Fatal anaphylaxis in the United States, 1999-2010: Temporal patterns and demographic associations

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Background: Anaphylaxis-related deaths in the United States have not been well characterized in recent years.

Objectives: We sought to define epidemiologic features and time trends of fatal anaphylaxis in the United States from 1999 to 2010.

Methods: Anaphylaxis-related deaths were identified by using the 10th clinical modification of the International Classification of Diseases system diagnostic codes on death certificates from the US National Mortality Database. Rates were calculated by using census population estimates.

Results: There were a total of 2458 anaphylaxis-related deaths in the United States from 1999 to 2010. Medications were the most common cause (58.8%), followed by "unspecified" (19.3%), venom (15.2%), and food (6.7%). There was a significant increase in fatal drug-induced anaphylaxis over 12 years: from 0.27 (95% CI, 0.23-0.30) per million in 1999 to 2001 to 0.51 (95% CI, 0.47-0.56) per million in 2008 to 2010 ($P < .001$). Fatal anaphylaxis caused by medications, food, and unspecified allergens was significantly associated with African American race and older age ($P < .001$). Fatal anaphylaxis to venom was significantly associated with white race, older age, and male sex ($P < .001$). The rates of fatal anaphylaxis to foods in male African American subjects increased from 0.06 (95% CI, 0.01-0.17) per million in 1999 to 2001 to 0.21 (95% CI, 0.11-0.37) per million in 2008 to 2010 ($P < .001$). The rates of unspecified fatal anaphylaxis decreased over time from 0.30 (95% CI, 0.26-0.34) per million in 1999 to 2001 to 0.09 (95% CI, 0.07-0.11) per million in 2008 to 2010 ($P < .001$).

Conclusion: There are strong and disparate associations between race and specific classes of anaphylaxis-related mortality in the United States. The increase in medication-related deaths caused by anaphylaxis likely relates to increased medication and radiocontrast use, enhanced diagnosis, and coding changes. (J Allergy Clin Immunol 2014;134:1318-28.)

Key words: *Fatal anaphylaxis, drug, food, venom, death certificate, epidemiology*

Abbreviation used
ICD-10: *International Classification of Diseases, 10th revision*

Anaphylaxis has been dubbed "the latest allergy epidemic."[1] The United States and Australia have some of the highest rates of severe anaphylaxis among developed countries.[2] Analyzing fatal anaphylaxis trends is challenging in the United States because unlike the United Kingdom,[3] it does not have a national registry for anaphylaxis-related deaths. There is a voluntary registry of fatal food-induced anaphylaxis, which documented 32 cases of fatal anaphylaxis caused by food between 1994 and 1998 and an additional 31 cases between 2001 and 2006.[4,5] Anaphylaxis admissions have increased over time in the United States, Australia, and the United Kingdom for both food- and non–food-related causes.[6-11] In Australia the incidence of fatal anaphylaxis doubled between 2002 and 2004 compared with that between 1997 and 2001.[9] It has been suggested that overall rates of fatal anaphylaxis in the United States are stable[6]; however, little is known about changes in anaphylaxis-related mortality rates by cause and how they differ among racial/ethnic groups and by age and sex. Furthermore, although racial disparities have been reported for other allergic conditions, such as food allergies and asthma,[12-14] it is not clear whether the same tendencies exist in fatal anaphylaxis.

The *International Classification of Diseases, 10th revision* (ICD-10), system introduced drug-related anaphylaxis as a new category and also added specific codes that allow for more exact identification of the cause of anaphylaxis. This enabled the identification of medications involved in anaphylactic shock in the United Kingdom and probable causes of fatal anaphylaxis in Australia.[11,15]

To understand the features and time trends in fatal anaphylaxis, we analyzed the National Mortality Database in the United States between 1999 and 2010 using ICD-10 coding of US death certificates. With this study, we characterized recent trends in fatal anaphylaxis and its associations with demographic characteristics, such as age, sex, race, and geographic distribution, in the United States.

METHODS

Case identification and selection

Mortality data were obtained from the Vital Statistics Database of the National Center for Health Statistics' Multiple Cause of Death Data,[16] which contains the codes provided on all annually reported death certificates from the United States. Data were analyzed for the time period starting 1999 (the first year ICD-10 codes were used)[17] through 2010 (the last year for which data were available in the Vital Statistics database at the time of the analysis). All mortality data for this period were entered from death

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certificates into the database by using the Automated Mortality Medical Data System.[18]

Categories were assigned by using specific anaphylaxis codes (food, drug, serum, and unspecified) and certain causality codes (eg, venom and medications; see Table E1 in this article's Online Repository at www.jacionline.org).

In the Multiple Cause of Death Database, anaphylaxis is disallowed as the underlying cause of death,[19] and therefore anaphylaxis-related deaths were defined as all deaths that had at least 1 anaphylaxis code among the remaining cause-of-death fields. Additional deaths that fulfilled algorithmic definitions of anaphylaxis were identified (see Table E2 in this article's Online Repository at www.jacionline.org).[20,21]

The following groupings were identified as probable causes of fatal anaphylaxis[15]:

- *Drug-related anaphylaxis*: T88.6 (anaphylactic shock due to an adverse effect of correct drug or medicament properly administered) with or without medication-specific codes Y40.0 through Y59.0 and/or T88.7 (specific or unspecified adverse drug reactions, including allergic) or T78.2 (anaphylactic shock, unspecified) if recorded in combination with Y40.0-Y59.0 or T88.7.
- *Anaphylactic shock caused by serum*: T80.5;
- *Food-related anaphylaxis*: T78.0 (anaphylactic shock due to adverse food reaction) and/or T78.1 (other adverse reaction [including allergic] to ingested food) if it was recorded in combination with T78.2;
- *Venom-related anaphylaxis*: T63.4 (toxic effect of contact with venom of other arthropods [insect bite or sting]), X23 (contact [accidental] with bees, wasps, hornets, including yellow jacket), X25 (contact [accidental] or sting by venomous arthropod, insect, or ants), if it was recorded in combination with T78.2; and
- *Unspecified anaphylaxis*: T78.2 in the absence of other anaphylaxis codes or X/Y codes.

