

National estimates of emergency department visits for angioedema and allergic reactions in the United States

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ABSTRACT

Each year there are a substantial number of emergency department (ED) visits for angioedema and allergic reactions in the United States. Angioedema is commonly mistaken for an allergic reaction, possibly affecting the treatment rendered. We sought to determine the characteristics of U.S. ED visits for acute angioedema and to determine their differences from visits for allergic reactions. We used 2001–2009 data from the National Hospital Ambulatory Medical Care Survey. Using ED diagnoses (defined by the International Classification of Diseases, 9th Revision codes), we identified visits involving angioedema (ICD-9 277.6 and 995.1) or allergic reaction (ICD-9 995.6, 995.0, 995.4, 995.3, and 708). Accounting for the weighted sampling design, we determined the annual number of angioedema and allergic reaction cases, the characteristics of the affected patients, course of care, and patient outcomes. During 2001–2009 there were 1.05 billion ED visits, including 979,342 for angioedema and 8,814,601 for allergic reactions. These figures corresponded to 108,816 (95% CI, 82,246–132,386) annual visits for angioedema and 979,400 (CI, 874,562–1,084,238) annual visits for allergic reactions. Angioedema patients spent >3 hours in the ED and 11% were admitted to the hospital. Steroids and antihistamines were the most common treatments rendered for both angioedema and allergic reaction patients. There are >100,000 annual visits for angioedema in the United States, with key differences and similarities between allergic reaction and angioedema cases. These findings underscore the large number of angioedema cases presenting to U.S. EDs and the opportunities for novel angioedema therapy use in this setting.

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Angioedema is a medical condition manifesting with swelling of the deep dermal tissues, mucus membranes, and intestines. Although traditionally associated with angiotensin-converting enzyme inhibitor (ACEI) use, angioedema may also be hereditary or caused by other factors such as autoimmune conditions.^{1,2} Angioedema is typically classified as allergic (immunoglobulin E [IgE] mediated) or nonallergic (not IgE mediated). Examples of nonallergic angioedema include hereditary angioedema, acquired angioedema, pseudoallergic angioedema, ACEI-induced angioedema, and idiopathic angioedema.³ Most cases of nonallergic angioedema are related to dysfunction of the bradykinin/kallikrein system.³ Angioedema is of particular interest in the emergency department (ED) because the condition may lead to life-threatening airway obstruction. Angioedema is often difficult to differentiate from allergic

reaction, with up to 50% of patients presenting with both urticaria and angioedema.⁴

The absence of information regarding angioedema presenting to the ED is an important problem. ED clinicians often treat angioedema similarly to an allergic reaction, using primarily antihistamines and corticosteroids. However, there are novel therapies that have been approved for the treatment of hereditary angioedema, such as C1 esterase concentrate or kallikrein and bradykinin inhibitors.⁵ Information regarding the characteristics of patients afflicted by angioedema, their ED course of care, their outcomes, and their contrasting features compared with allergic reaction could aid strategies to target therapy and improve the care of these individuals.

We sought to determine the characteristics of patients presenting to U.S. EDs with acute angioedema or allergic reaction.

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METHODS

Study Design and Setting

We conducted a cross-sectional analysis using data from the National Hospital Ambulatory Medical Care Survey (NHAMCS). The study was approved by the Institutional Review Board of the University of Alabama at Birmingham.

Data Source

NHAMCS is a probability sample of ED and outpatient visits in the United States. The NHAMCS ED survey uses a four-stage probability design, accounting for geographic setting, hospitals within specific geographies, emergency service areas within hospitals, and patient visits to emergency service areas. The study systematically selects all patients in a target hospital ED over a 4-week period.⁶ The National Center for Health Statistics (NCHS) works with each hospital to abstract clinical data from selected charts for each ED visit, including patient demographics, diagnoses, diagnostic tests, procedures, and medical therapies. The weighted sampled design allows for national estimates of visit characteristics. For this analysis we used the 2001–2009 NHAMCS ED public-use data set.⁷

