



Rate of recurrent anaphylaxis and associated risk factors among Olmsted County, Minnesota, residents A population-based study

Sangil Lee, MD, MS^{*,†}; Curtis Bashore, BS^{*}; Christine M. Lohse, MS[‡]; M. Fernanda Bellolio, MD, MS^{*}; Alanna Chamberlain, PhD[‡]; Kumi Yuki, MD[§]; Erik P. Hess, MD, MSc^{*}; Ronna L. Campbell, MD, PhD^{*}

^{*} Department of Emergency Medicine, Mayo Clinic, Rochester, Minnesota

[†] Department of Emergency Medicine, Mayo Clinic Health System, Mankato, Minnesota

[‡] Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota

[§] The REACH Institute, New York, New York

ARTICLE INFO

Article history:

Received for publication August 2, 2016.

Received in revised form September 23, 2016.

Accepted for publication September 26, 2016.

ABSTRACT

Background: The rate and risk factors for recurrence of anaphylaxis are not well known.

Objective: To measure the rate and risk factors for recurrent anaphylaxis in a population-based cohort in Olmsted County, Minnesota.

Methods: We conducted a population-based cohort study using the Rochester Epidemiology Project, a comprehensive medical records linkage system, to obtain records of patients who presented to medical centers within the Olmsted County area with anaphylaxis from January 1, 2001, through December 31, 2010. We evaluated the rate and associations of risk factors with anaphylaxis recurrence.

Results: Among the 611 patients with anaphylaxis, 50 (8%) experienced a total of 60 recurrences within the 10-year period, resulting in a recurrence rate of 2.6 per 100 person-years. A history of atopic dermatitis (hazard ratio [HR], 5.6; 95% confidence interval [CI], 2.0–16.1; $P = .001$), presenting symptoms of cough (HR, 4.7; 95% CI, 2.1–10.7; $P < .001$) oral pruritus (HR, 9.9; 95% CI, 4.3–23.2; $P < .001$), and receiving corticosteroids (HR, 5.2; 95% CI, 2.3–11.7; $P < .001$) were associated with an increased risk of recurrence. The cardiovascular symptom of chest pain (HR, 0.24; 95% CI, 0.07–0.79; $P = .02$) was associated with a decreased risk of recurrence.

Conclusion: In this epidemiologic study, the rate of recurrence was 8% during the 10-year study period (recurrence rate of 2.6 per 100 person-years). Those with atopic dermatitis and mucocutaneous or respiratory symptoms were more likely to have a recurrent anaphylactic event. Our findings underscore the importance of early patient access to self-injectable epinephrine and referral to an allergist/immunologist for additional testing and education.

© 2016 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Introduction

Anaphylaxis is a systemic allergic reaction that can be fatal.¹ Several studies in different populations have reported increasing incidence rates of anaphylaxis over time.^{2–5} Clinical criteria for the

diagnosis of anaphylaxis were poorly defined until 2006 when the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network (NIAID/FAAN) diagnostic criteria for anaphylaxis were established.¹ One of the most feared aspects of anaphylaxis is its recurrence. Previous studies report frequent recurrence of anaphylaxis, particularly in patients with multiple triggers.⁶ Identification of those at greatest risk for recurrent anaphylaxis may enable patients to be more vigilant and prepared to mitigate the risk. Despite the dangers of recurrent anaphylactic reactions, few studies have examined the incidence of and risk factors for recurrence, and there have been no population-based studies.^{6–8} This study was designed to measure the rate and risk factors for recurrent anaphylactic reactions in the population of Olmsted County, Minnesota, from 2001 to 2010.

Reprints: Sangil Lee, MD, MS, Department of Emergency Medicine, Mayo Clinic Health System, 1025 Marsh St, Mankato, MN 56001; E-mail: Lee.Sangil@mayo.edu.

Disclosures: The contents are solely the responsibility of the authors and do not necessarily represent the official view of National Institutes of Health.

Funding Sources: This study was made possible using the resources of the Rochester Epidemiology Project, which is supported by the National Institute on Aging of the National Institutes of Health under award R01AG034676, and by Clinical and Translational Science Award grant UL1 TR000135 from the National Center for Advancing Translational Sciences, a component of the National Institutes of Health.

Methods

Study Design and Setting

We conducted a population-based observational cohort study among residents of Olmsted County between 2001 and 2010. We identified patients with anaphylaxis from the Rochester Epidemiology Project, a medical record linkage system connecting the records of all health care workers in Olmsted County, Minnesota.^{9–13} Every patient's diagnosis was coded with either the codes of the *Hospital Adaptation of the International Classification of Diseases, Second Edition (HICDA-2)*, or the codes of the *International Classification of Diseases, Ninth Edition (ICD-9)*. This study was approved by the Mayo Clinic and Olmsted Medical Center institutional review boards. Patients were included in the study only if they were residents of Olmsted County and had granted written permission for review of their medical records.

