Case fatality and population mortality associated with anaphylaxis in the United States

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Background: Anaphylaxis is a serious allergic reaction that can cause death; however, the actual risk of death is unclear.

Objective: We sought to estimate the case fatality rate among hospitalizations or emergency department (ED) presentations for anaphylaxis and the mortality rate associated with anaphylaxis for the general population.

Methods: This was a population-based epidemiologic study using 3 national databases: the Nationwide Inpatient Sample (NIS; 1999-2009), the Nationwide Emergency Department Sample (NEDS; 2006-2009), and Multiple Cause of Death Data (MCDD; 1999-2009). Sources for these databases are hospital and ED discharge records and death certificates, respectively.

Results: Case fatality rates were between 0.25% and 0.33% among hospitalizations or ED presentations with anaphylaxis as the principal diagnosis (NIS+NEDS, 2006-2009). These rates represent 63 to 99 deaths per year in the United States, approximately 77% of which occurred in hospitalized patients. The rate of anaphylaxis-related hospitalizations increased from 21.0 to 25.1 per million population between 1999 and 2009 (annual percentage change, 2.23%; 95% CI, 1.52% to 2.94%), contrasting with a decreasing case fatality rate among hospitalizations (annual percentage change, −2.35%; 95% CI, −4.98% to 0.34%). Overall mortality rates ranged from 0.63 to 0.76 per million population (186-225 deaths per year, MCDD) and appeared stable in the last decade (annual percentage change, −0.31%; 95% CI, −1.54% to 0.93%).

Conclusion: From 2006 to 2009, the overwhelming majority of hospitalizations or ED presentations for anaphylaxis did not result in death, with an average case fatality rate of 0.3%. Anaphylaxis-related hospitalizations increased steadily in the last decade (1999-2009), but this increase was offset by the decreasing case fatality rate among those hospitalized; both inpatient and overall mortality rates associated with anaphylaxis appeared stable and were well under 1 per million population. Although anaphylactic reactions are potentially life-threatening, the probability of dying is actually very low. With the prevalence of anaphylaxis on the increase, practitioners need to stay vigilant and follow the treatment guidelines to further reduce anaphylaxis-related deaths. (J Allergy Clin Immunol 2014;133:1075-83.)

Key words: *Anaphylaxis, mortality, case fatality, epidemiology, hospitalization, emergency department presentation, death certificate*

Anaphylaxis is a rapid-onset, potentially life-threatening systemic allergic reaction that can affect persons of any age or sex. It usually occurs as a result of an allergen response, which leads to activation of mast cells and basophils, although in many cases the cause of anaphylaxis is not known. The diagnosis of anaphylaxis is based on recognition of clinical symptoms and might require a detailed evaluation of the episode, including activities and events occurring within the minutes to hours preceding the event. Patients typically present with a combination of dermatologic, respiratory, cardiovascular, and gastrointestinal symptoms. The most common triggers are medications, insect stings, and foods, with reactions to medications accounting for most of the mortality.[1-7]

Population-based studies have estimated the anaphylaxis incidence rate in the United States, the United Kingdom, and other developed countries to be in the range of 40 to 500 per million person-years.[6] Lifetime prevalence estimates range from 0.05% to 2% and seem to be increasing.[3,6,8] Estimates of anaphylaxis-related mortality have been between 0.5 and 5.5 per million population, with death reportedly occurring in 0.65% to 2% of patients experiencing severe anaphylactic reactions.[3,9] Few studies of anaphylaxis in the US population have been conducted, and most studies were limited by small populations or a regional focus.[10-15] Among the population-based studies in the United States, the lowest case fatality rate of 0.20% was reported among hospitalized patients younger than 20 years in New York (1990-2006),[14] and the highest case fatality rate of 0.86% was reported among hospitalizations for anaphylaxis in Florida (2001).[15] The lowest mortality rate of 0.5 per million population was reported by a study using death records from Florida between 1996 and 2005,[13] whereas the highest rate of 5.5 per million population (1500 deaths annually) was estimated based on a review of anaphylaxis epidemiologic data.[7,16]

For the United States, more recent, broader, population-based epidemiologic data are needed to better assess the risk of anaphylaxis. This information will be useful both for informing patients and health care providers of the risk and for focusing and assessing efforts to reduce the mortality associated with anaphylaxis.[3,8,13,17,18] We sought to conduct a large population-based epidemiologic study using current data from 3 US national databases to estimate the case fatality and population mortality associated with anaphylaxis based on hospital and emergency department (ED) discharge records and death certificates.

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Abbreviations used
ED: Emergency department
GLM: Generalized linear model
HCUP: Healthcare Cost and Utilization Project
ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10: International Classification of Diseases, Tenth Revision
MCDD: Multiple Cause of Death Data
NEDS: Nationwide Emergency Department Sample
NIS: Nationwide Inpatient Sample

METHODS

Data sources

Three separate databases were used in this study: the Nationwide Inpatient Sample (NIS; 1999-2009), the Nationwide Emergency Department Sample (NEDS; 2006-2009), and Multiple Cause of Death Data (MCDD; 1999-2009).[19-21] These databases are deidentified for public use and were protected through data use agreements.

