

The Burden of Angioedema on United States Emergency Departments: 2006–2010

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Objectives/Hypothesis: Angioedema (AE) is a condition that may prompt a visit to an emergency department (ED), and can quickly progress to airway obstruction. To optimize treatment of AE, it is necessary to understand epidemiology and practice patterns. This study measured the magnitude of AE ED visits and characterized demographics, management, frequency of airway interventions, and mortality.

Study Design: Analysis of two national data sets.

Methods: From the Nationwide Emergency Department Sample and National Hospital Ambulatory Medical Care Survey, we identified all patients presenting from 2006 to 2010 with a primary diagnosis of AE, characterized by the International Classification of Diseases, Ninth Edition, Clinical Modification code 995.1. The discharges were weighted and stratified by comorbidities, age, treatments, and region. χ^2 , t test, and linear regression were employed for comparisons.

Results: Total discharges increased from 87,481 (29.3 of 100,000 people) to 111,116 (35.8 of 100,000 people). More females were afflicted (57%), and 41.1% were African American. The majority (83%) of patients were discharged from the ED. Twelve percent of cases were attributed to antihypertensive adverse reaction, and these patients were older ($P < .0001$, odds ratio [OR] = 1.02), and had more comorbidities ($P < .0001$, OR = 5.66), hospital admissions ($P < .0001$, OR = 4.83), and intubations ($P < .03$, OR = 2.07). Overall, patients required intubation infrequently (<1%) and mortality was low (0.08%).

Conclusions: The AE burden on EDs has increased over time. Patients with adverse reactions to antihypertensives are older, have more comorbidities, and require admission and intubation more frequently. Further investigation is needed to better delineate causation and outcome predictors, and to understand regional practice variance.

Key Words: Angioedema, allergic reaction, emergent airway.

Level of Evidence: 2c.

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INTRODUCTION

Angioedema (AE) involves the rapid escape of intravascular fluid into surrounding tissues, specifically resulting in the progressive swelling of the dermis and subcutaneous and/or submucosal tissue. Most commonly, the condition affects the mucosa of the lips, mouth, tongue, and throat.¹ One in 50,000 persons experiences AE because of hereditary AE, a genetic deficiency in a critical regulator of the complement cascade, C1 inhibitor.² However, there are other acquired etiologies (Table I), with approximately 30% of U.S. AE cases attributed to decreased degradation of bradykinin associated with

angiotensin-converting enzyme inhibitors (ACEi).³ Bradykinin-induced AE is usually a self-limiting reaction, predominantly manifesting in the face and extremities.⁴ However, each underlying cause of AE can progress to swelling of the roof of the mouth, tongue, or laryngeal mucosa—risking airway obstruction where airway intervention is critical until the AE resolves.

Overall, the mortality rate following AE is low because the condition is transient; however, there has been a relative increase in hospitalizations and complications from AE in recent years.⁵ Thus, proper management of this acute clinical condition remains crucial in EDs throughout the United States. Recently, there have been attempts to outline the specific clinical manifestations of various subtypes of nonhereditary AE—a promising first step toward the development of an algorithm for managing AE.⁶ In the past, classic intervention for airway obstruction from severe AE included surgical management—tracheotomy or cricothyrotomy.⁷ However, both procedures come with a host of complications, and presently, several institutions consider fiberoptic intubation to be first-line intervention for patients experiencing AE-induced airway obstruction.⁸ Others utilize fiberoptic laryngoscopy only if the patient is experiencing symptoms of airway involvement.⁹ Others prefer to utilize pharmaceutical solutions in an attempt to avoid intubation, only intervening if and when laryngeal

Additional supporting information can be found in the online version of this article.

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TABLE I.
Drug-Induced Causes of Angioedema.

