamines, and corticosteroids for patients with angioedema of an unknown cause or if concerned for histamine-mediated angioedema.[1,3,4,14,58] However, these therapies are unlikely to be effective in bradykinin-mediated forms given they do not target the pathophysiologic pathway. Allergy guidelines recommend against their routine use in patients with a definite diagnosis of bradykinin-mediated angioedema because they have been shown to be ineffective, although they have not been associated with harm.[1,3,4,24,29,59]

Several medications are available to treat bradykinin-mediated angioedema if this is the known cause (eg, hereditary angioedema), all of which reduce the production or activity of bradykinin, a peptide that increases vascular permeability and inflammation.[3,4,24,59-65] C1 esterase inhibitor (C1-INH) replacements inhibit proteases such as kallikrein and the complement system to reduce bradykinin production (Berinert [CSL Behring], Cinryze [Takeda], and Ruconest [Pharming Healthcare, Inc).[61-63] Kallikrein inhibitors reduce production of bradykinin (ecallantide or Kalbitor [Takeda]).[64] Bradykinin B2 receptor antagonists prevent bradykinin from binding the B2 receptor, thereby limiting the symptoms associated with angioedema (icatibant acetate or Firazyr [Takeda]) (Table 3).[3,4,24,61-65] These medications should be administered as soon as possible in those with suspected or known bradykinin-mediated angioedema, as treatment within 6 hours of onset has been associated with improved outcomes.[24,59,60,66] Patients with known hereditary angioedema and recurrent attacks may present with an individualized treatment action, which should be followed if possible.[3,4,59,60,67-69]

C1-INH concentrates are currently the first-line recommended therapies for bradykinin-mediated angioedema in those more than 2 years of age, but their use is limited by availability and cost.[1,3,4,14,29,60-63,67-69] Ruconest is currently the only available human recombinant C1-INH and can be self-administered.[61] Plasma-derived C1-INHs include Berinert and Cinryze.[3,4,60,62,63] Unfortunately, those with recurrent attacks may require higher doses of plasma-derived C1-INH, as C1-INH concentrates may become less effective over time.[1,3,4,14,29,67-69] The kallikrein inhibitor ecallantide may be used in those aged $\geq$12 years.[64] Icatibant can be self-administered.[65] These therapies may also be used for those with acquired angioedema.

