

Epidemiology of anaphylaxis in Olmsted County: A population-based study

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Background: Awareness of the clinical features of anaphylaxis and its causative triggers is important if recurrent episodes are to be avoided. The incidence of anaphylaxis in the general population is often underreported, and epidemiologic studies are few. Because an accurate profile of anaphylaxis could heighten awareness of this problem, we investigated the epidemiology of anaphylaxis in the general population of Olmsted County, Minn.

Objective: The purpose of this study was to describe the epidemiology of anaphylaxis in Olmsted County residents from 1983 through 1987.

Methods: This was a retrospective population-based cohort study. The medical records of 1255 Olmsted County residents identified by computer-linked, medical diagnostic indices (the Rochester Epidemiology Study) were reviewed retrospectively to identify residents whose clinical episodes met the criteria for anaphylaxis. We determined the incidence and rate of occurrence of anaphylaxis, rate of recurrence, prevalence of atopy, cause of anaphylaxis, frequency of referral to an allergy specialist, hospital admission rate, and case-fatality rate.

Results: There were 133 residents who experienced 154 anaphylactic episodes during the 5-year period: 116 residents had 1 episode of anaphylaxis, 13 residents had 2 episodes, and 4 residents had 3 episodes. The anaphylaxis occurrence rate was 30 per 100,000 person-years (95% confidence interval, 25-35). There were 110 residents who had a first lifetime episode of anaphylaxis (that was medically evaluated) during the years 1983 to 1987. The average annual incidence rate of anaphylaxis was 21 per 100,000 person-years (95% confidence interval, 17-25). Atopy was present in 53% of the cohort, and allergy consultation was obtained in 52%. A suspect allergen was identified in 68% of the cohort, most frequently a food, medication, or insect sting. The hospitalization rate was 7%, and 1 patient died.

Conclusion: The incidence of anaphylaxis is less than 1%, and death rarely occurs. People with atopy experience anaphylaxis

more frequently than people without atopy. Anaphylaxis frequently is not recognized by patients and physicians. (J Allergy Clin Immunol 1999;104:452-6.)

Key words: Allergens, anaphylaxis, atopy, epidemiology, medical emergencies

Portier and Richet¹ coined the term *anaphylaxis* to describe the phenomenon that occurred when a second vaccinating dose of sea anemone toxin caused a dog's death. They wished to distinguish this adverse event from prophylaxis, which describes protection from vaccination. Anaphylaxis is an acute, systemic reaction caused by mast cell-mediator release and is potentially life threatening. It is a medical emergency. The condition is identified by multiorgan involvement of the cutaneous, respiratory, cardiovascular, and gastrointestinal systems reacting to mast cell degranulation and mediator release temporally associated with a specific trigger, such as a drug, food, or insect sting.² The term *idiopathic anaphylaxis* describes patients who experience anaphylactic symptoms with no identifiable etiology.³ The term *anaphylactic reaction* implies occurrence of an IgE type I reaction triggered by an antigen, whereas the term *anaphylactoid reaction* implies a non-IgE-mediated cause, such as serum complement activation or direct mast cell degranulation by medications such as vancomycin, narcotic drugs, or radiocontrast agents.

Data on the epidemiology of anaphylaxis are generally available for only selected groups and not for the general population. In a retrospective study of all cases of anaphylactic shock occurring in a hospital catchment area of 48,000 in a 13-year period, 20 cases were found, for an incidence of 3.2 cases of anaphylaxis per 100,000 persons per year.⁴ Most estimates are based on reactions to specific drugs, such as penicillin, glafenine, and diclofenac.^{5,6} An estimate of the number of cases of idiopathic anaphylaxis occurring in the United States ranged from 20,000 to 47,000 cases per year.⁷ Atopy has been variably associated as predisposing to anaphylaxis.⁸⁻¹³ We previously estimated that the incidence of anaphylaxis is 90 per 100,000, based on emergency department visits to a tertiary hospital during a 4-month period.¹⁴

Studies of the epidemiology and incidence of anaphylaxis are complicated by several factors. The definitions of anaphylaxis vary and often do not distinguish between mucocutaneous symptoms alone and more severe cardio-

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Abbreviation used

CI: Confidence interval

vascular, respiratory, and gastrointestinal symptoms. Furthermore, surveys of patients can yield false-positive or false-negative responses, and the extent of anaphylaxis in the general population cannot be determined easily.^{2,14} An accurate profile of the epidemiology of anaphylaxis would heighten awareness of this condition among emergency department and primary care physicians for the purposes of diagnosis, treatment, and counseling.

