
Prescriptions for self-injectable epinephrine in emergency department angioedema management

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Background: Angioedema is often treated in the emergency department (ED). Few studies have evaluated self-injectable epinephrine (SIE) prescribing patterns for angioedema.

Objectives: To describe presentation and management of ED patients with angioedema and determine factors associated with epinephrine administration, hospital admission and SIE prescription.

Methods: We conducted a retrospective cohort study of all ED patients with angioedema between January 2005 and December 2006.

Results: Of 63 patients, 39 (61.9%) were female. Median age was 49 years. Precipitating factors were identified in 36 (57.1%) patients. History of other allergic conditions was seen in 37 (58.7%) patients. Seventeen (27.0%) patients received epinephrine, 55 (87.3%) received antihistamines, and 51 (81.0%) received steroids. Epinephrine was administered more commonly in patients with edema of the tongue (risk ratio [RR], 5.28, 95% confidence interval [CI] 1.95–14.33, $P = .0003$), tightness/fullness of throat (RR, 3.31, 95% CI 1.62–6.76, $P = .006$), and dyspnea/wheeze (RR, 3.04, 95% CI 1.41–6.59, $P = .005$). Hospitalization was more common in patients with dyspnea/wheeze ($P = .028$) and allergic history ($P = .006$). Thirteen patients (22.0%) were discharged with SIE. An SIE prescription was associated with younger patients (median age, 26 years [interquartile range (IQR) 15–50] vs a median age 57.5 years [IQR 43–68], $P = .004$) and patients with throat tightness/fullness (RR, 4.2, 95% CI 1.8–9.8, $P = .005$).

Conclusion: Patients with respiratory symptoms and allergic history were likely to be admitted. Epinephrine use was more frequent in patients with signs and symptoms of oropharyngeal edema. Younger patients and those with tightness/fullness of throat were likely to be prescribed SIE. Further studies are needed to determine who would benefit from epinephrine use and SIE prescription.

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INTRODUCTION

Angioedema is a self-limited swelling of the dermis, subcutaneous, and mucosal tissues. Swelling usually subsides in 24 hours. It commonly affects areas with loose connective tissue such as the face, mouth, and throat, but it also can involve the extremities and genitalia.¹ Angioedema can be broadly classified as allergic, drug-induced, hereditary, and idiopathic.¹ Allergic angioedema is often associated with urticaria. Involvement of the respiratory tract can result in life-threatening airway obstruction from laryngeal edema.²

Because of the potential for airway compromise, angioedema is often treated acutely in the emergency department (ED). Multiple studies suggest that hospitalizations for angioedema are increasing.^{3–5} This has been attributed to the increased use of angiotensin-converting enzyme inhibitors (ACEIs).⁶ Data describing ED angioedema presentations and

management are limited. Several studies have been published describing the use of self-injectable epinephrine (SIE) in anaphylaxis.^{7–9} However, very few studies have evaluated SIE prescribing patterns for angioedema, and no clear guidelines exist to assist emergency care providers in determining whether SIE is indicated or likely to be useful in these patients.¹⁰

The aim of our study was to analyze clinical features and management of patients presenting to the ED with angioedema. We also determined factors associated with administration of epinephrine, hospital or intensive care unit (ICU) admission, and the prescription of SIE in ED patients presenting with angioedema.

METHODS

Study Design and Setting

We conducted a retrospective cohort study of all ED patients who were diagnosed with angioedema from January 2005 to December 2006 based on the ICD-9 code for angioneurotic edema NOS (995.1) and hereditary angioedema (277.6). This study was conducted at an academic medical center in the upper midwest United States with 79,000 ED visits per year. During this time period, 69 patients were diagnosed with angioedema. Three patients denied research authorization and were therefore excluded from further study. Medical records

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of all patients were reviewed to confirm the presence of self-limited abrupt swelling of the dermis, subcutaneous, and mucosal tissues consistent with angioedema and then were included in the study. Three patients were excluded because the angioedema was likely to have been a component of anaphylaxis. Of the 63 patients, 1 patient presented to the ED 5 times, and 2 patients had 1 recurrence each. Only the first presentation for each patient during our study period was included in the data analysis. Two abstractors used a standard form to abstract data. The abstractors and investigators resolved any abstracting questions periodically. Demographics, mode of presentation, precipitating factors, treatment taken at home, presenting signs and symptoms, ED management and disposition, prescription of SIE, and medical history were recorded. The study was approved by the institutional review board.