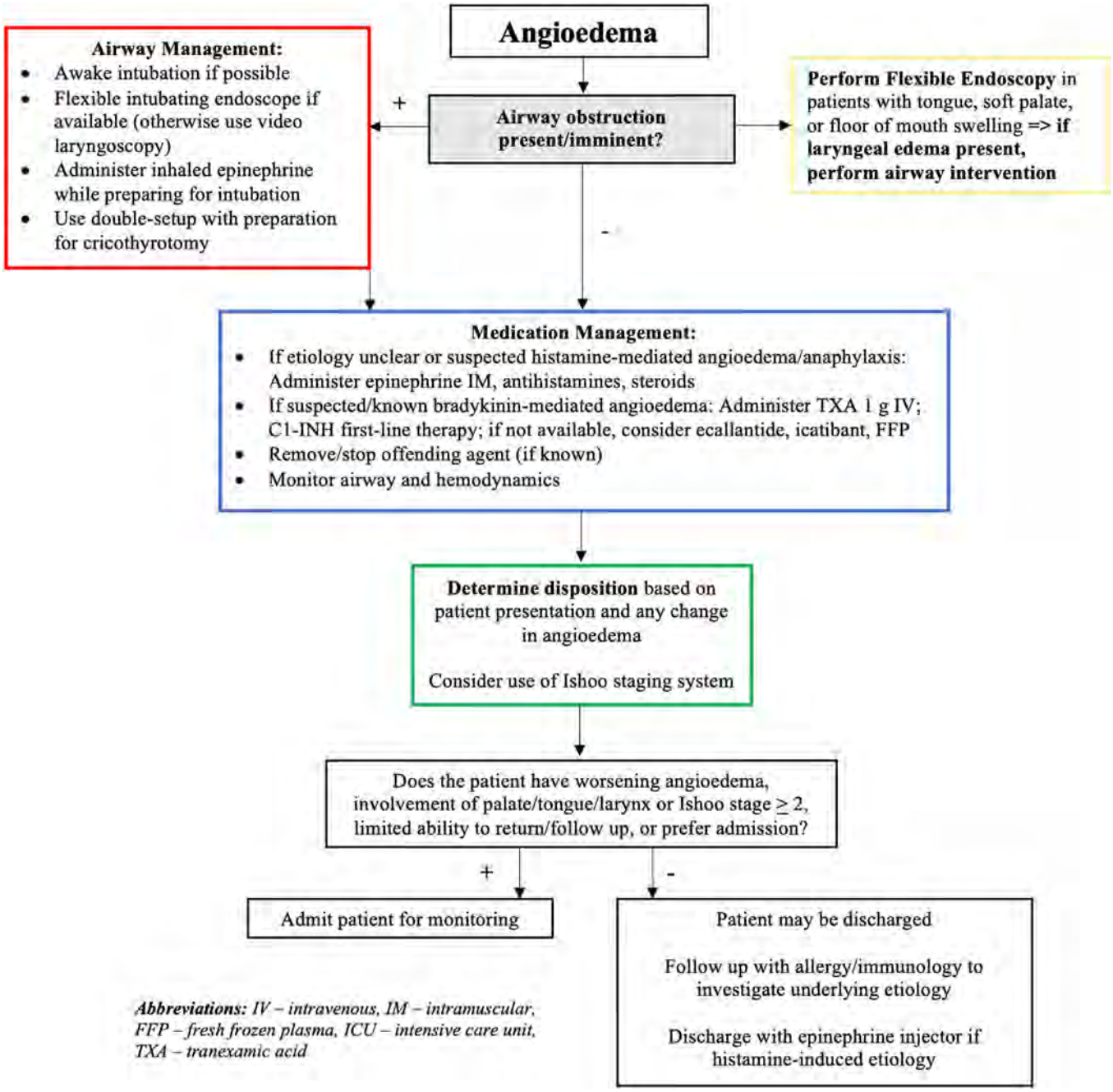

Figure 4. Angioedema evaluation and management.

For suspected ACEI-related angioedema, epinephrine, antihistamines, and corticosteroids can be administered but may be ineffective, as they do not decrease bradykinin.[3,14,59,70,71] C1-INH replacement, ecallantide, or icatibant has been evaluated in the literature, with case reports demonstrating a possible benefit with C1-INH therapy.[59,72,73] However, a randomized trial of 30 patients with ACEI-related angioedema found no benefit with C1-INH therapy.[74] Icatibant has demonstrated improvement in symptom resolution, but no studies have demonstrated a reduction in ICU admissions or intubation.[75] Thus, given the high cost of therapy, these should generally be reserved for hereditary angioedema.

Tranexamic acid has been proposed as a treatment for bradykinin-mediated forms, particularly for ACEI-induced angioedema.[3,14,29,72,76,77] Tranexamic acid inhibits the conversion of plasminogen to plasmin, which is an integral step in amplifying kallikrein activation. Several retrospective studies suggest that tranexamic acid may reduce symptoms, with no reported adverse events.[14,29,77-82] Dosing is 1-g intravenous push over 2 to 10 minutes,

Table 3. Angioedema medications.

Medication (Trade Name)	Mechanism	Route	Dose	Time To Onset	Minor Adverse Effects	Serious Adverse Effects
Plasma-derived C1-INH (Berinert, Cinryze)	C1-INH protein replacement	Intravenous	Berinert 20 units/kg; Cinryze 1,000 units	Median<50 min	Dysgeusia, headache, injection site reactions, nausea, diarrhea, fever	Hypersensitivity, thrombosis, and blood-borne infection
Recombinant human C1-INH (Ruconest)	C1-INH protein replacement	Intravenous	50 units/kg, maximum 4,200 units	Median 90 min	Pruritus, rash, sinusitis, headache, injection site reactions, nausea, fever	Hypersensitivity, anaphylaxis, and thrombosis
Ecallantide (Kalbitor)	Kallikrein inhibitor	SubQ	30 mg	Median 67 min	Headache, injection site reactions, nausea, fever	Hypersensitivity and anaphylaxis
Icatibant acetate (Firazyr)	Bradykinin B2 receptor antagonist	SubQ	12-25 kg: 10 kg 26-40 kg: 15 kg 35-50 kg: 20 mg 51-65 kg: 25 mg >65 kg: 30 mg	Median 2 h	Elevated LFTs, injection reaction, dizziness, headache, nausea, rash, and fever	Theoretical worsening of an ongoing ischemic event; caution warranted in those with coronary artery disease
Tranexamic acid	Inhibits conversion of plasminogen to plasmin	Intravenous	1 g over 10 min	Minutes to hours	Headache, seizure, back pain, nausea, vomiting, diarrhea,	Anaphylaxis, thrombosis
Fresh frozen plasma	C1-INH protein replacement (various amounts)	Intravenous	15 mg/kg	Minutes to hours		Hypersensitivity, worsening angioedema, volume overload, transfusion-related infection

LFT, Liver function test; *SubQ,* subcutaneous.