NIS, 1999-2009. The NIS is part of the Healthcare Cost and Utilization Project (HCUP), the largest all-payer inpatient care database in the United States, and contains data on approximately 8 million hospitalizations annually from approximately 1000 hospitals, approximating a 20% stratified sample of US community hospitals. The NIS includes data from up to 45 states that participate in the HCUP, covering more than 96% of the population. The unit of analysis for the NIS is the individual hospitalization rather than the individual patient, and no patient identifiers or keys are available. Weights are provided to calculate estimates for the entire US population. Diagnosis and procedure codes on the hospital discharge records in the NIS are based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The NIS has been widely used to study trends in hospital care and has been validated against the National Hospital Discharge Survey and the Medicare Provider Analysis and Review.[22]

NEDS, 2006-2009. The NEDS, also part of the HCUP, is a database of ED presentations that do not result in an admission (ie, treat-and-discharge presentations) and ED presentations that result in admission to the same hospital. The NEDS contains 25 to 30 million records for ED presentations from approximately 1000 hospitals, approximating a 20% stratified sample of US hospital EDs. Similar to the NIS, weights are provided for US projection, and diagnoses and procedures are coded based on the ICD-9-CM. The NEDS was first released in 2006 and has been validated against other national data sources on ED presentations.[23]

MCDD, 1999-2009. MCDD contains mortality data derived from death certificates for US residents. Each death certificate records an underlying cause of death (disease or injury that initiated the events resulting in death), 20 or less multiple causes leading to death, and demographic data. Causes of death are coded by using the International Classification of Diseases, Tenth Revision (ICD-10). Mortality data compiled in MCDD include death certificates from all 50 states and the District of Columbia. Death certificates for nonresident aliens, US nationals living abroad, and residents of US territories are excluded, as are fetal deaths.

Case definition and study end point

Selection of anaphylaxis cases. In previous research various ICD-9-CM or ICD-10 codes have been used for the selection of anaphylaxis cases.[13,14,17,18,24] Some studies included anaphylaxis-nonspecific codes, such as "allergic reaction" or "angioneurotic edema (angioedema),"[16,24] whereas others included only anaphylaxis-specific codes or a subset of those codes.[13,17,18] Use of additional non–anaphylaxis-specific codes enhances the sensitivity in case selection but decreases specificity.[18]

For the analysis of NIS and NEDS data, anaphylaxis cases were selected based on the principal diagnosis code on a discharge record using the following ICD-9-CM codes: 995.0 (anaphylactic shock or reaction, unspecified), 995.60 to 995.69 (various food items), and 999.4 (serum). The principal diagnosis is defined as that condition established after study to be chiefly responsible for occasioning the admission of the patient to the hospital for care and has been used to capture anaphylaxis in most of the epidemiologic studies using ICD-9-CM codes.[13-15] For MCDD, cases were selected based on 4 ICD-10 codes including the key word anaphylactic: T78.0 (food), T78.2 (unspecified), T80.5 (serum), and T88.6 (drug). Anaphylaxis might have been entered as the main underlying cause in the original death certificate but will only show up as one of the multiple causes of deaths in MCDD because it is not permissible as the main underlying cause of death under the data-processing guidance of CDC.[25]

ICD-9-CM offers very specific codes capturing food-related anaphylaxis cases but no codes for drug-related anaphylaxis cases, which are likely captured under code 999.50 (unspecified). On the other hand, ICD-10 provides a specific code for drug-related anaphylaxis cases but no codes for types of food causing anaphylaxis.

Primary outcomes. The primary outcomes were the annual anaphylaxis case fatality rate and population mortality rate. The case fatality rate was defined as the percentage of deaths among hospitalizations or ED presentations for anaphylaxis-associated cases. The overall mortality rate (deaths per million population) was estimated by dividing the total number of deaths by the US resident population from the census data, and inpatient and ED mortality rates were calculated by using the same denominators.[21] We also estimated the age-adjusted mortality rate based on the 2000 US standard population.[26]

Statistical analysis

For MCDD, numbers of deaths and mortality rates were obtained through http://wonder.cdc.gov/ (record-level data were also obtained to validate the results for 2007-2009). We assumed that the number of deaths arises from a Poisson distribution[27] and calculated the SEs and 95% CIs based on the Taylor expansion.[28] Population estimates were used as the denominators for calculations of annual mortality rates and were assumed to be free of sampling error. To assess whether there is any trend in the mortality rate, we used a generalized linear model (GLM) with the Poisson distribution and log link. To guard against misspecification of the variance, such as the overdispersion commonly observed with Poisson data, we used the Huber-White robust sandwich estimator for variance.[29-31] The relative risk for deaths was explored among demographics factors, such as age, sex, and race, and it was estimated by using a similar GLM with Poisson distribution and log link.

For the NIS and NEDS, we used SAS SurveyMeans software (version 9.2; SAS Institute, Cary, NC) to obtain estimates for hospitalizations, ED presentations, and deaths, accounting for the sampling design (discharge weight, stratification, and clustering) of these databases.[32] To assess trends associated with hospitalization and death rates, we used the same GLM described earlier as the primary approach. One advantage of the GLM with log link was that change could be measured as an annual percentage change.

