

Epidemiology and trends of anaphylaxis in the United States, 2004-2016

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Background: No national study has examined the epidemiology of anaphylaxis after introduction of the codes of the International Statistical Classification of Diseases and Health Related Problems, Tenth Revision, Clinical Modification (ICD-10 CM). Our objective was to examine the trends in incidence and hospitalization rates in the United States utilizing ICD-9 and ICD-10 CM codes.

Methods: We used the Clinformatics database from 2004 to 2016. Our outcome measures included incidence of anaphylaxis and hospitalization trends. Multivariable logistic regression was used to assess the predictors of anaphylaxis and hospitalization.

Results: There were a total of 462,906 anaphylaxis cases. The incidence increased from 153 in 2004 to 218 in 2016 (per 100,000). Women were 1.19 (95% confidence interval, 1.18-1.20) times more likely to present with anaphylaxis. Medication-induced anaphylaxis increased 15-fold.

Conclusion: This is the first population-based study that included ICD-10 CM codes to describe the epidemiology of anaphylaxis in the United States. ICD-10 codes improved the accuracy of medication-induced anaphylaxis, the most likely etiology to result in hospitalization. © 2019 ARS-AAOA, LLC.

Key Words:

anaphylaxis; allergens; food allergy; medication allergy; venom anaphylaxis

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Anaphylaxis as defined by the American Academy of Allergy Asthma and Immunology (AAAAI) is an acute, life-threatening systemic reaction with varied mechanisms, clinical presentations, and severity.¹ There has been a steady increase in the incidence of anaphylaxis in many countries around the world.²⁻⁵ In the United States (US), a 2.2% increase per year in hospitalizations and a >100% increase in emergency department (ED) admissions over a 10-year period have been reported.⁵ Etiologic triggers for anaphylaxis include food, medications, venom, serum, and

idiopathic causes. When examining the triggers of anaphylaxis, studies have yielded variable results depending on study designs. In a large US database study using codes established by the International Statistical Classification of Diseases and Health Related Problems, Ninth Edition, Clinical Modification (ICD-9), idiopathic anaphylaxis was the most common trigger,⁴ and the largest rise in the incidence of anaphylaxis was observed for medication-induced anaphylaxis (212%) and food (124%), which parallels the rise in the incidence of food allergy.⁶ All ICD-9 CM codes that have been used for medication-induced anaphylaxis were nonspecific, including adverse reactions to drugs.

With the introduction of ICD-10 CM, specific medication-induced anaphylactic codes were introduced. To date, no large database study has examined the incidence and hospitalization rates of anaphylaxis in the US utilizing ICD-10 CM codes. In addition, previous epidemiologic studies examined the trends of anaphylaxis in a single setting (ED or inpatient).

Our goal in this study was to examine the trends of anaphylaxis utilizing ICD-9 and ICD-10 CM codes during the period from 2004 to 2016 in all patient settings (ED, inpatient, and outpatient) in the US.

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Materials and methods

Data source

In this retrospective cohort study we used administrative health data from Clinformatics DataMart (CDM). These data represent one of the nation's largest national commercial health insurance programs and have been validated in a number of studies.^{7–12} Persons enrolled in this insurance program may be included in either a fee-for-service plan or a managed care plan, which includes health maintenance organizations (HMOs), preferred provider organizations (PPOs), and exclusive provider organizations (EPOs). The CDM database contains approximately 13% Medicare patients and 87% commercial insurance patients. The majority of enrollees are point of service (POS, 43.7%) and HMO (31.4%), followed by PPO (11.6%) and EPO (8.9%). Other and indemnity cases make up the remaining 3.8% and 0.6%, respectively. For each of these plans, providers are required to submit complete claims to receive reimbursement. The data are from a single commercial insurance that is widely used in the US across all states. During the study period (2004–2016), a total of 217,556,764 beneficiaries, with no age restriction, were included in the overall study population with a minimum of 15,502,169 in any year. We used a combination of outpatient, inpatient, and pharmacy claims data. Inpatient (or hospitalization status) was determined by using “confinement” tables in the data. For this reason, only patients who had an inpatient status were included in our hospitalization. Patients who were observed for 23 hours were not included in the inpatient database. This study protocol was reviewed by the institutional review board at the University of Texas Medical Branch.