Selection of Participants

All patients with codes representing anaphylactic shock, anaphylactic shock caused by food, anaphylactic shock not classified elsewhere, and anaphylactic shock after sting were obtained (HICDA-2 codes 09894110 and 09994110-2; ICD-9 codes, 995.6, 995.60-69, 999.4, 999.41-42, 999.49, 995.0, and V13.81). In addition, 3 sublists with diagnoses representing potential anaphylactic reactions were generated. Twenty percent of the medical records from each subgroup were chosen for review by random-number sampling to identify additional cases of anaphylaxis. The sublists are as follows:

1. Diagnosis of venom, bee sting, or toxic effect of venom (HICDA-2 codes, 09894120-4, 09894210-1, and 09894310; ICD-9 codes, V15.06, E905.0-.9, and 989.5)
2. Diagnosis of allergy, foodstuff; adverse effect, food; dermatitis caused by food taken internally; or toxic effect of specific food (HICDA-2 codes, 06928540-2, 06928610-1, and 34608120; ICD-9 codes, 692.5, 693.1, 995.7, V15.01-.05, 988, 988.0-2, and 988.8-.9)
3. Diagnosis of medication reactions (ICD-9 codes, 995.2, 995.20-.21, 995.27, 999.4, 999.41-.42, and 999.49)

The record of each patient was reviewed to confirm the diagnosis of anaphylaxis and to identify recurrences within the study period, using the NIAID/FAAN criteria to identify positive cases (eFig 1). Only cases that met the criteria for anaphylaxis were included in the study. Patients evaluated in the emergency department (ED), primary care clinics, allergy clinic, urgent care, and hospital ward were included. This method is similar to a prior study of anaphylaxis in Olmsted County that used Rochester Epidemiology Project resources.^{2,13}

Data Collection, Variables, and Outcome Measures

The health records of all included patients were independently reviewed and abstracted by 2 previously trained investigators (C.B., S.L.); data were extracted in duplicate for a sample of the cohort to ensure quality and consistency and to reduce bias. A calibration of the abstractors was performed after the duplicate abstraction, and interobserver agreement was measured. The abstractor (C.B.) and principal investigator (S.L.) met frequently to review and discuss coding rules. Quality assurance of abstracted data was performed on a weekly basis. Data were entered into a REDCap (Research Electronic Data Capture, Vanderbilt University, Nashville, TN) database. A data abstraction form was created specifically for this study and was tested before starting data retrieval. This data abstraction tool was hosted at Mayo Clinic and was constructed to support the collection of data for research studies by providing an interface for data collection, tracking data manipulation,

automating the export of data to statistical software, and allowing the import of data from external sources.¹⁴

Data were collected on demographic variables, medical history, signs and symptoms, clinical presentation, clinical management, trigger, and allergy follow-up. The inciting allergens of contrast and latex were combined with other triggers. For those who developed either index or recurrent anaphylaxis, we reviewed the medical records and determined access to epinephrine before arrival to the health care setting. The total number of recurrent reactions within the study period for each patient was recorded. Recurrence of anaphylaxis was defined as the recurrence of symptoms that met the NIAID/FAAN criteria during the study period. Biphasic reactions were excluded based on the duration of symptom recurrence and reexposure to the trigger after the initial reaction. If the variable of interest was not mentioned in the records, including notes by the ED physician, allergy clinic, primary care appointment, and/or nurse, it was left as a missing value.

Statistical Analysis

We present the variables collected with frequency counts and percentages. We report the rate of recurrent events per 100 person-years. Associations of features with time to recurrence were evaluated using Cox proportional hazards regression models and summarized with hazard ratios (HRs) and 95% confidence intervals (CIs). The duration of follow-up was calculated from the index date of anaphylaxis to the date of first recurrence, the date of last follow-up if the patient was lost to follow-up before December 31, 2010, or December 31, 2010, if the patient was still being followed up on that date. A multivariable model was developed using stepwise selection with the *P* value for a feature to enter or leave the model set to 0.05. The modeling was done on a per-patient basis to account for those with multiple recurrences. Statistical analyses were performed using version 9.3 of the SAS software package (SAS Institute Inc, Cary, NC). All tests were 2-sided, and *P* < .05 was considered statistically significant.

Results

Interobserver Agreement

Twenty medical records were reviewed by a trained medical assistant (C.B.) and the principal investigator (S.L.), and interrater agreement was very good, with an overall agreement of 95% and a κ of 0.88 (95% CI, 0.64–1.00).

Participants

Using the resources of the Rochester Epidemiology Project, we identified 631 patients who had at least one anaphylactic reaction that met the NIAID/FAAN criteria (Fig 1) in Olmsted County from January 1, 2001, through December 31, 2010. One patient did not have research authorization after the initial phase of the study. Nineteen patients who did not have follow-up after the index date of anaphylaxis were excluded, leaving 611 patients for the recurrence analysis. Features of interest for the 611 patients are summarized in Table 1 and eTable 1.