Statistical Analyses

The independent predictor variables of interest included signs and symptoms on presentation, age, sex, use of home medications for the angioedema, presence of an identifiable precipitating factor, and medical history. The administration of epinephrine, ED management and disposition, and prescription of SIE were the outcome variables of interest. Statistical analyses were performed in JMP 7.01. Distributions were calculated for each of the variables, with median and interquartile range (IQR) reported for skewed variables and means and standard deviations reported for normally distributed variables. Nonparametric tests were used for age because of the skewed distribution. The χ^2 test was used for categorical variables.

RESULTS

Sixty-three patients were identified and included in the study. The median patient age was 49 years (interquartile range, 28–67 years). There were 39 (61.9%) women and 24 men. A precipitating factor was identified in 36 (57.1%) of the cases. Medication was the most commonly identified precipitating factor (Fig 1). Three patients had recurrences during the study period. One patient presented to the ED 5 times, and the cause of angioedema was not determined. Two patients had one

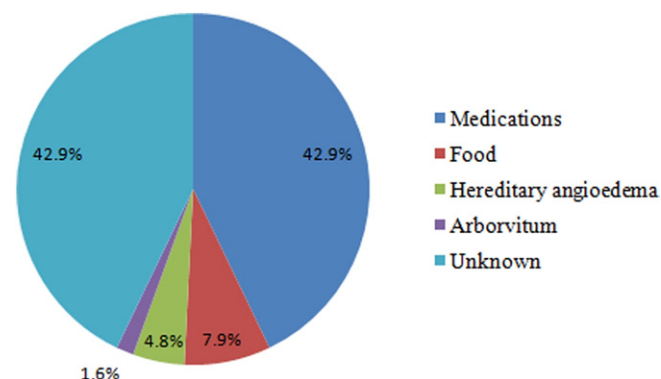


Figure 1. Inciting agents.

Table 1. Medical management of patients

Treatment	Total N (N %)
Medications taken at home	
Antihistamines	16 (25.4%)
Steroids	3 (4.8%)
Epinephrine	2 (3.2%)
Albuterol	1 (1.6%)
Other medications	1 (1.6%)
EMS medications	
Antihistamines	6 (9.5%)
Epinephrine	2 (3.2%)
Albuterol	2 (3.2%)
Steroids	0
ED medications	
Steroids	51 (81.0%)
H1 antihistamines	46 (73.0%)
H2-blockers	25 (39.7%)
Other medications	22 (34.9%)
Epinephrine	13 (20.6%)
Inhaled β -agonists	6 (9.5%)
Epinephrine nebulization	2 (3.2%)

Abbreviations: ED, emergency department; EMS, emergency medical services.

recurrence each. In 1 patient, the precipitating factor was identified as ACEI after the second episode. In the second patient, the precipitating factor was believed to be an ACEI after the first ED presentation, and the ACEI was discontinued. The patient presented again approximately 1 month later, and aspirin was identified as the cause.

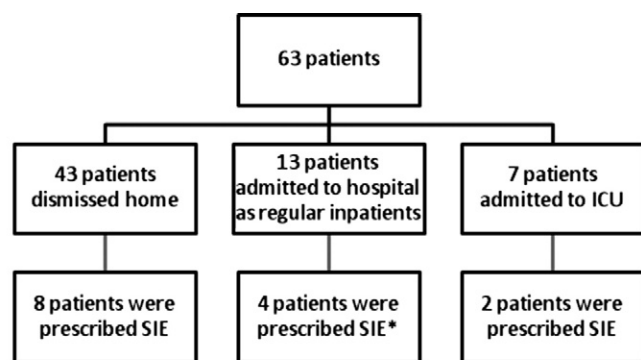
A history of angioedema was noted in 24 (38.1%) of the 63 patients, and a history of other allergic conditions was seen in 37 (58.7%) patients. Twenty-four (39.3%) had a history of taking ACEIs, and 2 (3.3%) were taking angiotensin II receptor blockers (ARBs). The ACEIs were discontinued after the episode in 20 (83.3%) of the patients taking them. The patients on angiotensin II receptor blockers continued taking their medication after the episode.

Table 1 summarizes the at-home, emergency medical services, and ED medical management of patients presenting with angioedema to the ED. A total of 17 (27.0%) patients received epinephrine, 55 (87.3%) received antihistamines, and 51 (81.0%) received steroids. Age, sex, precipitating factors, and history of allergies did not have any significant relationship with use of epinephrine. Epinephrine was administered more commonly in patients with edema of the tongue (risk ratio [RR], 5.28; 95% confidence interval [CI], 1.95–14.33; $P = .0003$), tightness/fullness of throat (RR, 3.31; 95% CI, 1.62–6.76; $P = .006$) and dyspnea/wheeze (RR, 3.04; 95% CI, 1.41–6.59, $P = .005$). Table 2 shows the use of epinephrine in our cohort with regards to the localization of angioedema.