Measures

Anaphylaxis was defined using codes based on the following etiologic subgroups (ICD-9 CM: 999.41 [blood and blood products]; 995.6x [food allergy]; 999.42 [immunization]; 995.4 [anesthesia]; 989.5 [venom]; 995.1 [angioneurotic edema]; and 995.0 [unspecified]; ICD-10 CM: T63.4 [venom]; T78.0X [food allergy]; T78.2 [anaphylactic shock, unspecified]; T80.5 [serum]; T88.2 [anesthesia]; T78.3 [angioneurotic edema]; and T88.6XXA [medication-induced anaphylaxis]). ICD-9 CM codes were used from January 2004 until September 30, 2015. ICD-10 CM codes were used starting October 1, 2015 until December 30, 2016.

Analysis

To estimate the annual incidence of anaphylaxis, separate study cohorts were identified for each calendar year from 2004 to 2016. Persons at the start of each calendar year with continuous benefits during the 12-month period for the previous year were included in the study population for that year. Number of eligible follow-up months for each calendar year were counted for the calculation of person-

years. Incidence was defined as the percentage of persons in a given year's cohort who had at least one diagnosis of anaphylaxis divided by total person-year during that year. For each patient, only the first episode in a given year was counted. We assessed the incidence of overall anaphylaxis and the incidence of anaphylaxis by etiology subtype (food, angioneurotic edema, drug, venom/sting, and other), each by calendar year. Second, we examined the proportion of persons with anaphylaxis who were hospitalized by etiology and calendar year. Third, we assessed the median length of stay for each anaphylaxis-related hospitalization by calendar year. Finally, we conducted a multivariable logistic regression to assess the trend of anaphylaxis incidence over time, adjusted for demographic and clinical factors. The regulations set for Optum CDM is to restrict reporting any number that is <10. Numbers that are ≤10 are reported as <11 in our study. All analyses were performed using SAS version 9.4 (SAS Institute, Inc, Cary, NC).

Results

A total of 217,522,366 patients with an average of 12,884,332 person-years per year were included in our analysis for the time period 2004–2016. A total of 462,906 anaphylaxis cases were reported during the study period.

Demographics

Patients' characteristics are presented in Table 1. There were 121,173 (26%) pediatric patients between 0 and 17 years old, 239,847 adults (53% of cases) aged 18–59 years, and 101,886 older adults (21%) aged 60+ years.

There was a rise in the overall incidence of anaphylaxis over the observed time period from 2.1 per 1000 person-years in 2004 to 3.3 per 1000 person-years in 2013 (57% increase). When comparing 2004–2007 with 2008–2016, there was a 32% increase in incidence of reported anaphylaxis (Fig. 1). The change in incidence of anaphylaxis by age, demographic region, gender, and etiology was reported over the time period studied (Fig. 2). The incidence of anaphylaxis cases from the pediatric population increased from 2.3 per 1000 person-years in 2004 to 5.0 per 1000 person-years in 2016 (117% increase). The biggest changes were seen in the 6- to 12-year age group (151% increase), the 13- to 17-year age group (132% increase), and the 70+-year age group (108% increase).

The results of our multivariate analysis show that women were 1.188 (95% confidence interval [CI], 1.181–1.195) times more likely to have anaphylaxis compared with men (Table 2). Patients in the Northeast were most likely to develop anaphylaxis (odds ratio [OR], 1.684; 95% CI, 1.460–1.484) compared with those living in the West.