We conducted a retrospective cohort study of all Olmsted County residents who experienced episodes of anaphylaxis from 1983 through 1987. The main objective was to describe the epidemiology of anaphylaxis in a defined general population. Secondary objectives were to determine the incidence of anaphylaxis in the population, the rate of occurrence of episodes of anaphylaxis, the rate of recurrence of anaphylaxis in the identified cohort, the prevalence of atopy in the cohort, the cause of the anaphylactic event, the signs and symptoms of the anaphylactic episode, the frequency of subsequent evaluation by an allergist, the percentage of episodes resulting in hospitalization, and the case-fatality rate.

METHODS

Medical record review

Olmsted County, Minn, is isolated from urban areas, and a unit record system allows all medical information about each person to be accumulated in a single file. Records can be accessed by indexes to the clinical diagnoses incorporated in what is known as the Rochester Epidemiology Project. This system provides a computer-linked, medical diagnostic index for all providers of care to Olmsted County residents and access to the original medical records of all Olmsted County residents.¹⁵ The population of Olmsted County has been the source of numerous population-based incidence studies and has proved a reliable indicator of disease incidence.¹⁵ With the exception of a higher proportion of the working population employed in the health care industry (and correspondingly higher educational levels), the demographics of Olmsted County residents generally reflect those of the US white population.¹⁶

The medical records of Olmsted County residents with diagnoses suggesting the presence of anaphylaxis during the years 1983 through 1987 were reviewed by physician investigators. The diagnostic codes searched for by the computer included the following: anaphylaxis, food allergy, drug allergy, hypersensitivity not otherwise specified, adverse effect of immunotherapy, adverse effect of injectable diagnostic agent, subglottic or pharyngeal edema, bee sting allergy, and unspecified allergic reaction. The episodes of anaphylaxis identified must have occurred between January 1, 1983, and December 31, 1987, and residency in Olmsted County at the time of the anaphylactic event was verified.

Definition of atopy or the allergic state

Patients were considered to be atopic, or prone to produce IgE antibody, if the medical record contained a diagnosis of allergic rhinitis, bronchial asthma, atopic dermatitis, or eczema.¹³ Additionally, patients were considered atopic if they had a known history of immediate reactions to foods or medications or a history of nasal or respiratory symptoms to an aeroallergen documented in the medical record.

Definition of anaphylaxis

Identification of anaphylaxis was based on symptoms and signs of generalized mast cell–mediator release plus mucocutaneous, oral or gastrointestinal, respiratory, or cardiovascular system involvement, as defined below. These criteria were established before the medical records review.

To classify an event as anaphylaxis, we required 1 symptom of generalized mediator release, such as flushing; pruritus or paresthesias of lips, axilla, hands, or feet; general pruritus; urticaria or angioedema; lip tingling or paresthesia; and conjunctivitis or chemosis. In addition to 1 symptom of generalized mediator release, we required at least 1 of the following additional symptoms to be present during the event, involving the oral and gastrointestinal, respiratory, or cardiovascular system, as discussed below.

1. Oral and gastrointestinal: oral mucosal pruritus; intraoral angioedema of buccal mucosa, tongue, palate, or oropharynx; nausea, emesis, dysphagia, abdominal cramps, or diarrhea.
2. Respiratory: rhinitis, stridor, cough, hoarseness, aphonia, tightness in the throat, dyspnea, wheezing, hypopharyngeal or laryngeal edema, cyanosis.
3. Cardiovascular: chest pain, arrhythmia, hypotension, presyncope, syncope, tachycardia, bradycardia, orthostasis, seizures, and shock.

Only 2 exceptions to these criteria could classify an event as anaphylaxis: isolated laryngeal edema or immediate shock and a syncope event after injection of medication or a radiocontrast agent.

