Predicting airway risk in angioedema: Staging system based on presentation

EDWIN ISHOO, MD, UDAYAN K. SHAH, MD,* GREGORY A. GRILLONE, MD, JOHN R. STRAM, MD, and **NABIL S. FULEIHAN, MD,***
Boston, Massachusetts

Angioedema is an immunologically mediated, anatomically limited, nonpitting edema that can lead to life-threatening airway obstruction. To predict the risk of airway compromise in angioedema, we retrospectively reviewed 93 episodes in 80 patients from 1985 to 1995. Intubation or tracheotomy was necessary in 9 (9.7%) cases. Angiotensin-converting enzyme inhibitor use in 36 cases (39%) was associated with intensive care unit (ICU) admission ($P = 0.05$). ICU stay correlated significantly with presentation with voice change, hoarseness, dyspnea, and rash ($P < 0.05$). Voice change, hoarseness, dyspnea, and stridor were present in patients requiring airway intervention ($P < 0.05$). On the basis of our data, we propose a staging system by which airway risk may be predicted from the anatomic site of presentation. Patients with facial rash, facial edema, lip edema (stage I), and soft palate edema (stage II) were treated as outpatients and on the hospital ward. Patients with lingual edema (stage III) usually required ICU admission. All patients with laryngeal edema (stage IV) were admitted to the ICU. Airway intervention was necessary in 7% of stage III patients and in 24% of stage IV cases. No deaths were caused by angioedema. Airway risk in angioedema may be predicted by anatomic site of presentation, allowing appropriate triage with preparation for airway intervention in selected cases. (Otolaryngol Head Neck Surg 1999; 121:263-8.)

From the Department of Otolaryngology–Head and Neck Surgery, Boston University School of Medicine.

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*Dr Shah is currently with the Division of Pediatric Otolaryngology, Children's Hospital of Philadelphia and University of Pennsylvania School of Medicine, Philadelphia, and Dr Fuleihan is currently with the Department of Otolaryngology, American University of Beirut, Beirut, Lebanon.

Reprint requests: Udayan K. Shah, MD, Pediatric Otolaryngology, Children's Hospital of Philadelphia, Richard D. Wood Building, 1st Floor, 34th and Civic Center Blvd, Philadelphia, PA 19104-4399.

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Angioedema is an immunologic disorder characterized by an acute onset of anatomically limited nonpitting edema. Ten percent of Americans may have angioedema during their lifetimes.[1] Men and women are affected equally, usually in their third and fourth decades of life. Most angioedema presents in the head and neck.[2,3] Airway compromise remains the principal cause of mortality.

Airway management requires patients in extremis and those likely to worsen to be separated from those requiring therapy but not intensive care unit (ICU) monitoring or airway intervention by intubation or tracheotomy. Although angioedema caused by angiotensin-converting enzyme inhibitors (ACEIs) or hereditary angioedema (HAE) is reported to be more severe,[1,4] there is no formal means of determining, at presentation, which patients are at risk for progressive airway compromise.

We sought to clarify airway management in angioedema by reviewing our experience during the past decade to (1) determine criteria for the identification of patients at risk from progressive airway compromise, and (2) guide the triage of patients into the appropriate treatment setting—outpatient, ward, or ICU.

METHODS AND MATERIAL

Retrospective chart review was performed for all patients in whom angioedema was diagnosed at Boston Medical Center (formerly Boston University Medical Center Hospital and Boston City Hospital) for the years 1985 to 1995.

In addition to demographic, etiologic, and therapeutic information, the anatomic site of edema and symptoms on presentation were determined for each episode. The episodes were categorized by treatment setting into 1 of 3 groups: (1) those treated on an outpatient basis; (2) those admitted to the hospital but not into an ICU, termed the "ward" group; and (3) those admitted to the ICU.

Airway intervention was defined as the need for intubation, cricothyrotomy, or tracheotomy.