Descriptive Data

The median age of this cohort at first visit was 31 years (interquartile range [IQR], 18–45 years), including 148 children (24%) (age <18 years). Two hundred ninety-nine patients (49%) were female, and 476 (85%) were white. On the first visit, 101 patients (17%) had a history of asthma, 61 (10%) had a history of allergic rhinitis, 21 (3%) had a history of atopic dermatitis, and 28 (5%) had a history of hives. Table 1 lists the patient encounter settings and inciting triggers. Four hundred sixty-seven of the 610 patients (77%) were seen in the ED, 40 (7%) were seen in the allergy clinic, 57 (9%)

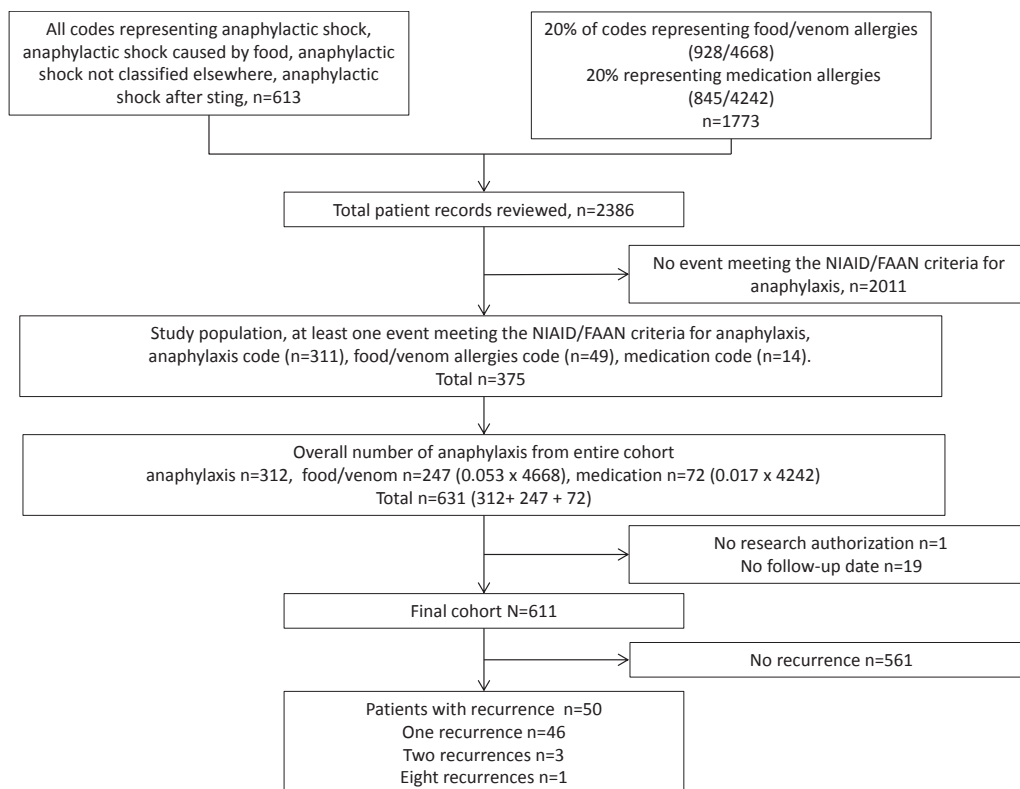


Figure 1. Flowchart of the selection process. NIAID/FAAN indicates National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network.

were seen in a nonallergist/immunologist outpatient clinic, 33 (5%) were seen in urgent care, and 13 (2%) were either seen elsewhere or in an unspecified location.

As indicated in Table 1 and eTable 1, an inciting trigger was identified in 543 cases (89%). Two hundred twenty-three of 611 patients (36%) had an inciting trigger of food, of which the largest proportion was peanut or tree nut (91/611, 15% overall). One hundred thirty patients (21%) had a medication as a trigger, including 45 antibiotics (7% overall). Insect venom was the inciting trigger in 146 reactions (24%), with bee stings accounting for 112 (18%) of the reactions.

Treatment and follow-up of the first reaction are summarized in Table 1 and eTable 1. Steroid therapy was administered in 392 reactions (64%), and epinephrine was administered in 288 reactions (47%). Of the 288 anaphylactic reactions, 283 had records of the locations of epinephrine administration, and 208 of 283 patients (74%) were treated with epinephrine in the ED. Four hundred ninety-eight patients (82%) did not have access to an epinephrine autoinjector when their symptoms began. Four hundred forty-nine of 606 patients (74%) were dismissed home after treatment in the outpatient setting, and 85 (14%) were admitted to either a hospital ward or the intensive care unit. After the first reaction, 289 of the 611 patients (47%) followed up with an allergist/immunologist, who identified a trigger in 213 of the 289 patients (74%).

