Multicenter study of patients with angiotensin-converting enzyme inhibitor–induced angioedema who present to the emergency department

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Background: Recent data are lacking about the number of patients with angiotensin-converting enzyme inhibitor (ACEI)–induced angioedema who present to the emergency department (ED). Current management of the condition and clinical outcomes also are not known.

Objective: To describe the clinical epidemiology of ACEI-induced angioedema in patients who present to the ED.

Methods: We performed a medical record review of ACEI-induced angioedema in patients who presented to 5 EDs in the Emergency Medicine Network. A structured data abstraction form was used to collect each patient's demographic factors, medical history, and details about the angioedema that prompted the ED visit. The medical record review also focused on treatment provided in the ED and subsequent need for hospitalization.

Results: We identified a total of 220 patients with ACEI-induced angioedema. The frequency of ACEI-induced angioedema among all patients with angioedema who presented to the ED was 30% (95% confidence interval, 26%–34%). The annual rate of visits for ACEI-induced angioedema was 0.7 per 10,000 ED visits. The most frequent presenting signs were shortness of breath, lip and tongue swelling, and laryngeal edema. Most patients (58%) were sent home directly from the ED, whereas 12% were regular inpatient admissions, 11% were admitted to the intensive care unit, and 18% were admitted under observation status (<24 hours). Pharyngeal swelling and respiratory distress were independent predictors of hospital admission and longer length of stay.

Conclusion: ACEI-induced angioedema accounted for almost one-third of angioedema treated in the ED, although it remains a rare ED presentation. A subgroup of these patients still needs inpatient hospitalization for management of upper airway angioedema.

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INTRODUCTION

Angioedema is a life-threatening adverse event associated with angiotensin-converting enzyme inhibitor (ACEI) therapy. The number of patients taking ACEIs continues to rise, leading to increasing rates of angioedema.[1] In 2001, there were 35 million to 40 million prescriptions written for ACEIs worldwide,[2] and in 2007, ACEIs remain the most frequent class of medications prescribed for the treatment of hypertension.[3] Angioedema occurs in approximately 0.1% to 2.2% of patients treated with ACEIs,[4–7] with a higher incidence in women and African Americans.[8,9]

Because of the large number of patients treated with this class of medication, ACEIs became the most common cause of angioedema in patients who presented to the hospital and the ED in the early 1990s.[10–13] Unfortunately, these data regarding the frequency of ACEI-induced angioedema in patients who presented to the ED are at least 10 years old and more recent data are not available. Three retrospective studies from that period found that among patients who presented to the ED with angioedema (identified using the *International Classification of Diseases, Ninth Revision [ICD-9]* code 995.1 for angioedema), 30% to 40% of cases were associated with ACEIs.[10,13,14] Also, despite the relatively high incidence of angioedema, few data exist regarding current management and short-term outcomes of patients who develop angioedema from ACEIs. The aim of the current study is to address the lack of recent data regarding the frequency, current treatment practices, and outcomes of ACEI-induced angioedema in patients who present to the ED.

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MATERIALS AND METHODS

This study is a retrospective medical record review of angioedema in patients who presented to 5 EDs in the Emergency Medicine Network (www.emnet-usa.org). Each site obtained approval from their institutional review board and was asked to review all cases of angioedema in patients who presented to the ED between 2003 and 2005. The target sample size was 1,000 patients across the 5 sites. Prior studies from a decade ago suggested that approximately 30%[10,13,14] of these 1,000 patients will have ACEI-induced angioedema, yielding 300 cases. Therefore, each of the 5 sites needed to abstract data on a minimum of 60 patients with angioedema whose condition was caused by an ACEI. If the number of patients with ACEI-induced angioedema did not reach this predetermined threshold of 60 patients, study sites were asked to review medical records before 2003 or after 2005 to try to reach this target sample.

All patients with a primary *ICD-9* code of 995.1 (angioedema) who presented to the ED during the study period were eligible for medical record review. All medical records identified for review were reviewed to determine whether the allergic reaction was associated with an ACEI. The medical records were abstracted by physicians, researchers with PhD degrees, or college graduates under the supervision of physician site principle investigators. Each site data abstractor received a detailed training document to review before beginning data abstraction. The 19-page training document included detailed information about how to answer each of the questions included in the data abstraction form. A standard form was used to collect detailed information on patients with ACEI-induced angioedema, including demographic factors, history of asthma and/or allergies, prior episodes of angioedema, length of treatment with ACEIs, and details about the current episode of angioedema that prompted the ED visit. Specifics about the treatment provided in the ED, response to treatment, and need for further hospitalization were also recorded. Patients with a diagnosis of ACEI-induced angioedema were included for statistical analysis.

