

A Population-Based Study of the Incidence, Cause, and Severity of Anaphylaxis in the United Kingdom

Michael M. Peng, PhD; Hershel Jick, MD

Background: Anaphylaxis is an acute and potentially fatal systemic reaction usually caused by mast cell-mediated release of histamine. Symptoms can vary in onset, appearance, and severity. Some common symptoms include weakness, dizziness, flushing, angioedema, urticaria, nasal congestion, and sneezing. Severe symptoms include upper respiratory tract obstruction, hypotension, vascular collapse associated with angioedema and urticaria, gastrointestinal distress, cardiovascular arrhythmias, and/or arrest.

Methods: We conducted an observational follow-up study encompassing approximately 8 million person-years based on the UK General Practice Research Data-

base for the period January 1, 1994, to December 31, 1999, which quantified the frequency, type, and severity of a clinical diagnosis of anaphylaxis.

Results: Based on 675 cases of anaphylaxis, we estimate the incidence to be 8.4 per 100 000 person-years. Approximately 10% of cases had hypotension and shock that required urgent treatment. The most common causes were insect stings and oral medicines.

Conclusion: Anaphylaxis is an uncommon illness that has multiple causes and can be life-threatening.

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ANAPHYLAXIS IS A SUDDEN-onset, acute, and potentially fatal systemic reaction usually caused by mast cell-mediated release of histamine. Symptoms can vary in onset, appearance, and severity. Some common symptoms include weakness, dizziness, flushing, angioedema, urticaria, nasal congestion, and sneezing. Severe symptoms include upper respiratory tract obstruction, hypotension, vascular collapse associated with angioedema and urticaria, gastrointestinal distress, cardiovascular arrhythmias, and/or arrest.^{1,2} Because affected patients can have any combination of symptoms, the criteria for the diagnosis are likely to vary among clinicians.

Few studies have provided reliable data on the frequency and severity of anaphylaxis. Based on a review of the admittedly sparse and imprecise literature, Neugut et al¹ concluded that “the problem of anaphylaxis may, in fact, affect 1.21% to 15.04% of the US population.” Medicines, insect stings, radiologic contrast medium, and food are thought to be the most common causes. Yocum et al² conducted a population-based study in Olmsted

County, Minnesota. Based on 154 episodes of anaphylaxis, they reported an “occurrence rate” of 30 per 100 000 person-years and an “incidence rate” of 21 per 100 000 person-years. They concluded that “the incidence of anaphylaxis is less than 1% and death rarely occurs.” The current study was based on the General Practice Research Database (GPRD) in the United Kingdom and was designed to estimate the cause-specific frequency and severity of anaphylaxis in this population.

METHODS

Since 1988, more than 4 million residents of the United Kingdom have registered with selected general practitioners (GPs) who provide computerized patient data, which include patient demographics, drugs dispensed, clinical diagnoses, and referrals to hospitals. The computer record also includes a place for word comments made by the GP. The high quality and completeness of data recording in the general practices used by our research group have been demonstrated during the past 10 years.³⁻⁶

The base population from which frequencies of anaphylaxis were calculated was derived from people who were enrolled in the GPRD during 1994 to 1999 and born between 1912 and 1999. Potential cases of anaphylaxis were identified from the computer record be-

From the Boston Collaborative Drug Surveillance Program, Boston University School of Medicine, Lexington, Mass. The authors have no relevant financial interest in this article.

Table 1. Distribution of Causes and Severity of Anaphylaxis in the Random Sample of Cases*

Cause	Severity, No. (%)				Total
	Mild	Moderate	Severe	Uncertain	
Insect sting or bite	8	11	3	6	28 (32)
Medicine	10	10	2	4	26 (30)
Nuts or other foods	5	11	0	3	19 (22)
Other	2	7	3	2	14 (16)
Total	25 (29)	39 (45)	8 (9)	15 (17)	87 (100)

*Mild is defined as limited to urticaria not requiring treatment in emergency departments or hospitals; moderate, requiring hospital visit and treatment with adrenaline; and severe, including hypertension or shock considered life-threatening.

cause they either had a coded diagnosis of anaphylaxis during the study period or were noted to have this diagnosis as a comment. The anaphylaxis codes are as follows:

Oxford Medical Information Systems Code

9779AK
9779AR
9894HA
9894HB
9894HN
9899AN
9994
9994CC
9994MN
9994RM

Diagnosis

Medication causing anaphylactic shock
Anaphylactic reaction to medicine or drug
Bite(s), animal anaphylactic reaction
Allergy bee sting (anaphylactic)
Anaphylactic reaction to bite
Anaphylactic reaction to nonmedicinal agent
Anaphylactic shock or reaction
Anaphylactic reaction to vaccination
Anaphylactic reaction to immunization
Allergy serum (anaphylactic)

CASE DEFINITION

Patients were included as potential cases if during the study period they were younger than 80 years at the time of the event and had at least 6 months of computer-recorded clinical data. To evaluate the evidence for the diagnosis of anaphylaxis, case records were requested for a random sample of the potential cases (identified from the computer record). The records were reviewed and results tabulated.

Initially, we identified 898 patients with either a coded diagnosis of anaphylaxis (n=783) or with anaphylaxis noted in the comments field (n=115). To further evaluate the evidence for and circumstances related to the diagnosis of anaphylaxis, we asked the attending GP for information relating to the diagnosis, including any referral letters from specialists, accident rooms, or hospitalization, for a random sample of 70 patients (9%) with a coded diagnosis of anaphylaxis and 50 patients (43%) with a comment diagnosis. Relevant information on the diagnosis was available in more than 90% of requests. (Only one person in the random sample had the anaphylaxis attributed to a vaccine. Given the special interest in this matter, we reviewed the complete computer records of all patients with a diagnosis of anaphylaxis due to a vaccine.) Based on the case histories received, we derived criteria for considering that a patient qualified as having anaphylaxis and developed 3 categories of severity.

We noted that the GPs consistently considered a patient to have anaphylaxis if an acute, sudden allergic reaction occurred (most often preceded by an apparent exposure) and was manifested by systemic generalized urticaria often accompanied by swollen tongue requiring immediate treatment. The syndrome was also often accompanied by wheezing, flushing, and gastrointestinal symptoms and occasionally by hypotension and shock.

In this report, anaphylaxis was considered mild if it was primarily limited to generalized urticaria (angioedema) and did not lead to an emergency department admission or hospitalization. Treatment was generally limited to an oral antihistamine and the patient recovered rapidly. The illness was considered to be of moderate severity if a hospital visit was initiated and the illness was treated with adrenalin often accompanied by parenteral corticosteroids and antihistamines. The illness was considered to be severe if there was hypotension or shock that was described as life-threatening.

ANALYSIS

Based on the results of both case history and computer-recorded information, population-based summary statistics in particular, frequency estimates of anaphylaxis were tabulated by cause (food, medicine or drug, bite or sting). Incidence rate estimations were calculated as the number of cases divided by the person-time at risk, which we estimated to be approximately 8 million person-years for the 6-year period of the study.

RESULTS

Of the 120 records reviewed in detail, we considered 87 to be cases of anaphylaxis. Most of the 33 subjects excluded from the case series had a computer entry that signified only a history of anaphylaxis that required prophylactic protection from a future attack rather than an acute episode. In a few instances of anaphylaxis, the diagnosis was not confirmed. Of the 897 people initially identified as having a computer-recorded diagnosis of anaphylaxis, we estimated, based on the random sample of 120 case histories reviewed, that 675 had an acute episode of anaphylaxis. From these findings, we calculated a crude estimate of the incidence of anaphylaxis to be 675 per 8 million person-years at risk (8.4 per 100 000 person-years).

Based on the review of the 87 case records received, together with the computer-recorded information on those cases (**Table 1**), we estimate that the most common cause of anaphylaxis was insect sting or bite, which accounted for 32% of cases. All but 2 cases occurred in June through September. The second most common cause was medicines (30%). Penicillin (n=5) and nonsteroidal anti-inflammatory drugs (n=4) were the most frequent causes. Allergy to food was estimated to represent 22% of cases. More than half of these were due to nuts, primarily peanuts. Shellfish and dairy products accounted for most of the remaining cases. Other causes were present in the remaining 16% of cases.

Table 1 provides the distribution of causes and severity of anaphylaxis derived from the sample of 87 cases fully reviewed. Among the cases, 29% were considered to be mild, 45% moderate, and 9% severe. In 17% of cases, severity could not be determined from the information available.

