

Original Article

Anaphylaxis among elderly emergency department patients in a large health system in New York



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ABSTRACT

Background: Anaphylaxis in the elderly is poorly understood.

Objective: To elucidate demographic, clinical, and management characteristics of older adults presenting to emergency departments (EDs) with National Institute of Allergy and Infectious Diseases (NIAID) criteria-confirmed anaphylaxis vs milder, non-anaphylactic acute allergic reactions (AARs).

Methods: A retrospective analysis of ED patients more than or equal to 65 years was conducted, using anaphylaxis International Classification of Diseases, Ninth Revision (ICD-9) codes or ICD-9–based algorithms incorporating the NIAID diagnostic criteria. Descriptive statistics were generated, and the abovementioned characteristics were compared between cohorts.

Results: Of 164 eligible visits, 71 (43.3%), 90 (54.9%), and 3 (1.8%) cases were identified by ICD-9 codes, the algorithms, or both, respectively. Only half fulfilled NIAID diagnostic criteria. Compared with the non-anaphylactic AAR group, criteria-confirmed anaphylaxis group had lower drug allergy rates (43.9% vs 61.0%, $P = .03$) but higher food allergy rates (26.8% vs 12.2%, $P = .02$). For the criteria-confirmed anaphylaxis group, presenting signs and symptoms in descending frequency were mucocutaneous, respiratory, cardiovascular, and gastrointestinal. Criteria-confirmed anaphylaxis group had higher rates of prior anaphylaxis (13.4% vs 2.4%, $P = .009$), pre-ED (12.2% vs 0.0%, $P = .001$) or ED (72.0% vs 4.9%, $P < .001$) epinephrine administration, and allergy referral (17.1% vs 2.4%, $P = .002$). Tryptase levels were rarely ordered, occurring once in the criteria-confirmed anaphylaxis group and never in the non-anaphylactic AAR group. Despite low mortality ($n = 1$), 64.6% of the criteria-confirmed anaphylaxis cohort required hospitalization, with 23.2% admitted to intensive care unit.

Conclusion: Diagnosis of elderly ED patients with anaphylaxis remains suboptimal. Identifying NIAID criteria-confirmed cases remain challenging, using the existing methods. Management of these patients poorly adheres to current guidelines.

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Introduction

The impact of anaphylaxis, a potentially lethal allergic reaction that requires immediate diagnosis and treatment, continues to grow.^{1–4} In

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the United States, recent estimates suggest an anaphylaxis incidence rate of approximately 42 per 100,000 person-years, with lifetime prevalence between 1.6% and 5.1%.^{1–6} However, exact anaphylaxis incidence and prevalence are difficult to determine owing to the lack of universal agreement on diagnostic criteria and suboptimal detection of anaphylaxis in health care data.^{7–10} Although prevalence and hospitalization rates may be increasing, anaphylaxis is rarely fatal.^{1,10–12}

Anaphylaxis is a clinical diagnosis that relies on the clinician recognizing key findings in the history and clinical presentation in a timely manner. Unfortunately, clinicians, regardless of training level, consistently demonstrate difficulty in recognizing, diagnosing, and

managing anaphylaxis.^{13–17} An expert panel, convened in 2005 by the National Institute of Allergy and Infectious Disease (NIAID), defined anaphylaxis as 1 of the following 3 clinical scenarios: (1) acute onset of a reaction with involvement of the skin, mucosal tissue, or both and at least 1 of the following: (a) respiratory compromise or (b) reduced blood pressure or symptoms of end-organ dysfunction; (2) 2 or more of the following that occur rapidly after exposure to a likely allergen for that patient: involvement of the skin or mucosal tissue, respiratory compromise, reduced blood pressure or associated symptoms, or persistent gastrointestinal symptoms; or (3) reduced blood pressure—after exposure to a known allergen.¹⁸ This definition has been validated prospectively and retrospectively, demonstrating high sensitivity and negative predictive value (both >95%).^{19,20} However, it is not universally accepted or routinely used in clinical practice or research.^{1–3,10,21–23} Optimal patient outcomes require timely treatment with intramuscular epinephrine. Because appropriate management is predicated on correct diagnosis, suboptimal recognition of anaphylaxis leads to delays in treatment, including but not limited to underutilization or incorrect dosing of epinephrine and use of second-line agents.^{1,24–29}

The elderly constitute an understudied, vulnerable population for whom anaphylaxis is considered infrequently, despite presenting with concerning signs and symptoms.^{30–37} We recently published that anaphylaxis hospitalization rates increased substantially among the elderly who were hospitalized in New York State (NYS) from 2000 to 2010 using data from the NYS Department of Health State-wide Planning and Research Cooperative System administrative database.³⁶ Almost half (46.3%) of probable anaphylaxis cases who met the NIAID anaphylaxis criteria were undiagnosed by clinicians, and those aged 85 years or older were less likely to be diagnosed with anaphylaxis despite the presence of symptoms consistent with the diagnosis.³⁶ Using cross-sectional analyses of nationally representative samples of US population, others have shown that older adults aged 65 years or older had higher anaphylaxis-related hospitalization rates compared with younger adults and that anaphylaxis-related emergency department (ED) visits and hospitalizations have increased from 2006 to 2014.³⁷ The available literature suggests that the elderly have higher rates of serious anaphylaxis, requiring more intensive treatment or resulting in death, regardless of cause.^{3,12,23,35,38,39} Severe anaphylaxis, requiring hospital or intensive care unit (ICU) admission or intubation or experiencing a near fatal reaction, is highly associated with age 65 years or older, presence of cardiac or lung disease, and medication-induced anaphylaxis.³⁸ Overall, frailty, polypharmacy, comorbidities, and less robust physiological compensatory mechanisms contribute to this increased risk for poor outcomes.^{23,34,36,38,39} Our previous work also suggested that older age, male sex, and being non-White or unknown race were associated with increased risk of not being diagnosed with anaphylaxis in an inpatient setting even when symptoms consistent with the NIAID anaphylaxis criteria were present.³⁶ Equally troubling, the limited data show that clinicians are less likely to prescribe or administer self-injectable epinephrine to elderly patients presenting with anaphylaxis to the ED.^{12,31,37,39–44}

This current work explored anaphylaxis among elderly patients presenting to the EDs of a large multihospital health care system. Our objective was to elucidate the demographic, clinical, and management characteristics of older adults presenting to EDs with NIAID criteria-confirmed anaphylaxis vs milder, non-anaphylactic acute allergic reactions (AARs).