All analyses were performed using STATA statistical software, version 9.0 (StataCorp, College Station, Texas). Data were presented as proportions (with 95% confidence intervals [CIs]), means (with SDs), or medians (with interquartile ranges). Associations are examined using χ^2 test, *t* test, and Wilcoxon rank sum test, as appropriate. Associations were further evaluated using multivariate logistic regression. All *P* values are 2-tailed, with $P < .05$ considered statistically significant.

RESULTS

Frequency of ACEI-Induced Angioedema

Among the 5 participating sites, we identified a total of 586 patients who presented to the ED with angioedema between 2003 and 2005. Among these 586 patients with angioedema, 175 patients (30% [95% CI, 26%–34%]) were found to have ACEI-induced angioedema. The percentage of angioedema cases associated with ACEIs was consistent across years (Fig 1).

Three sites did not reach the predetermined goal of 60 ACEI-induced angioedema cases per site and therefore gathered data from other years (ie, 1998 to 2002 and 2006). This approach led to a final collection of detailed information from 220 patients with ACEI-induced angioedema (including 2 patients with angioedema from angiotensin receptor blockers).

Annual Rate of ED Visits

To determine the annual rate of ACEI-induced angioedema ED visits, we focused on cases during 2003 to 2005. Using these data, in addition to the number of angioedema visits to each ED site during the same period, we calculated the annual rate of visits (per 10,000 ED visits) for both angioedema and ACEI-induced angioedema. The annual rate of visits for angioedema and ACEI-induced angioedema varied across sites, but we found an average of 2.2 visits for angioedema and 0.7 visit for ACEI-induced angioedema per 10,000 ED visits (Table 1).

Demographics and Medical History

The mean (SD) age of the 220 ED patients with ACEI-induced angioedema was 60 (14) years. There was a slight female predominance (62%). Most of the population was either white (46%) or African American (42%), with the remainder of Hispanic (9%) or Asian (1%) descent.

Although most patients had a history of hypertension (98%), prompting treatment with an ACEI, the prevalence of atopy (including asthma, 11%; food allergy, 6%; allergic rhinitis, 4%; and atopic dermatitis, 1%) was much lower than in the general population. Diabetes mellitus was recorded in 24%, coronary artery disease in 22%, congestive heart failure in 7%, and chronic idiopathic urticaria in 1%.

ED Visit

The onset of ACEI-induced angioedema in patients before they presented to the ED was variable, from less than 1 hour

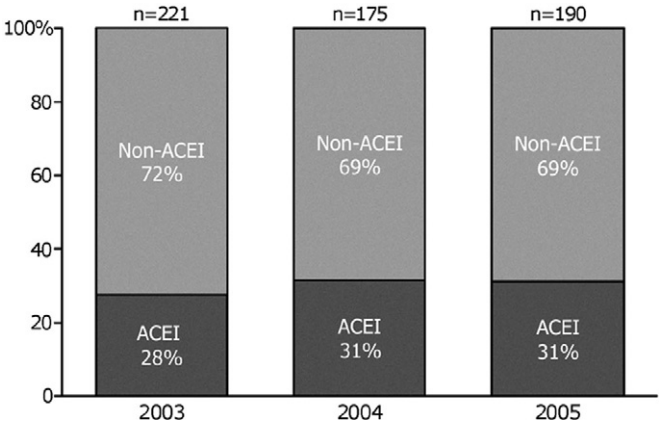

Figure 1. Proportion of all patients with angioedema who had angiotensin-converting enzyme inhibitor (ACEI)–induced angioedema by year.

Table 1. Annual Rates of ED Visits for Angioedema and ACEI-Induced Angioedema

Site	ED visits from 2003 to 2005	Patients presenting to EDs with angioedema from 2003 to 2005	Patients presenting to EDs with angioedema annually (per 10,000)	Patients presenting to EDs with ACEI angioedema from 2003 to 2005	Patients presenting to EDs with ACEI angioedema annually (per 10,000)
1	227,610	172	2.5	35	0.5
2	192,318	49	0.8	17	0.3
3	193,287	210	3.6	85	1.5
4	151,500	62	1.4	19	0.4
5	106,382	93	2.9	19	0.6
All	871,097	586	2.2	175	0.7

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ED, emergency department.

to more than 12 hours, but the median duration was 4 to 6 hours. Most patients came from home (82%) and did not arrive by ambulance (73%). Arrival by ambulance was associated with a significant increase in pre-ED treatment ($P < .001$), including H_1-blockers, H_2-blockers, epinephrine, steroids, and inhaled β-agonists or oxygen and intravenous fluids.