Recurrent Anaphylaxis

Fifty patients (8%) experienced recurrence at a mean of 1.8 years after the index date of anaphylaxis (median, 0.6 years; IQR, 0.1–4.1 years; range, 1 day to 7.5 years). The mean duration of follow-up for the 561 patients who did not experience a recurrence was 3.7 years (median, 3.1 years; IQR, 1.3–5.7 years; range, 1 day to 9.9 years). There were 46 patients who experienced 1 recurrence, 3 patients who experienced 2, and 1 patient who experienced 8 during the

period under study, for a total of 60 recurrences observed during 2,290 patient-years of follow-up, resulting in a recurrence rate of 2.6 per 100 person-years. The mean age at the date of recurrence was 34.3 years (median, 32 years; IQR, 18–53 years; range, 5–75 years). Steroid treatment was provided in 45 recurrent reactions (75%), and epinephrine was provided in 39 recurrent reactions (65%). Forty-four patients (73%) had epinephrine available during their recurrent reactions. Twenty-five patients (42%) with recurrence had visited an allergist/immunologist after their first reaction, and in 15 of the 25 patients (60%), the allergist/immunologist identified the trigger on a visit before the recurrence. The remaining features collected for the 60 recurrences are summarized in Table 2 and eTable 2.

Risk Factor Analysis

Univariable associations with recurrence are summarized in Table 3. The multivariable model to evaluate time to recurrence is summarized in Table 4. A history of atopic dermatitis (HR, 5.6; 95% CI, 2.0–16.1; $P = .001$), the presenting symptoms of cough (HR, 4.7; 95% CI, 2.1–10.7; $P < .001$), oral pruritus (HR, 9.9; 95% CI, 4.3–23.2; $P < .001$), and receiving steroid therapy for the index reaction (HR, 5.2; 95% CI, 2.3–11.7; $P < .001$) were significantly associated with recurrence, whereas the cardiovascular symptom of chest pain (HR, 0.24; 95% CI, 0.07–0.79; $P = .02$) was associated with a decreased risk of recurrence after multivariable adjustment.

Discussion

Main Findings

In this population-based, epidemiologic study, we found that recurrent anaphylaxis occurred in 8% of the patients during the 10-year study period (2.6 per 100 patient-years). The median time to recurrence was 0.6 years. We found an association between

Table 1
Summary of Features at Index Date of Anaphylaxis in the 611 Study Patients

Feature	Finding ^a
Age at index anaphylaxis, mean (SD), y	
Pediatric	148 (24)
Adult	463 (76)
Sex	
Women	299 (49)
Men	312 (51)
Race/ethnicity (N = 562) ^b	
White	476 (85)
Hispanic	1 (<1)
Black	18 (3)
Asian/Pacific Islander	38 (7)
Other	29 (5)
Visit setting (N = 610)	
Emergency department	467 (77)
Urgent care	33 (5)
Clinic	57 (9)
Allergy clinic	40 (7)
Other	13 (2)
Disposition (N = 606)	
Home	449 (74)
Observation unit	72 (12)
Hospital ward	57 (9)
Intensive care unit	28 (5)
Medical history	
Asthma	101 (17)
Allergic rhinitis	61 (10)
Atopic dermatitis	21 (3)
Hives	28 (5)
Inciting allergen	
Food	223 (37)
Medication	130 (21)
Contrast	6 (1)
Latex	1 (<1)
Venom	146 (24)
Unknown	68 (11)
Other	37 (6)
Mucocutaneous symptom	594 (97)
Gastrointestinal tract symptom	121 (20)
Cardiovascular symptom	222 (36)
Respiratory tract symptom	482 (79)
Steroid provided as therapy	392 (64)
Epinephrine provided as therapy	288 (47)
Location of first epinephrine (N = 283)	
Self/home	22 (8)
Emergency Medical Services/resuscitation team	26 (9)
Emergency department	208 (74)
Intensive care unit/hospital ward	5 (2)
Other	22 (8)
Access to epinephrine autoinjector	113 (18)

^aData are presented as number (percentage) of patients unless otherwise indicated.

^bSample sizes for features with missing data or for subsets of interest are noted.

recurrence and a history of atopic dermatitis and the presenting symptoms of cough, oral pruritus, and receiving steroid therapy for the index reaction, whereas the cardiovascular symptom of chest pain was significantly associated with a decreased risk of recurrence.

Interpretation of Results

Eight percent of our patient population experienced a recurrence during the study. As might be expected, this percentage is lower than those reported in studies of allergy clinic patients.^{6,8} Mullins⁶ reported that 43% of allergy clinic patients surveyed experienced a recurrence during a 5.5-year period. It is possible that patients with recurring reactions were more likely to be followed up at an allergy clinic. In addition, patients with more recurrences may have been more likely to participate in the survey.⁶ Another study⁸ conducted in an allergy clinic found a recurrence rate of 76%. However, this study was conducted before the introduction of the NIAID/FAAN criteria, and the definition