Selection of Participants

We studied patients receiving treatment for angioedema or allergic reactions. NHAMCS contains three fields for ED diagnoses, each classified using International Classification of Disease, ninth revision (ICD-9) codes. We defined angioedema cases as ED visits with diagnosis codes for hereditary and acquired angioedema (ICD-9 codes 277.6 and 995.1). We defined allergic reactions as visits with an ED diagnosis for anaphylaxis due to food (ICD-9 code 995.6), other anaphylactic reaction (995.0), anaphylaxis serum (995.4), unspecified allergy (995.3), and urticaria (708). If a visit contained codes for both angioedema and an allergic reaction, we classified the visit as angioedema.

Covariates

For each ED visit we identified age, race, ethnicity, sex, insurance status, geographic region, metropolitan statistical area, length of stay, admission rate, arrival by ambulance, and therapies given in the ED for both angioedema and allergic reaction groups. Sex, race, and ethnicity were missing for some of the study population (0.9% missing sex information, 12.4% missing race, and 17.5% missing ethnicity). Therefore, we used imputed values provided by NHAMCS.⁶ We classified insurance as Medicare, Medicaid, private, or other insurance, using the hierarchy recommended by NHAMCS.⁶ Geographic regions were grouped into Northeast, Southeast, Midwest, and West census regions. Length of stay (hours), admission rate, and arrival by ambulance were determined from variables in the data set. Information pertaining to ethnicity and arrival by emergency medical services was not available for 2001 or 2002.

We determined administered medications from specific drug class and identification codes specified by the NCHS (Lexicon Plus; Cerner Multum, Inc., Denver, CO).⁸ We identified the use of antihistamines, bronchodilators, steroids, epinephrine, and i.v. fluids in the ED.

Analysis

We analyzed the data using descriptive statistics, annualizing all frequency estimates. We used sampling design and weight variables to calculate nationally weighted estimates and corresponding 95% CIs. Because the NCHS considers estimates with >30% relative standard error or based up <30 raw observations to be unreliable, we collapsed subcategories to ensure that table cells satisfied the requisite number of observations. For variance and 95% CI calculations, we used ultimate cluster design (single stage sampling), using “masked” stratum and primary sampling unit identifiers provided with the NHAMCS public-use data set.⁷ Prior efforts have confirmed the conservative nature of variance estimates using these methods.⁹ We compared patient and visit characteristics between angioedema and allergic reaction cases using logistic regression for categorical variables or F-tests (Wald) for continuous variables.

In the primary analysis we included urticaria (ICD-9 708) in the allergic reaction group, because ED clinicians often do not differentiate the two conditions. In a sensitivity analysis, we repeated the estimates of allergic reactions, excluding urticaria cases.

We conducted all analyses using Stata v.12.0 (Stata Corp., College Station, TX).

RESULTS

Patient Characteristics

During the study period of 2001–2009 there were 1.05 billion ED visits, including 979,342 (95% CI, 767,212–1,191,472) visits for angioedema and 8,814,601 (CI, 7,871,058–9,758,144) visits for allergic reactions (Table 1). Annualized, these figures corresponded to 108,816 (CI, 82,246–132,386) ED visits for angioedema and 979,400 (CI, 874,562–1,084,238) ED visits for allergic reactions.

Patients presenting with angioedema were older than those with allergic reactions (44.4 years versus 28.9 years) and were more commonly Medicare beneficiaries (24.3% versus 9.3%). African Americans comprised over one-fourth of angioedema ED visits, a larger percentage than was observed for allergic reaction patients (28.7% versus 21.2%). The largest number of angioedema cases occurred in the South Census region (37,015 ED visits/year; Table 2). However, relative to the total number of ED visits, the percentage of visits for angioedema was similar across all census regions ($p = 0.07$). We observed no variation in the percentage of visits for allergic reactions in each region ($p = 0.39$).