Statistical analysis of data was performed to determine relationships of individual case variables and clinical outcome.

RESULTS

Eighty patients were identified—40 men and 40 women. Ages ranged from 18 to 86 years (mode 36

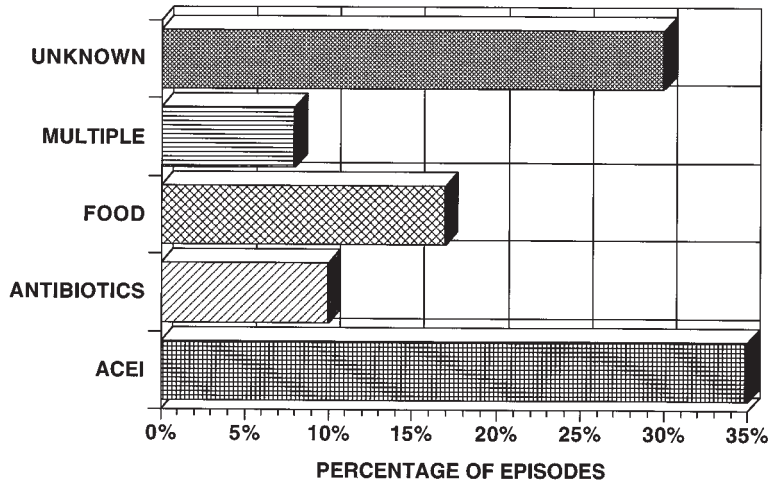

Fig 1. Cause of angioedema in 80 patients (93 episodes), 18 to 86 years of age, from 1985 to 1995.

Table 1. Symptoms and outcomes

	ICU placement		Airway intervention	
Symptom	%	*P*	%	*P*
Odynophagia	43	0.18	11	0.095
Voice change	82	0.001	100	0.001
Dyspnea	33	0.002	44	0.006
Rash	12	0.02	22	0.956
Hoarseness	98	0.001	100	0.001
Stridor	100	0.016	44	0.001

Table 2. Sites and symptoms

Site	Odynophagia (%)	Voice change (%)	Dyspnea (%)	Rash (%)	Hoarseness (%)	Stridor (%)
Tongue	46	73	21	13	73	4
Lip	29	26	9	23	29	3
Face	21	25	11	39	36	7
Soft palate	67	70	26	11	78	4
Larynx	48	90	38	10	97	21

years). These 80 patients accounted for 93 hospital visits; 11 (14%) had multiple episodes, 25 (31%) had prior episodes of angioedema. Fifty-one patients (64%) were black, 23 (29%) white, 5 (6%) Hispanic, and 1 (1%) Asian.

Of the 93 episodes of angioedema, 23 (25%) were treated on an outpatient basis, 21 (23%) were admitted to the floor, and 49 (53%) were admitted to the ICU for airway monitoring; 9 required airway intervention (1 tracheotomy, 1 cricothyrotomy, and 7 intubation). Neither age greater than 60 years ($P = 0.182$) nor sex ($P = 0.464$) was statistically related to ICU admission. All patients admitted to the hospital were seen in consultation by the otolaryngology–Head and Neck Surgery service.

Serum complement studies were not ordered routinely. No abnormal values for C1-esterase inhibitor (C1-INH), C2, or C4 levels were reported. No cases of HAE were encountered. T-cell lymphoma was later diagnosed in 1 patient with repeated bouts of angioedema.

ACEIs were responsible for 36 episodes (39%). The inciting cause was food in 18 cases (19%) and antibiotics in 10 cases (11%). Multiple agents were blamed in 8 episodes (9%). No etiologic agent could be identified in 31 instances (33%) (Fig 1). Patients using ACEI required ICU monitoring for 47% of their episodes ($P = 0.05$) and airway intervention 33% of the time ($P = 0.78$).