Methods

Design and Study Population

A retrospective cohort study that included all adults aged 65 years or more who presented to the ED of any hospital

belonging to the Northwell Health System from January 1, 2016, to December 31, 2017, was performed. By using retrospective chart review, we aimed to circumvent inherent limitations in data accuracy, which are predicated on well-documented clinician deficiencies in recognizing and diagnosing anaphylaxis and shortcomings in how medical records capture the information.^{1,2,8–10,12,14–16,31,39,41–44}

Northwell Health is the largest healthcare provider in NYS, with 23 hospitals, spanning the gamut with community hospitals and tertiary academic medical centers, serving racially, socioeconomically diverse communities in the metro New York City area, including Long Island and Westchester County. These catchment areas include urban, suburban, and rural settings. The study was approved by the Northwell Health Institutional Review Board with a waiver of informed consent.

Case Ascertainment

Electronic medical records (EMRs) of adult ED patients aged 18 years or older who presented to any Northwell ED during the study period were queried by the Northwell Health Research Informatics team. To identify the elderly, this query was filtered by age 65 years or older. There were 2 complementary query methods utilized to identify anaphylaxis cases to maximize case ascertainment in this elderly target group.⁴⁵ The International Classification of Diseases, Ninth Revision (ICD-9)—derived method utilized 995.0 (other anaphylactic reaction) or 995.60 to 995.69 (anaphylactic shock because of food and other triggers). The algorithm-derived method used validated algorithms in identifying cases fulfilling the NIAID criteria for anaphylaxis which were likely missed and not coded by physicians. Thus, the algorithm method helps circumvent potential physician-dependent deficiencies that lead to under-recognizing or under-diagnosing anaphylaxis. Because the algorithm method was originally validated using ICD-9 codes, we used ICD-9 codes in this study even though the United States had transitioned to International Classification of Diseases, Tenth Revision, before this study started.⁴⁵ Using the International Classification of Diseases, Tenth Revision, codes to query the EMR resulted in the same number of cases (data not shown). The algorithm method identifies a potential anaphylaxis case if respiratory compromise or skin or mucosal involvement was found in conjunction with shock owing to anesthesia; respiratory compromise or reduced blood pressure level was found in conjunction with skin or mucosal involvement; or a combination of gastrointestinal symptoms, respiratory compromise, reduced blood pressure level, or skin/mucosal involvement was found in conjunction with a potential allergen (including venom, drug, food, or a biological substance).⁴⁵ A total of 20 algorithms were applied to the elderly cohort (eTable 1). These algorithms enabled the identification of likely missed cases of anaphylaxis in the elderly population. The number of cases that were identified by both methods was also calculated ($N = 3$).

There were 2 research fellows who reviewed eligible medical records using a standardized data abstraction tool adapted from the literature.^{7,8} The abstracted data were entered into Research Electronic Data Capture database. To assess inter-rater reliability between the 2 fellows, 10% ($N = 16$) of the eligible cases were randomly chosen and reviewed independently by both fellows at study start. The 2 research fellows demonstrated high inter-rater reliability (Cohen's kappa ≥ 0.8 , data not shown). The rest of the eligible cases ($N = 148$) were divided equally among the 2 fellows who abstracted the data independently. All records were reviewed by a board-certified allergist-immunologist. Any discrepancies were discussed and adjudicated together with the allergist.

Data Variables

Data were collected for subject demographic characteristics, comorbidities, suspected causes, timing of symptom onset, presenting signs and symptoms, medications administered before and during ED arrival, emergency medical services management, ED management, ED disposition, ED follow-up, and incidence of biphasic reactions. Any of the 164 cases that met the NIAID criteria was considered criteria-confirmed anaphylaxis, whereas those that did not were considered non-anaphylactic AARs.

Statistical Analysis

Descriptive statistics utilizing frequencies and percentages were generated. The χ^2 or Fisher exact tests were used to test the association between demographic or clinical or management variables and group membership. A log binomial regression model was used to identify independent risk factors of having criteria-confirmed anaphylaxis. An observed *P* value of less than .05 was considered significant. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, North Carolina).

Results

Ascertainment of Anaphylaxis Cases

As Figure 1 shows, of 47,793 adult ED visits during the study period, 164 (0.3%) visits were from elderly patients aged 65 years or older who were diagnosed with having an anaphylaxis ICD-9 code or identified using one of the algorithms. These 164 visits consisted of 153 unique patients, 3 of whom had 3 visits, 5 of whom had 2 visits, and the remainder only with 1 visit over the study period. None of the patients with multiple visits were repeat visits to the ED up to 72 hours after the initial visit. There were no biphasic reactions. There were 71 (43.3%), 90 (54.9%), and 3 (1.8%) cases identified by the ICD-9 codes, algorithms, and

both, respectively. eTable 2 lists the distribution of subjects by case ascertainment. Less than half (43.3%) of the cases were recognized by ED physicians and assigned an ICD-9 anaphylaxis code. More than half (54.9%) were identified by one of the algorithms, suggesting these could represent missed cases.

To assess the accuracy of case ascertainment, in-depth chart review of the 164 visits showed that 82 (50.0%) cases met the NIAID criteria regardless of ascertainment method. The remainder comprised milder non-anaphylactic AARs. The data were analyzed further to better understand the demographic, clinical, and management characteristics of these elderly ED patients with diverse allergic reactions.

Characteristics of the Cohorts

The median age for the sample and the 2 cohorts was 75.0 years (interquartile range 69–81 for the sample, 69–81 for the criteria-confirmed anaphylaxis group, 69–82 for the non-anaphylactic AAR group). Table 1 summarizes the demographic characteristics. The racial composition of the 2 cohorts differed (*P* = .03); the criteria-confirmed anaphylaxis group had fewer Whites (52.4% vs 62.2%). The 2 groups also differed by ascertainment method (*P* < .001); 74.4% of the criteria-confirmed anaphylaxis group was identified by ICD-9 codes compared with 22.0% using algorithms, whereas 12.2% of the non-anaphylactic AAR group was identified by the ICD-9 codes compared with 87.8% by means of algorithms. The 2 cohorts were comparable in terms of distribution by age group, sex, insurance, and ED type.