Course of Care

Angioedema patients spent >3 hours in the ED, and 11% were admitted to the hospital. Compared with allergic reaction patients, length of stay was longer (3.1

Table 1 Characteristics of ED visits for angioedema or allergic reactions, 2001–2009

Characteristic	All ED Visits (<i>n</i> = 116,990,477 annual visits) (%)	Angioedema ED Visits (<i>n</i> = 108,816 annual visits) % (95% CI)	Allergic Reaction ED Visits (<i>n</i> = 979,400 annual visits) % (95% CI)	Angioedema vs Allergic Reactions	
				OR (95% CI)	<i>p</i> Value
Age					
<10 yr	15.7	6.3‡ (3.7–10.3)	25.0 (22.7–27.5)		
10–19 yr	11.7	8.7‡ (4.9–15.0)	14.4 (12.8–16.2)		
20–39 yr	30.8	24.4 (18.3–31.7)	29.8 (27.4–32.4)		
40–59 yr	23.5	33.8 (25.9–42.8)	20.3 (18.3–22.4)		
60+ yr	18.3	26.9 (20.5–34.4)	10.4 (9.0–12.1)		
Mean age (years)	36.2	44.4 (41.1–47.7)	28.9 (27.8–30.0)		<0.01*§
Sex					
Female	54.1	55.6 (45.8–64.9)	58.2 (55.3–61.0)	0.9 (0.6–1.3)	0.60
Male	45.9	44.4 (35.1–54.2)	41.8 (39.0–44.7)	Ref	—
Race					
White	73.6	69.0 (60.0–76.8)	74.0 (71.3–76.7)	Ref	—
African American	22.9	28.7 (21.2–37.7)	21.2 (18.7–23.8)	1.5 (1.0–2.2)	0.07
Other	3.5	2.3¶ (1.1–4.5)	4.8 (3.9–6.0)	0.5 (0.2–1.1)	0.08
Ethnicity#					
Hispanic	13.6	10.5‡ (6.5–16.4)	15.2 (12.8–18.0)	0.7 (0.4–1.1)	0.11
Non-Hispanic	86.4	89.5 (83.6–93.5)	84.8 (82.0–87.2)	Ref	—
Health Insurance					
Medicare	17.7	24.3 (17.7–32.4)	9.3 (7.9–11.0)	2.8 (1.7–4.6)	<0.01*
Medicaid	23.1	17.6 (12.0–25.3)	25.5 (22.9–28.3)	0.7 (0.4–1.3)	0.27
Private	37.7	44.0 (34.9–53.6)	47.0 (44.3–49.8)	Ref	—
Self-pay/other	21.5	14.0 (10.1–19.2)	18.2 (16.3–20.2)	0.8 (0.5–1.3)	0.37
Region					
Northeast	19.1	11.6 (7.6–17.3)	20.4 (17.0–24.3)	Ref	—
Midwest	23.1	31.3 (21.7–42.8)	23.0 (18.9–27.8)	2.4 (1.3–4.4)	<0.01*
South	39.6	34.0 (24.3–45.3)	39.7 (34.3–45.3)	1.5 (0.9–2.6)	0.13
West	18.2	23.1 (15.9–32.5)	16.9 (13.6–20.8)	2.4 (1.4–4.3)	<0.01*
Metropolitan statistical area					
No	16.5	26.3 (14.6–42.7)	18.9 (12.6–27.3)	1.5 (0.8–2.8)	0.18
Yes	83.5	73.7 (57.3–85.4)	81.1 (72.7–87.4)	Ref	—
Initial systolic BP (mm Hg)	132.3	143.7 (139.9–147.6)	128.2 (127.1–129.3)		<0.01*§
Initial HR (beats/min)	92.1	85.3 (82.2–88.4)	93.6 (92.4–94.7)		<0.01*§
Length of stay (hr)	3.3	3.1 (2.4–3.9)	2.2 (2.1–2.3)		0.01*§
Admitted to hospital	12.7	11.0‡ (6.4–18.3)	2.2 (1.6–3.2)	6.5 (3.3–12.5)	<0.01*
Arrival by EMS#	16.1	11.1‡ (6.5–18.2)	7.7 (6.5–9.1)	1.5 (0.8–2.8)	0.19
Treatment rendered in ED					
Antihistamine	10.2	70.1 (62.3–76.8)	75.7 (73.4–77.9)	0.8 (0.5–1.1)	0.12
Steroids	4.6	64.1 (53.7–73.4)	52.2 (49.6–54.7)	1.6 (1.1–2.6)	0.03*
Bronchodilator	5.2	14.7 (10.2–20.7)	13.9 (12.1–15.8)	1.1 (0.7–1.7)	0.72
Epinephrine	0.6	11.2 (7.5–16.6)	11.0 (9.4–12.9)	1.0 (0.6–1.7)	0.91
i.v. Fluids	23.6	37.7 (28.7–47.6)	17.2 (15.2–19.3)	3.0 (1.9–4.6)	<0.01*