Voice change, defined as muffled or stertorous, correlated with ICU stay ($P = 0.001$). Hoarseness ($P = 0.001$), stridor ($P = 0.016$), dyspnea ($P = 0.002$), and rash ($P = 0.02$) also were predictive of the need for ICU monitoring. Voice change ($P = 0.001$), hoarseness ($P = 0.001$), stridor (p = 0.01), and dyspnea ($P = 0.006$) were present in those patients requiring airway intervention (Table 1).

Voice change was most common in patients with soft palate (70%), lingual (73%), and laryngeal edema (90%). Hoarseness was present in 97% of patients with laryngeal edema, and stridor was present in 21%. Dyspnea was present mostly in soft palate (26%), lingual (21%), and laryngeal edema (38%) (Table 2).

Patients were categorized by anatomically defined stages (Table 3) and were considered to be at the highest stage when their angioedema presented in more than

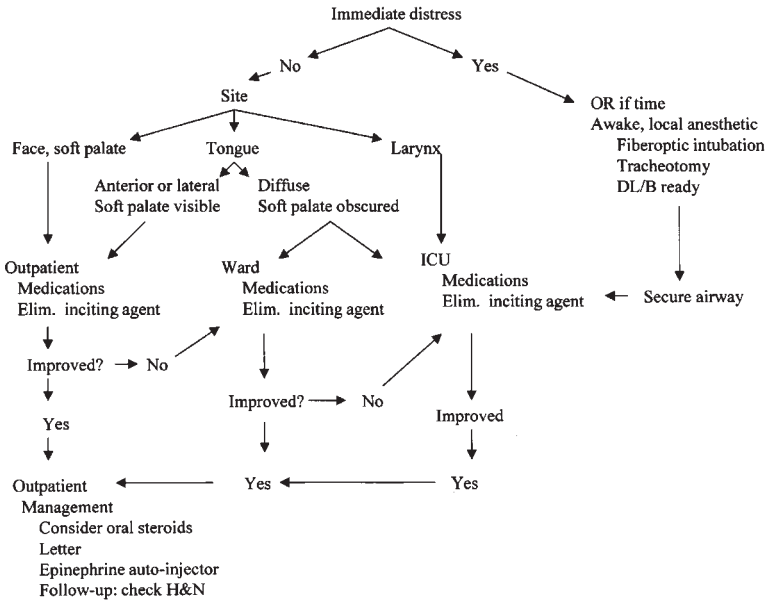

Fig 2. Triage algorithm. Guide for management of angioedema based on anatomic site of presentation. *DL/B,* Direct laryngoscopy and bronchoscopy; *H&N,* head and neck.

Table 3. Staging by site

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

Table 4. Stage, treatment location, and intervention

Stage	Outpatient (%)	Floor admittance (%)	ICU admittance (%)	Intervention (%)	*P*
I	48	52	0	0	0.001
II	60	40	0	0	0.001
III	26	7	67	7	0.001
IV	0	0	100	24	0.012

1 site. All stage I and stage II patients were treated as outpatients and on the hospital ward. Stage III patients were mostly cared for in the ICU. All stage IV patients were treated in the ICU (Table 4).

No stage I or stage II patients required airway intervention. Two (7%) stage III patients required intervention: 1 by intubation and 1 by tracheotomy ($P = 0.001$). Airway protection was required in 7 (24%) of the stage IV patients: 5 by intubation, 1 by cricothyrotomy, and 1 by tracheotomy ($P = 0.012$). No patient died of angioedema during the study period.

