Original Article

Prospective Validation of the NIAID/FAAN Criteria for Emergency Department Diagnosis of Anaphylaxis

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What is already known about this topic? Anaphylaxis diagnostic criteria were proposed at the Second Symposium on the Definition and Management of Anaphylaxis. These criteria were 97% sensitive and 82% specific when retrospectively validated.

What does this article add to our knowledge? This first prospective analysis of the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network criteria shows that the criteria are 95% sensitive and 71% specific and are likely to be a useful tool for diagnosing anaphylaxis in the emergency department.

How does this study impact current management guidelines? These results support the use of the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network criteria in anaphylaxis management guidelines because they are sensitive and likely to increase the recognition of anaphylaxis in the emergency department.

BACKGROUND: Anaphylaxis diagnostic criteria were proposed at the Second Symposium on the Definition and Management of Anaphylaxis. These criteria were 97% sensitive and 82% specific when retrospectively validated.

OBJECTIVE: To prospectively evaluate the diagnostic accuracy of the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria for diagnosis of anaphylaxis in the emergency department (ED).

METHODS: We conducted a prospective observational study of patients seen in our institution's ED from April 2010 to March 2013. Patients seeking care for an allergic reaction and possible anaphylaxis were enrolled. Patients and providers completed questionnaires regarding onset, trigger, and signs and symptoms. Records were reviewed independently and blindly by 2 board-certified allergist-immunologists, and their final diagnosis (anaphylaxis vs no anaphylaxis) was used as the reference standard. Two-by-two tables were built, and test characteristics were calculated.

RESULTS: Among the 174 enrolled patients, 91 (52%) met the NIAID/FAAN criteria for anaphylaxis. The allergist-immunologists diagnosed 61 cases of anaphylaxis (35%), of which 58 (95%) also satisfied the NIAID/FAAN criteria. The interrater agreement between allergist-immunologists was substantial ($\kappa = 0.7$). Test characteristics (95% CIs) of the NIAID/FAAN criteria were as follows: sensitivity, 95.1% (85.4%-98.7%); specificity, 70.8% (61.4%-78.8%); positive predictive value, 63.7% (52.9%-73.4%); negative predictive value, 96.4% (89.1%-99.1%); positive likelihood ratio, 3.26; and negative likelihood ratio, 0.07.

CONCLUSIONS: Prospectively, the NIAID/FAAN criteria continued to be highly sensitive (95%) but had lower specificity (71%) than on retrospective assessment. These criteria are likely to be useful for the diagnosis of anaphylaxis in the ED. © **2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;4:1220-6)**

Key words: *Anaphylaxis; Diagnostic criteria; Test characteristics*

Anaphylaxis is a potentially life-threatening allergic reaction that is underrecognized and underdiagnosed,[1-5] largely because it can present clinically with variable target organ involvement and a wide array of associated signs and symptoms. There is currently no universally accepted definition of or diagnostic criteria for anaphylaxis.[6] The lack of reliable criteria has not only led to impairments in this field of research but also affected patient care, resulting in inconsistent management in the emergency department (ED), where most anaphylactic reactions are treated.[1,2,7,8] Given the lack of serum markers that are both

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Abbreviations used
ED- emergency department
FAAN- Food Allergy and Anaphylaxis Network
LR- likelihood ratio
NIAID- National Institute of Allergy and Infectious Diseases

sensitive and specific, validated clinical criteria for the diagnosis of anaphylaxis are needed.

The current existing diagnostic criteria are from the National Institutes of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) (Figure 1).[6] A multinational and multidisciplinary expert panel established the content validity. The proposed definitions aimed to "establish clinical criteria that would accurately identify cases of anaphylaxis with high precision."[6] The overall goal was to establish clinical criteria that would be acceptable not only to allergy immunologists but also to all types of medical practitioners who diagnose and manage anaphylaxis.

The NIAID/FAAN criteria were retrospectively validated and found to have 96.7% sensitivity and 82.4% specificity.[9] However, the criteria have not been prospectively validated. Therefore, we sought to conduct a prospective assessment of the criteria, which is essential for establishing their utility and determining any need for further revision.

METHODS

The Standards for Reporting of Diagnostic Accuracy guidelines for reporting studies of diagnostic test accuracy were followed.[10]

Design and setting

We conducted a prospective observational study of patients seeking care at the ED of Mayo Clinic Hospital—Saint Marys Campus, Rochester, Minnesota, a tertiary care academic ED that has a volume of approximately 73,000 annual patient visits. Overall, 20% of the patients in the ED are children, and most patients come from Olmsted County and 6 adjacent counties in southeastern Minnesota. The study was approved by the Mayo Clinic Institutional Review Board.