Lisinopril was implicated in 60% of cases of ACEI-induced angioedema. Enalapril was the next most frequent cause (12%), followed by benazepril (6%). In most patients, this was their first episode of angioedema. Patients were taking an ACEI for an average of 6 months (interquartile range, 1–18 months) before the development of the angioedema that prompted the ED visit.

Initial vital signs on presentation to the ED showed a mean (SD) respiratory rate of 19/min (7/min), heart rate of 84/min (17/min), a systolic blood pressure of 151 (26) mm Hg, diastolic blood pressure of 82 (16) mm Hg, temperature of 97.6°F (1.3°F), and oxygen saturation of 97% (2%). Restricting the oxygen saturation to those breathing room air (n = 139) yielded an average of 98% (2%).

The most prominent presenting signs documented in the ED were shortness of breath, lip swelling, laryngeal edema, and tongue swelling (Fig 2). Most patients were treated with corticosteroids (75%) and diphenhydramine (73%). Relatively few patients were treated with epinephrine (10%). Intravenous fluids were used in 42%, oxygen in 9%, and inhaled β-agonists in only 4% of patients with ACEI-induced angioedema.

ED Disposition

Most patients were sent home directly from the ED (58%), with a smaller number requiring regular inpatient admission (12%) or admission to the intensive care unit (ICU) (11%). The other 18% were admitted and discharged under observation status (ie, planned stay of <24 hours). Overall, 14 patients (7%) required ventilatory support in the ED. The type of ventilatory support was determined for 13 patients: noninvasive ventilation (n = 1), intubation (n = 10), and surgical airway (n = 2). All 14 patients who received ventilatory support in the ED were admitted to the hospital. Patients who received ventilatory support had a longer hospital length of stay in days (3 [95% CI, 2–6] days vs 1 [95% CI, 1–2] days; $P < .001$). Although statistical power was limited, no statistically significant difference was found in the number of hours spent in the ICU (48 [95% CI, 17–60] hours vs 22 [95% CI, 17–24] hours; $P = .10$). No deaths occurred from ACEI-induced angioedema among the 5 sites during the years evaluated.

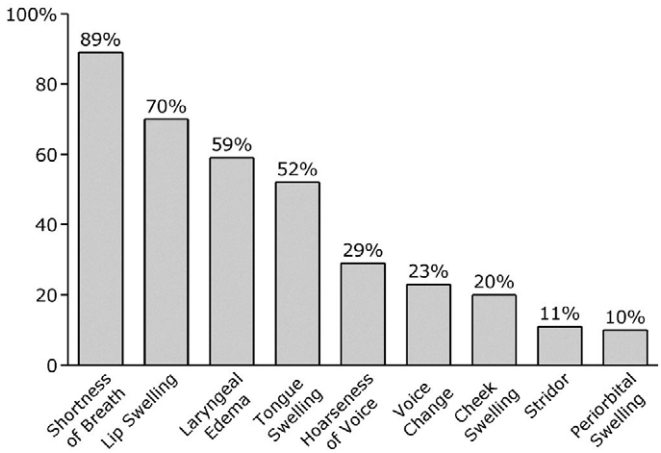

Figure 2. Symptoms of angiotensin-converting enzyme inhibitor–induced angioedema at initial presentation to the emergency department.

Admitted patients (observation, regular floor, or ICU admission) were similar to patients who were discharged to home with respect to mean (SD) age (60 [15] years vs 61 [13] years; $P = .94$), sex (female, 63% vs 60%; $P = .72$), and race/ethnicity (race other than white, 60% vs 50%; $P = .17$) on univariate analysis. The time of symptom onset before ED presentation, arrival by ambulance, any pre-ED treatment, and the initial vital signs in the ED did not predict the need for subsequent hospital admission. Patients were more likely to be admitted to the hospital if they presented to the ED with pharyngeal swelling ($P < .001$) and respiratory distress ($P < .001$) but not if they presented with oral or facial swelling (Table 2). This finding was confirmed by a multivariate analysis of which factors at ED presentation predicted hospital admission (Table 3). Our multivariate analysis further

Table 2. ED Presentation and Clinical Course of ACEI-Induced Angioedema Patients Treated in the ED According to Disposition