RESULTS

Anaphylaxis-related hospitalizations and inpatient deaths (NIS)

Between 1999 and 2009, the annual number of anaphylaxis-related hospitalizations increased from 5681 to 7708 (Table I), which corresponds to an increase in hospitalization rates from 21.0 to 25.1 per million population (Fig 1), with an annual increase of approximately 2.23% (95% CI, 1.52% to 2.94%; $P < .01$). In contrast, the case fatality rate among hospitalizations for anaphylaxis appeared to be decreasing, with an annual change of −2.35% (95% CI, −4.98% to 0.34%; $P = .09$). Case fatality rates ranged from 0.42% to 1.27% (average, 0.92%), with the

TABLE I. Anaphylaxis-related hospitalizations, ED presentations, case fatalities, and population mortality

	Anaphylaxis as the principal diagnosis				
	Hospitalizations or ED visits		Deaths in hospital or ED		Case fatality rate among hospitalizations or ED visits (95% CI)†
Year	Count	Rate per million (95% CI)*	Count	Mortality rate per million (95% CI)*	
NIS (hospitalizations)					
1999	5,863	21.0 (19.2 to 22.8)	48	0.17 (0.05 to 0.29)	0.82% (0.25% to 1.39%)
2000	5,938	21.1 (19.3 to 22.9)	63	0.22 (0.10 to 0.34)	1.06% (0.49% to 1.63%)
2001	5,681	19.9 (18.3 to 21.5)	62	0.22 (0.10 to 0.34)	1.09% (0.50% to 1.68%)
2002	5,907	20.5 (18.8 to 22.1)	61	0.21 (0.10 to 0.33)	1.04% (0.47% to 1.60%)
2003	5,807	20.0 (18.4 to 21.5)	61	0.21 (0.10 to 0.32)	1.05% (0.48% to 1.62%)
2004	6,365	21.7 (20.0 to 23.4)	81	0.28 (0.15 to 0.41)	1.27% (0.68% to 1.87%)
2005	6,670	22.5 (20.1 to 24.9)	28	0.10 (0.02 to 0.17)	0.42% (0.08% to 0.77%)
2006	7,302	24.4 (21.5 to 27.2)	61	0.20 (0.09 to 0.32)	0.84% (0.38% to 1.30%)
2007	7,062	23.4 (21.4 to 25.4)	49	0.16 (0.06 to 0.26)	0.69% (0.25% to 1.13%)
2008	7,310	24.0 (21.9 to 26.2)	64	0.21 (0.08 to 0.34)	0.88% (0.34% to 1.42%)
2009	7,708	25.1 (23.0 to 27.2)	71	0.23 (0.11 to 0.36)	0.93% (0.43% to 1.42%)
NEDS (ED presentations without admission)					
2006	18,027	60.2 (54.5 to 66.0)	22	0.07 (0.00 to 0.15)	0.13% (0.00% to 0.25%)
2007	17,735	58.8 (53.5 to 64.1)	14	0.05 (0.00 to 0.10)	0.08% (0.00% to 0.17%)
2008	21,039	69.2 (63.0 to 75.4)	13	0.04 (0.00 to 0.09)	0.06% (0.00% to 0.13%)
2009	21,822	71.1 (64.6 to 77.6)	27	0.09 (0.02 to 0.16)	0.12% (0.02% to 0.23%)
NIS+NEDS (hospitalizations and ED presentations without admission)					
2006	25,329	84.6 (78.2 to 91.0)	83	0.28 (0.14 to 0.41)	0.33% (0.00% to 0.81%)
2007	24,797	82.2 (76.5 to 87.9)	63	0.21 (0.09 to 0.32)	0.25% (0.00% to 0.70%)
2008	28,349	93.2 (86.7 to 99.8)	77	0.25 (0.12 to 0.39)	0.27% (0.00% to 0.82%)
2009	29,530	96.2 (89.4 to 103.0)	99	0.32 (0.18 to 0.46)	0.33% (0.00% to 0.84%)

Note: All counts derived from the NIS and NEDS are projected national estimates based on the discharge weights and are subject to rounding error.
*The denominator was the US population.
†Deaths among hospitalizations or ED presentations (without admission) with a principal diagnosis of anaphylaxis.

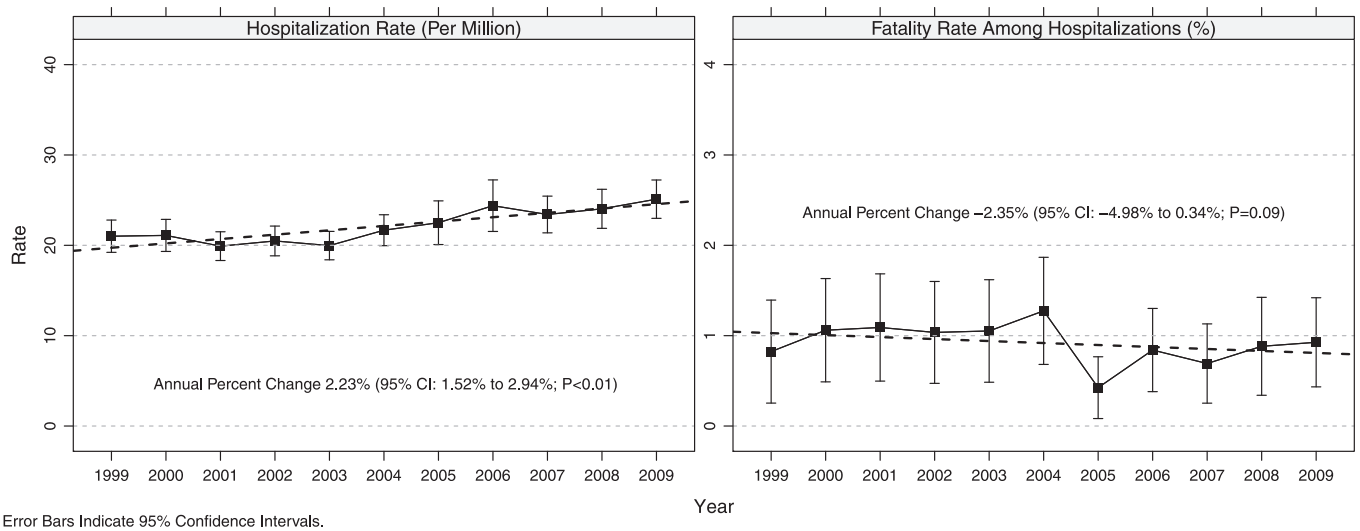

FIG 1. Trend in hospitalization rate for anaphylaxis and case fatality rate among hospitalizations (NIS).

