

Epidemiology of anaphylaxis at a tertiary care center

A report of 730 cases

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ABSTRACT

Background: Recent data reveal that the rate of anaphylaxis is increasing and suggest that idiopathic anaphylaxis may account for most of these cases.

Objective: To determine the pattern of anaphylaxis at a tertiary care referral center.

Methods: A retrospective electronic medical record review spanning 12 years (2002–2013) identified patients with anaphylaxis.

Results: Of the 4,777 records reviewed, 730 patients met our anaphylaxis definition. Median age was 34.0 years; 72.7% were adults, 58.6% were female, and 86.8% were white. Median time to evaluation by an allergist was 8.8 months. Foods were the most common cause (29.9%), followed by Hymenoptera venom (24.6%), idiopathic anaphylaxis (13.7%), and medications (13.3%). The most common foods were peanuts (23.9%), tree nuts (21.6%), shellfish (16.1%), and egg and milk (both 10.1%). The most common cause of anaphylaxis in adults was Hymenoptera venom. The most frequent symptoms were urticaria and/or angioedema, reported in 84.7% of cases. Atopy was present in 43.8%. In 15.4% of cases, anaphylaxis was not the chief reason for the office visit.

Conclusion: We found food allergy was the most common overall cause of anaphylaxis, with peanut the most frequent food trigger. Idiopathic anaphylaxis was not the most common cause but accounted for 13.7% of all cases. Approximately 1 in 6 cases of anaphylaxis may be missed if a comprehensive evaluation is not performed.

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Introduction

Anaphylaxis is an acute, systemic, potentially life-threatening reaction that often results in emergency department visits and hospital admissions. A surge in the rate of anaphylaxis has been observed. Epidemiologic studies from the United States and other countries have reported more than a 3-fold increase in the incidence of anaphylaxis in the past 3 decades.^{1–15} Causes of anaphylaxis include foods, Hymenoptera stings, medications, diagnostic agents, perioperative agents, latex, allergen skin testing, immunotherapy, and systemic mast cell disorders.^{16–18}

Idiopathic anaphylaxis is diagnosed when no cause can be identified despite a detailed history, allergen skin or in vitro testing,

and challenge tests.¹⁹ A recent report found idiopathic anaphylaxis to be the most common cause of anaphylaxis.¹ If the observation that most anaphylaxis cases occur without a recognizable external trigger is confirmed in additional studies, this would be important for patients and health care professionals. We sought to investigate the cases identified at our tertiary care center to identify recent and possibly changing patterns of anaphylaxis.

Methods

Medical Record Review

Electronic medical records of all patients evaluated in the Allergy and Immunology Department at Cleveland Clinic from July 2002 to October 2013 were searched for all patients with a diagnosis compatible with anaphylaxis. Patients of all age groups were included, and all patients were seen for outpatient consultation by a board-certified allergist/immunologist. The *International Classification of Diseases, Ninth Revision (ICD-9)* codes used were 995.0 (other anaphylactic shock, fish, crustaceans, food additives, milk

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Table 1
Demographic Characteristics of the Study Participants

Characteristic	No. (%) of patients (N = 730)
Female	428 (58.6)
Adults (≥18 years old)	531 (72.7)
Atopy	320 (43.8)
Race	
White	634 (86.8)
African American	55 (7.5)
Asian/Pacific Islander	22 (3.0)
Hispanic	6 (0.8)
Native American	1 (0.1)

products, eggs, other specified food), 989.82 (toxic effect of latex), 989.5 (toxic effect of venom), 202.6 (malignant mast cell tumors), 995.20 (adverse effect of medical/biological substance not otherwise specified), and 995.27 (other drug allergy). This study was approved by the Cleveland Clinic Institutional Review Board.