Variable	Sent home (n = 129)	Admitted (n = 91)	*P* value
Time of onset, %			.71
<1 hour	6	6	
1–3 hours	42	44	
4–6 hours	19	27	
7–12 hours	16	10	
>12 hours	17	13	
Arrived by ambulance, %	23	36	.07
Pre-ED treatment, %	47	60	.17
Initial respiratory rate, median (IQR)	18 (16–20)	19 (18–20)	.07
Initial pulse rate, median (IQR)	87 (74–96)	80 (70–98)	.34
Initial systolic blood pressure, median (IQR)	148 (135–167)	147 (134–170)	.81
Initial diastolic blood pressure, median (IQR)	81 (71–94)	79 (70–88)	.39
Initial temperature, median (IQR)	97.9 (97.0–98.4)	97.7 (97.0–98.4)	.59
Initial oxygen saturation, median (IQR)	98 (97–99)	98 (97–99)	.71
Pharyngeal swelling, %	13	36	<.001
Oral or facial swelling, %	94	90	.31
Respiratory distress, %	9	29	<.001
Other pain, itching, or swelling, %	17	10	.25
Received oxygen, %	6	14	.03
IV line established, %	64	84	.001
Epinephrine given in ED, %	6	15	.04
Diphenhydramine given in ED, %	66	83	.008
H_1-blocker given in ED, %	2	8	.02
H_2-blocker given in ED, %	52	72	.003
Steroids given in ED, %	70	83	.03
Inhaled β-agonists given in ED, %	1	9	.005
Any ventilatory support given in ED, %	0	16	<.001
Additional medications given in ED, %	4	19	<.001

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ED, emergency department; IQR, interquartile range; IV, intravenous.

Table 3. Multivariate Predictors of Hospital Admission Among ACEI-Induced Angioedema Patients Treated in the Emergency Department

Predictor	Odds ratio (95% confidence interval)	*P* value
Age (per increasing 10-year increments)	1.1 (0.8–1.5)	.47
Female	1.0 (0.5–2.2)	.96
Race/ethnicity other than white	2.2 (1.0–4.9)	.049
Arrived by ambulance	1.6 (0.7–3.6)	.22
Pharyngeal swelling	3.6 (1.5–8.4)	.003
Respiratory distress	3.1 (1.1–8.4)	.03

Abbreviation: ACEI, angiotensin-converting enzyme inhibitor.

suggests that race/ethnicity other than white also predicts the need for subsequent hospital admission ($P = .049$). Patients who received ventilatory support had a longer hospital length of stay in days (3 [95% CI, 2–6] days vs 1 [95% CI, 1–2] days; $P < .001$). Although statistical power was limited, no statistically significant difference was found in the number of hours spent in the ICU (48 [95% CI, 17–60] hours vs 22 [95% CI, 17–24] hours; $P = .10$).

DISCUSSION

Our study found an overall frequency of 30% of ACEI-induced angioedema among all patients with angioedema who presented to the ED. ACEI-induced angioedema accounts for almost one-third of angioedema treated in the ED. This percentage is similar to data from studies completed more than a decade ago, which reported values of approximately 30% to 38%.[10,13,14] Although there was slight variability among the 5 different sites in this study, ACEI-induced angioedema is a rare ED presentation (0.7 case per 10,000 ED visits). Thus, the typical academic ED, with approximately 50,000 annual visits,[15] might expect to see 11 patients with angioedema during a year, of which 3 to 4 cases would have been associated with ACEI. The most frequent presenting signs at the time of initial ED presentation were shortness of breath, lip and tongue swelling, and laryngeal edema. However, pharyngeal swelling and respiratory distress were inde-

pendent predictors of hospital admission and longer length of stay.

Our data are consistent with prior studies suggesting a higher incidence of ACEI-induced angioedema among women and African Americans.[1,16,17] Our results further suggest that patients of races other than white were more likely to need hospital admission (Table 3). The reason for a higher incidence of ACEI-induced angioedema among African Americans remains unclear but may be due to differences in sensitivity to bradykinin.[18–20]

Interestingly, we found atopy, including asthma, food allergy, allergic rhinitis, and atopic dermatitis, to be low compared with the general population among all patients who developed ACEI-induced angioedema. This finding is consistent with the findings of the study by Pigman et al[13]; however, Kostis et al[7] report seasonal allergies as a potential risk factor (odds ratio, 1.65). Our data did not specifically differentiate between seasonal and perennial allergic rhinitis.

Initial vital signs suggest that many of the patients were relatively stable without significant tachycardia, hypotension, fever, or hypoxia at initial presentation to the ED. An underlying diagnosis of hypertension in almost all of the patients helps to explain why the average initial blood pressure was elevated. Angioedema of the tongue and lips with no urticaria and pruritus is the classic presentation of ACEI-induced angioedema.[2,16] Our data show that, despite a normal pulse oximetry, shortness of breath was the most commonly documented presenting sign of ACEI-induced angioedema, followed by lip or tongue swelling and laryngeal edema. Our review did not find patients who presented with significant urticaria or pruritus in the ED. Previous studies report odynophagia and tongue swelling at the time of presentation as risk factors for further intervention and hospitalization.[10] We found that pharyngeal swelling and respiratory distress in the ED were independent predictors of subsequent hospital admission (Table 2) and longer length of stay.