Data collection and analysis

The medical records of 1255 Olmsted County residents were reviewed individually by the physician investigators who then selected patients who met the criteria for an episode of anaphylaxis. All the medical records of patients identified as having experienced an anaphylactic event by the physician investigators were further reviewed by an experienced nurse abstractor. The physician investigators then met again with the nurse abstractor to review individual patient records when questions arose regarding symptoms or whether an episode qualified as an anaphylactic event. A final cohort of patients who had experienced anaphylaxis was identified. The demographic characteristics, clinical features, associated allergens, and hospitalization for the first medically evaluated episode in the 1983 to 1987 period were abstracted from the medical record. Results are summarized as means $\pm$ SD.

The incidence of anaphylaxis was calculated by using the number of Olmsted County residents with a first lifetime episode of anaphylaxis during the specified 5-year period in the numerator and the number of Olmsted County person-years in the denominator. The occurrence of episodes of anaphylaxis was calculated by using the number of episodes of anaphylaxis in Olmsted County residents during the 5-year period in the numerator and the number of Olmsted County person-years in the denominator. The incidence and the occurrence rates of anaphylaxis were adjusted to the 1980 US white population because the population of Olmsted County was approximately 95% white.

RESULTS

Epidemiology of anaphylaxis

The numbers of first anaphylactic events during the 5-year study period were distributed as follows: 28 events (21%) in 1983, 28 events (21%) in 1984, 19 events (14%) in 1985, 27 events (20%) in 1986, and 31 events (23%) in 1987. Anaphylaxis occurred more frequently in July through September. Fig 1 shows the distribution of the episodes of anaphylaxis by suspected allergen and by

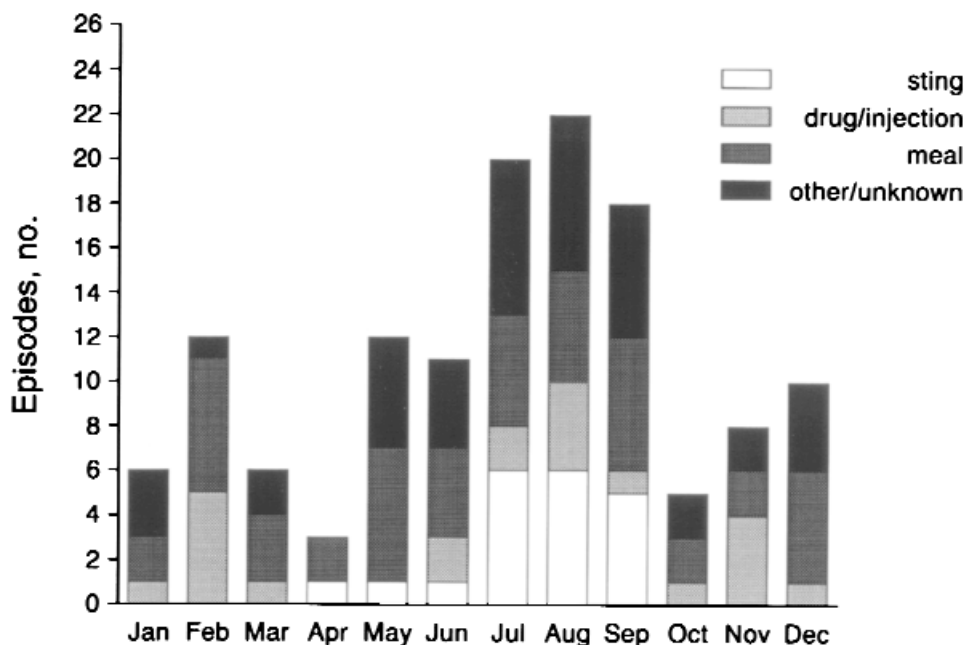


FIG 1. Distribution of first episodes of anaphylaxis (n = 133) by suspected allergen and by month.

month. The peak incidence during the summer months was the result of insect stings, which occurred only from May through September.

There was a temporal relationship of a few minutes to 2 hours between exposure to a suspected allergen and most of the 133 first anaphylactic events. In 48 of 133 events (36%), the allergen consisted of an ingestant; in 22 of 133 events (17%), the trigger was oral or parenteral administration of a medication, allergy immunotherapy injection, or injection of a diagnostic agent or a foreign protein; and in 20 of 133 events (15%), it was an insect sting. Therefore an allergen was suspected by temporal association in 90 of 133 anaphylactic events (68%). The implicated foods included fish, shellfish, tree nuts, eggs, peanuts, and seeds. The suspected medications, therapeutic and diagnostic agents, and other allergens included radiocontrast dye, nonsteroidal anti-inflammatory agents, antibiotics, allergy immunotherapy injection, and human semen.