Definition of Anaphylaxis

Using World Allergy Organization guidelines,¹⁷ anaphylaxis was defined as sudden onset of characteristic symptoms and signs within minutes to hours after exposure to a known or potential trigger, often followed by rapid progression of symptoms and signs over hours. Criteria for the diagnosis of anaphylaxis were as follows:

1. Sudden onset of an illness (minutes to several hours), with involvement of the skin, mucosa tissue, or both (eg, generalized hives, itching and flushing, swollen lips, tongue, or uvula), and at least one of the following: sudden respiratory symptoms and signs (eg, shortness of breath, wheeze, cough, stridor, and hypoxemia), sudden reduced blood pressure, or symptoms of end-organ dysfunction (eg, collapse, incontinence).

2. Two or more of the following that occur suddenly after exposure to a likely allergen or other trigger for that patient (minutes to several hours): sudden skin or mucosal symptoms and signs (eg, generalized hives, itching or flushing, swollen lips, tongue, or uvula), sudden respiratory symptoms and signs (eg, shortness of breath, wheeze, cough, stridor, hypoxemia), sudden reduced blood pressure or symptoms of end-organ dysfunction (eg, collapse, incontinence), or sudden gastrointestinal symptoms (eg, crampy abdominal pain, vomiting).
3. Reduced blood pressure (BP) after exposure to a known allergen for that patient (minutes to hours): in infants and children, a low systolic BP (age specific) or greater than 30% decrease in systolic BP; in adults, a systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline.

Patients were considered to be atopic if the medical record contained a diagnosis of atopic dermatitis or rhinitis and/or asthma with evidence of positive immediate hypersensitivity aeroallergen skin and/or in vitro (>0.35 kU/L) testing.

Data Collection

Physician investigators reviewed 4,777 unique medical records containing potential anaphylaxis-related ICD-9 codes individually and then selected patients who met the criteria for anaphylaxis. In some cases, episodes occurred more than once for the same patient.

Cases with suspected food, Hymenoptera venom, or latex allergy were further probed for skin and/or in vitro testing. When the history was equivocal and skin test results were negative, with or without performance of provocative challenges as relevant (eg, for latex allergy), these cases were excluded. For drug-related anaphylaxis, where validated skin or in vitro testing have not been established^{20,21} (eg, sulfa or quinolone antibiotics), a convincing history alone was regarded as sufficient for diagnosis. The same was applied for penicillin because approximately 80% of patients with a penicillin allergy will lose penicillin specific IgE antibodies after 10 years.²² A diagnosis of idiopathic anaphylaxis