The anatomic staging was not statistically associated with demographic or etiologic variables. Staging was independent of age greater than 60 years ($P = 0.181$), male sex ($P = 0.256$), race ($P = 0.380$), tobacco use ($P = 0.356$), ACEI use ($P = 0.170$), and prior episodes of angioedema ($P = 0.212$)

DISCUSSION

> Sometimes the lips inside of the mouth, palate, and uvula are attacked, giving rise to a very considerable inconvenience. Were such tumors to occur in the neighbourhood of the glottis, I need not say that they would be pregnant with danger of no ordinary character.—*Robert Graves, 1888*[5]

Angioedema, like gestation, carries importance because of its tendency to progress. Predicting airway risk on presentation would allow appropriate triage of patients and preparation for airway intervention. Our experience during the past decade has allowed us to propose a staging system that stratifies patients by risk of airway obstruction, on the basis of initial presentation (Table 3). Treatment location and the need for airway intervention were our indicators of the severity of angioedema. We found that patients with stage I and II facial, lip, and soft palate edema were treated as outpatients or on the ward and did not require airway intervention. Patients with stage III lingual edema required ICU stay most of the time and occasionally airway intervention. All patients with laryngeal angioedema

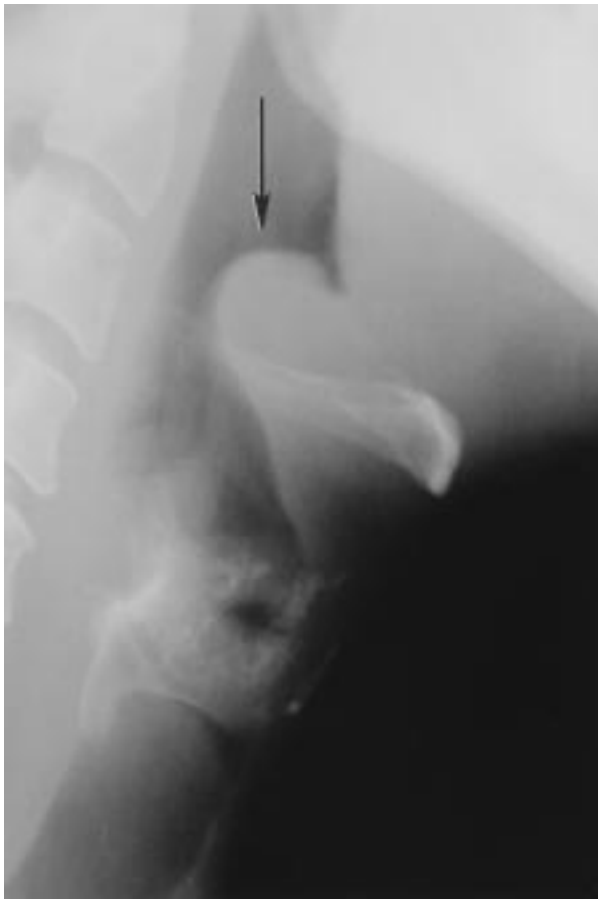

Fig 3. Plain film of the lateral neck in a 36-year-old woman with stridor and dyspnea. She had had recurrent episodes of laryngeal angioedema caused by foods and medications. No clear cause could be found for this episode. This plain film of the lateral neck shows a thickened epiglottis *(arrow),* much as would be seen in acute supraglottitis. Indirect laryngoscopy revealed epiglottic, right aryepiglottic fold, and right arytenoid edema. She was successfully treated by intravenous hydrocortisone in a ward setting.