number of inpatient deaths between 28 and 81. The inpatient mortality rates ranged from 0.10 to 0.28 per million population and were stable (annual percentage change, −0.23%; 95% CI, −2.77% to 2.38%; $P = .86$). The year 2005 was notably a departure from other years with respect to inpatient anaphylaxis-related deaths. However, the trend was similar without year 2005; the annual percentage change for case fatality rates was −1.90% (95% CI, −4.30% to 0.56%; $P = .13$), and the annual percentage change for inpatient mortality rates was 0.25% (95% CI, −1.94% to 2.49%; $P = .83$).

The discharge diagnosis most frequently linked to anaphylaxis-related hospitalizations was 995.0 (unspecified) and accounted for 63% to 71% of all anaphylaxis-related hospitalizations (Table II). Peanut-related anaphylaxis (995.61) hospitalizations almost doubled in the last decade, from 256 (4%) in 1999 to 512 (7%) in 2009. The breakdown of deaths

TABLE II. Anaphylaxis-related hospitalizations and ED presentations by ICD-9-CM diagnosis code

Year	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
NIS (hospitalizations)	5,863	5,938	5,681	5,907	5,807	6,365	6,670	7,302	7,062	7,310	7,708
Anaphylaxis ICD-9-CM code, no. (%)											
995.0, Unspecified	4,037 (69%)	4,197 (71%)	3,997 (70%)	4,065 (69%)	4,118 (71%)	4,254 (67%)	4,255 (64%)	4,587 (63%)	4,553 (64%)	4,955 (68%)	5,008 (65%)
995.60, Unspecified food	240 (4%)	158 (3%)	158 (3%)	99 (2%)	148 (3%)	169 (3%)	196 (3%)	262 (4%)	246 (3%)	251 (3%)	194 (3%)
995.61, Peanuts	256 (4%)	284 (5%)	248 (4%)	354 (6%)	301 (5%)	375 (6%)	540 (8%)	562 (8%)	578 (8%)	470 (6%)	512 (7%)
995.62, Crustaceans	202 (3%)	179 (3%)	165 (3%)	89 (2%)	156 (3%)	207 (3%)	202 (3%)	176 (2%)	255 (4%)	202 (3%)	258 (3%)
995.63, Fruits, vegetables	134 (2%)	124 (2%)	108 (2%)	156 (3%)	84 (1%)	132 (2%)	198 (3%)	182 (2%)	118 (2%)	178 (2%)	206 (3%)
995.64, Tree nuts, seeds	182 (3%)	218 (4%)	167 (3%)	220 (4%)	254 (4%)	313 (5%)	290 (4%)	345 (5%)	268 (4%)	255 (3%)	344 (4%)
995.65, Fish	227 (4%)	224 (4%)	233 (4%)	278 (5%)	272 (5%)	251 (4%)	207 (3%)	359 (5%)	255 (4%)	300 (4%)	285 (4%)
995.66, Food additives	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
995.67, Milk products	85 (1%)	67 (1%)	NR	NR	58 (1%)	113 (2%)	111 (2%)	117 (2%)	140 (2%)	55 (1%)	113 (1%)
995.68, Eggs	NR	NR	NR	NR	NR	NR	67 (1%)	NR	NR	NR	NR
995.69, Other food	369 (6%)	364 (6%)	371 (7%)	389 (7%)	313 (5%)	390 (6%)	487 (7%)	428 (6%)	465 (7%)	484 (7%)	631 (8%)
999.4, Serum	77 (1%)	68 (1%)	101 (2%)	84 (1%)	64 (1%)	83 (1%)	99 (1%)	130 (2%)	136 (2%)	103 (1%)	117 (2%)
NEDS (ED presentations without admission)								18,027	17,735	21,039	21,822
Anaphylaxis ICD-9-CM code, no. (%)											
995.0, Unspecified	—	—	—	—	—	—	—	9,196 (51%)	8,709 (49%)	10,236 (49%)	10,559 (48%)
995.60, Unspecified food	—	—	—	—	—	—	—	985 (5%)	1,118 (6%)	1,329 (6%)	1,404 (6%)
995.61, Peanuts	—	—	—	—	—	—	—	2,158 (12%)	1,899 (11%)	2,633 (13%)	2,540 (12%)
995.62, Crustaceans	—	—	—	—	—	—	—	704 (4%)	742 (4%)	827 (4%)	883 (4%)
995.63, Fruits, vegetables	—	—	—	—	—	—	—	443 (2%)	464 (3%)	544 (3%)	611 (3%)
995.64, Tree nuts, seeds	—	—	—	—	—	—	—	1,153 (6%)	1,256 (7%)	1,372 (7%)	1,425 (7%)
995.65, Fish	—	—	—	—	—	—	—	1,078 (6%)	1,097 (6%)	1,230 (6%)	1,169 (5%)
995.66, Food additives	—	—	—	—	—	—	—	77 (0%)	74 (0%)	69 (0%)	98 (0%)
995.67, Milk products	—	—	—	—	—	—	—	244 (1%)	254 (1%)	287 (1%)	360 (2%)
995.68, Eggs	—	—	—	—	—	—	—	143 (1%)	136 (1%)	219 (1%)	266 (1%)
995.69, Other food	—	—	—	—	—	—	—	1,576 (9%)	1,658 (9%)	1,916 (9%)	2,217 (10%)
999.4, Serum	—	—	—	—	—	—	—	271 (2%)	328 (2%)	379 (2%)	289 (1%)

Note: All counts derived from the NIS and NEDS are projected national estimates based on the discharge weights and are subject to rounding error.
NR, Not reported for count of 10 or less per data user agreement.

by ICD-9-CM code could not be reported because most of the counts were 10 or less.