A flow diagram of the patients showing ED disposition and prescription of SIE is shown in Figure 2. No case fatalities occurred in our cohort. Twenty (31.7%) patients were admitted to the hospital, including 7 to the ICU. Intensive care unit

Table 2. Localization of angioedema and use of epinephrine

Localization of angioedema	No. of patients (N = 63)	Patients who received epinephrine No (%)
Edema of lips	45	12 (26.7)
Edema of face	26	9 (34.6)
Edema of tongue	24	13 (54.2)
Edema of pharynx	9	5 (55.6)
Edema of extremities	6	2 (33.3)
Edema of neck	5	2 (40.0)
Gastrointestinal edema	2	0
Edema of genitalia	1	0



* Includes one patient with prior prescription of SIE

Figure 2. ED disposition and prescription of self-injectable epinephrine.

admission was more common in patients in whom ACEIs were the precipitating factors as compared with those who had other inciting agents (22.2% vs 6.7%). Two patients were intubated. The precipitating factor in one patient was ACEI, and it was unknown in the other. Both patients presented with edema of lips and tongue, and one of them had dyspnea/wheeze and edema of the pharynx.

No significant associations were seen between age, inciting agents, and hospital admission. Females were more likely to be admitted to the hospital (OR = 5.41; 95% CI, 1.38–21.19, $P = .01$) as well as patients presenting with dyspnea/wheeze (52.9% vs 23.9%, $P = .028$), and a history of other allergic conditions (46.0% vs 11.5%, $P = .006$). Age, sex, and precipitating factors were not significantly associated with either ICU admission or intubation. Patients presenting with edema of tongue were more commonly admitted to the ICU (29.2% vs 0%, $P = .0006$) as compared with patients without edema of the tongue. Intensive care unit admission was also found to be more frequent in patients who had epinephrine as part of management as compared with those who did not (29.4% vs 4.4%, $P = .013$). These results could have been the result of a difference in presenting symptoms and area of localization of angioedema. Intensive care unit admission was significantly more common in patients who had a history

of allergic conditions as compared with those who did not (18.9% vs 0%, $P = .035$).

Among the patients who did not have a prior prescription of epinephrine ($N = 59$), 13 patients (22.0%) were discharged home with a prescription for SIE (Table 3). Younger age was significantly associated with an increased rate of receiving a SIE prescription ($P = .004$). The median age for patients discharged home with an SIE was 26 years (IQR 15–50) vs a median age of 57.5 years (IQR 43–68) for those who were not discharged with SIE. Among the signs and symptoms recorded, presence of tightness/fullness of throat was significantly associated with prescription of SIE (RR, 4.2; 95% CI, 1.8–9.8, $P = .005$). The presence of urticaria did not predict an increased likelihood of receiving an SIE prescription ($P = .48$).

An allergy referral was made in 16 patients (25.4%), and a primary care referral was made in 32 (53.3%). An allergist referral was made by the ED physician in 9 (64.3%) of the patients who were prescribed an SIE as compared with 7 (14.3%) of the patients who were not prescribed SIE (RR, 4.5; 95% CI, 2.0–9.9, $P = .0002$). Of the 16 patients who received an allergy referral, 15 were seen in follow-up by an allergist. An additional 9 patients followed up with allergy; thus, a total of 24 patients were evaluated by an allergist, and the allergist diagnoses were angioedema in 19, hereditary angioedema in 3, urticaria in 1, and medication allergy in 1. In patients who did not have a prior diagnosis of hereditary angioedema, 17 patients were evaluated for hereditary angioedema, and the workup was negative for the condition in all of them.

DISCUSSION

Angioedema is an infrequently presenting symptom in the ED. Similar to data presented in other studies, we found more women than men presented with angioedema.^{3,11} The mean age of our cohort was 47.8 years, which is comparable to the mean age found in the study by Banerji et al¹¹ on ACEI-induced angioedema.