Drug Type	Drug
Antihypertensives	Angiotensin-converting enzyme inhibitors
	Angiotensin II receptor blockers
	Calcium channel blockers
Anti-inflammatories	COX-2 inhibitors
	Nonsteroidal anti-inflammatory drugs
	Aspirin
Antidepressants	Bupropion
	Selective serotonin reuptake inhibitors
	Statins
Others	Proton pump inhibitors
	Tissue plasminogen activator
	Intravenous contrast
	Vaccinations

edema occurs.¹⁰ Recently, some departments have looked into avoiding intubation depending on etiology. For example, icatibant (a bradykinin B2 receptor antagonist) has been shown to successfully address airway obstruction for ACEi-related AE even when intubation had failed.¹¹ Literature in recent years has supported the notion of pharmaceutical intervention reducing the complications associated with procedural interventions.¹²

Ultimately, it is necessary to understand the epidemiology, current practices, and complication rates. Therefore, this study was undertaken to measure the magnitude of AE emergency department (ED) visits with an evaluation of demographic variables, medical management, frequency of airway interventions, and mortality.

MATERIALS AND METHODS

Data collected through the Agency for Healthcare Research and Quality, Healthcare Cost and Utilization Project from the Nationwide Emergency Department Sample (NEDS; 2006–2010) was selected to measure the magnitude of AE, as this database is the largest nationally representative, all-payor ED database in the United States.¹³ The 2006–2010 NEDS varies just slightly by year, containing a 20% stratified sample of 955 to 980 hospitals in 24 to 29 states. NEDS contains limited demographic information and hospital information from ED; charges; International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) coding; and mortality information.

The data analysis for this paper was generated using SAS software, version 9.4 (SAS Institute, Cary, NC) using the appropriate Taylor Series linearization for a primary ICD-9-CM diagnosis of AE (995.1). These patients were stratified by age group, comorbidities, adverse reaction to an antihypertensive (E942.6, E942.9), and geographic region. We obtained data from the U.S. census, similarly stratified by year, age group, and geographical region, and determined incidence of AE.¹⁴ Those suffering from hereditary C1 esterase inhibitor deficiency were omitted. χ^2 tests for equal proportions for each categorical variable were performed as well as trends across the years using linear regression and χ^2 tests for association. The years 2006–2010 were also combined into a single cohort, and the analysis described above was repeated.

Simple logistic regressions were implemented for the single cohort to identify significant predictors. Backward model selection was performed to identify the optimal multiple logistic regression model. Additional dichotomous predictors were created and utilized in the logistic regression to analyze more specific aspects of the demographic and hospital characteristics including admission status, mortality, comorbidity status, individual comorbidity status, and intubation status (procedure codes 96.04 and 96.05). All statistical tests were assessed at the $\alpha = .05$ level.

NEDS is lacking an ethnicity component in its study design. Therefore, we aimed to use a comparable data set, the National Hospital Ambulatory Medical Care Survey (NHAMCS), to examine ethnicity among AE diagnoses. NHAMCS is based on a national probability sample of visits.¹⁵ The demographic and hospital characteristics for the analysis were selected to emulate the variables found in NEDS with the addition of ethnicity. The above analysis was repeated on the NHAMCS 2006–2011 database to the best extent possible.

All members of the study team completed the online data use agreement produced by the U.S. Agency for Healthcare Research and Quality (AHRQ) available at https://www.hcup-us.ahrq.gov/tech_assist/dua.jsp. Those columns with <10 discharges were omitted due to AHRQ limitations set forth in the data use agreement. Two authors (A.S. and M.R.) had full access to all of the data and take responsibility for the integrity and accuracy of the data analysis. Because this study was a secondary analysis of a public database, institutional review board exemption was obtained.

RESULTS

NEDS

The number of primary AE diagnoses increased for years 2006–2010, from 87,488 (29.3 of 100,000 people) to 111,116 (35.8 of 100,000 people). Within each year, there was a significant difference of proportions across gender, location of patient's residence, month of admission (Fig. 1), disposition of patient from the ED, death, and hospital region. Age, primary source of payment, total charges for ED services, and weekend admission were all