Table 2 shows that those with criteria-confirmed anaphylaxis had higher rates of previous anaphylaxis (13.4% vs 2.4%, *P* = .009) and owning an epinephrine autoinjector (EAI) (14.6% vs 0.0%, *P* = .001), although most subjects in either group did not have prior history of anaphylaxis (86.6% vs 97.6%) or owning an EAI (85.4% vs 100.0%), respectively. As expected, the criteria-confirmed anaphylaxis group had a higher proportion of subjects presenting with

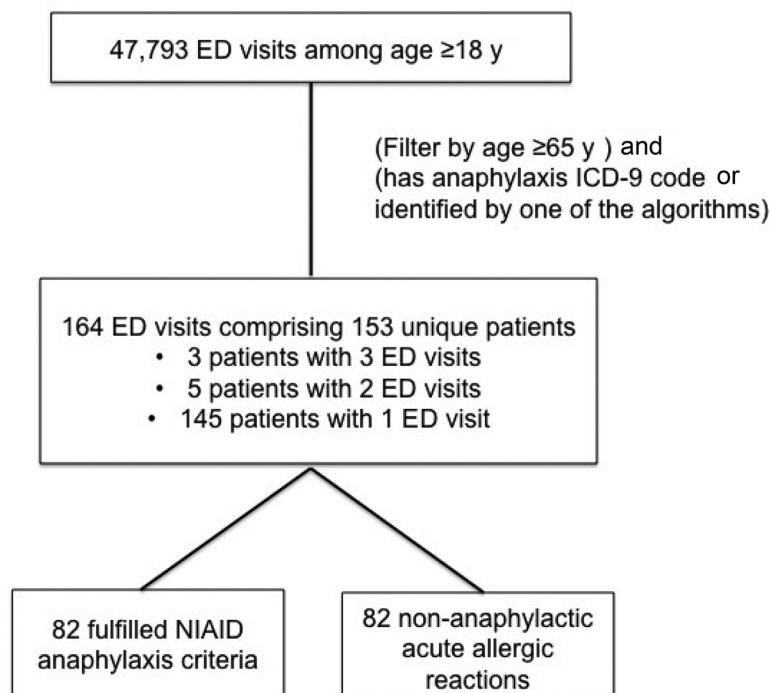


Figure 1. Case ascertainment flowchart. ED, emergency department; ICD-9, International Classification of Diseases, Ninth Version; NIAID, National Institute of Allergy and Infectious Disease.

Table 1
Sample Demographics (N = 164)

Characteristic	Total sample (N = 164)	Anaphylaxis (N = 82)	Non-anaphylactic acute allergic reaction (N = 82)	P value
Age group (y)				NS ^a
Early old (65–74)	80	41 (50.0)	39 (47.6)	
Middle old (75–84)	58	31 (37.8)	27 (32.9)	
Late old (≥ 85)	26	10 (12.2)	16 (19.5)	
Sex				NS ^a
Female	102	50 (61.0)	52 (63.4)	
Male	62	32 (39.0)	30 (36.6)	
Race				.03 ^a
African American	34	14 (17.1)	20 (24.4)	
Other ^b	36	25 (30.5)	11 (13.4)	
White	94	43 (52.4)	51 (62.2)	
Insurance type				NS ^a
Commercial	4	2 (2.4)	2 (2.4)	
Governmental	160	80 (97.6)	80 (97.6)	
ED type				NS ^a
Community	48	21 (25.6)	27 (32.9)	
Tertiary	116	61 (74.4)	55 (67.1)	
Ascertainment method				<.001 ^a
Algorithm	90	18 (22.0)	72 (87.8)	
ICD-9	71	61 (74.4)	10 (12.2)	
Mixed	3	3 (3.6)	0 (0.0)	

Abbreviations: ED, emergency department; ICD-9, International Classification of Diseases, Ninth Revision; NS, not significant.

^aχ² test.

^bOther = Asian or declined or unknown or not specified.

more than one organ system involved (92.7% vs 7.3%, $P < .001$). Those with criteria-confirmed anaphylaxis had lower rates of having asthma (17.1% vs 37.8%, $P = .003$), but most subjects in both groups did not have asthma (82.9% vs 62.2%). The distribution of suspected trigger types differed between the 2 cohorts ($P < .001$); for the criteria-confirmed anaphylaxis, medications were the most common trigger (37.8%) but only second for the non-anaphylactic AAR group (26.8%). eTable 3 summarizes the 43 identifiable medication triggers found in the criteria-confirmed anaphylaxis group compared with 21 in the non-anaphylactic AAR group; the most frequently identified medication trigger was radiocontrast (14.6%) and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (13.4%) for the 2 groups, respectively.

Table 3 demonstrates that drug allergy was common in both groups, but subjects with criteria-confirmed anaphylaxis had lower

rates (43.9% vs 61.0%, $P = .03$). eTable 4 demonstrates the 51 drug allergens reported in the criteria-confirmed anaphylaxis cohort compared with 79 in the non-anaphylactic AAR cohort; antibiotics were the most frequent drug allergen in both groups (22.0% vs 34.1%, respectively). Having food allergy was the second most reported allergy, with higher rate among the criteria-confirmed anaphylaxis group (26.8% vs 12.2%, $P = .02$). eTable 5 summarizes the 28 food allergens reported in the criteria-confirmed anaphylaxis group compared with 16 in the non-anaphylactic AAR group; shellfish was the most common food allergen (11.0% vs 9.8%) in both cohorts. Having allergies to aeroallergens (0.0% vs 3.6%), latex (1.2% vs 3.6%), or venom (2.4% vs 0.0%) was rare.

eTable 6 tabulates the 279 non-allergic comorbidities in the criteria-confirmed anaphylaxis group compared with 362 in the non-anaphylactic AAR group; cardiovascular conditions were the most reported (79.3% vs 87.8.9%) in both groups.

Table 4 summarizes the presenting signs and symptoms. Because a subject can present with multiple signs and symptoms, these characteristics are not mutually exclusive. For those with criteria-confirmed anaphylaxis group, the frequency of presenting signs and symptoms in descending order was mucocutaneous, respiratory, cardiovascular, and gastrointestinal. For those with non-anaphylactic AARs, the symptom breakdown in descending order was cardiovascular, mucocutaneous, respiratory, and gastrointestinal. Angioedema (58.5% vs 26.8%), dyspnea (58.5% vs 13.4%), and nausea (18.3% vs 11.0%) were the most common presenting mucocutaneous, respiratory, and gastrointestinal symptoms, respectively. Hypotension (28.0%) was the most common cardiovascular symptom for the criteria-confirmed anaphylaxis group compared with syncope (15.9%) for the non-anaphylactic AAR group.

