Increase in anaphylaxis-related hospitalizations but no increase in fatalities: An analysis of United Kingdom national anaphylaxis data, 1992-2012

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Background: The incidence of anaphylaxis might be increasing. Data for fatal anaphylaxis are limited because of the rarity of this outcome.
Objective: We sought to document trends in anaphylaxis admissions and fatalities by age, sex, and cause in England and Wales over a 20-year period.
Methods: We extracted data from national databases that record hospital admissions and fatalities caused by anaphylaxis in England and Wales (1992-2012) and crosschecked fatalities against a prospective fatal anaphylaxis registry. We examined time trends and age distribution for fatal anaphylaxis caused by food, drugs, and insect stings.
Results: Hospital admissions from all-cause anaphylaxis increased by 615% over the time period studied, but annual fatality rates remained stable at 0.047 cases (95% CI, 0.042-0.052 cases) per 100,000 population. Admission and fatality rates for drug- and insect sting–induced anaphylaxis were highest in the group aged 60 years and older. In contrast, admissions because of food-triggered anaphylaxis were most common in young people, with a marked peak in the incidence of fatal food reactions during the second and third decades of life. These findings are not explained by age-related differences in rates of hospitalization.
Conclusions: Hospitalizations for anaphylaxis increased between 1992 and 2012, but the incidence of fatal anaphylaxis did not. This might be due to increasing awareness of the diagnosis, shifting patterns of behavior in patients and health care providers, or both. The age distribution of fatal anaphylaxis varies significantly according to the nature of the eliciting agent, which suggests a specific vulnerability to severe outcomes from food-induced allergic reactions in the second and third decades. (J Allergy Clin Immunol 2015;135:956-63.)

Key words: *Anaphylaxis, drug allergy, epidemiology, food allergy, hospitalization, insect sting allergy*

Acute, life-threatening systemic allergic reactions (anaphylaxis) can lead to cardiorespiratory arrest within minutes.[1] For those affected, the threat of further episodes can lead to significant lifestyle restrictions and psychological consequences.[2,3] Recent Australian data suggest that episodes of anaphylaxis, particularly those triggered by drugs or food, might be increasing.[4] Recent US data suggest that at least 1.6% of the population have a history of anaphylaxis,[5] although this might be an overestimate.[6] Although anaphylaxis is a relatively

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P.J.T. has received a Clinician Scientist award from the UK Medical Research Council (grant no. MR/K010468/1). R.J.B. and P.J.T. are supported by the National Institute for Health Research (NIHR)'s Imperial Biomedical Research Centre, and the MRC–Asthma UK Centre in Allergic Mechanisms of Asthma.

Disclosure of potential conflict of interest: P. J. Turner has received research support from the UK Medical Research Council and the NHS National Institute for Health Research. M. H. Gowland has consultant arrangements through Allergy Action with the Anaphylaxis Campaign and the Laboratory of the Government Chemist and has provided training through Allergy Action in partnership with Hygiene Audit Systems, Allergy and Hygiene Solutions, the Royal Environmental Health Institute of Scotland, the Royal Borough of Kensington and Chelsea, the Royal Society of Public Health, and the Wolverhampton City Council; has provided expert testimony for Her Majesty's Coroners and Police; has received research support from the Food Standards Agency; has received royalties and payment for development of educational presentations through Allergy Action Training from Hygiene Audit Systems; has received payments for delivering presentations from the University Caterers Organisation, the Chartered Institute of Environmental Health, the Trading Standards Institute, and their members; and has received travel support from the Food Standards Agency, the Allergy Academy in London, the European Academy of Allergy and Clinical Immunology, the French Cercle d'Investigations Cliniques et Biologiques en Allergologie Alimentaire, and the Universities of Cambridge, Southampton, Bath, Surrey, and Portsmouth. V. Sharma has received research support from ALK-Abelló, Meda, and Emmerade; has received travel support from ALK-Abelló, Meda, and Stallergenes; and is a member of the North West Paediatric Allergy Network, which has received grants from ALK-Abelló, Meda, Stallergenes, Nutricia, and Mead Johnson Nutrition toward organization of their annual educational event. N. Harper is employed by Central Manchester University Hospitals NHS Foundation Trust, has received research support from Manchester Allied Health Sciences Centre, and has received royalties from Nerve Stimulator. R. Pumphrey has received consulting fees and travel support from Her Majesty's Coroners; has received payment for lectures from NHS hospitals; has received travel support from ALK-Abelló, Meda, iMed Systems, and Lincoln Medical; has provided a device review for Meda; and is a medical advisor to the Anaphylaxis Campaign, UK. R. J. Boyle has received research support from Lincoln Medical and has received travel support from Meda Pharmaceuticals. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication July 3, 2014; revised October 3, 2014; accepted for publication October 8, 2014.

Available online November 25, 2014.

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0091-6749

http://dx.doi.org/10.1016/j.jaci.2014.10.021

Abbreviations used
ASR: Age-standardized rate
ICD: International Classification of Diseases
ONS: Office for National Statistics
UK: United Kingdom

common occurrence, at least as defined by the patient, severe immediate outcomes, such as fatality or admission to an intensive care unit, are rare.[6-8] Indeed, a recent report from a European anaphylaxis registry relating to severe anaphylaxis found that only 2% of more than 3000 cases of significant anaphylaxis involved cardiorespiratory arrest.[9]

For this reason, there is a paucity of data relating to trends in fatal (or near-fatal) allergic reactions over time. The apparent increase in hospitalization caused by anaphylaxis might be due to a real increase in disease or a change in health care provider or patient behavior, such as improved management. A parallel increase in fatal anaphylaxis incidence would provide supportive evidence for the former. Therefore we assessed trends in hospital admissions and fatalities caused by anaphylaxis in a population-based data set that includes the largest reported series of cases of fatal anaphylaxis. We explored time trends in all-cause and specific-cause anaphylaxis events in different age groups and by sex to understand which patients are at highest risk for severe allergic reactions. Previous small case series suggest that teenagers and young adults might be at the highest risk of fatal food-induced anaphylaxis for unknown reasons,[10] but this has not been confirmed in large population-based data sets and might be confounded by age-related differences in the incidence of anaphylaxis.