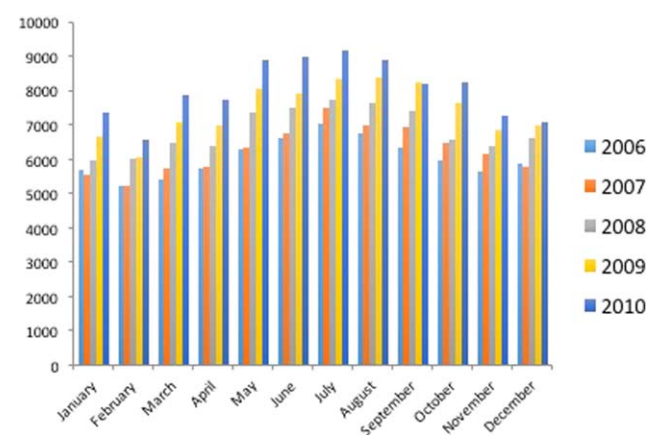


Fig. 1. Seasonal representation of angioedema presenting to the Nationwide Emergency Department Sample database by year. On crude analysis, every month except January and May had significantly more discharges than the reference month, February. On adjusted analysis, this characteristic was no longer significant. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

TABLE II.
NEDS Versus NHAMCS for Combined Cohort Years 2006–2010 Showing Discharge Characteristics From Each Database.

NEDS Variable	Frequency (%)	NHAMCS Variable	Frequency (%)
Age, mean yr	49.11	Age, mean yr	45.25
Gender of patient, $P < .001^*$		Gender of Patient, $P < .0331^*$	
Male	209,936 (42.97)	Male	167,462 (39.02)
Female	278,684 (57.03)	Female	261,664 (60.98)
Location of patient's residence, $P < .001^*$		Urban/rural classification of patient's ZIP code, $P < .1106^*$	
Large central metropolitan	120,146 (24.7)	Large central metropolitan	114,420 (26.66)
Large fringe metropolitan	107,364 (22.07)	Large fringe metropolitan	74,599 (17.38)
Medium metropolitan	112,084 (23.04)	Medium metropolitan	64,517 (15.03)
Small metropolitan	48,676 (10.01)	Small metropolitan	78,171 (18.22)
Micropolitan	60,972 (12.54)	Micropolitan [nonmetropolitan]	79,061 (18.42)
Not metropolitan or micropolitan	37,126 (7.63)		
Payor, $P < .001^*$		Payor, $P < .0206^*$	
Medicare	141,666 (29.1)	Unknown	4,862 (5.01)
Medicaid	61,850 (12.7)	Medicare	21,099 (21.73)
Private	206,222 (42.36)	Medicaid	20,703 (21.32)
Self-pay	57,370 (11.78)	Private insurance	36,669 (37.76)
No charge	3,146 (0.65)	Self-pay	6,819 (7.02)
Other	16,590 (3.41)	No charge	2,514 (2.59)
Total charge for ED services, rounded to nearest dollar, mean	\$1,173	Worker's compensation	2,455 (2.53)
Weekend admission, $P < .001^*$		Weekend admission, $P < .0015^*$	
Monday–Friday	335,100 (68.61)	Weekday	300,372 (70.00)
Saturday–Sunday	153,338 (31.39)	Weekend	128,754 (30.00)
Month of admission, $P < .001^*$		Month of admission, $P < .5457$	
January	31,202 (7.51)	January	25,337 (5.9)
February	29,064 (7)	February	49,931 (11.64)
March	32,560 (7.84)	March	32,372 (7.54)
April	32,612 (7.85)	April	56,514 (13.17)
May	36,968 (8.9)	May	26,090 (6.08)
June	37,826 (9.11)	June	32,992 (7.69)
July	39,748 (9.57)	July	11,369 (2.65)
August	38,652 (9.31)	August	55,895 (13.03)
September	37,094 (8.93)	September	36,527 (8.51)
October	34,914 (8.41)	October	46,414 (10.82)
November	32,290 (7.78)	November	29,557 (6.89)
December	32,360 (7.79)	December	26,128 (6.09)
Disposition of patient from the ED, $P < .001^*$		Race/ethnicity, $P < .001^*$	
Routine discharge	399,824 (81.81)	Non-Hispanic white	204,529 (47.66)
Transfer to short-term hospital	3,966 (0.81)	Non-Hispanic black	176,332 (41.09)
Other transfers—skilled nursing facility, intermediate care, or another type	2,694 (0.55)	Hispanic	46,123 (10.75)
Against medical advice	2,798 (0.57)	Asian/Non-Hispanic other	2,142 (0.5)
Admitted as an inpatient	72,818 (14.9)		
Mortality, $P < .001^*$	350 (0.07)	Mortality	0
Hospital region, $P < .001^*$		Hospital region, $P < .001^*$	
Northeast	77,170 (15.79)	Northeast	53,194 (12.4)
Midwest	106,698 (21.83)	Midwest	88,856 (20.71)
South	225,786 (46.2)	South	18,1815 (42.37)
West	79,046 (16.17)	West	105,261 (24.53)

Probability values compare variables within each database, not between databases.