Etiology

The percentage of anaphylactic cases due to venom and stings fell from 57% in 2004 to 38% in 2016. Over this entire period, this category still accounted for the majority

TABLE 1. Characteristics of all patients with incident anaphylaxis from 2004 to 2016

	All patients, person-years	Number of anaphylaxis patients	Percentage of anaphylaxis patients	Rate of anaphylaxis per 1000 person-years
Gender				
Male	81,534,095	207,605	0.25%	2.55
Female	85,938,213	255,235	0.30%	2.97
Age group (years)				
0-1	2,289,359	5,181	0.23%	2.26
2-5	6,937,188	36,938	0.53%	5.32
6-12	13,338,758	51,704	0.39%	3.88
13-17	10,161,760	27,350	0.27%	2.69
18-29	23,466,023	47,191	0.20%	2.01
30-39	23,527,703	54,234	0.23%	2.31
40-49	25,879,006	68,854	0.27%	2.66
50-59	23,888,886	69,568	0.29%	2.91
60-69	17,635,957	52,394	0.30%	2.97
70-79	13,614,365	35,420	0.26%	2.60
80+	6,757,310	14,072	0.21%	2.08
Region				
Midwest	40,128,394	114,160	0.28%	2.84
Northeast	15,928,060	54,376	0.34%	3.41
South	70,245,760	213,262	0.30%	3.04
West	39,612,294	79,741	0.20%	2.01
Year				
2004	12,319,444	25,544	0.21%	2.07
2005	12,903,797	28,769	0.22%	2.23
2006	13,304,187	31,594	0.24%	2.37
2007	13,418,982	32,078	0.24%	2.39
2008	12,951,589	34,111	0.26%	2.63
2009	12,619,641	35,491	0.28%	2.81
2010	12,237,682	35,373	0.29%	2.89
2011	12,408,178	36,140	0.29%	2.91
2012	12,583,397	39,536	0.31%	3.14
2013	12,848,927	42,301	0.33%	3.29
2014	12,261,225	39,685	0.32%	3.24
2015	13,053,301	41,117	0.31%	3.15
2016	14,585,968	41,167	0.28%	2.82
Asthma	13,943,580	76,865	0.55%	5.51
COPD	11,765,951	22,130	0.19%	1.88
Allergic rhinitis	31,734,648	127,868	0.40%	4.03
Overall	217,556,764	462,906	0.21%	2.13

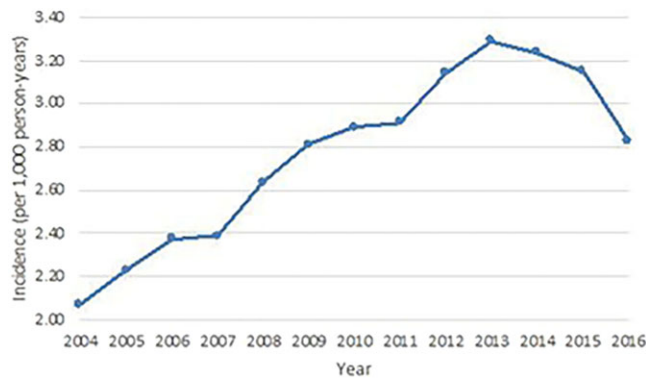


FIGURE 1. Total incidence of anaphylaxis cases. The incidence appears to increase, reaching a peak in 2013 and followed by a decrease in 2014–2016.

of reported cases. On average, 47% of anaphylaxis cases due to venom and stings occurred in the South, 28% in the Midwest, 15% in the West, and 10% in the Northeast. The percentage of anaphylaxis cases caused by medications

increased in 2015 and 2016 years, from 0.14% (2004–2014) to 0.63% in 2015 and 2.20% in 2016.

The incidence of food-related anaphylaxis cases increased from 86.3 per 1000 person-years in 2004 to 239.2 per 1000 person-years in 2016 (177% increase). The majority of food-related anaphylaxis cases were reported as food—unspecified (33% of food-related cases). The percentage of nut/seed-related anaphylaxis cases increased the most, from 11.6% in 2004 to 30.8% in 2016 (166% increase). The percentage of shellfish-related anaphylaxis cases increased from 6.2% in 2004 to 10.2% in 2016 (64% increase). In addition, the percentage of peanut-related anaphylaxis cases increased from 22.6% in 2004 to 34.0% in 2016 (50% increase). The diagnosis of food—unspecified anaphylaxis decreased from 36.6% of food-related anaphylaxis to 16.2% in 2016. Unspecified food allergies, on average, comprised the greatest percentage of food-related anaphylaxis cases from 2004 to 2016 in the study, at 35% (Fig. 3).