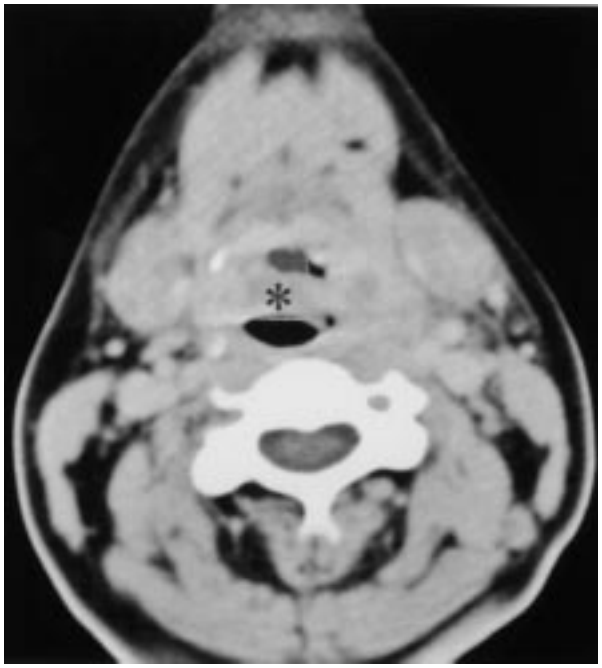

Fig 4. CT scan of the neck in axial section, with intravenous contrast, of patient in Fig 3. Scan shows epiglottic edema *(asterisk)* that partially obstructs the airway.

(stage IV) required ICU care; one fourth of these patients required airway intervention (Tables 3 and 4).

Lingual angioedema is not uniformly life threatening. Approximately one fourth of patients with lingual angioedema were treated as outpatients. Anatomic distinction must be made between the safer anterior and lateral edema versus the more dangerous diffuse lingual angioedema. Inability to visualize the soft palate suggests a dangerous airway. Edema is unlikely to progress if tongue size is diminished during or shortly after the administration of intravenous steroids; these patients may be safely observed in the outpatient setting or on the ward.

Site of presentation is an easily applied, reproducible criterion. A complete head and neck examination with indirect laryngoscopy is the optimal means of evaluating the upper airway. If this cannot be performed, the site of airway involvement may be predicted by clinical signs. The findings of voice change, hoarseness, stridor, and dyspnea indicate airway risk by the need for ICU stay and airway intervention (Table 1). Voice change was used to describe patients who sounded muffled or stertorous and was most common in soft palate, lingual, and laryngeal edema. Hoarseness and stridor indicated laryngeal involvement. Dyspnea, as expected, is not localizing and was present in soft palate, lingual, and laryngeal edema (Table 2).

Rash was statistically associated with ICU admission (P = 0.02, Table 1). This association is difficult to explain. Although rash may indicate severity because it is a systemic reaction, the lack of statistical correlation between rash and need for airway intervention (P = 0.956), as well as our clinical experience with rash as a ubiquitous, nonspecific finding, led us to withhold rash from our decision-making algorithm (Fig 2).

Radiographic evaluation, by anteroposterior or lateral neck plain film (Fig 3) or CT scan (Fig 4), supplements but does not replace physical examination of the obstructed airway. Imaging a compromised airway in a rapidly progressive disease such as angioedema may be a dangerous waste of valuable time.

Age and sex were not associated with severity of

angioedema. Children, in general, rarely require airway intervention because their presentation of angioedema is usually less severe than adults'.[6] The exception to this is in cases of HAE, an autosomal codominant cause of an often quantitative but sometimes qualitative deficit in C1-INH.[4,7,8] HAE usually presents with some combination of abdominal pain, peripheral edema, and airway obstruction. HAE should be suspected in younger patients with repeated bouts of angioedema and in patients with positive family histories. Diagnosis is confirmed by serum testing for quantitative or qualitative deficiency in C1-INH and an acute drop in C2 and/or C4 levels.[9] The lack of HAE patients in our review is reflected by the absence of serum complement abnormalities in our series.

An inciting factor could be identified in two thirds of cases. Iatrogenic causes predominated, with ACEI and antibiotics together accounting for half of all cases. Food was a cause in nearly 20% of episodes, and multiple causes were seen in 9% (Fig 1). The severity of ACEI-related angioedema warranted ICU stay for nearly half of these patients, approaching statistical significance ($P = 0.05$). Airway intervention was required in one third of episodes related to ACEI. The prevalence of ACEI-related angioedema was high during our study period. The incidence and severity of ACEI-related angioedema may be reduced by structural modifications of these agents. Angioedema has also been reported because of the blockade of the angiotensin II receptor by the antihypertensive losartan (Cozaar).[10]