*Statistically significant.

ED = emergency department; NEDS = Nationwide Emergency Department Sample; NHAMCS = National Hospital Ambulatory Medical Care Survey.

TABLE III.

Healthcare Cost and Utilization Project Demographic Characteristics for Those With Angioedema From Adverse Antihypertensive Reaction Versus Those Not Attributed to Adverse Antihypertensive Reaction for Years 2006–2010 Combined.

Variable	2006–2010 Combined, n = 488,700, Frequency (%)	
	Adverse Medication Reaction, n = 55,871	No Adverse Reaction, n = 432,829
Age, mean yr, $P < .001^*$	61.69	47.49
Gender of patient, $P = .5988$		
Male	24,151 (43.23)	185,785 (42.92)
Female	31,717 (56.77)	246,968 (57.06)
Location of patient's residence, $P < .001^*$		
Large central metropolitan	18,012 (32.24)	102,134 (23.6)
Large fringe metropolitan	10,815 (19.36)	96,549 (22.31)
Medium metropolitan	12,770 (22.86)	99,313 (22.95)
Small metropolitan	5,234 (9.37)	43,442 (10.04)
Micropolitan	5,615 (10.05)	55,357 (12.79)
Not metropolitan or micropolitan	3,147 (5.63)	33,979 (7.85)
Payor, $P < .001^*$		
Medicare	25,547 (45.73)	116,119 (26.83)
Medicaid	5,434 (9.73)	56,417 (13.03)
Private	17,931 (32.09)	188,291 (43.5)
Self-pay	4,664 (8.35)	52,707 (12.18)
No Charge	478 (0.85)	2,668 (0.62)
Other	1,649 (2.95)	14,941 (3.45)
Total mean charges for ED services, rounded to nearest dollar, $P < .001^*$	\$1462.4	\$1141
Disposition of patient from the ED, $P < .001$		
Routine	28,212 (50.5)	371,612 (85.86)
Transfer to short-term hospital	298 (0.53)	3,668 (0.85)
Other transfers—skilled nursing facility, intermediate care, or another type	291 (0.52)	2,404 (0.56)
Home health care	38 (0.07)	480 (0.11)
Against medical advice	263 (0.47)	2,534 (0.59)
Admitted as an inpatient to this hospital	26,316 (47.1)	46,502 (10.74)
Not admitted, destination unknown	447 (0.8)	5,595 (1.29)
Hospital region, $P = .1905$		
Northeast	8,739 (15.64)	68,431 (15.81)
Midwest	13,098 (23.44)	93,601 (21.63)
South	25,512 (45.66)	200,274 (46.27)
West	8,522 (15.25)	70,524 (16.29)
Comorbidities		
Hypertension, $P < .001^*$	40,574 (72.62)	136,625 (31.57)
Diabetes, $P < .001^*$	12,043 (21.55)	43,539 (10.06)
Tobacco use, $P < .001^*$	8,306 (14.87)	31,704 (7.32)
Hyperlipidemia, $P < .001^*$	13,590 (24.32)	30,871 (7.13)
Asthma, $P < .001^*$	2,928 (5.24)	16,784 (3.88)
GERD, $P < .001^*$	5,123 (9.17)	15,107 (3.49)
Hypothyroid, $P < .001^*$	3,985 (7.13)	15,635 (3.61)
Coronary artery disease, $P < .001^*$	3,958 (7.08)	8,870 (2.05)
Emergent airway intervention		
Intubation, $P = .0265^*$	60 (0.11)	231 (0.047)
Mortality, $P = .1348$	60 (0.12)	265 (0.06)

*Statistically significant.