Medication-induced anaphylaxis cases in the older population increased from 2004 to 2016. During this period,

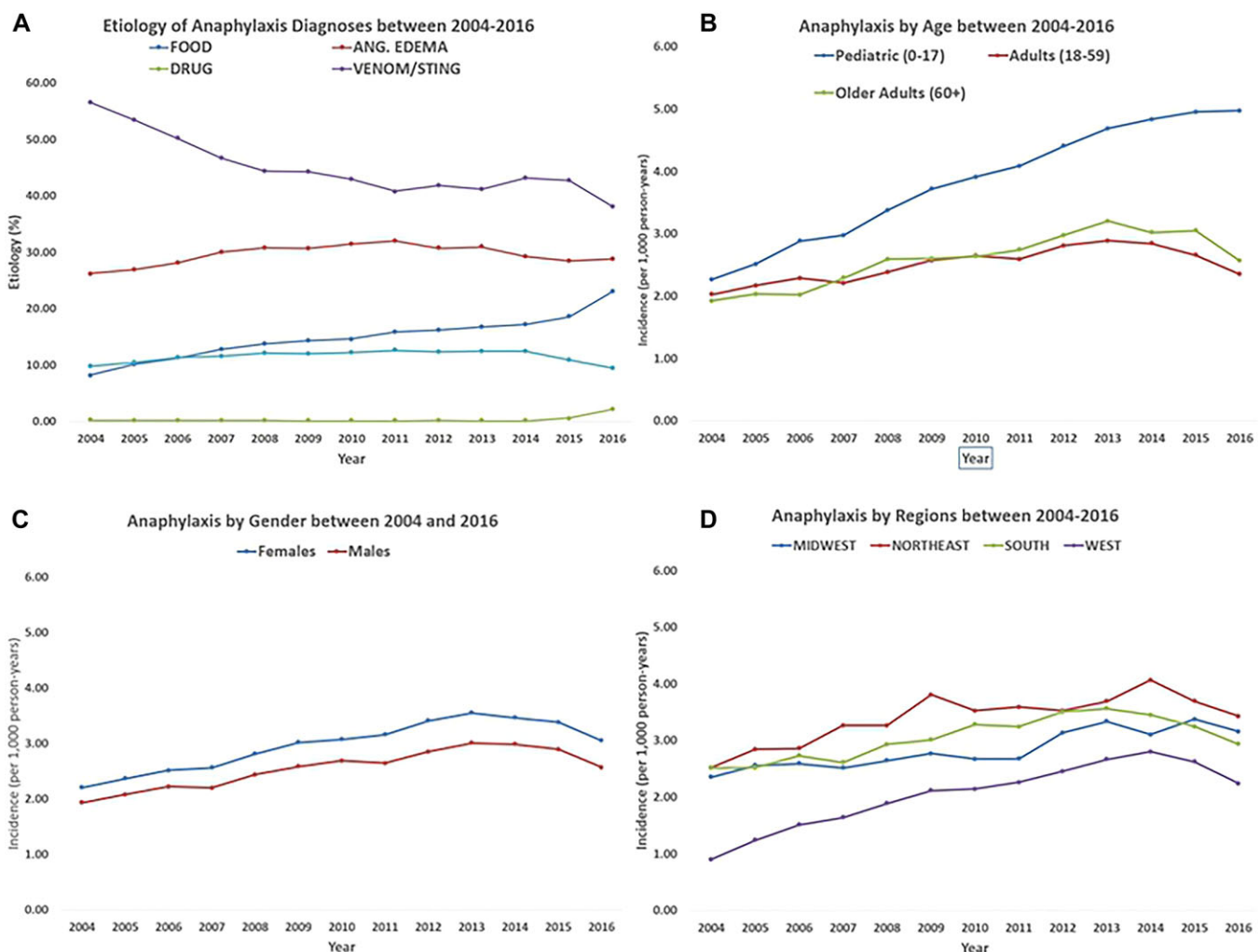


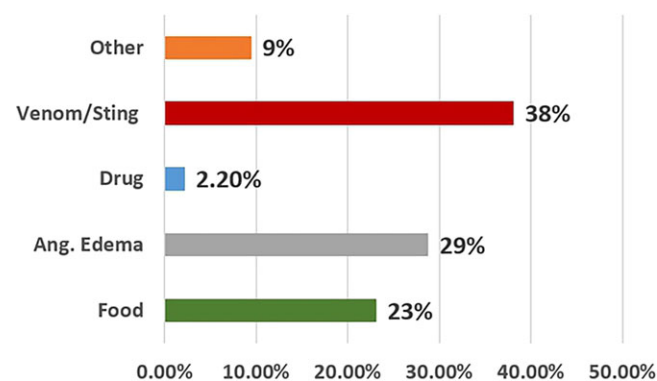
FIGURE 2. (A) Percentage of types of anaphylaxis diagnoses (etiology) over time. The incidence of anaphylaxis over time per 1000 person-years is stratified by age (B), sex (C), and region (D).

TABLE 2. Multivariable logistic regression model predicting anaphylaxis

	Odds ratio (95% CI)
Year	
2004	Referent
2005	1.061 (1.043-1.079)
2006	1.117 (1.098-1.135)
2007	1.099 (1.080-1.117)
2008	1.172 (1.154-1.192)
2009	1.207 (1.187-1.226)
2010	1.239 (1.220-1.260)
2011	1.242 (1.222-1.262)
2012	1.348 (1.327-1.370)
2013	1.446 (1.423-1.468)
2014	1.508 (1.484-1.532)
2015	1.504 (1.481-1.528)
2016	1.435 (1.413-1.458)
Gender	
Male	Referent
Female	1.109 (1.102-1.115)
Age (years)	
0-1	1.912 (1.851-1.974)
2-5	2.918 (2.860-2.976)
6-12	1.971 (1.934-2.009)
13-17	1.401 (1.372-1.430)
18-29	1.267 (1.243-1.292)
30-39	1.347 (1.322-1.373)
40-49	1.442 (1.416-1.469)
50-59	1.505 (1.478-1.533)
60-69	1.492 (1.464-1.520)
70-79	1.264 (1.239-1.289)
80+	Referent
Region	Referent
West	
Northeast	1.502 (1.486-1.519)
South	1.285 (1.274-1.300)
Midwest	1.299 (1.287-1.311)
Asthma	2.529 (2.509-2.549)
COPD	1.851 (1.831-1.870)
Allergic rhinitis	2.844 (2.826-2.861)

$p < 0.0001$ for all covariates.

CI = confidence interval; COPD = chronic obstructive pulmonary disease.