In our study, we found that medications were the most common identifiable precipitating agent (42.9%). An ACEI was identified as a precipitating factor in 18 (28.6%) patients. The definitive treatment of ACEI-induced angioedema is the discontinuation of all ACEIs.² In our cohort, ACEIs were stopped in 83.3% of patients. Emergency department management and disposition in our study were comparable to those in the study by Banerji et al,¹¹ with some differences: Epinephrine was administered in more patients in our cohort (20.6% vs. 10%), as were inhaled β agonists (9.5% vs 4%). This is likely because our cohort included all acquired causes of angioedema rather than only ACEI-induced angioedema.

No significant difference was found between use of epinephrine and the prescription of SIE in patients who had urticaria as a symptom, suggesting that a suspected allergic cause did not increase the use of epinephrine or SIE.

Table 3. Characteristics of patients who were prescribed self-injectable epinephrine

Factor	No. of patients (N = 59)	No. prescribed self-injectable epinephrine, n (%)
Females	35	10 (28.6%)
Males	24	3 (12.5%)
Precipitating factor		
ACEI	18	2 (11.1%)
NSAIDs	2	1 (50.0%)
Other medications	7	1 (14.3%)
Food	5	1 (20.0%)
Hereditary angioedema	1	0
Arborvitae	1	0
Unknown	25	8 (32.0%)
Localization of edema		
Edema lips	44	12 (27.3%)
Edema face	26	4 (15.4%)
Edema tongue	23	5 (21.7%)
Edema pharynx	8	3 (37.5%)
Edema extremities	6	3 (50.0%)
Edema neck	4	1 (25.0%)
Edema genitalia	1	1 (100%)
Gastrointestinal edema	0	0
Presenting signs and symptoms		
Pruritus	20	6 (30.0%)
Urticaria	18	5 (27.8%)
Dyspnea/wheeze	16	2 (12.5%)
Tightness/fullness of throat	10	6 (60.0%)
Pain	1	0
Abdominal pain	1	0
Epinephrine use in management	15	5 (33.3%)
History of other allergic conditions	34	8 (23.5%)
ED disposition		
Home	41	8 (19.5%)
Hospital admission	18	5 (27.8%)
ICU admission	7	2 (28.6%)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ED, emergency department; ICU, intensive care unit; NSAID, nonsteroidal anti-inflammatory drugs.

The potential for rapid airway obstruction accounts for the life-threatening nature of this disorder. Determining the underlying pathogenesis of the angioedema in the ED is difficult, underscoring the importance of follow-up with an allergist for further evaluation. Despite this, only a little more than one-fourth of patients were referred to an allergist.

Guidelines regarding prescription of SIE in patients presenting with anaphylaxis to the ED have been developed.¹² However, no guidelines exist regarding prescriptions of SIE in patients with angioedema. We found that SIE was prescribed in 22.0% of the patients who did not have a prior prescription of epinephrine and presented to the ED with angioedema. In our cohort, younger age and the presence of tightness or fullness of the throat were significantly associated with an increased rate of receiving an SIE prescription. No association was seen between localization of angioedema and SIE prescription. Patients with a history of laryngeal edema or life-threatening reactions should be given an SIE in case of recurrence. A Medic Alert bracelet also should be considered.¹³

Epinephrine has been shown to be effective in anaphylaxis.¹⁴ The efficacy of epinephrine in the management of

allergic angioedema is inferred based on the common underlying pathogenesis. However, epinephrine is not believed to be effective for hereditary or ACEI-induced angioedema.^{11,15} Further studies are needed to determine who would benefit from a prescription for SIE when dismissed from the ED after treatment for angioedema.

Limitations

This is a retrospective case study. Our dataset is ED based; hence, these findings may not apply to other clinical settings. Based on the exploratory nature of this study, we did not correct *P*-values to account for testing multiple hypotheses; therefore, the probability of finding significance is not controlled at the overall nominal .05 level under the null hypothesis, and thus considerably more than 5% of the significant findings may be spurious. Further studies need to be done with patients in other medical settings.

CONCLUSION

Angioedema was commonly seen in those with a history of other allergic problems. Patients presenting with dyspnea/

wheeze and patients who had a history of other allergic conditions were more likely to be admitted to the hospital. Patients presenting with edema of tongue were more commonly admitted to the ICU. Epinephrine was administered more commonly in patients with edema of the tongue, tightness or fullness of the throat, and dyspnea/wheeze. Only one fifth of all patients presenting with angioedema to the ED were prescribed SIE. Younger age and presence of tightness/fullness of throat as a symptom were significantly associated with the likelihood of being discharged home with a prescription for SIE. Further studies are needed to determine who would benefit from a prescription for SIE when dismissed from the ED after treatment for angioedema.

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