Incidence of anaphylaxis

There were 133 Olmsted County residents who experienced anaphylaxis during the 5-year period: 116 residents had 1 episode of anaphylaxis, 13 residents had 2 episodes, and 4 residents had 3 episodes, for a total of 154 episodes. The entire cohort was composed of 66 females and 67 males; the patients' mean age was 29 ± 19 years (range, 6 months to 89 years). One hundred ten Olmsted County residents had a first lifetime episode of anaphylaxis during the study period, and 23 residents (17%) had experienced an episode of anaphylaxis before 1983 (1961 through 1982). The average annual incidence of anaphylaxis was 21 per 100,000 person-years (95% confidence interval [CI], 17-25 per 100,000 person-

years). The anaphylaxis occurrence rate was 30 per 100,000 person-years (95% CI, 25-35 per 100,000).

Prevalence of atopy

Among the cohort of residents who experienced anaphylaxis, 42 (32%) had allergic rhinitis; 44 (33%) had bronchial asthma, and 20 (15%) had atopic dermatitis. In the total cohort 62 (47%) were nonatopic and 71 (53%) were atopic.

Signs and symptoms of anaphylaxis

Among the 133 residents who experienced anaphylaxis, 100% had cutaneous manifestations, 69% had respiratory symptoms, 24% had oral and gastrointestinal symptoms, and 41% had cardiovascular symptoms. The percentages of the cohort that experienced symptoms and signs in the 4 target organ systems are shown in Table I. The percentages exceed 100% because the people in the cohort experienced multiple signs and symptoms in the 4 target organ systems.

Frequency of allergy consultation

Allergy consultation was obtained in 52% of the anaphylaxis cohort. Allergy skin tests were performed in 31% to penicillin, Hymenoptera venom, aeroallergens, and foods. In vitro allergen-specific IgE antibody testing was performed in 9% of the cohort to penicillin, Hymenoptera venom, aeroallergens, and foods. Overall, 53 of the 133 patients (40%) in the anaphylaxis cohort underwent either skin testing or RASTs.

Hospital admission and case-fatality rates

Among the anaphylaxis cohort, 9 of 133 (7%) were admitted to the hospital. The diagnosis of anaphylaxis

was made in 6 patients at admission. The diagnosis of anaphylaxis was not made either at admission or at dismissal in 3 patients. The length of hospitalization was 2.1 ± 2.3 days. One death occurred in the emergency department, for a case-fatality rate of 0.91%. The cause of this death was acute laryngeal edema that occurred during exercise. The fatality rate for all episodes of anaphylaxis during the 5-year period was 0.65% (1 in 154).

DISCUSSION

We believe this is the first study to examine the overall incidence of anaphylaxis in a defined community. This report is unique in that we have identified essentially all anaphylactic events in the medical records of Olmsted County residents during a 5-year period. We included all anaphylactic episodes of defined cause and idiopathic cases. This approach distinguishes the present study from previous reports that investigated narrow subtypes of anaphylaxis.^{2-8,12} The incidence of anaphylaxis reported here is surely an underestimate because it is frequently unrecognized and undiagnosed by physicians, and milder episodes, although potentially fatal, do not prompt patients to seek medical care.¹⁴

Our criteria for anaphylaxis included symptoms and signs of generalized mast cell–mediator release and symptoms of another target organ involvement. This excluded purely cutaneous reactions, such as urticaria and pruritus, and ensured that the process was truly systemic. The anaphylaxis cohort did not experience trivial symptoms: 54% had throat tightness and wheezing; 32% had intraoral angioedema, emesis, and abdominal cramps; and 34% had presyncope, hypotension, syncope, and shock. One patient died.

We report the incidence of anaphylaxis as 21 cases per 100,000 person-years. A previous retrospective study of all cases of anaphylactic shock in a hospital catchment area reported 3.2 cases per 100,000 inhabitants per year.³ The difference in incidence between these studies may be that we included all cases of anaphylaxis, mild to severe, and did not limit cases to shock alone.