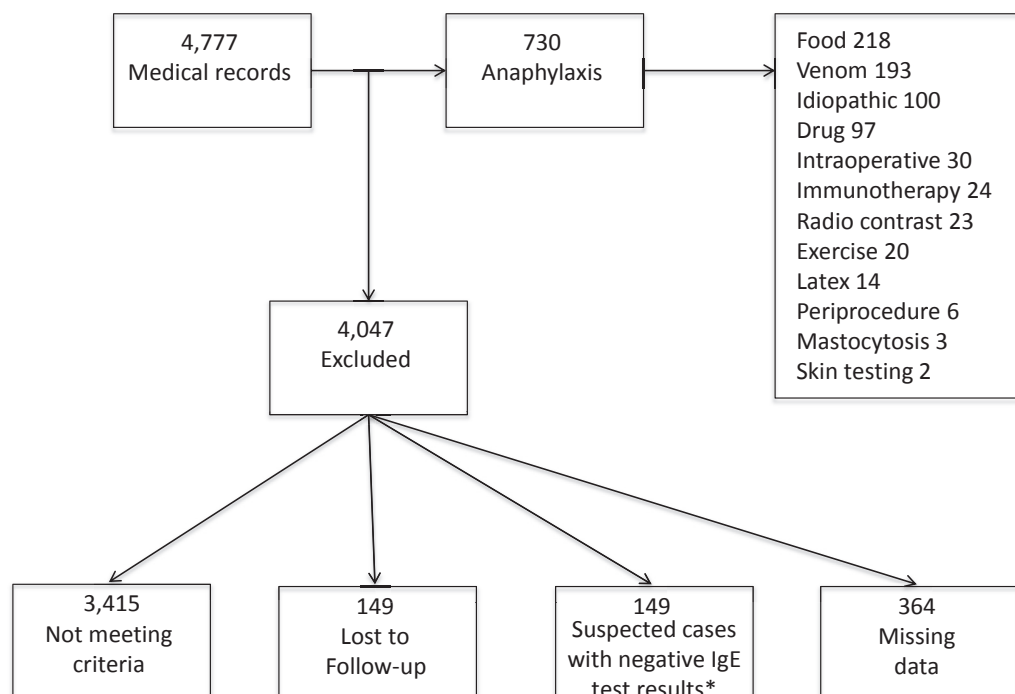


Figure 1. Review of 4,777 medical records with possible anaphylaxis-related *International Classification of Diseases, Ninth Revision* codes. *A total of 149 patients suspected of having anaphylaxis to food, venom, or latex had negative immediate hypersensitivity test results.

was established when no cause could be identified despite a detailed history, allergen skin and/or in vitro testing, or challenge testing.

Exclusion criteria included missing data (records lacking documentation of signs and symptoms of anaphylaxis), not meeting clinical criteria for anaphylaxis, or lost to follow-up (skin prick testing, in vitro testing, or challenge testing not performed). When suspected cases of food, Hymenoptera, or latex fulfilled clinical criteria for anaphylaxis but immediate hypersensitivity test results were negative, these cases were classified as suspected anaphylaxis with negative immediate hypersensitivity testing. These cases were reviewed on a case-by-case basis, so that in some instances associated with a high pretest probability, a cause of or anaphylaxis was established by a convincing history.²³

When questions emerged regarding symptoms or diagnostic criteria, investigators met on a bimonthly basis with the principal investigator to further review those cases. Results were compiled to evaluate demographic data, prescribing of injectable epinephrine, cause, presenting symptoms, and the presence of atopy. Anaphylaxis cases were further categorized by reason for consultation as anaphylaxis consultations (eg, chief concern of anaphylaxis) or nonanaphylaxis consults (eg, chief concern of asthma). All patients seen in Allergy and Immunology Department at Cleveland Clinic undergo a comprehensive evaluation, including a collateral allergic history (eg, inquiring about adverse reactions to insect stings or latex when presenting with asthma). Dates of the diagnosis by an allergist of anaphylaxis were recorded, as well as the date of the event reported by the patient. When there was only a year for the reported date of the anaphylactic event by the patient, the date of June 1 (midpoint of the year) was assigned.

Statistical Analyses

Patient characteristics were described using medians and interquartile ranges (IQRs) for all continuous variables and counts and percentages for all categorical variables. The Cochran-Armitage test was used to check for trends across time, the Wilcoxon rank sum (or Kruskal-Wallis, where appropriate) was used to compare medians, and the χ^2 test was used to assess associations between categorical variables. All analyses were 2-tailed and were performed at a significance level of .05. SAS statistical software, version 9.3 (SAS Institute Inc, Cary, North Carolina) was used for all analyses.

Results

There were 730 cases of anaphylaxis identified from 4,777 medical records reviewed. The median age of the patients was 34.0 years (IQR, 16.0–50.0 years). Of the 730 patients, 634 (86.8%) were

Table 2
Causes of Anaphylaxis

Cause	No. (%) of patients (N = 730)	No. (%) of adults (n = 531)	No. (%) of children (n = 199)
Food	218 (29.9)	90 (16.9)	128 (64.3)
Hymenoptera venom	193 (26.4)	154 (29.0)	39 (19.6)
Idiopathic anaphylaxis	100 (13.7)	90 (16.9)	10 (5.0)
Medication	97 (13.3)	89 (16.8)	8 (4.0)
Perioperative	30 (4.1)	29 (5.5)	1 (0.5)
Immunotherapy	24 (3.3)	18 (3.4)	6 (3.0)
Radiopaque media	23 (3.2)	22 (4.1)	1 (0.5)
Exercise	20 (2.7)	15 (2.8)	5 (2.5)
Latex	14 (1.9)	13 (2.4)	1 (0.5)
Periprocedure	6 (0.8)	6 (1.1)	0 (0.0)
Mastocytosis	3 (0.4)	3 (0.6)	0 (0.0)
Immediate hypersensitivity skin testing	2 (0.3)	2 (0.4)	0 (0.0)