ED = emergency department; GERD = gastroesophageal reflux disease; NA = not applicable.

TABLE IV.

Adjusted Odds Ratios From Modeling (Logistic Regression) the Odds of Having an Adverse Effect of Medication Resulting in Diagnosis of Angioedema Compared to the Odds of Being Diagnosed With Angioedema With No Adverse Reaction to Medication Combining Years 2006–2010.

Predictor Variables, Category Level vs. Referent Level	Adjusted Odds Ratio (95% Confidence Interval)	χ^2 [P]
Age, yr	1.021 (1.018-1.024)	166.6229 [<.0001]*
Expected primary payer		
Medicaid vs. Medicare	0.619 (0.481-0.796)	13.9116 [.0002]*
Private including HMO vs. Medicare	0.955 (0.829-1.099)	0.4138 [.52]
Self-pay vs. Medicare	0.584 (0.376-0.905)	5.7904 [.0161]*
No charge vs. Medicare	0.996 (0.53-1.87)	0.0002 [.9898]
Other vs. Medicare	0.776 (0.503-1.198)	1.3082 [.2527]
Expected secondary payer		
Medicare vs. private including HMO	1.151 (0.931-1.423)	1.6796 [.195]
Medicaid vs. private including HMO	1.256 (1.086-1.453)	9.4609 [.0021]*
Self-pay vs. private including HMO	1.772 (1.498-2.095)	44.6099 [<.0001]*
No charge vs. private including HMO	1.323 (0.703-2.49)	0.7535 [.3854]
Other vs. private including HMO	1.003 (0.791-1.272)	0.0006 [.9803]
Total charge for ED services (nearest dollar)	1.00 (1.00-1.00)	12.6943 [.0004]*
Admission to hospital, inpatient		
Admitted to hospital vs. not admitted to hospital	4.829 (4.233-5.508)	550.0971 [<.0001]*
Individual comorbidities		
Hypertension, 401.9 [†]	2.265 (2.003-2.561)	170.1078 [<.0001]*
Tobacco use, 305.1 [†]	1.58 (1.367-1.827)	38.252 [<.0001]*
Hyperlipidemia, 272.4 [†]	1.254 (1.071-1.469)	7.8926 [.005]*
Intubation status		
Intubated vs. not intubated	2.982 (1.037-8.574)	4.1127 [.0426]*

*Significant results at the alpha = .05 level.

[†]International Classification of Diseases, Ninth Edition, Clinical Modification code.

ED = emergency department; HMO = health maintenance organization.

significantly associated with time or had linear trend across the years (see Supporting Table 1 in the online version of this article). The top 10 secondary diagnoses across all years included: hypertension (401.9), diabetes mellitus (250.0), tobacco use (305.1), swelling of the face (784.2), hyperlipidemia (272.4 or 272.0), asthma/chronic obstructive pulmonary disease (493.9), gastroesophageal reflux disease (530.81), hypothyroidism (244.9), allergy (995.3), renal failure (586.9), and coronary artery disease (414.01).

When combined into a single AE cohort, gender, location of patient's residence, payor, weekend admission, month of admission, disposition of patient from the ED, death, and hospital region proved to have significantly different proportions (Table II, significant variables denoted with asterisks).

Adverse Effect

The combined single AE cohort stratified by adverse effect from antihypertensive medications also proved to have significantly associated proportions, as shown in Table III (significant variables denoted with asterisks). Specifically, average age and total charges were higher in the adverse effects group. Age, location of patient's residence, national quartile for median household income of patient's ZIP code, payor, total charges for ED

services, month of admission, admission status, comorbidities, and intubation status proved to be significant univariate predictors of experiencing AE due to antihypertensive medication effect (see Supporting Table 2 in the online version of this article).