Table 2
Summary of Features at Recurrence in 60 Patients

Feature	Finding ^a
Age at recurrence, mean (SD), y	
Pediatric	14 (23)
Adult	46 (77)
Sex	
Women	33 (55)
Men	27 (45)
Race/ethnicity	
White	52 (87)
Asian/Pacific Islander	7 (12)
Other	1 (2)
Visit setting	
Emergency department	52 (87)
Clinic	1 (2)
Allergy clinic	5 (8)
Other	2 (3)
Disposition	
Home	45 (75)
Observation unit	4 (7)
Hospital ward	4 (7)
Intensive care unit	7 (12)
Inciting allergen	
Food	20 (33)
Medication	5 (8)
Contrast	1 (2)
Venom	7 (12)
Unknown	17 (28)
Other	10 (17)
Allergist saw patient after index anaphylaxis	25 (42)
Inciting allergen identified by allergist (N = 25) ^b	15 (60)
Allergy tests performed	12 (20)
Mucocutaneous symptom	57 (95)
Gastrointestinal tract symptom	12 (20)
Cardiovascular symptom	30 (50)
Respiratory tract symptom	39 (65)
Steroid provided as therapy	45 (75)
Epinephrine provided as therapy	39 (65)
Location of first epinephrine (N = 39)	
Self/home	16 (41)
Emergency Medical Services/resuscitation team	3 (8)
Emergency department	18 (46)
Other	2 (5)
Access to epinephrine autoinjector	44 (73)

^aData are presented as number (percentage) of patients unless otherwise indicated.

^bSample sizes for features with missing data or for subsets of interest are noted.

used did not require multisystem involvement.⁸ A more recent study¹⁵ conducted in 2013 found that 22% of children who presented to the ED with allergic reactions to food experienced a recurrence of allergic reactions in a 3-year period. However, this study did not specifically examine anaphylaxis but instead looked for recurrence of any allergic symptoms, so a lower rate would be expected than if only patients with anaphylaxis were included.¹⁵ Thus, our finding of an 8% recurrence rate of anaphylaxis during a 10-year period in a population-based cohort is lower than rates reported in previously published literature. However, sampling and referral bias are likely to have been present in studies performed in allergy clinics compared with this population-based epidemiologic study.

Patients who experienced recurrent reactions typically experienced the recurrence in a relatively short period because the median time between the index and recurrent anaphylaxis was approximately 7 months, with an IQR of 1 month to 4 years. These findings support the need for patients to immediately begin carrying an epinephrine autoinjector and to seek expedited outpatient allergist/immunologist follow-up for further evaluation to confirm the diagnosis and establish the trigger whenever possible.

Table 3
Univariable Associations With Recurrence

Feature	HR (95% CI)	P value
Age at index anaphylaxis	1.07 (0.93–1.24) ^a	.36
Age at index anaphylaxis		
Pediatric	1.0 [Reference]	
Adult	1.36 (0.66–2.81)	.40
Sex		
Women	1.0 [Reference]	
Men	0.58 (0.33–1.03)	.06
Race/ethnicity (N = 562) ^b		
White	1.0 [Reference]	
Nonwhite	1.07 (0.50–2.29)	.85
Medical history		
Asthma	1.39 (0.71–2.71)	.34
Allergic rhinitis	1.86 (0.87–3.96)	.11
Atopic dermatitis	3.41 (1.21–9.61)	.020
Hives	2.12 (0.84–5.36)	.11
Inciting allergen		
Food	1.0 [Reference]	
Medication	0.63 (0.28–1.41)	.26
Venom	0.34 (0.14–0.84)	.02
Unknown	1.14 (0.50–2.58)	.76
Contrast, latex, and other	1.58 (0.67–3.72)	.30
Mucocutaneous symptom		
Diffuse urticarial	0.78 (0.43–1.41)	.40
Local angioedema	1.04 (0.55–1.96)	.90
Oral pruritus	6.03 (2.69–13.49)	<.001
Pruritus	1.58 (0.79–3.16)	.20
Flushing	1.75 (0.90–3.43)	.10
Local urticarial	0.97 (0.53–1.78)	.93
Conjunctivitis	0.73 (0.04–12.25) ^c	.83
Oropharyngeal edema	2.35 (1.11–5.02)	.03
Diffuse angioedema	0.61 (0.08–4.38)	.62
Diaphoresis	0.50 (0.03–8.42) ^c	.63
Chemosis/edema ocular conjunctiva	0.85 (0.21–3.51)	.82
Tightness or fullness of throat	1.60 (0.94–2.86)	.08
Rhinitis	0.62 (0.09–4.53)	.64
Any of above	1.20 (0.17–8.74)	.85
Gastrointestinal tract symptom		
Emesis	0.50 (0.16–1.60)	.24
Nausea	0.49 (0.12–2.02)	.32
Abdominal cramping	1.09 (0.27–4.50)	.90
Diarrhea	0.20 (0.01–3.35)	.26
Any of above	0.44 (0.18–1.12)	.09
Cardiovascular symptom		
Presyncope/lightheadedness	0.98 (0.48–2.02)	.96
Chest pain	0.32 (0.10–1.03)	.06
Hypotension	0.44 (0.11–1.80)	.25
Arrhythmia	12.39 (0.71–216.78)	.08
Syncope	0.26 (0.04–1.92)	.19
Orthostatic hypotension	0.61 (0.04–10.33)	.73
Any of above	0.55 (0.29–1.03)	.06
Respiratory tract symptom		
Dyspnea/difficulty breathing	1.30 (0.71–2.38)	.40
Wheezing/bronchospasm	1.07 (0.50–2.29)	.85
Cough	3.93 (1.75–8.80)	<.001
Hoarseness/raspy voice	3.89 (1.98–7.65)	<.001
Cyanosis	0.52 (0.03–8.70)	.65
Stridor	1.81 (0.25–13.12)	.56
Aphonia	3.01 (0.18–50.53)	.44
Any of above	1.51 (0.73–3.13)	.26
Steroid provided as therapy	4.30 (1.93–9.59)	<.001
Epinephrine provided as therapy	1.44 (0.82–2.52)	.20