white, 428 (58.6%) were female, and 531 (72.7%) were adults (18 years or older). Atopy was found in 320 (43.8%); 294 (40.3%) had allergic rhinitis, 142 (19.5%) had allergic asthma and allergic rhinitis, and 70 (9.6%) had atopic dermatitis. Anaphylaxis as the chief concern to be evaluated was found in 617 (84.5%) of all cases; 15.4% of all anaphylaxis cases were associated with a chief concern other than anaphylaxis. The median date of diagnosis by an allergist after the initial event was 8.8 months. Demographic data are summarized in Table 1.

From the 4,777 medical records reviewed, 4,047 cases were not included in the analysis because of the following: not meeting clinical criteria for anaphylaxis (n = 3,415), lost to follow-up (n = 149), suspected anaphylaxis (food, venom, or latex), negative immediate hypersensitivity test results (n = 119), or missing data (364) (Fig 1).

Causes of Anaphylaxis

The most common cause of anaphylaxis was food (29.9%), followed by Hymenoptera venom (26.4%), idiopathic anaphylaxis (13.7%), and medications (13.3%). All causes of anaphylaxis are listed in Table 2. Twenty-six patients were identified as having more than a single cause of anaphylaxis (Table 3). Of the 218 cases of food-related anaphylaxis (Table 4), the most common were peanuts (23.9%), followed by tree nuts (21.6%), and shellfish (16.1%). The median age of a patient with food anaphylaxis was 10.0 years. In children, the most common foods were peanuts (32.0%), tree nuts (22.7%), milk (17.2%), and eggs (16.4%). The median ages of patients with milk (1.0 year) and egg (1.0 year) anaphylaxis were each significantly lower than the median age for those who had peanut (3.5 years) and tree nut (7.0 years) anaphylaxis (Table 5) (all $P < .001$). In adults, the most common food was shellfish (34.4%), followed by tree nuts (20.0%) and peanuts (12.2%). Of the top 5 most common food allergens, patients who had a shellfish allergy had the highest median age (42.0 years); this was statistically significantly different compared with the other 4 most common causes of food anaphylaxis (Table 5) (all $P < .001$). There was no statistically significant difference in the most common foods causing

Table 3
Twenty-six Patients With Anaphylaxis With More Than a Single Cause

Patient No.	Cause
1	β -lactam and RCM
2	Macrolide, neosporin, and RCM
3	Peanut and shellfish
4	Venom and IT
5	Venom and mushroom
6	Venom and shellfish
7	Venom and β -lactam
8	Venom and β -lactam
9	β -lactam and peanut
10	β -lactam and RCM
11	Latex and tree nut
12	Venom and idiopathic anaphylaxis
13	Onion and tomato
14	Egg and milk
15	Latex and idiopathic
16	Venom and peanut
17	Venom and RCM
18	Shellfish and tree nut
19	Venom and IT
20	Egg and milk
21	Peanut and tree nut
22	Egg and peanut
23	Egg and milk
24	β -lactam and macrolide
25	Venom and shellfish
26	Venom and IT

Abbreviations: IT, immunotherapy; RCM, radiocontrast media.

