

Angioedema-related emergency department visits in the United States: Epidemiology and time trends, 2006-2015



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Clinical Implications

- There were approximately 117,000 angioedema-related emergency department (ED) visits annually in the United States between 2006 and 2015, accounting for nearly 1 of every 1000 ED visits.

Angioedema is a condition characterized by swelling of subcutaneous or submucosal tissue secondary to the escape of intravascular fluid. Based on its pathophysiology, angioedema can be divided into 2 groups: (1) histamine-mediated angioedema, including IgE-mediated angioedema, drug-induced direct mastocyte degranulation, and idiopathic mastocyte degranulation; and (2) bradykinin-mediated angioedema including hereditary angioedema, acquired angioedema, and drug-induced angioedema (including angiotensin-converting enzyme inhibitor-induced angioedema).¹ Angioedema can be life threatening depending on the severity and the affected site(s) and therefore may warrant emergency medical attention. It has been previously estimated that approximately 109,000 to 115,000 emergency department (ED) visits in the United States are due to angioedema annually; however, these figures represent the burden of angioedema-related ED visits from 2001 to 2010.^{2,3} We sought to update the contemporary epidemiology and time trends of angioedema-related ED visits by describing angioedema-related ED visits in the United States between 2006 and 2015.

We performed an analysis of data from 2006 to 2015 collected from the National Hospital Ambulatory Care Survey (NHAMCS), which is a publicly available, annual survey by the Centers for Disease Control and Prevention and the National Center of Health Statistics (NCHS) of ambulatory care services (ED and outpatient clinics) of US hospitals.⁴ Population estimates on age, sex, race, and region from the US Census Bureau were used to compute US visit rates.⁵ All rates were reported per 1000 individuals per 2 years (2006-2007, 2008-2009, 2010-2011, 2012-2013, and 2014-2015) for the US resident population.

Angioedema-related ED visits were categorized by age group (<18, 18-39, 40-64, and 65 years and older), sex, race (white and non-white), region (Northeast, Midwest, South, West), and insurance status (private, public [Medicare, Medicaid], other [worker compensation, no charge, other, unknown]) for the analysis. ED visits due to angioedema were identified by International Classification of Diseases, Ninth Revision codes (995.1 and 277.6), and rates per 1000 ED visits were estimated and

described by relative risk ratio (RRR), 99% confidence intervals (CI), and *P* values. Comparisons for RRR were performed using the following references for each respective group: 2006 and 2007 for year, <18 years for age, male for sex, non-white for race, Northeast for region, and private for insurance.

Between 2006 and 2015, an estimated 1.2 million ED visits were angioedema-related (approximately 117,000 annually), accounting for 0.09% (99% CI, 0.07%-0.1%) of all ED visits annually (Table I). There was no significant change in the rate of angioedema-related ED visits over the study timeframe.

The median patient age was 52 years (99% CI, 33-67) (Table II). Most angioedema-related ED visits were patients aged 40 to 64 years (42%) followed by patients aged 65 years and older (30%). Most patients were female (59%) and white (68%). The majority of visits occurred in the Southern region (40%).

Patients aged ≥65 years (RRR, 4.2 [99% CI, 1.88-9.41], *P* < .001) and patients aged 40 to 64 years (RRR, 3 [99% CI, 1.40-6.43], *P* = .001) had higher rates of angioedema-related ED visits compared with patients under 18 years of age (Table I). There were no statistically significant differences in proportions of angioedema-related ED visits based on sex, race, US region, or insurance status.

Steroids were the most frequently administered (52.3%) and prescribed (24%) treatment (Table II); administration and prescription rates did not significantly change over time. Counts for prescriptions of epinephrine and H2-antihistamines as well as for additional subgroups based on race were too low to provide accurate estimates and are therefore not reported.

We report an estimated 117,000 angioedema-related ED visits annually without significant changes in this rate between 2006 and 2015, which is similar to what has been reported from 2001 to 2009.^{2,3} These 2 reports estimated the rates of angioedema-related ED visits annually, and the report by Zilberberg et al³ estimated these rates per 100,000 visits. Within this timeframe, there were no significant differences between female and male patients or between white and non-white patients. Similar to what Kelly et al² reported, prescription rates remained unchanged in our timeframe, and steroids continued to be frequently prescribed and administered. There are no data regarding the use of new treatments such as C1-inhibitor, bradykinin receptor antagonists, or plasma kallikrein inhibitors.

A limitation of this study is the inability to distinguish rates of IgE-mediated angioedema and angiotensin-converting enzyme inhibitor-induced angioedema, which represent the most common causes of histamine-mediated and bradykinin-mediated angioedema syndromes, respectively.⁶⁻⁸ In addition, it is possible that anaphylaxis-associated angioedema was coded as angioedema instead of anaphylaxis if angioedema was the most prominent manifestation of anaphylaxis. Furthermore, although the NCHS does its best to standardize coding across different institutions, there may be differences across participating NHAMCS institutions in the completeness of coding. Nonetheless, this is a contemporary epidemiologic study of angioedema-related ED visits that, due to our use of a large national dataset, is likely generalizable to similar populations in the United States.