Patient Management and Follow-up

Table 5 highlights notable differences in ED management and follow-up. Those with criteria-confirmed anaphylaxis had higher rates of pre-ED (12.2% vs 0.0%, $P = .001$) and ED (72.0% vs 4.9%, $P < .001$) epinephrine administration. The frequency of ED-administered epinephrine doses was similar; 1 dose was most common (69.5% vs 75.0%). In addition, those with criteria-confirmed anaphylaxis had higher rates of ED observation for at least 6 hours (69.5% vs 4.9%, $P < .001$) and being discharged with an EAI (34.1% vs 0.0%, $P < .001$). Although the criteria-confirmed anaphylaxis group had higher allergy referral rate for further evaluation (17.1% vs 2.4%, $P = .002$), referrals rarely occurred in both groups. Subjects with criteria-

Table 2
Sample Clinical Characteristics (N = 164)

Characteristic	Total sample (N = 164)	Anaphylaxis (N = 82)	Non-anaphylactic acute allergic reaction (N = 82)	P value
Prior anaphylaxis				.009 ^a
Yes	13	11 (13.4)	2 (2.4)	
No	151	71 (86.6)	80 (97.6)	
Had own autoinjector				.001 ^a
Yes	12	12 (14.6)	0 (0.0)	
No	152	70 (85.4)	82 (100.0)	
Suspected trigger type				<.001 ^a
Intravenous contrast	12	12 (14.6)	0 (0.0)	
Drug	53	31 (37.8)	22 (26.8)	
Food	30	27 (32.9)	3 (3.6)	
Venom	6	6 (7.3)	0 (0.0)	
Unknown	11	6 (7.3)	5 (6.1)	
Not applicable	52	0 (0.0)	52 (63.4)	
Presented with 1 system involvement				<.001 ^a
Yes	82	76 (92.7)	6 (7.3)	
No	82	6 (7.3)	76 (92.7)	
Has asthma				.003 ^a
Yes	45	14 (17.1)	31 (37.8)	
No	119	68 (82.9)	51 (62.2)	

^aχ² test.

Table 3
Comparison of Comorbid Allergies (N = 164)

Characteristic	Total sample (N = 164)	Anaphylaxis (N = 82)	Non-anaphylactic acute allergic reaction (N = 82)	P value
Drug allergy				.03 ^a
Yes	86	36 (43.9)	50 (61.0)	
No	78	46 (56.1)	32 (39.0)	
Food allergy				.02 ^a
Yes	32	22 (26.8)	10 (12.2)	
No	132	60 (73.2)	72 (87.8)	
Aeroallergens allergy				NS ^b
Yes	3	0 (0.0)	3 (3.6)	
No	161	82 (100.0)	79 (96.3)	
Latex allergy				NS ^b
Yes	4	1 (1.2)	3 (3.6)	
No	160	81 (98.2)	79 (96.3)	
Venom allergy				NS ^b
Yes	2	2 (2.4)	0 (0.0)	
No	162	80 (97.6)	82 (100.0)	

Abbreviations: NS, not significant.

^aχ² test.

^bFisher exact test.

Table 4
Comparison of Presenting Signs and Symptoms^a

Characteristic	Total sample (N = 164)	Anaphylaxis (N = 82)	Non-anaphylactic acute allergic reaction (N = 82)
	N	N (%)	N (%)
Mucocutaneous			
Flushing	21	21 (25.6)	0 (0.0)
Pruritus	33	31 (37.8)	2 (2.4)
Diffuse urticaria	34	24 (29.3)	10 (12.2)
Angioedema	70	48 (58.5)	22 (26.8)
Gastrointestinal			
Emesis	0	0 (0.0)	0 (0.0)
Abdominal pain	7	6 (7.3)	1 (1.2)
Nausea	24	15 (18.3)	9 (11.0)
Diarrhea	1	0 (0.0)	1 (1.2)
Respiratory			
Cough	9	7 (8.5)	2 (2.4)
Voice change	15	15 (18.3)	0 (0.0)
Dyspnea	59	48 (58.5)	11 (13.4)
Wheezing	22	22 (26.8)	0 (0.0)
Cyanosis	2	2 (2.4)	0 (0.0)
Stridor	3	3 (3.7)	0 (0.0)
Hypoxemia	11	11 (13.4)	0 (0.0)
Cardiovascular			
Hypotension	24	23 (28.0)	1 (1.2)
Chest pain	10	1 (1.2)	9 (11.0)
Presyncope	27	15 (18.3)	12 (14.6)
Syncope	25	12 (14.6)	13 (15.9)

^aCharacteristics are not mutually exclusive.

confirmed anaphylaxis had lower rate of exposure to an identifiable allergen (22.0% vs 36.6%, $P = .04$). Tryptase was rarely checked; it was drawn in only 1 subject in the criteria-confirmed anaphylaxis group

Table 5
Patient Management and Follow-up (N = 164)

Characteristic	Total sample	Anaphylaxis (N = 82)	Non-anaphylactic acute allergic reaction (N = 82)	P value
Given epinephrine before ED				.001 ^a
Yes	10	10 (12.2)	0 (0.0)	
No	154	72 (87.8)	82 (100.0)	
Disposition				NS ^a
CCU or ICU	29	19 (23.2)	10 (12.2)	
Non ICU ^b	71	34 (41.5)	37 (45.1)	
Deceased	1	1 (1.2)	0 (0.0)	
Discharged	63	28 (34.1)	35 (42.7)	
Exposed to identifiable allergen				.04 ^a
Yes	48	18 (22.0)	30 (36.6)	
No	116	64 (78.0)	52 (63.4)	
Repeat visit				<.001 ^a
Not applicable	82	0 (0.0)	82 (100.0)	
No	82	82 (100.0)	0 (0.0)	
Epinephrine administered in ED				<.001 ^a
Yes	63	59 (72.0)	4 (4.9)	
No	101	23 (28.0)	78 (95.1)	
Frequency of epinephrine doses		N = 59	N = 4	NS ^a
1	44	41 (69.5)	3 (75.0)	
2	16	15 (25.4)	1 (25.0)	
3	3	3 (5.1)	0 (0.0)	
Observed for at least 6 h				<.001 ^a
Yes	61	57 (69.5)	4 (4.9)	
No	101	25 (30.5)	78 (95.1)	
Referred to allergy				.002 ^a
Yes	16	14 (17.1)	2 (2.4)	
No	148	68 (82.9)	80 (96.6)	
Tryptase checked				NS ^c
Yes	1	1 (1.2)	0 (0.0)	
No	163	81 (98.8)	82 (100.0)	
Discharged with epinephrine autoinjector				<.001 ^a
Yes	28	28 (34.1)	0 (0.0)	
No	136	54 (65.9)	82 (100.0)	

Abbreviations: ED, emergency department; CCU, critical care unit; CDU, clinical decision unit; ICU, intensive care unit; NS, not significant.