Care of the patient with angioedema must heed airway and systemic signs. The possibility of central nervous system, abdominal, pulmonary, and gastrointestinal edema may require CT scanning with contrast for diagnosis,[11] intravenous fluid for intravascular volume repletion, or diuresis and ventilatory support for pulmonary management.[4] Steroid therapy with intravenous dexamethasone or hydrocortisone remains the main treatment for angioedema. Tapered oral steroids are used for outpatient management. Epinephrine (0.3 mL of 1:1000 dilution, subcutaneously, repeated up to 3 times) may be used to treat airway edema.[3,12] Inhaled albuterol and terbutaline have also been used for airway symptoms.[12] An antihistamine, such as diphenhydramine hydrochloride (Benadryl) or hydroxyzine (Atarax), is used to reduce the pruritis that patients experience and may help to reduce inflammation. Stress- and steroid-induced gastritis is prevented by H2-blockers and gastric cytoprotective agents.

Patients with HAE benefit from replacement of C1-INH by lyophilized C1-INH concentrate, aerosolized C1-INH, or fresh-frozen plasma.[9] Epsilon-aminocaproic acid (Amicar) may be used short- and long-term in children.[12] Attenuated androgens, such as danazol and stanozol,[12,13] also provide short- and long-term relief. Long-term therapy is sought for patients with frequent episodes (>2/month) or airway compromise,[4] because up to one third of patients used to die of laryngeal edema. Androgens, although successful in adults, are discouraged in pregnant women and children. Nonetheless, limited pediatric experience has been successful.[14] Side effects of androgens include virilization and weight gain. Prophylaxis against angioedema caused by surgical trauma is possible with attenuated androgens, steroids, fresh-frozen plasma, epsilon-aminocaproic acid, and C1-INH concentrate.[15]

Appraisal of airway risk is facilitated by an anatomically based staging system. Because a staging system must be simple, reproducible, and guide referrals and management, we offer an algorithm based on our experience (Fig 2).

Patients without airway distress may be evaluated and treated in an outpatient setting. Patients with airway compromise are evaluated in the emergency department or operating room. When admitted, they are observed in the ICU, and a tracheotomy tray is kept by the bedside. All hospitalized patients are monitored by continuous pulse oximetry in a bed close to the nursing station. Progression of symptoms and/or examination may require airway intervention. As much as possible, airway control is obtained in the operating room with awake fiberoptic intubation. Tracheotomy with the patient under local anesthesia is used if intubation fails to secure the airway. Equipment for direct laryngoscopy and rigid bronchoscopy is kept ready to use. Serial airway examination documents improvement before transfer from the ICU to the ward. Conversion from causative medications is made before discharge, in coordination with the patients' primary care providers. At discharge, patients are given an epinephrine autoinjector (EpiPen or EpiPen-Jr),[2] a recommendation to wear a medical alert bracelet,[4] a letter to keep with them regarding their propensity for angioedema (because 31% of our patients had more than 1 episode), and a follow-up appointment with their otolaryngologist in 2 to 4 weeks. At follow-up, a full head and neck examination is necessary to confirm complete resolution of their angioedema. Persistent lesions require further evaluation, including biopsy. Epidermoid and hematologic malignancies may present with localized edema.[16,17] One such patient in our series was diagnosed with T-cell lymphoma.

CONCLUSION

Mortality today from angioedema most likely is not caused by a lack of technical expertise, but from a failure to appreciate the potential for progressive airway

edema. Understanding the propensity for airway obstruction in patients with voice change, hoarseness, stridor, and dyspnea, and in patients using ACEI, should allow appropriate triage to an ICU setting with preparation for airway intervention. Outpatient and ward management may suffice when the presentation is limited to the face, lip, and/or soft palate. ICU care is recommended for selected patients with lingual edema and all patients with laryngeal edema. An anatomically based staging system should facilitate the safe triage of patients with angioedema, allowing staff and patient preparation for this potentially lethal disease.

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