METHODS

We examined time trends and age/sex distribution for hospital admissions and fatalities caused by anaphylaxis in England and Wales over a 21-year period (1992-2012). We further analyzed the data for differences in time trend and age distribution by triggering agent (food, iatrogenic causes [eg, oral and parenteral medication and contrast media], and insect stings).

Anaphylaxis admission data

Hospital admission data for England and Wales are collated by the Hospital Episodes Statistics database (coordinated through the Health & Social Care Information Centre) and the Patient Episode Database for Wales (National Health Service Wales Informatics Service), respectively. We extracted data relating to hospitalizations in which anaphylaxis was the primary diagnosis for the calendar years 1992 to 2012. We did not include emergency department visit that did not result in a hospital admission. For analysis of trigger-specific age distribution, we limited data extraction to the years 1998 to 2012 to avoid confounding because of International Classification of Diseases (ICD) coding changes from ICD-9 to ICD-10 that took place before 1998. Admissions before 1998 were identified by using ICD-9 codes 995.0 (anaphylaxis, unspecified) and 995.6 (food-induced anaphylaxis). All hospital admissions from 1998 onward were included where the principal diagnosis corresponded to the following ICD-10 (international version) codes: anaphylactic shock due to adverse food reactions (T78.0); anaphylactic shock, unspecified (T78.2); and anaphylactic shock due to adverse effects of correct drug or medicament properly administered (T88.6). Hospitalizations in which a primary T78 code was associated with a secondary X23 code were classified as being caused by insect sting–related anaphylaxis. We also analyzed the data to assess the possible effect of the introduction of a maximum 4-hour wait in emergency departments by the United Kingdom (UK) Government in 2004.

Fatal anaphylaxis data

All deaths in England and Wales are recorded by a medical doctor, and these data are collected by the Office for National Statistics (ONS). Since 1992, we (R.P. and M.H.G.) have collected data on all cases in which anaphylaxis was included as a cause of death. Cases were entered into a registry within the parameters permitted by the local research ethics committee and approved by the ONS. Additional notifications were collected from patient representative organizations, coroners, the police service, pathologists, and media reports, as previously described.[1]

Verification of fatal anaphylaxis data

The attribution and coding of deaths can be unreliable, and therefore caution is needed when interpreting fatal anaphylaxis statistics. It is important that both the probability that a death was due to anaphylaxis and that the trigger for the reaction was correctly determined are taken into account when analyzing the data. Since the inception of the registry in 1992, we (R.P. and M.H.G.) have attempted to investigate the circumstances of every fatal anaphylactic episode using a previously outlined methodology.[1] In brief, for each death, the probability that it was caused by anaphylaxis and the probability that the cause had been correctly identified were assessed. Deaths caused by an acute asthma exacerbation were included only where there was strong evidence that the episode was triggered by an identified allergen to which the deceased patient had a known allergy. Deaths caused by asphyxia from upper airways angioedema in patients with hereditary angioedema or in those taking angiotensin-converting enzyme inhibitors were excluded when an allergic cause for the reaction seemed improbable. We also excluded cases of amniotic fluid emboli (anaphylactoid syndrome of pregnancy). Because of difficulties in obtaining sufficient data to confirm the precise trigger for some cases of fatal anaphylaxis, particularly those caused by medication, we have included cases from the ONS database in which sufficient information was available to determine that anaphylaxis was the likely cause of death but not to confirm the specific cause (eg, medication) with high probability. We classified these as unconfirmed cases.

Prescription of epinephrine autoinjector devices

We extracted data from the National Health Service Business Services Authority Prescription Cost Analysis databases from 1998 to 2012, which record all prescriptions issued by health practitioners through the English public health system. We grouped epinephrine autoinjector devices into 150- and 300-μg doses, irrespective of device. We were unable to obtain similar data for Wales.

Statistics

Age-standardized rates (ASRs) for death and hospital admissions were calculated by standardizing to the age distribution of the population in mid-2001 (for 1992-2012) and mid-2006 (1998-2012), as reported by the ONS; thus cases (admissions or fatalities) are expressed per 100,000 population. Poisson regression was used to estimate the rate ratio for the annual increase in rates by calendar year, as previously described.[11] Results are presented as rate ratios and 95% CIs. A rate ratio of 1.0 indicates no annual change in rate, and a 95% CI that includes 1.0 indicates the observed rate ratio is not statistically significant.

RESULTS

Hospital admissions because of all-cause anaphylaxis increased steadily from 1992 for both sexes but appear to have reached a plateau since 2008 (Fig 1, *A*). Over the study period, there was an increase in hospital admissions of 615%, from 1.0 to 7.0 cases per 100,000 population per annum. The estimated rate ratio (multiplicative increase of the rate per year over the study period) was 1.073 (95% CI, 1.071-1.075; $P < .001$). This trend was not clearly related to either a change in ICD coding (ICD-9 to ICD-10) or the introduction of a 4-hour maximum observation in emergency departments in the UK (Fig 1, *A*),