^a χ^2 test.^bNon ICU, non-ICU floor or stepdown unit or CDU.^cFisher exact test.

and never in the non-anaphylactic AAR group. Disposition was comparable for the 2 groups. There was only 1 death in the entire sample which occurred in the criteria-confirmed anaphylaxis group (1.2% vs 0.0%). Despite low mortality rate, only 34.1% of the criteria-confirmed anaphylaxis cohort was discharged from the ED, whereas 64.6% required hospitalization, with 23.2% admitted to the ICU. For the non-anaphylactic AAR group, 42.7% were discharged from the ED, whereas 57.3% required hospitalization, with 12.2% requiring ICU care.

Correlates of Criteria-Confirmed Anaphylaxis

In an attempt to identify potential correlates of being diagnosed with criteria-confirmed anaphylaxis, all variables that had a P value of less than .20 in the bivariate analyses were considered in log binomial modeling to estimate the relative risk of having criteria-confirmed anaphylaxis. Only 1 variable, “had more than 1 system involvement,” which is encompassed by the NIAID criteria, remained in the final model, demonstrating that having multisystem involvement is 12.7 times more likely to result in criteria-confirmed anaphylaxis (risk ratio, 12.70; 95% confidence interval, 5.85–27.43).

Discussion

Data on the characteristics, management, and follow-up of anaphylaxis in elderly patients remain limited. This current work adds to the growing body of literature which shows that anaphylaxis occurs

in this vulnerable population and that clinicians continue to under-recognize and under-diagnose anaphylaxis despite the presence of signs and symptoms consistent with the diagnosis.^{30–37} The available data suggest that anaphylaxis ED visits and hospitalizations among the elderly are increasing.^{36,37} More research is needed to clarify whether this observation is the result of an increase in true anaphylaxis prevalence or improved awareness among clinicians and patients or a combination of these factors. Identifying cases that meet the NIAID criteria remains challenging, even when using complementary approaches for case ascertainment. This study found that the ICD-9 approach identified 74.4% (78.0% if the 3 subjects identified by both approaches are included) of criteria-confirmed anaphylaxis, whereas the algorithms only identified 22.0%. Our finding disagrees with prior studies showing that the algorithms could be a useful tool in estimating the number of potential missed anaphylaxis cases that are not being coded by clinicians and that the algorithms are more likely to identify older subjects compared with ICD-9 coding.^{36,45} A potential reason for this discrepancy is that prior studies were unable to verify the accuracy of diagnosis and case ascertainment without access to the medical record. Performing in-depth medical record review can help mitigate the bias and potential confounding arising from suboptimal coding accuracy in studies relying on claims or administrative data.^{8,9,46} Innovative, multipronged approaches are still needed to improve clinician recognition and diagnosis of anaphylaxis, which are prerequisites to enhancing case ascertainment and data accuracy.

Some of the demographic characteristics of our patients in the criteria-confirmed anaphylaxis group, such as age category and insurance status, did not match what has been published previously in other studies of elderly ED patients.^{27,31} Differences in inclusion criteria, ascertainment methods, and study populations probably account for these discrepancies.¹¹

History of previous anaphylaxis was rare in our sample, but more frequent among those with criteria-confirmed anaphylaxis (13.4% vs 2.4%). This observation has not been reported specifically in the elderly but is a known risk factor for subsequent anaphylaxis in children with food allergy.^{47,48} Comorbid asthma was uncommon in our sample but more frequent among those with non-anaphylactic AARs (17.1% vs 37.8%). History of asthma is associated with higher likelihood of a recurrent anaphylaxis-related ED visit within 1 year.³⁸ Whether this holds true for older adults remains to be seen.

Among our subjects, drug allergy, specifically to antibiotics, was the most common atopic comorbidity, but the criteria-confirmed anaphylaxis cohort had a lower rate (43.9% vs 61.0%). Similar to other reports, medications, particularly radiocontrast and antibiotics, were the most frequently identified triggers in our sample.^{23,31,34,37} Food allergy was the second most common allergic comorbidity in our sample, with shellfish being the most frequently reported allergen. Venom allergy, which was found to be the most common anaphylaxis trigger in the European Anaphylaxis Registry, was rare in our subjects, likely because venom allergy and resulting anaphylaxis are infrequent in the Northeast United States from which our sample is drawn.⁴⁹

Cardiovascular comorbidities were the most observed non-atopic comorbidity in our sample (79.3% vs 87.8%), which is unsurprising given the burden of cardiovascular disease in the elderly.⁵⁰ Although the presentation of anaphylaxis appears to differ depending on the population studied, cardiovascular signs and symptoms seem to predominate among the elderly.^{23,31,34,37} In contrast, mucocutaneous signs and symptoms were the most common presentation in our criteria-confirmed anaphylaxis cohort; cardiovascular symptoms ranked third with hypotension being the most frequent presentation. Older adults may be less able to manifest compensatory responses to anaphylaxis owing to underlying cardiovascular disease and medication use, such as beta blockers.^{30,34,51–53} In addition, managing shock in the elderly is challenging because of cardiovascular complications,

such as heart failure, that limit resuscitation with fluid administration or medications.^{30,34,52,53}

Although mortality owing to anaphylaxis appears to be low, other surrogates of severity, such as hospitalization or higher level of care or intervention, are reported to be increased among older adults drawn from different populations.^{7,10,12,23,31,35–37,54} Compared with children or younger adults, the elderly score poorly when anaphylaxis severity scoring systems are applied.^{23,54} Despite a low mortality rate (1.2%), 64.6% of our criteria-confirmed anaphylaxis cohort required hospitalization, with 23.2% requiring critical care unit or ICU level of care. Our observations corroborate previous studies demonstrating that the elderly are more likely to be hospitalized or experience severe anaphylaxis.^{23,52,55} This may be explained by comorbidities, atypical clinical presentation, delayed epinephrine administration, or adverse effects of epinephrine.^{23,37,55,56} Drug-related triggers, having a chronic medical condition, and older age are all consistently associated with severity and death, even after controlling for confounders.^{7,12,34,37,52} Larger studies of diverse populations are needed to investigate this further, so that specifically targeted interventions can be developed to improve outcomes in the elderly.