Anaphylaxis-related deaths were further analyzed for the place of death: (1) medical facility (including nursing home or hospice) as an inpatient (inpatient); (2) outpatient medical facility or emergency department (outpatient); or (3) decedent's home, other, or dead on arrival (community).

Anaphylaxis-related deaths were analyzed for the presence of asthma,[22] angioedema, or hypotension on death certificates (see Table E2).

Data and statistical analysis

Each of the above categories (drug, venom, food, or unspecified) was evaluated by age, sex, and race. Race was specified based on categories used by the US Census Bureau, and race information was obtained from death certificates. Race and ethnicity groupings were created as follows: white, African American, Hispanic, and "other."[23] Age was grouped by 20-year intervals: 0 to 19 years, 20 to 39 years, 40 to 59 years, 60 to 79 years, and 80 years and older. Three-year time intervals were used as follows: 1999 to 2001, 2002 to 2004, 2005 to 2007, and 2008 to 2010.

Per-person rates were calculated by using US Census population data. For the years 2000 and 2010, the actual population counts were used. Population estimates were used for the remaining years.[24] Mortality rates by age, sex, race, and time period per million persons were calculated. Rates were not calculated for "other" race because of the small number of cases in each category and a heterogeneous mix.

Ninety-five percent CIs were calculated for each time point of the analysis by applying the gamma method for estimates based on fewer than 100 deaths.[25-27] Negative binomial regression models (including all of the predictors) were used to assess the predictor effects of age, sex, race, time, and region on anaphylactic deaths. A dichotomous race variable was used in regression models as either white versus nonwhite, African American versus non–African American, or Hispanic versus non-Hispanic for each of the 4 anaphylaxis-related death groups. Information on US Census geographic regions (Northeast, Midwest, South, and West)[28] was available only for 1999 through 2004.[16] Modeling that included geographic region was performed as a subset analysis. STATA 11.2 (StataCorp, College Station, Tex) and SAS 9.3 (SAS Institute, Cary, NC) software were used for statistical analysis. The study was classified as exempt by the Albert Einstein College of Medicine Institutional Review Board.

RESULTS

General characteristics of anaphylaxis-related deaths

From 1999 through 2010, there were 2458 fatal anaphylaxis cases of all causes, with an overall prevalence of 0.69 persons per million. Among anaphylaxis causes, medications were the most common cause of fatal anaphylaxis in the United States, followed by unspecified anaphylaxis, venom-induced anaphylaxis, and food-induced anaphylaxis. The demographic characteristics for each anaphylaxis cause are shown in Table I.

Drug-induced anaphylaxis (including serum)

There were 1446 anaphylaxis-related deaths attributable to medications, comprising 58.8% of the anaphylaxis-related deaths in the United States during the 12 years of the study. Forty-nine (3.4%) of the fatalities were in persons aged 19 years or less. Most deaths (58.6%) occurred in inpatient facilities (Table I).

Higher rates of drug-related anaphylaxis were observed with increasing age and in African American subjects: 0.05 (95% CI, 0.04-0.07) per million among those aged 19 years or less versus 1.28 (95% CI, 1.09-1.50) per million among persons aged 80 years or greater and 0.54 (95% CI, 0.47-0.61) in African American subjects; results were 0.19 (95% CI, 0.15-0.23) per million in Hispanic subjects and 0.45 (95% CI, 0.43-0.48) per million in white subjects ($P < .001$ for all; Fig 1, *A* and *B*, and see Tables E3 and E4 in this article's Online Repository at www.jacionline.org).

The rates of drug-induced fatal anaphylaxis increased over time for all races from 0.27 (95% CI, 0.23-0.30) per million in 1999 to 2001 to 0.51 (95% CI, 0.47-0.56) per million in 2008 to 2010 ($P < .001$; Fig 1, *C*, and see Table E5 in this article's Online Repository at www.jacionline.org). There was no significant difference in rates of fatal drug-induced anaphylaxis between sexes (Fig 1, *C*, and see Table E5).

Between 1999 and 2004, the Northeast census region had significantly lower rates of drug anaphylaxis ($P = .01$; Fig 2, *A*). African American race, year, and age remained significant after adjusting for region ($P < .001$ for all).

The culprit drug was not specified in 1078 (74.5%) of all drug-related anaphylaxis-induced fatalities. Among 368 (25.4%) fatalities in which a culprit drug class was identified, 40.5% were due to antibiotics (149 deaths). Of these, only 77 had a specific antibiotic class assigned. Penicillins were identified most often (n = 35), followed by cephalosporins (n = 33), sulfa-containing medications, and macrolides. The remainder were due to unspecified antibiotics.

The next most common group of specified drug-induced anaphylaxis causes consisted of reactions to radiocontrast agents (100 deaths). When combined with the adverse reactions caused by other diagnostic agents, this group comprised 112 (30.4%) deaths.

The next most frequent group was anaphylaxis-related death caused by antineoplastic drugs (n = 46). The remaining specified drug-induced anaphylaxis-related deaths were due to serum (n = 10), opiates, antihypertensive agents, nonsteroidal anti-inflammatory drugs (NSAIDs), and anesthetic agents (Fig 1, *D*).