Table 4
Foods Causing Anaphylaxis^a

Food	No. (%) of patients (N = 218)	No. (%) of adults (n = 90)	No. (%) of children (n = 128)
Peanuts	52 (23.9)	11 (12.2)	41 (32.0)
Tree nuts	47 (21.6)	18 (20.0)	29 (22.7)
Shellfish	35 (16.1)	31 (34.4)	4 (3.1)
Milk	22 (10.1)	0 (0.0)	22 (17.2)
Eggs	22 (10.1)	1 (1.1)	21 (16.4)
Fish	7 (3.2)	3 (3.3)	4 (3.1)
Pitted fruits	7 (3.2)	6 (6.7)	1 (0.8)
Wheat	5 (2.3)	3 (3.3)	2 (1.6)
Sesame seed	3 (1.4)	2 (2.2)	1 (0.8)
Soybean	2 (0.9)	2 (2.2)	0 (0.0)
Poultry	2 (0.9)	0 (0.0)	2 (1.6)
Kiwi	2 (0.9)	2 (2.2)	0 (0.0)
Banana	1 (0.5)	1 (1.1)	0 (0.0)
Beef	1 (0.5)	1 (1.1)	0 (0.0)
Buckwheat	1 (0.5)	1 (1.1)	0 (0.0)
Cotton seed	1 (0.5)	1 (1.1)	0 (0.0)
Green pea	1 (0.5)	0 (0.0)	1 (0.8)
Mushroom	1 (0.5)	1 (1.1)	0 (0.0)
Mustard	1 (0.5)	1 (1.1)	0 (0.0)
Onion	1 (0.5)	1 (1.1)	0 (0.0)
Sun flower seed	1 (0.5)	1 (1.1)	0 (0.0)
Sulfite	1 (0.5)	1 (1.1)	0 (0.0)
Tarragon leaves	1 (0.5)	1 (1.1)	0 (0.0)
Tomato	1 (0.5)	1 (1.1)	0 (0.0)

^aAll cases were confirmed by skin and/or in vitro testing.

anaphylaxis by race ($P = .21$). Seven cases of food anaphylaxis were identified by oral challenge.

Hymenoptera venom anaphylaxis was the second most frequent cause overall, with 193 cases (26.4%), and was the most common cause observed in adults. The median age for patients with venom anaphylaxis was 38.0 years. Skin and/or in vitro testing was used to confirm all venom cases. Idiopathic anaphylaxis was the third most common cause of anaphylaxis (13.7%), and the median age of these patients was 41.0 years.

Ninety-seven patients (13.3%) experienced medication-related anaphylaxis. Medication-induced anaphylaxis was more common in adults (16.8%) than in the pediatric population (4.0%) ($P < .001$). In addition, adults with drug-related anaphylaxis had an older median age (41.0 years) compared with adults with other causes of anaphylaxis (32.0) ($P < .001$). Antibiotics were the most common medication, with 61 cases (62.9%), followed by nonsteroidal anti-inflammatory drugs (20.6%). The most common type of antibiotic was β -lactams. All causes of medication-induced anaphylaxis are listed in Table 6. There were 30 cases of perioperative anaphylaxis (4.1%), which have been described in a previous report.²⁴ The most common cause of perioperative anaphylaxis was antibiotics.

Table 5
Comparison by the Most Common Food Causes

Cause	Age, median (IQR), y ^a	No. (%) of children ^b	No. (%) of adults ^b	No. (%) of nonwhite patients ^c	No. (%) of white patients ^c
Total (n = 178)	5.0 (2.0–25.0)	117 (65.7)	61 (34.3)	37 (20.8)	141 (79.2)
Peanut (n = 52)	3.5 (2.0–11.0) ^{d,e,f}	41 (78.8)	11 (21.2)	9 (17.3)	43 (82.7)
Tree nut (n = 47)	7.0 (3.0–25.0) ^{d,e,f}	29 (38.3)	12 (25.5)	35 (74.5)	10 (28.6)
Shellfish (n = 35)	42.0 (27.0–52.0) ^{e,f,g,h}	4 (11.4)	31 (88.6)	10 (28.6)	25 (71.4)
Milk (n = 22)	1.00 (0.58–3.0) ^{d,g,h}	22 (100)	0	1 (4.5)	21 (95.5)
Egg (n = 22)	1.00 (1.00–3.0) ^{d,g,h}	21 (95.5)	1 (4.5)	5 (22.7)	17 (77.3)

Abbreviation: IQR, interquartile range.