Current guidelines recommend the use of intramuscular epinephrine as first-line treatment of anaphylaxis.¹ Our findings underscore the continuing undertreatment of anaphylaxis in various settings, such as pre-ED and ED, and the need to develop effective educational interventions to improve clinician recognition, diagnosis, and adherence to evidence-based guidelines and best practices.^{10,15,17,21,26–29} It is unclear how much of these deficiencies are because of under-recognition and underdiagnosis vs undertreatment or some combination of these factors. Although older adults are less likely to be prescribed EAI after presenting to the ED,³¹ no difference has been reported in epinephrine-dispensing patterns between the sexes in the elderly population.⁴⁶ There are sparse data on whether older adults are at increased risk of adverse cardiac events from epinephrine, and more research is needed to determine what risk factors might predispose the elderly to such adverse outcomes.^{31,34,51,56}

Our modeling showed that having multisystem organ involvement was the only predictor of criteria-confirmed anaphylaxis. This is unsurprising because the NIAID criteria embody this. Unfortunately, none of the other demographic or clinical or management variables reached statistical significance. Because tryptase was not routinely drawn, we could not evaluate whether this is a useful biomarker or correlate for anaphylaxis among older adults. More research is needed to clarify correlates of anaphylaxis vs milder allergic reactions in this population. Having this information would aid in risk-stratifying patients, which in turn could improve patient outcomes and quality of life.

Our study demonstrates that current anaphylaxis management in the elderly poorly adheres to guidelines, specifically regarding epinephrine administration, observation in the ED for at least 6 hours, discharge with an EAI, and referral to allergist on discharge.⁵⁷ Furthermore, tryptase was checked rarely (only once in the entire data set), even though documenting tryptase elevations can help clarify whether anaphylaxis truly occurred when analyzed after the acute event; when available, this information positively impacts patient management and anticipatory guidance. These deficits affect all patients with anaphylaxis presenting to EDs, but additional studies looking at how to address these concerns specifically among the elderly are required, given the unique characteristics and needs of this vulnerable population. Although the current state of affairs appears bleak, this study serves as an encouraging starting point by outlining the existing knowledge gaps and opportunities for improvement. For example, early studies evaluating the impact of implementing anaphylaxis order sets in the ED show promise, but the effect of these types of multifaceted interventions need to be studied in the elderly specifically.⁵⁸

Study limitations include that it was a retrospective chart review over a 2-year period in a single health care system. Despite the relatively short study period owing to funding constraints, this study adhered to best practices of retrospective chart review.⁵⁹ The information quality of the EMR is a major determinant of the quality of the study, and our health care system's EMR has been used extensively for research and has generated many high quality publications on myriad topics, including geriatric medicine.⁶⁰ In addition, the generalizability of our findings may be limited because the data were drawn from a single health care system. However, the data came from 23 different hospitals, which span the gamut of community hospitals through tertiary care centers that serve the diverse populations of metro New York City. In addition, the expertise and skills of the doctors staffing these EDs are heterogeneous, and hopefully reasonably reflect what occurs outside NYS. Furthermore, we did not formally compare our cohorts to younger adults who presented to the same EDs during the study period or other older adults drawn from different populations. However, our findings generally corroborate what has been reported in the limited literature.

We acknowledge that allergic reactions occur within a spectrum of severity. Our focus on anaphylaxis is not meant to diminish the impact of non-anaphylactic AARs, which are milder but still negatively affect patient outcomes and quality of life. This study is a reminder that current knowledge, attitudes, and practices regarding allergic reactions in the elderly remain suboptimal and that additional, larger studies are needed to address these shortcomings.

Supplementary Data

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.anai.2022.03.020>.