Participants

Patients of all ages who came to the ED with a chief concern of symptoms suggestive of an allergic reaction or anaphylaxis were prospectively enrolled between April 2010 and March 2013. Patients were identified if they had a chief concern that included "allergic," "reaction," "anaphy-," "angio-," "sting," "hives," or "rash." The chief concern was entered into the ED electronic patient-tracking system whenever a patient was registered. The ED electronic patient-tracking system was programmed to automatically generate a text page to the study coordinators when the specified text was entered. Study coordinators then approached the ED provider caring for the patient to determine whether the patient was eligible for the study. Any patient whom the ED provider suspected of having anaphylaxis or an allergic reaction was considered eligible for enrollment and was approached for participation. Consent was obtained from all enrolled patients or their caregivers.

Variables

Patients or caregivers and ED providers completed questionnaires regarding allergy history, symptom onset, trigger, presenting signs and symptoms, and prehospital management. Data on ED anaphylaxis management and disposition were extracted from the electronic health record using a standardized extraction procedure. All data obtained from the patient and provider questionnaires and electronic health records were entered into a password-protected SAS database. The database was programmed to determine whether NIAID/FAAN criteria were met for the diagnosis of anaphylaxis.

Two American Board of Allergy and Immunology—certified allergist-immunologists (J.B.H. and J.T.L.) independently reviewed the prospectively collected patient data and electronic health records to determine whether the cases represented anaphylaxis on the basis of their expert opinion. Both allergist-immunologists were blinded to the results regarding fulfillment of NIAID/FAAN criteria. Any diagnostic differences between the allergist-immunologists were resolved through careful joint review. All data were collected before the allergist-immunologists' final diagnosis.

Statistical methods

Using the final diagnosis made by the 2 allergist-immunologists as the reference standard, test characteristics were determined for the NIAID/FAAN diagnostic criteria for anaphylaxis. Two-by-two tables were created to calculate the measurements of diagnostic test accuracy, including true positives, true negatives, false positives, false negatives, and likelihood ratios (LRs). We calculated 95% CIs for sensitivity, specificity, positive predictive value, and negative predictive value using the score method incorporating a continuity correction.[5]

Sensitivity is the probability that a patient with the disease (anaphylaxis) will have a positive test result (meets the NIAID/FAAN criteria), and *specificity* is the probability that a patient without anaphylaxis will have a negative test result (does not meet the NIAID/FAAN criteria). *Positive predictive value* is the probability that a person who meets the NIAID/FAAN criteria has anaphylaxis, and *negative predictive value* is the probability that a person with a negative result (does not meet NIAID/FAAN criteria) does not have anaphylaxis. LR—sensitivity/(1 − specificity)—is a different way to incorporate sensitivity and specificity and provide a direct estimate of how much a test result will change the odds of having the disease. The LR of a negative test result indicates how much the odds of the disease (anaphylaxis) decrease when the NIAID/FAAN criteria are negative. The sensitivity, specificity, and LRs are properties of the test. The positive and negative predictive values are properties of both the test and the population being tested. The predictive value of a test in 2 populations with different disease prevalence will be different.

Associations of features of anaphylaxis with the consensus diagnosis of anaphylaxis and the NIAID/FAAN diagnostic criteria for anaphylaxis were evaluated using logistic regression models and summarized with odds ratios and 95% CIs. Agreement in the diagnosis of anaphylaxis between the 2 allergist-immunologists was evaluated using the κ statistic. Statistical analyses were performed using version 9.3 of the SAS software package (SAS Institute, Inc, Cary, NC), and a P value of less than .05 was considered statistically significant.

RESULTS

A total of 174 patients met the inclusion criteria and were enrolled in the study; 115 (55%) were female, and 36 (21%) were younger than 18 years. The median age of the study population was 37 years (interquartile range, 22-58 years), with the youngest age 6 months. Demographic characteristics and suspected causes of anaphylaxis for all patients, those who met NIAID/FAAN criteria, and those who were given a diagnosis of

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 (eg, 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 PEF, hypoxemia)

b. Reduced 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

FIGURE 1. NIAID/FAAN clinical criteria for the diagnosis of anaphylaxis. *BP*, Blood pressure; *PEF*, peak expiratory flow. *Low systolic BP for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years. (Adapted with permission from Sampson et al.[6])

TABLE I. Demographic characteristics for all patients and those who met NIAID/FAAN criteria or diagnosis of anaphylaxis by 2 allergist-immunologists*

Feature	All patients (N = 174)	NIAID/FAAN criteria (n = 91)	Diagnosis by allergists (n = 61)
Age at visit (y)	37 (0-93)	36 (0-93)	36 (1-80)
Age ≥18 y	138 (79)	73 (80)	48 (79)
Women	115 (66)	58 (64)	38 (62)
Suspected allergen			
Food	40 (23)	29 (32)	19 (31)
Medicine	56 (32)	25 (27)	14 (23)
Venom	16 (9)	11 (12)	10 (16)
Latex	1 (1)	0	1 (2)
Contrast medium	8 (5)	7 (8)	7 (11)
Other	9 (5)	3 (3)	0
Unknown	44 (25)	16 (18)	10 (16)
Race			
White	162 (93)	86 (95)	57 (93)
Other or unknown	12 (7)	5 (5)	4 (7)

*Values are median (range) or no. of patients (%).