Values reported as column percentages unless otherwise indicated.

*Significant at $p < 0.05$ level.

#Based on years 2003–2009 only.

§The p value from adjusted Wald (F) test of equal means.

¶Fewer than 30 raw observations. The NCHS considers estimates based on <30 raw observations to be unreliable.

ED = emergency department; EMS = emergency medical services; BP = blood pressure; HR = heart rate; OR = odds ratio; Ref = referent.

Table 2 Percentage of ED visits for angioedema and allergic reactions in each U.S. census region, 2001–2009

U.S. Census Region	Annual ED Visits 2001–2009 (estimated)	Percentage of ED Visits with Angioedema Diagnosis % (95% CI)	Annual ED Visits for Angioedema 2001–2009 (estimated)	<i>p</i> Value*	Percentage of ED Visits with Allergic Reaction Diagnosis % (95% CI)	Annual ED Visits for Allergic Reaction 2001–2009 (estimated)	<i>p</i> Value*
Northeast	22,282,611	0.06 (0.04–0.08)	12,588	0.07	0.90 (0.81–1.00)	199,560	0.39
Midwest	27,023,721	0.13 (0.08–0.20)	34,036	—	0.83 (0.74–0.94)	225,515	—
South	46,363,986	0.08 (0.05–0.12)	37,015	—	0.84 (0.77–0.92)	388,934	—
West	21,320,159	0.12 (0.08–0.18)	25,176	—	0.78 (0.70–0.86)	165,391	—
Total	116,990,477	0.09 (0.07–0.12)	108,816	—	0.84 (0.79–0.88)	979,400	—

Values reported as row percentages unless otherwise indicated. The differences in regional rates did not reach statistical significance at the 0.05 level for angioedema ($p = 0.07$) or allergic reactions ($p = 0.39$).

**P*-value from Pearson χ^2 -test of independence.

ED = emergency department.

hours versus 2.2 hours) and admission rate was higher (11.0% versus 2.2%) for angioedema patients. Approximately one-tenth of angioedema and allergic reaction patients arrived by emergency medical services (11.1% versus 7.7%). Most angioedema patients received antihistamines and steroids, and over one-third received i.v. fluids. Antihistamine use was similar between groups (70.1% versus 75.7%), whereas angioedema patients were more likely to receive steroids (64.1% versus 52.2%) and i.v. fluids (37.7% versus 17.2%). Bronchodilators or epinephrine were used in less than one-sixth of angioedema and allergic reaction cases. Between angioedema and allergic reaction patients, bronchodilator (14.7% versus 13.9%) and epinephrine (11.2% versus 11.0%) use was similar.

In the sensitivity analysis, we identified that 3,745,371 of 8,814,601 (42.5% CI, 40.0–45.0%) allergic reactions received an ED diagnosis of urticaria. When excluding urticaria cases from the allergic reaction group, we observed largely similar comparisons between angioedema and allergic reaction ED visits.