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Supplementary Data

eTable 1

Specific ICD-9 Combinations Used for the Algorithm-Derived Model

Algorithm 1	Skin or mucosal tissue involvement (372.73 or 374.82 or 478.6 or 478.25 or 782.62 or 708 or 708.0 or 708.1–708.5 or 708.8–708.9 or 698 or 698.1 or 698.8 or 698.9) and shock caused by anesthesia (995.4)
Algorithm 2	Respiratory compromise (518.81 or 518.82 or 786 or 786.00–786.09 or 786.1 or 493.0 or 493.9) and shock caused by anesthesia (995.4)
Algorithm 3	Respiratory compromise (518.81 or 518.82 or 786 or 786.00–786.09 or 786.1 or 493.0 or 493.9) and angioneurotic edema (995.1)
Algorithm 4	Reduced blood pressure (458 or 458.0 or 458.2 or 458.8 or 458.9 or 780.2) and angioneurotic edema (995.1)
Algorithm 5	Reduced blood pressure (458 or 458.0 or 458.2 or 458.8 or 458.9 or 780.2) and skin or mucosal involvement (372.73 or 374.82 or 478.6 or 478.25 or 782.62 or 708 or 708.0 or 708.1–708.5 or 708.8–708.9 or 698 or 698.1 or 698.8 or 698.9)
Algorithm 6	Reduced blood pressure (458 or 458.0 or 458.2 or 458.8 or 458.9 or 780.2) and the toxic effect of venom (989.5)
Algorithm 7	Reduced blood pressure (458 or 458.0 or 458.2 or 458.8 or 458.9 or 780.2) and an Ecode indicating the cause of poisoning was a venomous animal or plant (E905 or E905.3 or E905.5 or E905.8 or E905.9)
Algorithm 8	Reduced blood pressure (458 or 458.0 or 458.2 or 458.8 or 458.9 or 780.2) and gastrointestinal symptoms (558.3 or 787.0 or 787.01 or 787.03 or 789.0) and an unspecified adverse effect caused by the correct administration of a drug, medicinal, and biologic substance (995.2) or an unspecified allergic reaction (995.3)
Algorithm 9	Reduced blood pressure (458 or 458.0 or 458.2 or 458.8 or 458.9 or 780.2) and skin or mucosal tissue involvement (372.73 or 374.82 or 478.6 or 478.25 or 782.62 or 708 or 708.0 or 708.1–708.5 or 708.8–708.9 or 698 or 698.1 or 698.8 or 698.9) and an unspecified adverse effect caused by the correct administration of a drug, medicinal, and biologic substance (995.2) or an unspecified allergic reaction (995.3)
Algorithm 10	Respiratory compromise (518.81 or 518.82 or 786 or 786.00–786.09 or 786.1 or 493.0 or 493.9) and reduced blood pressure (458 or 458.0 or 458.2 or 458.8 or 458.9 or 780.2) and an unspecified adverse effect caused by the correct administration of a drug, medicinal, and biologic substance (995.2) or an unspecified allergic reaction (995.3)
Algorithm 11	Respiratory compromise (518.81 or 518.82 or 786 or 786.00–786.09 or 786.1 or 493.0 or 493.9) and gastrointestinal symptoms (558.3 or 787.0 or 787.01 or 787.03 or 789.0) and an unspecified adverse effect caused by the correct administration of a drug, medicinal, and biologic substance (995.2) or an unspecified allergic reaction (995.3)
Algorithm 12	Respiratory compromise (518.81 or 518.82 or 786 or 786.00–786.09 or 786.1 or 493.0 or 493.9) and gastrointestinal symptoms (558.3 or 787.0 or 787.01 or 787.03 or 789.0) and skin or mucosal involvement (372.73 or 374.82 or 478.6 or 478.25 or 782.62 or 708 or 708.0 or 708.1–708.5 or 708.8–708.9 or 698 or 698.1 or 698.8 or 698.9)
Algorithm 13	Respiratory compromise (518.81 or 518.82 or 786 or 786.00–786.09 or 786.1 or 493.0 or 493.9) and gastrointestinal symptoms (558.3 or 787.0 or 787.01 or 787.03 or 789.0) and the toxic effect of venom (989.5)
Algorithm 14	Respiratory compromise (518.81 or 518.82 or 786 or 786.00–786.09 or 786.1 or 493.0 or 493.9) and gastrointestinal symptoms (558.3 or 787.0 or 787.01 or 787.03 or 789.0) and an Ecode indicating the cause of poisoning was a venomous animal or plant (E905 or E905.3 or E905.5 or E905.8 or E905.9)
Algorithm 15	Respiratory compromise (518.81 or 518.82 or 786 or 786.00–786.09 or 786.1 or 493.0 or 493.9) and skin or mucosal tissue involvement (372.73 or 374.82 or 478.6 or 478.25 or 782.62 or 708 or 708.0 or 708.1–708.5 or 708.8–708.9 or 698 or 698.1 or 698.8 or 698.9) and an unspecified adverse effect caused by the correct administration of a drug, medicinal, and biologic substance (995.2) or an unspecified allergic reaction (995.3)
Algorithm 16	Respiratory compromise (518.81 or 518.82 or 786 or 786.00–786.09 or 786.1 or 493.0 or 493.9) and skin or mucosal tissue involvement (372.73 or 374.82 or 478.6 or 478.25 or 782.62 or 708 or 708.0 or 708.1–708.5 or 708.8–708.9 or 698 or 698.1 or 698.8 or 698.9) and the toxic effect of venom (989.5)
Algorithm 17	Respiratory compromise (518.81 or 518.82 or 786 or 786.00–786.09 or 786.1 or 493.0 or 493.9) and skin or mucosal tissue involvement (372.73 or 374.82 or 478.6 or 478.25 or 782.62 or 708 or 708.0 or 708.1–708.5 or 708.8–708.9 or 698 or 698.1 or 698.8 or 698.9) and an Ecode indicating the cause of poisoning was a venomous animal or plant (E905 or E905.3 or E905.5 or E905.8 or E905.9)
Algorithm 18	Gastrointestinal symptoms (558.3 or 787.0 or 787.01 or 787.03 or 789.0) and skin or mucosal tissue involvement (372.73 or 374.82 or 478.6 or 478.25 or 782.62 or 708 or 708.0 or 708.1–708.5 or 708.8–708.9 or 698 or 698.1 or 698.8 or 698.9) and an unspecified adverse effect caused by the correct administration of a drug, medicinal, and biologic substance (995.2) or an unspecified allergic reaction (995.3)
Algorithm 19	Gastrointestinal symptoms (558.3 or 787.0 or 787.01 or 787.03 or 789.0) and skin or mucosal tissue involvement (372.73 or 374.82 or 478.6 or 478.25 or 782.62 or 708 or 708.0 or 708.1–708.5 or 708.8–708.9 or 698 or 698.1 or 698.8 or 698.9) and the toxic effect of venom (989.5)
Algorithm 20	Gastrointestinal symptoms (558.3 or 787.0 or 787.01 or 787.03 or 789.0) and skin or mucosal tissue involvement (372.73 or 374.82 or 478.6 or 478.25 or 782.62 or 708 or 708.0 or 708.1–708.5 or 708.8–708.9 or 698 or 698.1 or 698.8 or 698.9) and an Ecode indicating the cause of poisoning was a venomous animal or plant (E905 or E905.3 or E905.5 or E905.8 or E905.9)

Abbreviation: ICD-9, International Classification of Diseases, Ninth Revision.

eTable 2

Distribution of Cases by Ascertainment Method (N = 164)