TABLE I. Overall estimates and rates for angioedema ED visits

Characteristic	Actual number of visits	Estimated number of visits	Total US population	Estimated number of all ED visits	Rate per 1000 ED visits (99% CI)	Rate per 1000 US population (99% CI)	Relative risk ratio (99% CI)*	P value
Overall	263	1,165,768	3,396,866,055	1,301,553,214	0.90 (0.69, 1.11)	0.34 (0.26, 0.43)		
Year								
2006 and 2007	47	149,823	304,899,000	235,993,594	0.63 (0.19, 1.08)	0.49 (0.16, 0.82)	Reference	
2008 and 2009	71	302,702	310,568,090	259,833,549	1.16 (0.53, 1.80)	0.97 (0.45, 1.50)	1.84 (0.77, 4.38)	.07
2010 and 2011	55	206,351	305,325,203	266,139,777	0.78 (0.40, 1.15)	0.68 (0.34, 1.01)	1.23 (0.52, 2.94)	.53
2012 and 2013	51	235,738	320,178,609	261,222,653	0.90 (0.44, 1.36)	0.74 (0.36, 1.11)	1.39 (0.59, 3.31)	.32
2014 and 2015	39	271,154	324,806,792	278,363,641	0.97 (0.44, 1.51)	0.83 (0.37, 1.30)	1.53 (0.61, 3.84)	.23
Age								
<18	32	132,750	73,757,714	293,528,632	0.45 (0.14, 0.76)	1.80 (0.58, 3.02)	Reference	
18-39	48	199,089	92,055,817	444,732,539	0.45 (0.17, 0.73)	2.16 (0.77, 3.56)	1.02 (0.36, 2.91)	.97
40-64	111	485,855	102,680,915	364,880,585	1.33 (0.87, 1.79)	4.73 (3.06, 6.40)	3.00 (1.40, 6.43)	<.001
65+	72	348,074	36,649,798	198,411,458	1.75 (1.02, 2.49)	9.50 (5.53, 13.46)	4.20 (1.88, 9.41)	<.001
Sex								
Female	143	685,723	1,726,429,510	714,984,352	0.96 (0.66, 1.26)	0.40 (0.27, 0.52)	1.13 (0.69, 1.87)	.52
Male	120	480,045	1,670,436,545	586,568,862	0.82 (0.52, 1.12)	0.29 (0.18, 0.40)	Reference	
Race								
White	175	789,898	249,276,057	943,751,522	0.84 (0.60, 1.08)	3.17 (2.21, 4.12)	0.69 (0.44, 1.09)	.04
Non-white	88	375,870	64,689,112	357,801,692	1.05 (0.63, 1.47)	5.81 (3.38, 8.24)	Reference	
Region								
Northeast	54	148,430	609,074,985	233,371,466	0.64 (0.38, 0.89)	0.24 (0.15, 0.34)	Reference	
Midwest	57	281,681	735,873,402	296,823,271	0.95 (0.48, 1.42)	0.38 (0.19, 0.57)	1.51 (0.81, 2.83)	.09
South	104	465,605	1,260,404,426	511,569,985	0.91 (0.60, 1.22)	0.37 (0.24, 0.50)	1.50 (0.87, 2.56)	.05
West	48	270,052	791,513,242	259,788,492	1.04 (0.43, 1.65)	0.34 (0.12, 0.56)	1.71 (0.83, 3.52)	.06
Insurance								
Private	107	377,602	†	394,609,454	0.96 (0.59, 1.32)	†	Reference	
Public	106	577,629	†	574,056,306	1.01 (0.65, 1.37)	†	0.822 (0.48, 1.42)	.36
Other	50	210,537	†	332,887,454	0.63 (0.33, 0.94)	†	0.69 (0.38, 1.25)	.10

CI, Confidence interval; ED, emergency department.

*P values are for relative risk ratios, which correspond to the rates per 1000 ED visits.

†Data not available.

TABLE II. Characteristics of angioedema ED visits

Characteristic	% (99% CI)
Age	
Median (IQR)	52.5 (33.0, 67.2)
Mean (SD)	49.8 (2.12)
<18	11.39 (3.92, 18.86)
18-39	17.08 (7.19, 26.97)
40-64	41.68 (30.28, 53.07)
65+	29.86 (19.45, 40.27)
Sex	
Female	58.82 (47.09, 70.55)
Male	41.18 (29.45, 52.91)
Race	
White	67.76 (56.93, 78.59)
Non-white	32.24 (21.41, 43.07)
Region	
Northeast	12.73 (8.89, 16.58)
Midwest	24.16 (15.48, 32.84)
South	39.94 (30.24, 49.64)
West	23.17 (12.87, 33.46)
Insurance	
Private	32.39 (21.45, 43.33)
Public	49.55 (37.24, 61.86)
Other	18.06 (10.17, 25.95)
Administered	
Epinephrine	13.76 (6.50, 21.03)
H1-Antihistamine	44.92 (34.24, 55.60)
H2-Antihistamine	37.93 (26.74, 49.12)
Steroid	52.29 (41.69, 62.89)
Prescribed	
H1-Antihistamine	13.83 (6.95, 20.72)
Steroid	23.82 (14.80, 32.85)
Arrival by EMS	13.31 (5.36, 21.25)
Admit to hospital	14.32 (6.02, 22.62)

CI, Confidence interval; ED, emergency department; EMS, emergency medical services; IQR, interquartile range; SD, standard deviation.

Angioedema-related ED visit rates in the United States remained stable between 2006 and 2015, accounting for approximately 1 of every 1000 ED visits. Future prospective studies are warranted to more accurately assess the epidemiology

of ED visits for angioedema given the wide array of causes, management considerations, and outcomes. Finally, these data reinforce the need for ED preparedness to manage this potentially life-threatening condition.

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No funding was received for this work.

Conflicts of interest: R. L. Campbell has been a peer reviewer for EB Medicine and an author for UpToDate. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication December 19, 2019; revised March 27, 2020; accepted for publication March 31, 2020.

Available online April 14, 2020.

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2213-2198

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<https://doi.org/10.1016/j.jaip.2020.03.046>

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