**FIGURE 3.** Etiology of anaphylaxis in 2016. Ang. Edema = angioedema.

the age group 60-69 years had an increase from <11 to 152 cases, whereas those 70-79 years had an increase from <11 to 132 cases and those 80-89 years an increased from 0 to 64 cases.

Hospitalizations

The overall number of anaphylaxis cases requiring hospitalization remained stable at an average of 2.3% during the study period. The average length of hospital stay increased from 2.47 days in 2004 to 3.63 days in 2016. Women were less likely to be hospitalized for anaphylaxis (odds ratio [OR], 0.830; 95% CI, 0.801-0.866 (Table 3)).

Venom- and sting-related anaphylaxis hospitalization rates decreased from 1.3% in 2004 to 0.3% of cases in 2016 (77% decrease). In every region, there were noticeable decreases in venom/sting hospitalizations when comparing 2004 with 2016. The South went from 116 cases to 12 cases, whereas the Midwest went from 38 cases to 12 cases. The West went from 16 cases to <11 cases, and the Northeast from 11 cases to <11 cases. Medication-induced anaphylaxis hospitalization rates were the highest, with an overall average of 12.1% of cases, and increased from 3.6% of cases requiring hospitalization in 2004 to 21.0% of cases in 2016 (483% increase). In 2016, every region had medication-induced hospitalizations. The South had the most at 70, followed by the Midwest at 60, the West with 30, and the Northeast with 28.