The 5 sites that were part of this study were all academic centers with high-volume EDs. In general, the approach to the treatment of a patient with angioedema was similar at each site. A patient with severe angioedema (pharyngeal swelling, respiratory distress) was observed more cautiously, received more aggressive treatment, and was more likely to be admitted to the hospital. Patients with mild angioedema were simply observed in the ED and often discharged home without subsequent hospital admission. This finding is consistent with the approach one would expect in the treatment of a patient who presents to the ED with mild vs severe symptoms.

We do not report any deaths among all patients who presented to the ED with ACEI-induced angioedema similar to other large studies.[16] Indeed, fatalities from ACEI-induced angioedema are extremely rare, with only isolated case reports in the literature.[21–23] Our study is novel in showing that although most patients appear to have angioedema not requiring intensive treatment in the ED, a subgroup (n = 51 of 220 patients with ACEI-induced angioedema [23%]) was admitted to either the inpatient ward or the ICU. This information is important to our understanding of the ongoing management of ACEI-induced angioedema to improve current and future therapies for these patients.

Similar to recent single-center studies,[16,24] our multicenter study confirmed that lisinopril was the most frequent ACEI to cause ACEI-induced angioedema. This finding may be reflective of data showing that lisinopril has been the most frequently prescribed ACEI.[16,25] Although our patients were taking ACEIs for an average of 6 months before developing angioedema, the literature suggests that 25% to 60% of patients present within the first month of beginning to take an ACEI.[5,10,16,26] However, patients can present with angioedema anywhere from a few days to several years after starting to take an ACEI.[14,27]

The mechanism of ACEI-induced angioedema remains unclear but may be related to increases in bradykinin levels.[28,29] Bradykinin would normally be degraded by ACE but is inhibited in the presence of ACEI. Other enzymes such as aminopeptidase P could degrade bradykinin but have also been reported to be deficient in patients with ACEI-induced angioedema.[30] If elevated bradykinin levels or an altered sensitivity to bradykinin are the main culprits, then current treatments (including antihistamines, corticosteroids, and epinephrine) will presumably not be helpful.[31] Rather, newer agents such as bradykinin receptor antagonists or kallikrein inhibitors may provide novel alternatives for the treatment of ACEI-induced angioedema; such medications are currently under development for hereditary angioedema.[32,33] Lefebvre et al[34] further suggest a role for substance P accumulation as a result of low levels of dipeptidyl peptidase IV levels, leading to an alternative explanation for ACEI-induced angioedema. Clinical research on these new medications requires a basic understanding of the clinical epidemiology of ACEI-induced angioedema, which our study provides.

Nevertheless, our study has several potential limitations. The first is the retrospective design. Using this study design allowed us to quickly gather data for a median 3-year period at 5 different sites. The frequency of ACEI-induced angioedema determined by this study suggests that prospective studies would need to be run for several years and/or across many sites to reach comparable numbers. Second, we were limited by evaluating data that were documented in the ED record. Although there undoubtedly is some variability from record to record, as well as from site to site, we used standard forms and were reassured by the relative similarity of data across the years from 2003 to 2005 and among the 5 sites involved in this study. Also, we did not sample any other *ICD-9* codes for the possibility of ACEI angioedema. We believed that code 995.1 represented the best *ICD-9* code for our objective, and this was similar to how prior studies from a decade ago were conducted, therefore allowing our recent data to be compared with data previously published. This approach could have led to an underestimation of the actual number of cases of ACEI-associated angioedema. Additionally, one could sample patients with diagnoses other than

angioedema who presented to the ED to gather additional data on the frequency of ACEI use. Lastly, our data are only from the ED setting, so extrapolation to other clinical settings remains uncertain.

In summary, ACEI-induced angioedema accounts for one-third of angioedema treated in the ED. Although fatalities are exceedingly rare, patients still need inpatient hospitalization and intensive care treatment for management of respiratory compromise and upper airway angioedema. Further research into the exact mechanism of ACEI-induced angioedema and development of novel treatment options is still needed. Results from our study provide a foundation to assist with study planning and to help determine the potential benefit of future novel treatments in either reducing the frequency of ACEI-induced angioedema or improving outcomes of patients who present to the ED with ACEI-induced angioedema.

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