Anaphylaxis-related ED presentations and deaths (NEDS)

From 2006 to 2009, the number of anaphylaxis-related ED presentations (without admission) ranged from 17,735 to 21,822, and the number of deaths ranged from 13 to 27 (Table I). The case fatality rates were between 0.06% and 0.13% (average, 0.10%) among ED presentations (without admission). The mortality rates were between 0.04 and 0.09 per million population. A trend was not assessed because only 4 years of data were available from NEDS. As with hospitalizations, anaphylaxis-related ED presentations were most frequently coded with 995.0 (unspecified; 48% to 51%) or 995.61 (peanut related; 11% to 13%; Table II).

TABLE III. Anaphylaxis-related deaths from the MCDD

Year	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	Total
US population (million)	279.0	281.4	285.3	288.4	290.8	293.7	296.4	299.4	301.6	304.1	307.0	3227.1
No. of anaphylaxis-related deaths	213	209	186	189	208	188	188	206	199	225	218	2229
Mortality rate (per million)	0.76	0.74	0.65	0.66	0.72	0.64	0.63	0.69	0.66	0.74	0.71	0.69
95% CI	0.67-0.87	0.65-0.85	0.56-0.75	0.57-0.76	0.62-0.82	0.55-0.74	0.55-0.73	0.6-0.79	0.57-0.76	0.65-0.84	0.62-0.81	0.66-0.72
Age-adjusted rate (per million)*	0.78	0.76	0.66	0.65	0.71	0.64	0.64	0.65	0.64	0.69	0.70	0.68
Anaphylaxis cause of death (%)												
T78.0 (food reaction)	4%	5%	6%	4%	5%	6%	6%	5%	6%	7%	6%	5%
T78.2 (unspecified)	79%	85%	71%	77%	73%	66%	78%	74%	73%	73%	77%	75%
T80.5 (serum)	0%	0%	0%	1%	1%	1%	1%	0%	1%	0%	0%	0%
T88.6 (drug)	17%	11%	23%	20%	22%	27%	17%	21%	22%	21%	18%	20%
Underlying cause of death, top 4 (%)†‡												
Y57.9 (Drug or medicament, unspecified)	13%	7%	11%	13%	36%	35%	41%	38%	34%	40%	35%	28%
X23 (Contact with hornets, wasps, and bees)	12%	19%	15%	16%	13%	9%	14%	13%	11%	12%	12%	13%
X57 (Unspecified privation)	15%	23%	20%	19%	NA	NA	NA	NA	NA	NA	NA	7%
X59 (Exposure to unspecified factor)	6%	10%	8%	8%	6%	7%	7%	3%	NA	NA	NA	5%
Place of death, top 4 (%)												
Medical facility, inpatient	55%	59%	52%	48%	49%	54%	48%	49%	51%	50%	51%	52%
Medical facility, outpatient or ED	27%	27%	32%	37%	35%	32%	37%	35%	37%	33%	32%	33%
Medical facility, dead on arrival	3%	3%	2%	3%	2%	3%	2%	2%	2%	4%	4%	3%
Decedent's home	8%	6%	6%	7%	9%	9%	6%	7%	6%	6%	5%	7%
Mortality rate by select subgroup (per million)												
0-17 y	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	0.10
18-34 y	0.45	0.36	NR	NR	0.35	0.32	0.29	0.29	0.33	0.30	0.42	0.32
35-44 y	0.58	0.58	0.55	0.58	0.52	0.50	UR	0.55	UR	0.49	0.58	0.52
45-54 y	1.01	0.90	1.20	0.97	0.86	0.77	0.89	1.20	1.07	1.10	0.79	0.98
55-64 y	1.39	2.18	0.91	1.24	1.51	1.38	1.29	1.30	0.95	1.81	1.64	1.42
65-74 y	1.85	1.58	1.47	1.92	1.80	1.57	1.88	2.22	1.86	1.69	1.83	1.79
75-84 y	2.37	2.18	2.38	1.96	2.25	1.62	2.30	UR	2.53	1.84	2.05	2.04
Female	0.75	0.67	0.63	0.57	0.67	0.59	0.59	0.65	0.45	0.73	0.60	0.63
Male	0.78	0.82	0.68	0.75	0.76	0.69	0.68	0.73	0.88	0.75	0.82	0.76
Black or African American	0.77	0.57	0.97	0.74	1.05	0.75	0.64	1.14	0.75	0.97	0.88	0.84
White	0.79	0.80	0.61	0.67	0.68	0.65	0.65	0.64	0.67	0.73	0.72	0.69

NA, Not available; *UR*, unreliable for deaths <20.

*Rate was adjusted based on year 2000 standard population. Not all death certificates reported age information. As a result, the year 2000 age-adjusted rate was slightly different from the unadjusted rate.