A retrospective study by the National Office of Vital Statistics¹⁷ of fatal envenomations in the United States estimated an average death rate of 0.28 per 1,000,000 persons per year from Hymenoptera stings alone. Our case-fatality rate was 0.65%.

A previous study found that atopy did not predispose Boy Scouts to an increased risk of Hymenoptera allergy.⁸ In 1975, the Penicillin Study Group⁹ reported no correlation between penicillin reactions and family or personal history of atopy. However, it has been reported that asthmatic people experience significantly more severe reactions to Hymenoptera stings than do nonatopic people.¹⁸ The prevalence of atopy in a European white population is 20%.¹⁹ We found that 53% of Olmsted County residents with an anaphylactic episode were atopic. Thus atopy appears to be more prevalent among persons experiencing anaphylaxis than in the general population.

We found a temporal relationship to a suspected aller-

TABLE I. Symptoms and signs associated with anaphylaxis

Symptom or sign	Patients (N = 133)	
	N	%
Cutaneous		
Urticaria	73	55
Angioedema	74	56
Pruritus	73	55
Flushing	48	36
Conjunctivitis or chemosis	30	23
Respiratory		
Dyspnea	57	43
Throat tightness	37	28
Wheezing	34	26
Rhinitis	22	17
Laryngeal edema	9	7
Hoarseness	9	7
Oral and gastrointestinal		
Intraoral angioedema	20	15
Emesis	12	9
Nausea	12	9
Abdominal cramps	11	8
Dysphagia	7	5
Oral pruritus	5	4
Diarrhea	1	1
Cardiovascular		
Tachycardia	36	27
Presyncope	20	15
Hypotension	15	11
Syncope	4	3
Shock	7	5
Chest pain	4	3
Bradycardia	2	2
Orthostasis	2	2

gen, such as food, medication, diagnostic agent, or Hymenoptera stings, in 58% of the cohort; thus most anaphylactic events probably resulted from an allergen. However, causation could not be proved (by rechallenge) for ethical reasons. In a previous, retrospective report on 179 patients with anaphylactic episodes, a cause was suspected in 66%, and only 19% were thought to be idiopathic.² In that report, 79% of the patients were seen by an allergist compared with 52% of our patients. Immediate treatment with epinephrine, instruction in the self-administration of epinephrine, and immediate referral to an allergist are recommended for all patients who experience anaphylaxis.²⁰ A thorough allergy history and selective skin and allergen-specific IgE antibody tests are the most important subsequent diagnostic tools.

Idiopathic anaphylaxis is a diagnosis of exclusion, although it can be characterized by some unique symptoms, such as the triad of syncope, abdominal symptoms, and onset during sleep.²¹ There were no characteristic features in the history or physical examination that distinguished anaphylaxis because of other/unknown causes from those related to known triggers (Fig 1). The percentage of idiopathic anaphylaxis in our series (32%) is similar to that reported in another recent review (37%).¹⁰

Patients who experience recurrent anaphylaxis should be seen immediately after each episode so that an accurate recall of items ingested, medications taken, and events preceding the episode can be recorded.²⁰

There are few data in the literature to compare with our case-fatality rate of 0.65% among all anaphylaxis episodes. The fatality rate from penicillin anaphylaxis reported by the US Public Health Service was 0.015% to 0.020%.⁴ The International Rheumatic Fever Study Group²² reported a 0.2% incidence of anaphylaxis in 1790 patients who received monthly intramuscular injections of benzathine penicillin. There were 2736 patient-years of observation and 1 patient death, for a case-fatality rate of 0.05%.²² Our case-fatality rate was based on only 1 death. Nevertheless, our case-fatality rate was 32 times greater than the US Public Health Service report and 13 times greater than that reported by the International Rheumatic Fever Study Group.²²

In summary, this is the first report of anaphylaxis from all causes in a defined general population. We found an incidence rate and occurrence rate of 21 and 30 per 100,000 person-years, respectively. Of the anaphylaxis cohort, 53% were atopic. An allergy consultation was obtained for 52%, and an allergen was identified in 58% of the patients. Anaphylaxis is frequently unrecognized by both patient and physician. The case-fatality rate of anaphylaxis was 0.65%. We recommend that all patients who experience anaphylaxis have an allergy consultation to identify the cause and to prevent further episodes.

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