Backward model selection identified age, payor, total charges, comorbidities (hypertension, tobacco use, and hyperlipidemia), and intubation status as predictors

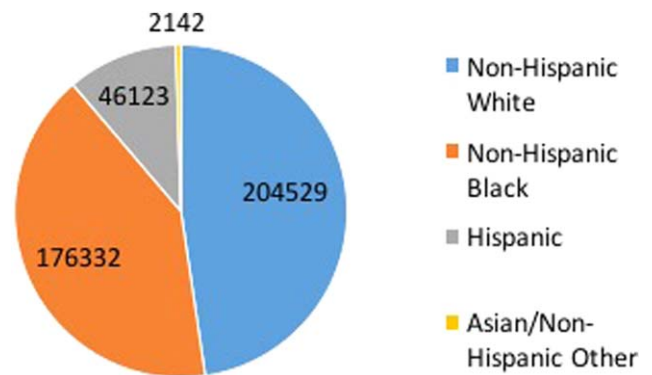


Fig. 2. Ethnicity of those patients presenting with angioedema from the combined cohort 2006–2010 National Hospital Ambulatory Medical Care Survey database. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

of experiencing AE due to an adverse effect from antihypertensive medication. Adjusted odds ratios are available in Table IV.

NHAMCS

The number of primary AE diagnoses for NHAMCS increased from 51,315 (17.2 of 100,000 people) to 95,966 (30.9 of 100,000 people) from 2006 to 2010. Due to the sampling scheme of NHAMCS, individual year stratification produced a large proportion of missing values and thus was excluded. When combined into a single cohort with all years of data combined, gender, race/ethnicity (Fig. 2), primary source of payment, weekend admission, and hospital region proved to have significantly different proportions. The NHAMCS combined cohort is compared with the NEDS combined cohort in Table II. Age, gender, region, month of presentation, payor, and patient's residence ZIP code were similar in proportion to NEDS.

DISCUSSION

AE represents one of the most common and deadly airway emergencies. The need to act quickly and deliberately could mean the life or death of a patient. We identified a frightening trend in that AE is presenting more commonly to our nation's EDs.

Additionally, AE related to the use of ACEi occurs in up to 1% of all patients taking ACEi for hypertension control. Due to the low incidence of this life-threatening sequela, these medications continue to be utilized at high rates.¹⁶ However, 12% of the overall cohort had adverse reactions related to antihypertensives. We believe that this proportion may be underreported among AE cases in NEDS, as it was in contradistinction to other reported association rates.⁴ Further elucidation within this study showed that this subgroup is more often older, with more comorbidities and subsequently more intubations and admissions to the hospital.

A well-known predictor for development of ACEi-related AE is African American ethnicity.¹⁷ Unfortunately, ethnicity is not a variable within NEDS; however, results from NHAMCS were consistent with previous literature.^{18–20} The proportions of other demographics were similar between the two data sets for the combined cohort of NEDS versus the combined cohort of NHAMCS. The sampling design of NHAMCS unfortunately had multiple missing variables in the more detailed analysis and is not included herein. Further exploration of demographic and regional disparities may identify at risk groups, leading to prevention efforts.

A seasonal variation appears to exist favoring the summer months; whether this corresponds with better weather and the likelihood of someone going to the doctor for an ACEi prescription is unknown. One potential correlation to explain this involves AE triggered by seasonal allergies.²¹ Due to the severity of this condition, one would expect an affected patient to go to the ED regardless of the weather. Conversely, AE does not correlate with the spike in upper airway infections seen in the winter.

Patients with symptoms of AE (orofacial swelling, drooling, dyspnea) who are evaluated in an ED may

undergo fiberoptic evaluation (FOE) of the larynx to determine severity of airway involvement and need for airway intervention. Otolaryngologists most often enter the management paradigm at the point of ED consultation request for laryngeal FOE. Unfortunately, neither NEDS nor NHAMCS includes information on consultations in the emergency room including FOE performed by an otolaryngologist.

CONCLUSION

The AE burden on U.S. EDs increased over the years studied. The reasons for the increase and any observed management variability are unclear from this data set, and further investigation is warranted.

Those patients with adverse antihypertensive reactions associated with AE were older, had more comorbidities, were more likely to be admitted to the hospital, and demonstrated a twofold need for airway intervention. Mortality was also twice as common, albeit <1%. Associated adverse reaction to antihypertensives proved to be an important predictor of poorer outcomes in this cohort. Efforts to recognize patients at higher risk for ACEi-related AE appear to be justified from this analysis.

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