†X57 was no longer reported as the underlying cause of death after 2002, which might explain the increase in Y57.9 after 2002.

‡A single subject could have multiple causes of death listed on his or her death certificate.

Anaphylaxis-related hospitalizations, ED presentations, and deaths (NIS+NEDS)

Between 2006 and 2009, the total hospitalizations and ED presentations (without admission) with anaphylaxis-related principal diagnosis ranged from 24,797 to 29,530, and the total deaths were between 63 and 99 (Table I). Of these deaths, approximately 77% happened in the hospital (range, 72% to 84%). The case fatality rates were between 0.25% and 0.33% (average, 0.30%). The anaphylaxis mortality rates for deaths in a hospital or ED were between 0.21 and 0.32 per million population. Although 75% to 89% (1999-2009) of hospitalizations for anaphylaxis were admitted from the ED, 74% to 78% of the anaphylaxis-related ED visits were not considered severe enough to warrant hospital admission from 2006 to 2009.

Anaphylaxis-related deaths (MCDD)

There were 2229 anaphylaxis-related deaths between 1999 and 2009 (0.69 per million population). The annual number of deaths related to anaphylaxis ranged from 186 to 225, corresponding to mortality rates of between 0.63 and 0.76 per million population (Table III). Mortality rates associated with anaphylaxis remained stable in the last decade, with an estimated annual decrease of −0.31% (95% CI, −1.54% to 0.93%; $P = .62$). Age-adjusted rates based on the 2000 US standard population were similar to crude rates (annual percentage change, −1.02%; 95% CI, −2.26% to 0.24%; $P = .11$).

Anaphylaxis-related mortality was less frequent in women (1026 deaths; 0.63 per million population) than in men (1203 deaths; 0.76 per million population). By age group, the

mortality rate was highest in persons aged 75 to 84 years (287 deaths; 2.04 per million population) and lowest in children 17 years or younger (84 deaths; 0.10 per million population). The relative risk was 19.5 (95% CI, 15.3-24.9; $P < .01$) between the 2 age groups. Seventy-five percent (n = 1675) of all anaphylaxis-related deaths were coded with T78.2 (anaphylactic shock). Overall, 87% (n = 1943) of the deaths occurred in a medical facility (inpatient, outpatient/ED, or dead on arrival), and approximately 7% (n = 148) occurred at the decedent's home. In cases in which the cause was reported, most anaphylaxis-related deaths were coded with Y57.9 (drug; n = 617 [28%]) or X23 (contact with hornets, wasps, and bees; n = 295 [13%]); etiology was not specified for most cases.

DISCUSSION

There are many aspects of an anaphylactic reaction that make it frightening to both patients and health care providers, including rapidity of onset and potential for fatality. Because the onset of symptoms can occur rapidly and outside the health care setting, patients who have had anaphylactic reactions need to remain vigilant to try to prevent re-exposure to the causative allergen. Sometimes avoidance is not possible because the patient cannot prevent the exposure (eg, insect sting), the patient is not aware that the allergen is present (eg, ingredients in food), or the relevant allergen cannot be discerned or does not exist. There has been a concerted effort in recent years to clearly label foods that contain common allergens and make food handlers more aware of the risks of food allergies and how to minimize these risks. In addition to reducing the risk of allergen exposure, guidelines universally recommend that patients who have had an anaphylactic reaction be supplied with an epinephrine autoinjector with instructions regarding when and how to self-treat.[4,33-35] Epidemiologic data on the risk of fatal reactions might also be helpful for patients to put the risk into some perspective.

It is necessary to have accurate data regarding the risk of a fatal outcome from an anaphylactic reaction to effectively counsel patients about the potential that an anaphylactic reaction will be fatal. This is particularly important when recommending a therapeutic intervention that poses a risk of anaphylaxis, such as allergy immunotherapy or vaccination. The Epidemiology of Anaphylaxis Working Group (sponsored by the American College of Allergy, Asthma & Immunology) concluded that data on anaphylaxis incidence and prevalence are sparse and often imprecise.[8] Case fatality and mortality data related to anaphylaxis are even more limited, with no robust US national estimates currently available.[7,13,16]

The present study was designed to address these information gaps by using 3 national databases. Mortality rates ranged from 0.63 to 0.76 per million population (average, 0.69) based on MCDD and from 0.21 to 0.32 per million population (average, 0.26) with anaphylaxis as the primary cause of death occurring in the hospital or ED based on the NIS and NEDS (Fig 2). The higher mortality rates from MCDD might reflect that anaphylaxis is captured as one of up to 20 causes leading to death, whereas mortality rates based on hospital or ED discharge coding only captured cases in which an anaphylaxis-rated code was used as the primary diagnosis. According to death certificate data, 87% of all anaphylaxis-related deaths occur in the hospital or ED setting, and therefore deaths outside the hospital cannot fully explain the difference. Despite the increased prevalence of anaphylaxis,[3,6,8] our study showed that mortality rates remained stable in the 11-year period between 1999 and 2009 and were considerably less than 1 per million population. A number of factors could have contributed to this, such as patients receiving diagnoses early and being treated properly, the wide availability of epinephrine autoinjectors, or increased awareness of anaphylaxis, resulting in more mild cases being presented.