Abbreviations: CI, confidence interval; HR, hazard ratio.

^aHR represents a 10-year increase in age.^bSample sizes for features with missing data or for subsets of interest are noted.^cHR estimated using the Firth penalized maximum likelihood.

A history of atopic dermatitis was associated with an increased risk of recurrence in multivariable analysis. Mullin⁶ reported in a survey-based study from Australia that female sex was associated with increased recurrence, yet history of asthma or atopic dermatitis were not. Kemp et al⁸ reported that the patients presenting to the allergy clinic had a higher prevalence of atopic dermatitis (37%) and hypothesized that mast cell and basophils in atopic individuals

Table 4
Multivariable Model to Predict Recurrence

Feature	HR (95% CI)	P value
Atopic dermatitis	5.60 (1.95–16.13)	.001
Oral pruritus	9.93 (4.25–23.21)	<.001
Chest pain	0.24 (0.07–0.79)	.02
Cough	4.70 (2.06–10.71)	<.001
Steroid provided as therapy	5.16 (2.28–11.67)	<.001

Abbreviations: CI, confidence interval; HR, hazards ratio.

are more active than in nonatopic individuals. These findings were not reported by Vetander et al,¹⁵ who reported that known food allergy and previously prescribed epinephrine were associated with ED revisit among children. Although specific risk factors have not been identified consistently in previous studies,^{6,8,15} atopy has been shown to be a risk factor for severe allergic reactions.¹⁶ In addition, the presenting symptoms of cough, oral pruritus, and steroid therapy for the index reaction remained significantly associated with recurrence, whereas the cardiovascular symptom of chest pain was associated with a decreased risk of recurrence. These findings have not been identified in prior studies.^{6,8,15} Despite statistically significant results, there are not enough data to implicate the prediction of future recurrence for those with positive risk factors. Further studies are needed to confirm or dispute these findings.

One encouraging finding was an increase in epinephrine availability at the time of the recurrent reaction relative to the first reaction. Although only 18% of patients had an epinephrine autoinjector available at the time of the index reaction, 73% of the patients who had a recurrence had an autoinjector available. Those patients with first-time anaphylaxis may not have had a reason to carry epinephrine previously. Self-injectable epinephrine availability is a crucial life-saving treatment for the management of anaphylaxis. Although availability appears to be increasing, improvements are still needed.¹⁷

Limitations and Strengths

Our study has several potential limitations. First, we used ICD-9 and HICDA-2 codes for identification of patients, so we may have missed some patients with anaphylaxis who were miscoded. Second, the study is based on medical record review, and the data collected are therefore limited to the information in the medical record. Third, we analyzed all patients with anaphylaxis diagnoses but only a sampling of the patients with diagnoses of sting, allergic reactions, or medication reactions, which could introduce selection bias. Fourth, decision making regarding diagnosis and management was left to the clinical team caring for the patients; thus, there may be bias intrinsic to practice variation, and it is difficult to capture all elements that influence decision making. Fifth, data abstractors were not masked to the outcomes measured or study objectives. Sixth, this study was conducted in a region with a predominantly white population, and the results may not be generalizable to other populations. Seventh, multiple variables were tested for associations, and external validation is needed to confirm these findings.

Despite these limitations, this is the first study, to our knowledge, describing the recurrence of anaphylaxis in a population-based cohort. This study used a medical records linkage system to track each patient's progress throughout a 10-year period. This enabled us to review visits to any clinic within the county, providing a comprehensive capture of each patient's medical history and outcomes. Of note, we used NIAID/FAAN criteria to define anaphylaxis in our cohort; the use of objective criteria likely increased the accurate identification of index and recurrent events.

Implication for Clinical Practice and Policy

Eight percent of the patients experienced anaphylaxis recurrence within 10 years, (recurrence rate of 2.6 per 100 person-years), with most patients having the first recurrence within 4 years. These findings reinforce guidelines that recommend that patients be prescribed and carry self-injectable epinephrine and follow up promptly with an allergist/immunologist to help confirm the diagnosis and likely trigger. Fear of recurrent anaphylaxis can be a stressful burden on a patient and his or her family or caregivers, particularly if a trigger is unknown. Increased anxiety attributable to anaphylactic reactions has been associated with an increase in future reactions.¹⁸ Understanding the overall risk of recurrence and specific associated risk factors will enable health care professionals to more accurately educate and prepare patients regarding their risk of future recurrence and potentially avoid recurrences and adverse outcomes.