Based on the computer-recorded information and the records received, we estimate that 65% to 70% of patients were either hospitalized or seen in the emergency department. More than half were treated with epinephrine and prescribed adrenaline 0.15-mg self-injection device to be available for immediate use when necessary.

Among the 8 patients who developed hypotension and shock, the cause was a wasp sting in 3 and an oral

medicine in 2. There was 1 case each attributed to suxamethonium chloride used during anesthesia, rubber gloves, and yeast. The reaction to suxamethonium was the only severe case noted that occurred in hospital.

There was only 1 death related to anaphylaxis among the original 675 cases identified—one 75-year-old man with computer-recorded diagnoses of anaphylactic shock and myocardial infarction on the same day. He died 7 days later. No further information on this person was available.

We reviewed all the computer records of the people who had a diagnosis of anaphylactic reaction to immunization. There were only 24 cases during the 6-year period of study. The most common cause was the diphtheria, pertussis, and tetanus (DPT) vaccine, which accounted for 7 cases; the diphtheria and tetanus vaccine accounted for an additional 2 cases and tetanus toxoid alone for 1 case. There were 2 cases each associated with flu vaccine and measles-mumps-rubella vaccine. Single cases were attributed to hepatitis B or typhoid vaccine, hepatitis A or meningococcal vaccine, rabies vaccine, pneumococcal vaccine, and typhoid alone. In 5 cases, the vaccine was not specified. All of the DPT cases occurred in children. Most of the other cases occurred in adults. Two patients were hospitalized, one of whom had to be resuscitated in the emergency department immediately after receiving the flu vaccine. The numbers of people who received most of the vaccines during the study period were large (**Table 2**).

COMMENT

Although allergic reactions due to many substances are ubiquitous, those severe enough to cause anaphylaxis are relatively uncommon. A large number of different exposures previously noted in case reports to cause anaphylaxis¹ were identified in this study. In addition to insect stings or bites, medicines, and common food allergies, there were cases attributed to throat lozenges (n=1), jellyfish, balloons, rubber gloves, fluorescein, latex, and extreme exercise. There were a few cases of anaphylaxis-like syndrome where the cause was unknown.¹ The cause of anaphylaxis is normally apparent because the illness most often occurs within minutes or hours of exposure, but cases of unknown cause have been reported.¹

We estimate the incidence in the UK population we studied to be 8.4 per 100 000 person-years. Approximately 10% of cases were associated with hypotension and shock that required resuscitation, providing an incidence of approximately 1 per 1 million person-years. The remaining cases appear to be readily reversible with adrenaline, steroids, and/or antihistamines. Insect stings or bites were the most common cause of anaphylaxis followed closely by medicines. Acute, severe allergic reactions to vaccines are rare and seldom life-threatening.

To our knowledge, the current population-based study of anaphylaxis is the largest yet published. Despite differences in study design, population, and time, the estimate of risk (8.4 per 100 000 person-years) is of

Table 2. Numbers of Persons Receiving Immunizations

Immunization	Persons Receiving Immunization, No.
Influenza	269 000
Typhoid	172 000
Tetanus	266 000
BCG	50 000
Pneumococcal	64 000
Rubella	99 000
Rabies	3900
DT	161 000
DPT	112 000
Polio	408 000
Hepatitis B IG	1200
MMR	143 000
Hepatitis B	37 000
Measles	98 000
Pertussis alone	2000
Meningococcal	21 000
Yellow fever	10 000

Abbreviations: BCG, bacille Calmette-Guérin; DPT, diphtheria, pertussis, and tetanus; DT, diphtheria and tetanus; IG, immunoglobulin; MMR, measles-mumps-rubella.

similar magnitude to those reported from the United States by Yocum et al² (21 per 100 000 person-years). By contrast, estimates of risk provided by Neugut et al¹ of 1.2% to 15% of the US population appear to be far too high.

The GPRD has repeatedly been shown to contain data of excellent quality and completeness.^{5,6} However, in this descriptive study, we cannot rule out the possibility that some cases of anaphylaxis may not have been recorded in the GP computer record, particularly those that occurred in hospital.

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Corresponding author: Hershel Jick, MD, Boston Collaborative Drug Surveillance Program, Boston University School of Medicine, 11 Muzzey St, Lexington, MA 02421.

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