The mortality rate is important from a population perspective, but most patients and health care providers are more interested in understanding the likelihood of a fatal outcome if a severe anaphylactic reaction occurs. This is especially important when the precipitating causes cannot be identified (idiopathic anaphylaxis) or avoided (bee stings or prescribed therapies). The present analysis demonstrates that the vast majority of hospital presentations, ED presentations, or both with anaphylaxis did not result in death, reflecting in part the quality of care provided in the urgent care setting. Among hospitalizations for anaphylaxis, an average of 0.92% of the cases resulted in death (range, 0.42% to 1.27%). NEDS data showed an even lower case fatality rate (average, 0.10%; range, 0.06% to 0.12%) among those who presented to an ED but were not admitted, although this might just reflect that patients with more severe anaphylaxis were rapidly admitted to the hospital or that anaphylactic reactions that occur in the hospital (ie, those likely to be related to medications or contrast agents) have a higher case fatality rate. When the cases that present for clinical care are combined (NIS+NEDS), the fatality rates ranged between 0.25% and 0.33% (average, 0.30%). Given that 87% of all anaphylaxis-related deaths occur in the hospital or ED setting, the combined NIS and NEDS data are a good estimate of the case fatality rates for severe anaphylactic reactions. Of course many, indeed most, anaphylactic reactions are mild or moderate,[2] and although there is no mechanism to discern this information, it seems likely that many patients with milder reactions (eg, isolated pruritus and flushing or acute urticaria) either do not seek medical attention or seek care outside hospitals or EDs. Therefore the case fatality rate from our study could be a vast overestimate of the case fatality rate when all anaphylactic reactions are considered.

Of the various demographic factors, age was most significantly associated with anaphylaxis-related deaths. From MCDD, the mortality rate was highest in persons aged 75 to 84 years (2.04 per million population) and lowest in children 17 years or younger (0.10 per million population; relative risk 19.5) and increased with advancing age. The relative risk of case fatality (NIS+NEDS) was 19.9 for the same age group comparison (case fatality rate, 1.19% for age 75-84 years and 0.06% for age ≤17 years). The higher risk associated with advancing age is likely explained by recognition that the elderly are less able to tolerate complications of anaphylaxis (hypotension, hypoxia, and arrhythmias) or treatment for anaphylaxis (epinephrine) than children or younger healthy adults because of the underlying comorbidities, such as cerebrovascular or cardiovascular diseases. However, we cannot rule out additional or alternative explanations, including, for example, the increasing risk that comes with age for exposure to causative agents, such as drugs.

It is also noteworthy that our data demonstrate an increase in anaphylaxis rates of approximately 2.23% per year from 1999 to 2009. This increase parallels the increase in the prevalence of allergic sensitization that has occurred during this same period,

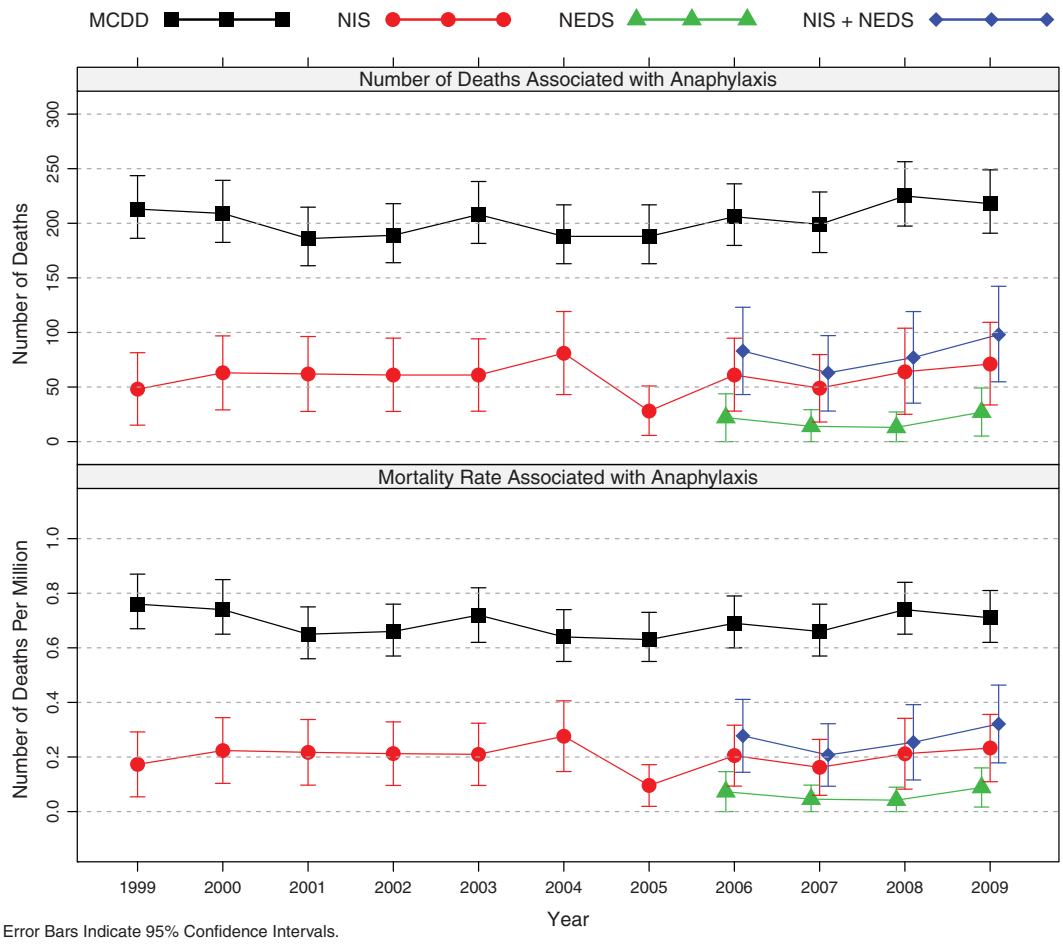

FIG 2. Mortality associated with anaphylaxis in the United States.

including sensitization to food allergens.[6,36] This is difficult to categorically assess because few of the putative causes of anaphylaxis have specific codes, and even when these codes are available, their validity cannot be discerned. However, support for increased allergic sensitization driving the increased rate of anaphylaxis is certainly consistent with our specific observation that peanut-related anaphylaxis (995.61) hospitalizations appeared to be on the increase during this same period, from 256 (4%) in 1999 to 512 (7%) in 2009.