Unanswered Questions and Future Research

Few studies have been dedicated to investigating recurrence in patients with anaphylaxis, and this is the first to be conducted since the establishment of the NIAID/FAAN criteria in 2006.¹⁹ More discrete data on the recurrence of anaphylaxis and identifying the causative factors can benefit the patients and clinicians. To gain a better understanding of factors that can lead to recurrent anaphylaxis, larger studies are needed.

In conclusion, we found that 8% of patients with anaphylaxis experienced a recurrence of within 10 years, and half of these experience a recurrence within 7 months. The risk of recurrence increased with a history of atopic dermatitis and the presence of mucocutaneous or respiratory symptoms during index reaction. Our findings can be used for risk stratification of patients and underscore the importance of early patient access to self-injectable epinephrine and referral to an allergist/immunologist for additional testing and education.²⁰

Acknowledgments

We appreciate Waqas Gilani, MD, and Dante Lucas Souza from Mayo Clinic for assistance in medical record review.

Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2016.09.444>.

References

- [1] Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report: second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *Ann Emerg Med*. 2006;47:373–380.
- [2] Decker WW, Campbell RL, Manivannan V, et al. The etiology and incidence of anaphylaxis in Rochester, Minnesota: a report from the Rochester Epidemiology Project. *J Allergy Clin Immunol*. 2008;122:1161–1165.
- [3] Sheikh A, Hippisley-Cox J, Newton J, Fenty J. Trends in national incidence, lifetime prevalence and adrenaline prescribing for anaphylaxis in England. *J R Soc Med*. 2008;101:139–143.
- [4] Tejedor-Alonso M, Moro-Moro M, Mosquera Gonzales M, et al. Increased incidence of admissions for anaphylaxis in Spain 1998–2011. *Allergy*. 2015;70:880–883.
- [5] Turner P, Gowland M, Sharma V, et al. Increase in anaphylaxis-related hospitalizations but no increase in fatalities: an analysis of United Kingdom national anaphylaxis data, 1992–2012. *J Allergy Clin Immunol*. 2015;135:956–963.
- [6] Mullins RJ. Anaphylaxis: risk factors for recurrence. *Clin Exp Allergy*. 2003;33:1033–1040.
- [7] Gold MS, Sainsbury R. First aid anaphylaxis management in children who were prescribed an epinephrine autoinjector device (EpiPen). *J Allergy Clin Immunol*. 2000;106:171–176.
- [8] Kemp SF, Lockey RF, Wolf BL, Lieberman P. Anaphylaxis: a review of 266 cases. *Arch Intern Med*. 1995;155:1749–1754.
- [9] Melton LJ III. History of the Rochester Epidemiology Project. *Mayo Clin Proc*. 1996;71:266–274.
- [10] Rocca WA, Yawn BP, St Sauver JL, Grossardt BR, Melton LJ III. History of the Rochester Epidemiology Project: half a century of medical records linkage in a US population. *Mayo Clin Proc*. 2012;87:1202–1213.
- [11] St Sauver JL, Grossardt BR, Yawn BP, Melton LJ III, Pankratz JJ, Brue SM. Data resource profile: the Rochester Epidemiology Project (REP) medical records-linkage system. *Int J Epidemiol*. 2012;41:1614–1624.
- [12] St Sauver JL, Grossardt BR, Yawn BP, Melton LJ, Rocca WA. Use of a medical records linkage system to enumerate a dynamic population over time: the Rochester Epidemiology Project. *Am J Epidemiol*. 2011;173:1059–1068.
- [13] Lee S, Hess EP, Lohse CM, Gilani W, Chamberlain AM, Campbell RL. Trends, characteristics and incidence of anaphylaxis in 2001–2010: a population study [published online June 4, 2016]. *J Allergy Clin Immunol*. <http://dx.doi.org/10.1016/j.jaci.2016.04.029>.
- [14] Harris PT, Thielke R, Payne R, Gonzalez J, Conde NJ. Research Electronic Data Capture (REDCap): a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42:377–381.
- [15] Vetander ML, Hakansson N, Lilja G, et al. Recurrent reactions to food among children at paediatric emergency departments. *Clin Exp Allergy*. 2013;44:113–120.
- [16] Sampson H. Anaphylaxis and Emergency Treatment. *Pediatrics*. 2003;111:1601–1608.
- [17] Simons FE. Epinephrine auto-injectors: first-aid treatment still out of reach for many at risk of anaphylaxis in the community. *Ann Allergy Asthma Immunol*. 2009;102:403–409.
- [18] Manassis K. Managing anxiety related to anaphylaxis in childhood: a systematic review. *J Allergy*. 2012;2012:316296.
- [19] Sampson HA, Munoz-Furlong A, Bock SA, et al. Symposium on the definition and management of anaphylaxis: summary report. *J Allergy Clin Immunol*. 2005;115:584–591.
- [20] Lieberman P, Nicklas RA, Oppenheimer J, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. *J Allergy Clin Immunol*. 2010;126:477–480.e1–42.