DISCUSSION

Our observations provide important perspectives of the national burden of angioedema care in the United States, which comprised >100,000 ED visits annually. On average, angioedema patients spent 3 hours in the ED, and ~1 in 10 were admitted to the hospital. Using the National Inpatient Sample, Zilberberg *et al.* estimated ~6000 annual hospital admissions for angioedema in the United States.¹⁰ Our higher estimate includes both patients admitted and discharged from the ED. In addition, our estimated number of angioedema admissions (11,000) is higher than projected by Zilberberg *et al.*¹⁰ Given that many patients with angioedema may be misclassified as allergic reaction, the true number of angioedema ED visits and hospital admissions

may be even higher. These observations highlight the large number of angioedema patients requiring care in the ED as well as the large number of individuals that may require follow-up care by specialists.

The contrasts between angioedema and allergic reaction patients highlighted key differences. Angioedema patients were older and more likely to be African American than allergic reaction patients, findings that may be caused by the different distribution of the conditions or higher rates of hypertension and ACEI use among the elderly and African Americans.¹¹ The regional variations in angioedema and allergic reaction were interesting, suggesting differences in health characteristics, comorbidities, behaviors, or practices. This observation highlights that strategies for angioedema and allergic reaction management may need to be tailored for different geographic regions. Angioedema cases were more likely to be admitted to the hospital, confirming the increased severity of these cases on ED presentation.

Angioedema may be caused by IgE immune-mediated mechanisms, which may respond to corticosteroid and antihistamine treatments. However, most cases of angioedema are bradykinin and complement mediated, rendering common treatments for allergic reaction ineffective.^{12,13} In our study, treatment practices were similar between angioedema and allergic reactions, with the majority of patients receiving antihistamines and corticosteroids. This finding is not surprising given that there are no diagnostic tools to differentiate the two distinct disease states. However, it is surprising that bronchodilator use was similar, indicating that angioedema may be initially treated as an allergic reaction during the course of care.

In the ED, traditional treatments for angioedema include airway management, steroids, antihistamines, and epinephrine. Novel therapies for angioedema that have not been implemented in the ED include C1 es-

terase concentrate, kallikrein inhibitors (ecallantide [Kalbitor]; Dyax Corp, Burlington, MA), and bradykinin inhibitors (icatibant [Firazyr]; Shire, Lexington, MA). Previous clinical trials have shown that ecallantide and icatibant are effective treatments for hereditary angioedema.^{14,15} Additionally, many ED physicians are not aware that fresh frozen plasma represents a viable treatment for angioedema. In the ED setting, these therapies could be beneficial for individuals who do not respond to the traditional treatment regimen, and could prove life-saving when clinicians are faced with undifferentiated angioedema. In characterizing the number of angioedema cases in the United States, our study highlights the need for further research into these alternative treatments and indicates a potential opportunity for their expanded use.

Analyses using NHAMCS are retrospective in nature and dependent on the probability sample design of the data set. However, the NHAMCS methodology is rigorous, and the data have been widely used in similar analyses.^{16–18} Because NHAMCS collects only three diagnoses per patient, we may have missed select cases of angioedema or allergic reactions. Abstractors may have varied in the selection and identification of ED diagnoses, and there was no way to independently validate the classifications. Although we classified ED visits with both angioedema and allergic reaction codes as angioedema, this occurred in only 10% of visits for angioedema.

Although we sought to shed light on the identification, treatment, and initial ED outcomes of angioedema and allergic reaction patients, we had only limited ability to ascertain specific details of treatment, such as admission to an intensive care unit or the details of airway management. We also could not characterize the in-hospital course of admitted patients or the outcomes of those discharged home. This analysis also could not identify causative factors such as the use of ACEIs. However, the current analysis reflects the best available data and provides one of the few cross-sectional perspectives of the ED presentation of and treatment for these patients.

In summary, there are >100,000 annual ED visits for angioedema in the United States, with key differences and similarities between angioedema and allergic reaction cases. These findings underscore the large number of angioedema cases presenting to U.S. EDs and the opportunities for novel angioedema therapy use in this setting.

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