A number of authors have reported anaphylaxis-related case fatality rates and population mortality rates. Yocum et al[11] published the first population-based study on anaphylaxis in the United States and identified a total of 154 anaphylaxis cases (1 death) among 1255 residents in Olmsted County, Minnesota (1983-1987), with a case fatality rate of 0.65% and a mortality rate of 1.36 per million population. However, the study was limited to the predominantly white, middle-class population of Olmsted County. In what is probably the largest US population-based study to date, Simon and Mulla[13] reported a mortality rate of 0.5 per million population based on death certificates in Florida (1996-2005). Using hospital discharge data, the same authors reported a case fatality rate of 0.86% among hospitalizations in Florida (2001).[15] In Switzerland Helbling et al[37] reported a case fatality rate of 1.2% (3 deaths out of 249 cases), with a mortality rate of 1 per million population for Canton Bern, which has a population of approximately 1 million (1996-1998). The highest case fatality rate of 2% (4 deaths out of 229 cases) was reported by Moneret-Vautrin et al[9] in the French Allergy Vigilance Network study involving food-induced anaphylaxis. The study focused on a specific cause for anaphylactic reactions, which might explain the higher case fatality rate than what was determined in the current study.

In contrast to previous studies, ours was based on 3 US national databases spanning the last decade. Not only do we report the case fatality rates separately for hospitalizations and ED presentations, but also this is the first study to report the case fatality rates among combined cases. Because deaths can occur outside medical facilities, we also obtained estimates from MCDD to validate and supplement results from the NIS and NEDS. In comparison, our results were at the lower end of the previously published results for both case fatality and population mortality. Furthermore, MCDD showed, among known causes, that drugs were the leading cause of anaphylaxis-related deaths, followed by contact with hornets, wasps, and bees and food reactions as a distant third.

Despite these methodological improvements, our study has several limitations. First, it relies on discharge records and death certificates for identification of anaphylaxis cases. The accuracy and completeness of the coding for anaphylaxis might significantly affect our results. Schneider et al[24] systematically

reviewed validated methods for identifying anaphylaxis using administrative and claims data and reported mixed positive predictive value based on use of ICD-9-CM codes. Simon and Mulla[13] compared anaphylaxis-related deaths reported based on death certificates and hospital discharges and concluded that anaphylaxis might be underreported by both sources. Second, the analysis for NIS and NEDS data was based on hospital and ED discharge records with the principal diagnoses for anaphylaxis, whereas the analysis for MCDD was based on having anaphylaxis as one of the multiple causes of death but not necessarily the underlying cause. The results from the NIS and NEDS might underestimate the number of anaphylaxis cases and are not directly comparable with the results from MCDD. Third, it is unclear how much the increase in anaphylaxis-related hospitalizations is attributable to the increased prevalence as opposed to the increased awareness of the condition. Fourth, because there were no patient identifiers in the NIS and NEDS, patients might appear more than once in hospitalizations or ED visits, but this limitation does not apply to death.

Nonetheless, to our knowledge, this is the largest and most comprehensive epidemiologic study to date on anaphylaxis mortality, and the results from 3 separate databases appear to corroborate and complement each other. With anaphylaxis being the most feared consequence for patients with allergic reactions,[36] these results might help health care professionals to better inform their patients as to the risks and outcomes of anaphylactic reactions. For example, there were 84 anaphylaxis-related deaths based on the death certificate data (MCDD) for children 17 years or younger over the 11-year study period between 1999 and 2009 compared with 115 children who died from influenza from September 2010 to August 2011, with most of them not vaccinated.[38]

In conclusion, from 2006 to 2009, the overwhelming majority of hospitalizations or ED presentations for anaphylaxis did not result in death, with an average case fatality rate of 0.3%, probably reflecting in part the quality of care provided in the urgent care setting. Anaphylaxis-related hospitalizations increased steadily in the last decade, but this increase was offset by the decreasing case fatality rate among those hospitalized; both inpatient and overall mortality rates associated with anaphylaxis appeared stable in the last decade (1999-2009) and were well under 1 per million population. Mortality rates varied greatly among different age groups, with persons 65 years or older having the highest rates and children 17 years or younger having the lowest rates. Although anaphylactic reactions are potentially life-threatening, the probability of dying is actually very low for those cases that require ED or hospital attention and is likely much lower when all anaphylactic reactions are considered. With the prevalence of anaphylaxis on the increase, practitioners need to stay vigilant and follow the treatment guidelines to further reduce anaphylaxis-related deaths, and continued effort is also needed to monitor the mortality trend associated with anaphylaxis.[33-35]

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Clinical implications: Although anaphylactic reactions are potentially life-threatening, the probability of dying is actually very low. However, practitioners need to stay vigilant and follow the treatment guidelines to further reduce anaphylaxis-related deaths.

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