Anaphylaxis is highly likely when any 1 of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST 1 OF THE FOLLOWING:
 - a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
 - b. Reduced blood pressure [BP] or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a *likely* allergen for that patient (minutes to several hours)
 - a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
 - b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
 - d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to *known* allergen for that patient (minutes to several hours)
 - a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
 - b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

eFigure 1. The National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network criteria. Reprinted with permission from Sampson et al¹.

eTable 1

Summary of Inciting Triggers and Details of Signs and Symptoms at Index Date of Anaphylaxis in 611 Patients

Feature	No. (%) of patients
Food inciting allergen (N = 211) ^a	
Peanut	51 (24)
Tree nut	40 (19)
Fruit or vegetable	31 (15)
Wheat	2 (1)
Shellfish	30 (14)
Milk	2 (1)
Fish	10 (5)
Soy	3 (1)
Egg	14 (7)
Other	28 (13)
Medication inciting allergen (N = 128)	
Aspirin	13 (10)
Other NSAID	13 (10)
Antibiotics	45 (35)
General anesthetic	7 (5)
Chemotherapy medication	6 (5)
Other	44 (34)
Venom inciting allergen (N = 145)	
Bee	112 (77)
Wasp	21 (14)
Other	12 (8)
Allergist saw patient after index anaphylaxis	289 (47)
Inciting allergen identified by allergist (N = 289)	213 (74)
Allergy tests performed (N = 608)	217 (36)
Mucocutaneous symptom	
Diffuse urticarial	238 (39)
Local angioedema	143 (23)
Oral pruritus	21 (3)
Pruritus	97 (16)
Flushing	92 (15)
Local urticarial	172 (28)
Conjunctivitis	6 (1)
Oropharyngeal edema	51 (8)
Diffuse angioedema	25 (4)
Diaphoresis	12 (2)
Chemosis/edema ocular conjunctiva	31 (5)
Tightness or fullness of throat	223 (37)
Rhinitis	15 (2)
Any of above	594 (97)
Gastrointestinal tract symptom	
Emesis	71 (12)
Nausea	46 (8)
Abdominal cramping	30 (5)
Diarrhea	21 (3)
Any of above	121 (20)
Cardiovascular symptom	
Presyncope/lightheadedness	98 (16)
Chest pain	96 (16)
Hypotension	49 (8)
Arrhythmia	1 (<1)
Syncope	34 (6)
Orthostatic hypotension	5 (1)
Any of above	222 (36)
Respiratory tract symptom	
Dyspnea/difficulty breathing	411 (67)
Wheezing/bronchospasm	97 (16)
Cough	34 (6)
Hoarseness/raspy voice	52 (9)
Cyanosis	13 (2)
Stridor	8 (1)
Aphonia	2 (<1)
Any of above	482 (79)

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

^aSample sizes for features with missing data or for subsets of interest are indicated.**eTable 2**

Summary of Inciting Triggers, Signs, and Symptoms at Recurrence in 60 Patients

Feature	No. (%) of patients
Food inciting allergen (N = 20) ^a	
Peanut	2 (10)
Tree nut	1 (5)
Fruit or vegetable	4 (20)
Shellfish	2 (10)
Milk	1 (5)
Fish	1 (5)
Other	9 (45)
Medication inciting allergen (N = 5)	
Other	5 (100)
Venom inciting allergen (N = 7)	
Bee	5 (71)
Wasp	2 (29)
Mucocutaneous symptom	
Diffuse urticarial	17 (28)
Local angioedema	20 (33)
Oral pruritus	5 (8)
Pruritus	26 (43)
Flushing	12 (20)
Local urticarial	1 (2)
Conjunctivitis	0
Oropharyngeal edema	13 (22)
Diffuse angioedema	0
Diaphoresis	1 (2)
Chemosis/edema ocular conjunctiva	1 (2)
Tightness or fullness of throat	17 (28)
Rhinitis	0
Any of above	57 (95)
Gastrointestinal tract symptom	
Emesis	8 (13)
Nausea	4 (7)
Abdominal cramping	2 (3)
Diarrhea	1 (2)
Any of above	12 (20)
Cardiovascular symptom	
Presyncope/lightheadedness	15 (25)
Chest pain	15 (25)
Hypotension	1 (2)
Arrhythmia	0
Syncope	5 (8)
Orthostatic hypotension	1 (2)
Any of above	30 (50)
Respiratory tract symptom	
Dyspnea/difficulty breathing	37 (62)
Wheezing/bronchospasm	7 (12)
Cough	10 (17)
Hoarseness/raspy voice	8 (13)
Cyanosis	0
Stridor	4 (7)
Aphonia	0
Any of above	39 (65)

^aSample sizes for features with missing data or for subsets of interest are indicated.