The percentage of food-related anaphylaxis cases resulting in hospitalization decreased from 2.00% in 2004 to 0.66% in 2016 (67% decrease). The most common food-borne cause of anaphylaxis was peanuts (1.86% of anaphylaxis cases requiring hospitalization during the study period), followed by nuts/seeds at 1.17% and fish (excluding shellfish) at 0.77%. The rate of hospitalization caused by anaphylactic reaction to peanuts decreased from 2.36% in 2004 to 1.22% in 2016 (48% decrease). Hospitalizations caused by nuts/seeds increased from 1.09% in 2004 to 1.56% in 2016 (43% increase). In comparing the 2004 and 2016 results for food-related anaphylaxis hospitalizations, the South showed little increase, going from 21 to 22

TABLE 3. Multivariable logistic regression model predicting hospitalization

Variable	Odds ratio (95% CI)
Year	
2004	Referent
2005	0.916 (0.813-1.032)
2006	0.951 (0.847-1.067)
2007	0.993 (0.888-1.112)
2008	1.028 (0.921-1.147)
2009	0.999 (0.896-1.115)
2010	0.846 (0.757-0.946)
2011	0.736 (0.657-0.825)
2012	0.987 (0.888-1.097)
2013	0.914 (0.823-1.015)
2014	0.856 (0.768-0.953)
2015	0.765 (0.687-0.853)
2016	0.730 (0.655-0.815)
Gender	
Male	Referent
Female	0.830 (0.801-0.866)
Age (years)	
0-1	0.097 (0.071-0.133)
2-5	0.083 (0.072-0.096)
6-12	0.087 (0.077-0.099)
13-17	0.154 (0.135-0.175)
18-29	0.156 (0.140-0.174)
30-39	0.200 (0.181-0.220)
40-49	0.269 (0.247-0.293)
50-59	0.380 (0.351-0.411)
60-69	0.538 (0.500-0.581)
70-79	0.653 (0.604-0.707)
80+	Referent
Region	
West	Referent
Northeast	0.991 (0.918-1.069)
South	1.173 (1.110-1.241)
Midwest	0.981 (0.9222-1.044)
Asthma	1.257 (1.192-1.324)
COPD	1.405 (1.330-1.484)
Allergic rhinitis	0.635 (0.605-0.666)

$p < 0.0001$ for all covariates.

CI = confidence interval; COPD = chronic obstructive pulmonary disease.

cases, and the Midwest showed no change from 15 cases when comparing the 2 years (Fig. 4).

Discussion

In this study of over 200 million persons enrolled in one of the nation's largest commercial insurance plans, we reviewed 462,906 anaphylactic cases over a 13-year study period to determine the epidemiology and hospitalization rates of anaphylaxis. To our knowledge, this is the first nationwide database study on the epidemiology of anaphylaxis in the US that included ICD-10 CM codes and examined the incidence in all patient care settings (ED, inpatient, and outpatient). Overall, there was an annual rise in the incidence of anaphylaxis, peaking in 2013 at 3.3 per 1000 person-years, with a subsequent decline in 2014-2016. The overall increased incidence of anaphylaxis is similar to that reported by Motosue et al,⁵ who showed an increase in the incidence of ED visits for anaphylaxis from 2004 to 2014. Our anaphylaxis rate of 3.3 per 1,000 person-years is much higher than their highest reported rate of 28.6 per 100,000 in 2014. This is largely explained by their exclusion of outpatient or inpatient settings for anaphylaxis.

The most common trigger for anaphylaxis in our study was venom/sting (44.5%), followed by food (15.3%). It is important to note that ICD-9 CM and ICD-10 CM codes for venom/sting are nonspecific and may overestimate the incidence of an anaphylactic event rather than a toxic effect. We believe that the decline in anaphylaxis after 2013 was largely due to the decline in venom/sting and idiopathic anaphylaxis. The rate of venom-induced anaphylaxis showed a similar pattern of an initial rise in incidence followed by a drop after the year 2014. This trend in venom-induced anaphylaxis has been reported in other studies,¹³⁻¹⁵ and has been postulated to be a result of the decreased populations of bees and wasps.^{16,17}

When examining demographic factors, we found that anaphylaxis was more common in women compared with men. Female gender has been a reported to be a risk factor for the development of anaphylaxis.¹⁸⁻²¹ Given that the reported difference is largely in the prepubertal years, it is believed that this could be hormonal.¹⁹

