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