ICD-9 derived	Frequency (%)
Anaphylactic shock caused by food (995.5) or other anaphylactic shock (995.0) or 995.60–995.69	71 (43.3)
Algorithm-derived ^a	90 (54.8)
Algorithm 1: Skin or mucosal tissue involvement and shock caused by anesthesia	0 (0.0)
Algorithm 2: Respiratory compromise and shock caused by anesthesia	0 (0.0)
Algorithm 3: Respiratory compromise and angioneurotic edema	35 (21.3)
Algorithm 4: Reduced blood pressure and angioneurotic edema	6 (3.7)
Algorithm 5: Reduced blood pressure and skin or mucosal involvement	20 (12.2)
Algorithm 6: Reduced blood pressure and the toxic effect of venom	2 (1.2)
Algorithm 7: Reduced blood pressure and an E-code indicating the cause of poisoning was a venomous animal or plant	0 (0.0)
Algorithm 8: Reduced blood pressure and gastrointestinal symptoms and an unspecified adverse effect caused by the correct administration of a drug, medicinal, and biologic substance or an unspecified allergic reaction	2 (1.2)
Algorithm 9: Reduced blood pressure and skin or mucosal tissue involvement and an unspecified adverse effect caused by the correct administration of a drug, medicinal, and biologic substance or an unspecified allergic reaction	0 (0.0)
Algorithm 10: Respiratory compromise and reduced blood pressure and an unspecified adverse effect caused by the correct administration of a drug, medicinal, and biologic substance or an unspecified allergic reaction	7 (4.3)
Algorithm 11: Respiratory compromise and gastrointestinal symptoms and an unspecified adverse effect caused by the correct administration of a drug, medicinal, and biologic substance or an unspecified allergic reaction	3 (1.8)
Algorithm 12: Respiratory compromise and gastrointestinal symptoms and skin or mucosal involvement	3 (1.8)
Algorithm 13: Respiratory compromise and gastrointestinal symptoms and the toxic effect of venom (989.5)	0 (0.0)
Algorithm 14: Respiratory compromise and gastrointestinal symptoms and an E-code indicating the cause of poisoning was a venomous animal or plant	0 (0.0)
Algorithm 15: Respiratory compromise and skin or mucosal tissue involvement and an unspecified adverse effect caused by the correct administration of a drug, medicinal, and biologic substance or an unspecified allergic reaction	13 (7.9)
Algorithm 16: Respiratory compromise and skin or mucosal tissue involvement and the toxic effect of venom	0 (0.0)
Algorithm 17: Respiratory compromise and skin or mucosal tissue involvement and an E-code indicating the cause of poisoning was a venomous animal or plant	0 (0.0)
Algorithm 18: Gastrointestinal symptoms and skin or mucosal tissue involvement and an unspecified adverse effect caused by the correct administration of a drug, medicinal, and biologic substance or an unspecified allergic reaction	1 (0.6)
Algorithm 19: Gastrointestinal symptoms and skin or mucosal tissue involvement and the toxic effect of venom	0 (0.0)
Algorithm 20: Gastrointestinal symptoms and skin or mucosal tissue involvement and an E-code indicating the cause of poisoning was a venomous animal or plant	0 (0.0)
Mixed ^b	3 (1.8)

Abbreviation: ICD-9, International Classification of Diseases, Ninth Revision.

^a1 patient was identified by algorithms 3 and 4, another patient by algorithms 3 and 10.^b1 patient each was identified by ICD-9 and algorithms 3, 10, and 15.**eTable 3**

Comparison of Identifiable Medication Triggers

Characteristic	Total sample (N = 164)	Anaphylaxis (N = 82)	Non-anaphylactic acute allergic reaction (N = 82)
ACE inhibitor or ARB	17	6 (7.3)	11 (13.4)
Analgesic	1	1 (1.2)	0 (0.0)
Anesthetic	1	1 (1.2)	0 (0.0)
Antiarrhythmic	0	0 (0.0)	0 (0.0)
Antibiotic	14	11 (13.4)	3 (3.2)
Anticonvulsant	0	0 (0.0)	0 (0.0)
Antihistamine	0	0 (0.0)	0 (0.0)
Antipsychotic	0	0 (0.0)	0 (0.0)
Immunosuppressive, biologic	6	6 (7.3)	0 (0)
Narcotic	3	3 (3.7)	0 (0)
NSAID, ASA	4	1 (1.2)	3 (3.7)
Other	6	2 (2.4)	4 (4.7)
Radiocontrast	12	12 (14.6)	0 (0.0)
Sedative	0	0 (0.0)	0 (0.0)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; NSAID, nonsteroidal anti-inflammatory; ASA, acetylsalicylic acid.

eTable 4

Comparison of Reported Drug Allergens

Characteristic	Total sample (N = 164)	Anaphylaxis (N = 82)	Non-anaphylactic acute allergic reaction (N = 82)
ACE inhibitor or ARB	16	5 (6.1)	11 (13.4)
Analgesic	1	0 (0.0)	1 (1.2)
Anesthetic	1	0 (0)	1 (1.2)
Antiarrhythmic	3	0 (0)	3 (3.7)
Antibiotic	46	18 (22.0)	28 (34.1)
Anticonvulsant	3	1 (1.2)	2 (2.4)
Antihistamine	3	2 (2.4)	1 (1.2)
Antipsychotic	2	1 (1.2)	1 (1.2)
Immunosuppressive, biologic	2	1 (1.2)	1 (1.2)
Narcotic	11	4 (4.9)	7 (8.5)
NSAID, ASA	13	2 (2.4)	11 (13.4)
Other	17	11 (13.4)	6 (7.3)
Radiocontrast	11	6 (7.3)	5 (6.1)
Sedative	1	0 (0.0)	1 (1.2)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; NSAID, nonsteroidal anti-inflammatory; ASA, acetylsalicylic acid.

eTable 5
Comparison of Reported Food Allergens

Characteristic	Total sample (N = 164)	Anaphylaxis (N = 82)	Non-anaphylactic acute allergic reaction (N = 82)
Cow's milk	1	0 (0.0)	1 (1.2)
Egg	0	0 (0.0)	0 (0.0)
Fish	0	0 (0.0)	0 (0.0)
Fruit	4	3 (3.7)	1 (1.2)
Other	9	8 (9.8)	1 (1.2)
Peanut	3	0 (0.0)	3 (3.7)
Shellfish	17	9 (11.0)	8 (9.8)
Soy	3	3 (3.7)	0 (0.0)
Tree nut	4	3 (3.7)	1 (1.2)
Vegetable	2	1 (1.2)	1 (1.2)
Wheat	1	1 (1.2)	0 (0.0)

eTable 6
Comparison of Non-Allergic Comorbidities^a

Characteristic	Total sample (N = 164)	Anaphylaxis (N = 82)	Non-anaphylactic acute allergic reaction (N = 82)
Cardiovascular	137	65 (79.3)	72 (87.8)
Dermatologic	16	1 (1.2)	15 (18.3)
Endocrine	82	35 (42.7)	47 (57.3)
Gastrointestinal	66	30 (36.6)	36 (43.9)
Hematology or oncology	48	22 (26.8)	26 (31.7)
Infectious disease	10	2 (2.4)	8 (9.8)
Musculoskeletal	55	28 (34.1)	27 (32.9)
Neurologic or psychiatric	70	31 (37.8)	39 (47.6)
None	5	5 (6.1)	0 (0.0)
Ophthalmologic	16	6 (7.3)	10 (12.2)
Otolaryngologic	10	6 (7.3)	4 (4.9)
Pulmonary	38	14 (17.1)	24 (29.3)
Renal	30	10 (12.2)	20 (24.4)
Rheumatology	17	9 (11.0)	8 (9.8)
Urogenital	41	15 (18.3)	26 (31.7)

^aCharacteristics are not mutually exclusive.