The incidence of anaphylaxis was also the highest in patients in the 2- to 5-year age group (OR, 2.285) compared with patients >80 years old. Pediatric patients (<18 years), in general, had an increased overall incidence of anaphylaxis compared with older patients. Our results regarding age are consistent with the literature, with the highest incidence of anaphylaxis reported in those 0-4 years of age.^{22,23} The increased incidence of anaphylaxis in this age group parallels the rise in the incidence of food-related anaphylaxis. The reported incidence of food allergies according to the US Centers for Disease Control and Prevention (CDC), in those <18 years old, have increased by 18% from the year 1997 to 2008.²⁴ It has also been suggested^{25,26} that the increased risk of food-induced anaphylaxis in teenagers

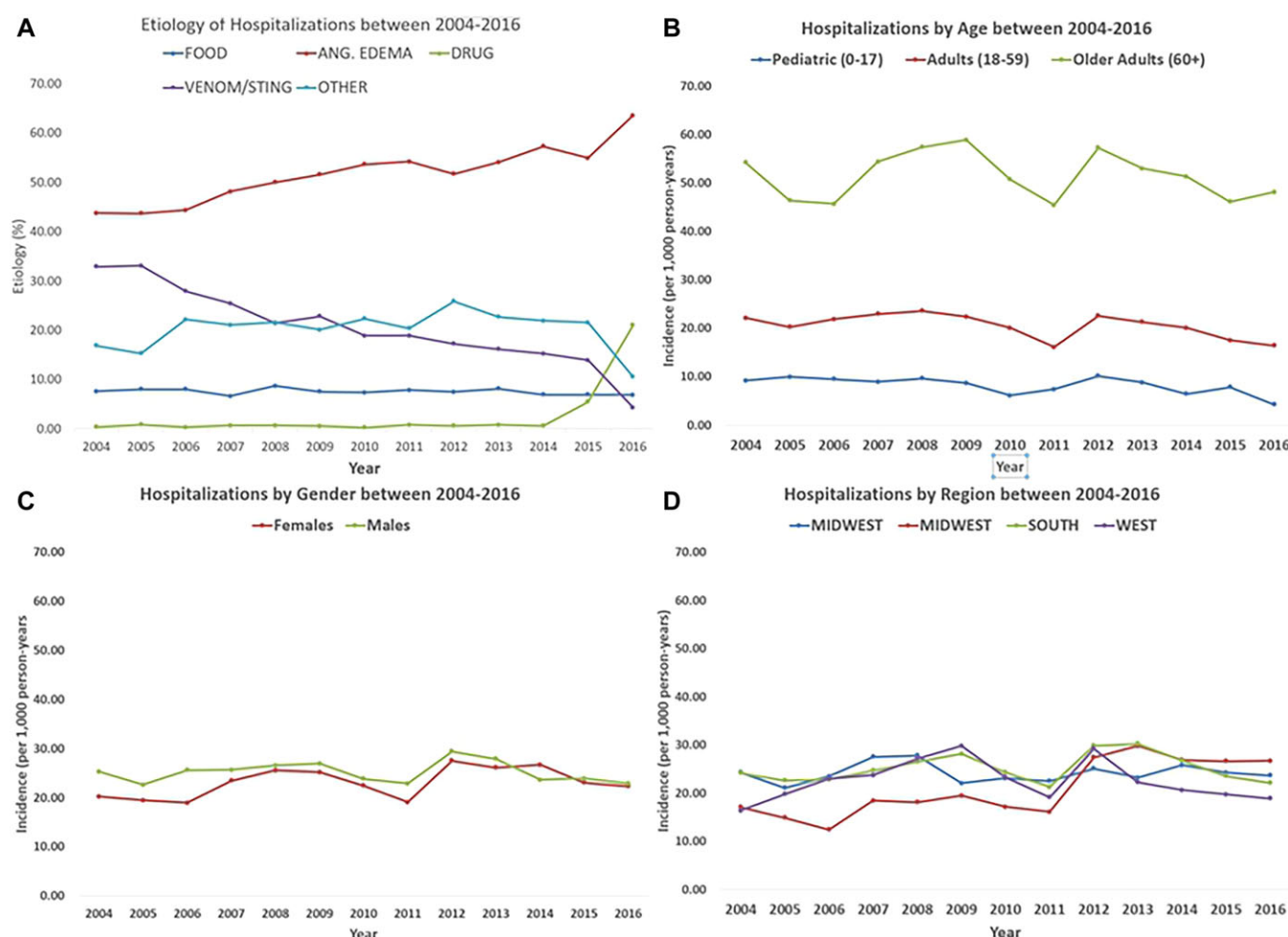


FIGURE 4. (A) Percentage of hospitalizations due to the different anaphylaxis diagnoses over time. The incidence of hospitalizations due to anaphylaxis per 1000 person-years is shown stratified by age (B), sex (C), and region (D).

and young adults can be explained by increased risk-taking behaviors.

Our study has demonstrated that patients living in the West have the lowest incidence of anaphylaxis compared with all other regions, and patients living in the Northeast have the highest incidence. Our study is similar to what has been reported in the literature regarding the increased incidence of anaphylaxis in the Northeast region.^{27,28} This has been postulated to be a result of sunlight exposure and vitamin D levels, which have been suggested to play a role in the development of food allergies and anaphylaxis.²⁷

Compared with 2004, patients in the years 2010-2011 and 2015-2016 had significantly lower admission rates for anaphylaxis. The hospitalization rates increased step-wise with age, similar to what has been reported in other studies.¹⁻⁴ This increase could be explained by the presence of comorbidities in older patients and a concomitant rise in the incidence of medication-induced allergies. In our study, medication-induced anaphylaxis spiked markedly in 2015 and 2016 with a 15-fold increase from 2004 to 2014. There were no medication-induced anaphylaxis codes in the

ICD-9 CM, and this increase is likely related to both an actual rise in the incidence of medication-induced anaphylaxis in the elderly^{14,29,30} and specific coding by physicians utilizing ICD-10 CM codes, which commenced in October 2015.