^a $P < .001$ (Kruskal-Wallis test).^b $P < .001$ (Pearson χ^2 test).^c $P = .21$ (Pearson χ^2 test).^dSignificantly different from shellfish.^eSignificantly different from milk.^fSignificantly different from eggs.^gSignificantly different from peanuts.^hSignificantly different from tree nuts.

Of the anaphylaxis causes with a sufficient number of observations to evaluate, only Hymenoptera venom-induced anaphylaxis exhibited a statistically significant trend in rates of anaphylaxis consultations during the period of the study ($P = .005$). For patients with a Hymenoptera venom allergy, there was a statistically significant trend for a decrease in the cases of venom allergy over time ($P < .001$).

Signs and Symptoms of Anaphylaxis

Of the 730 patients who experienced anaphylaxis, 618 (84.7%) reported urticaria and/or angioedema. Shortness of breath and/or cough was reported in 454 patients (62.2%). Other signs and symptoms, in order of greatest frequency, were syncope and/or presyncope, laryngeal involvement, nausea and/or vomiting, hypotension, diarrhea and/or abdominal cramps, and flushing. Table 7 summarizes the signs and symptoms of anaphylaxis.

Discussion

We performed a retrospective analysis of 730 cases of anaphylaxis during 12 years. To our knowledge, this is the largest retrospective study of anaphylaxis reported that includes both adults and children from the United States. The most common identified cause was food (29.9%), followed by venom (26.4%), both of which were more frequent than idiopathic anaphylaxis (13.7%). Venom and foods were the most commonly identified causes in adult and pediatric cases, respectively. The diagnosis of anaphylaxis caused by food, venom, and latex were confirmed by skin and/or in vitro testing. The median time of evaluation by an allergist after the initial event was approximately 9 months. Approximately 1 in 6 cases of anaphylaxis may be missed if a thorough history is not performed. Our findings reinforce the importance of allergists inquiring about a possible history of anaphylaxis, even when evaluating patients with a chief concern of asthma or rhinitis.

Foods were the most commonly identified cause of anaphylaxis in our series. The rate of approximately 30% is slightly lower than the rate in previous reports.^{5,6} However, in some previous studies,^{2,5,6} attribution of anaphylaxis to food was based on history alone without confirmatory skin or in vitro testing being performed. The most commonly identified foods in this series were peanuts (23.9%) followed by tree nuts (21.6%) and then shellfish (16.1%). A previous study¹ found shellfish was the most common cause followed by peanuts. It is possible this reflects the escalating prevalence of peanut allergy observed in recent years.²⁵

Venom was identified as the second most common cause of anaphylaxis overall and the most common cause of anaphylaxis in adults; 13.3% of the patients in our study had Hymenoptera venom anaphylaxis, a rate higher than reported in previous studies.^{2,5,6}

Table 6
Medications That Cause Anaphylaxis

Medication	No. (%) of patients (n = 97)
Antibiotics	61 (62.9)
β-Lactams	33 (34.0)
Macrolides	11 (11.3)
Sulfamethoxazole	7 (7.2)
Vancomycin	5 (5.2)
Bacitracin	1 (1.0)
Metronidazole	1 (1.0)
Clotrimazole	1 (1.0)
Tetracycline	1 (1.0)
Nitrofurantoin	1 (1.0)
NSAIDs	20 (20.6)
Succinate	4 (4.1)
Copaxone	3 (3.1)
Alendronic acid	1 (1.0)
Carvedilol	1 (1.0)
Chlorhexidine	1 (1.0)
Cyclizine	1 (1.0)
Hydrochlorothiazide	1 (1.0)
Interferon alpha	1 (1.0)
Lidocaine	1 (1.0)
Methotrexate	1 (1.0)
Protamine	1 (1.0)

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.