Table 4. Ishoo staging.

Stage	Site
1	Face, lip, periorbital, and extremities
2	Soft palate and posterior pharynx
3	Tongue
4	Larynx

followed by a second dose if necessary.[83] Although there are no high-quality data supporting its use, tranexamic acid is inexpensive, safe, and universally available.

Finally, fresh frozen plasma has been proposed as a treatment for angioedema if other medications are not available (15-mg/kg intravenous line or 2 units), as it contains angiotensin-converting enzyme, which can degrade bradykinin, and C1-INH.[1,3,4,14,29,60,67-69] Although retrospective literature suggests benefits with fresh frozen plasma if other therapies are not available, there are no high-quality randomized data demonstrating the efficacy of fresh frozen plasma in angioedema.[72,84-88] Fresh frozen plasma also contains varying levels of C1-INH and substrates of the kallikrein system, and thus, angioedema may theoretically worsen.[72,84-88] Notably, there are no case reports suggesting exacerbation of angioedema with fresh frozen plasma. Therefore, we recommend considering fresh frozen plasma in select cases if other medications are not available.

Importantly, there are several considerations regarding medications for bradykinin-mediated angioedema. Although there may be improvement in symptoms and edema with these medications, the literature evaluating the medical management of bradykinin-mediated angioedema has many limitations, particularly for ecallantide and icatibant.[3,4,60,75,89-91] These include low sample sizes, as well as significant bias and heterogeneity in patient selection, comparators, medication dosing, study design, and outcomes evaluated.[1,3,4,6,14,60,72,89-91] These medications also have a delayed onset of action with variable symptom relief. Given these limitations, we recommend the primary focus be on monitoring and managing the patient's airway.

DISPOSITION AND AFTERCARE

Any patient with airway involvement should be admitted to a closely monitored setting if they are not intubated. For other patients, disposition is controversial, with several studies seeking to predict patients who may experience airway compromise.[33,49] The Ishoo staging system was derived from a retrospective study of 80 patients with 93 episodes of angioedema and categorizes severity based on the location of angioedema (Table 4).[49] A subsequent retrospective chart review (n=320 patients) conducted in the ED setting found that patients with stage 4 findings required airway intervention in 67% of cases, compared with 16% for stage 3 and 8.6% for stage 2.[57] However, this system is limited by requiring direct visualization of laryngeal structures. Based on this score, patients with stage 1 findings may be discharged with follow-up after observation for several hours, whereas those with stage 2 findings or higher should be admitted.[11,53,57,67] A 2025 retrospective study (n=94 patients) found throat symptoms or throat or neck edema including difficulty speaking was associated with admission.[33] In general, all patients with angioedema should be observed for at least several hours to assess for progression of angioedema.[14] Any patients with progression after initial therapy should be admitted.

In patients appropriate for discharge, consider referral to allergy/immunology specialists for those with acute and recurrent angioedema for further evaluation.[1,3,6,59,60,92-94] These specialists can diagnose the underlying cause, educate the patient on triggers, and prescribe prophylactic medications.

Remove any triggers and discontinue any medication thought to be the underlying etiology, including ACEI, nonsteroidal anti-inflammatory drugs, and aspirin.[1,3-7,10-12,14,59,67] If the patient is on an ACEI, this should be listed as an allergy and the patient should be switched to another agent (eg, calcium channel blocker).[1,3,14,33,95-98] The incidence of angioedema with an angiotensin receptor blocker approximates 0.11%, which is no different than placebo. Although an angiotensin receptor blocker is likely safe in those with ACEI-induced angioedema, there may be a somewhat higher baseline risk of angiotensin receptor blocker angioedema in these patients.[97,98] Patients with angioedema who improve with therapy for anaphylaxis should be discharged with a prescription and training on the use of epinephrine autoinjectors, education on potential triggers, and follow-up with allergy/immunology to determine the underlying trigger.[3,59,60,94]

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