This trend also reflects the changing US population demographics, as the “Baby Boomer” generation ages. This flux in older persons and their associated comorbidities at a time of increasing medicalization of disease explains, at least in part, the rise in medication-induced anaphylaxis in the elderly.³⁰ Our results also show that the hospitalization rates for medication-induced anaphylaxis were the highest at an average of 11.8% of cases, and increased from 3.6% to 21.0% of cases in 2016.

When looking at the hospitalization rates according to trigger, venom had the highest rate of hospitalization. The increase in hospitalization rates in the elderly and in patients with venom-induced anaphylaxis may be related to cardiovascular compromise that more commonly occurs with rapid exposure to the allergen in medication- and venom-induced anaphylaxis.^{25,29,31-39} Our venom-induced anaphylaxis was highest in the South

(47%), which also explains the highest hospitalization rate in this region compared with the other regions in the US.

Our national study has provided the first national rates for incidence and hospitalization of anaphylaxis with the use of ICD-10 CM codes. In addition, the strengths of this study are that it included rates for all age groups and all hospital settings (ED, outpatient, and inpatient). Our study has several limitations. First, it was a retrospective study, utilizing a single, large commercial insurance administrative claims database. Second, our patients >65 years of age are not widely representative of patients in this age group, as most of these patients drop out of private commercial coverage and enroll in Medicare. Because these patients will file their claims under Medicare, our results in this particular subgroup (>65 years) cannot be generalized. Third, the ICD-9 CM and ICD-10 CM codes continue to have limitations in identifying specific triggers such as venom-induced anaphylaxis. Fourth, our study only included 1 full year of

ICD-10 CM codes, as these were introduced in October of 2015.

Conclusion

Our study is the first large population study that used the ICD-10 CM codes to describe the epidemiology of anaphylaxis in the US, establishing baseline characteristics of anaphylaxis with a full year of data utilizing the updated coding system. There was an overall increase in the incidence of anaphylaxis over the period from 2004 to 2016, with a peak incidence in 2013. The most common trigger was venom/sting, followed by food. Medication-induced anaphylaxis spiked markedly in 2015 and 2016, with a 15-fold increase from 2004 to 2014. Specific codes for medication-induced anaphylaxis were used for the first time in our study, and its incidence was highest in older patients. 

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