This may be because our study was performed at a referral center. A similar study⁷ performed in Switzerland found venom (58.8%) was the most common cause of anaphylaxis. Venom is the third leading cause of anaphylaxis-related death in the United States,²⁶ and patients only follow up with an allergist/immunologist 14% to 20% of the time.^{27,28} We also found a statistically significant trend for a decrease in cases of stinging insect anaphylaxis cases over time ($P < .001$). This was unexpected. Additional studies will be required to confirm and clarify this unanticipated finding.

Idiopathic anaphylaxis accounted for 13.7% of our cases. Our findings are consistent with previous reports,^{7,8,29} one of which included immediate hypersensitivity testing.² Webb and Lieberman¹ found idiopathic anaphylaxis accounted for almost 3 in 5 cases (59%) of anaphylaxis; however, their series of 601 cases did not include patients with anaphylaxis attributable to Hymenoptera venom. In our study, causes of anaphylaxis were elucidated in 86.3% of cases.

Medication reactions accounted for 13.3% of our cases, which is similar to previous reports.^{3,4} Medications are the most common cause of fatal anaphylaxis in the United States.²⁶ We found β-lactams as the most common medication identified, followed by nonsteroidal anti-inflammatory drugs. We assigned a cause of penicillin-induced anaphylaxis based on a convincing history, without need of wheal and flare reaction to penicillin

Table 7
Signs and Symptoms of Anaphylaxis

Sign or symptom	No. (%) of patients (N = 730)
Urticaria or Angioedema	618 (84.7)
Shortness of breath or cough	454 (62.2)
Syncope or presyncope	205 (28.1)
Laryngeal involvement	203 (27.8)
Nausea or vomiting	150 (20.5)
Hypotension ^a	105 (14.4)
Diarrhea or abdominal cramps	81 (11.1)
Flushing	74 (10.1)
Pruritus without rash	27 (3.7)
Chest pain	24 (3.3)
Rhinitis	16 (2.2)
Headache	4 (0.5)

^aHypotension was defined as systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline.

determinants. Previous reports indicate that in most cases of penicillin-induced anaphylaxis, skin and in vitro test results will become negative with time.^{20,30} Omission of these patients would decrease the proportion of medication-induced anaphylaxis cases from 97 to 64 cases.

Clinical manifestations^{2,3,6,7} and the rate of atopy in the series were consistent with previous studies.^{2–4,7} The most common presentation of anaphylaxis in our cohort was urticaria and angioedema (84.7%). The combination of urticaria and angioedema, flushing, and pruritus without a rash approaches 100%. These data provide further support for the contention that the absence of cutaneous symptoms on history should be regarded by the clinician as strong evidence against the diagnosis of anaphylaxis, implying that the diagnosis should be questioned. However, for management of acute anaphylaxis, clinicians should be aware that severe, potentially fatal (eg, perioperative) anaphylaxis may not entail cutaneous manifestations. Administration of epinephrine and other measures should not be delayed solely based on the absence of skin involvement.

There are several limitations to our study, including the retrospective nature and patients being seen exclusively in the Department of Allergy and Immunology. This is a report from a tertiary care center; our findings may not be generalizable to a community practice setting. Although our skin test protocol for penicillin³¹ does not include a minor determinant mixture, we do perform oral β-lactam challenge routinely when skin test results are negative, thereby validating the negative predictive value of our skin test protocol.³¹ A large proportion of medical records had to be reviewed to recognize a study cohort that met the criteria for anaphylaxis. This implies that many cases coded for anaphylaxis to food, venom, or latex are commonly suspected, but many cases are not confirmed by validated testing (skin and/or in vitro).

In conclusion, we conducted a retrospective analysis of the epidemiology of anaphylaxis during a 12-year period. We found that foods were the most common cause of anaphylaxis, with peanut being the most common. Our findings are important given the increasing incidence of food anaphylaxis reported in studies from around the world.^{2,5,6} Venom was the most common cause of anaphylaxis in adults. Because the most important aspect of anaphylaxis management continues to be prevention, our findings also highlight the importance of performing a comprehensive evaluation; without which, approximately 1 in 6 anaphylaxis cases would have been missed.

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