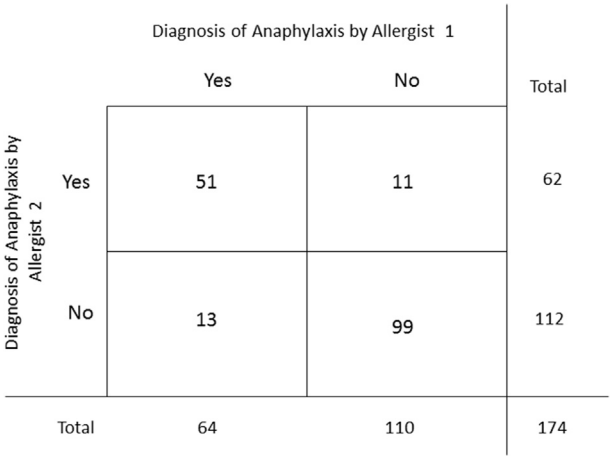

FIGURE 2. Comparison of anaphylaxis diagnoses by 2 allergist-immunologists. Contingency table shows the diagnostic agreement between Allergist 1 and Allergist 2 for 174 patients.

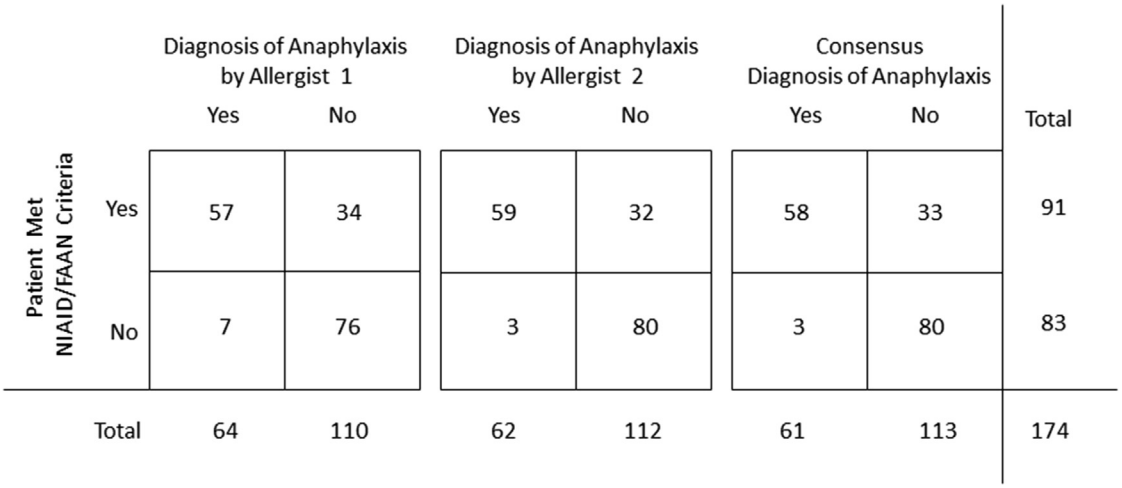

FIGURE 3. Comparison of NIAID/FAAN criteria with anaphylaxis diagnoses. Contingency tables show the diagnostic agreement for Allergist 1, Allergist 2, and the consensus diagnoses versus the NIAID/FAAN criteria for 174 patients.

TABLE II. Test characteristics of NIAID/FAAN criteria compared with the consensus diagnosis of anaphylaxis

	Criterion*			
Characteristic	**1, 2, or 3**	**1**	**2**	**3**
Patients meeting criterion	91	84	84	3
Patients with anaphylaxis diagnosis	58	52	55	2
Sensitivity, %	95.1 (85.4-98.7)	85.2 (73.3-92.6)	90.2 (79.2-95.9)	3.3 (0.6-12.4)
Specificity, %	70.8 (61.4-78.8)	71.7 (62.3-79.6)	74.3 (65.1-81.9)	99.1 (94.5-100)
Positive predictive value, %	63.7 (52.9-73.4)	61.9 (50.6-72.1)	65.5 (54.2-75.3)	66.7 (12.5-98.2)
Negative predictive value, %	96.4 (89.1-99.1)	90.0 (81.4-95.0)	93.3 (85.5-97.3)	65.5 (57.8-72.5)
LR of positive criteria	3.26	3.01	3.51	3.70
LR of negative criteria	0.07	0.21	0.13	0.98

*Data are no. of patients, value (95% CI), or value.

anaphylaxis by the allergist-immunologists are presented in Table I.

Figure 2 compares the diagnosis of anaphylaxis by the 2 allergist-immunologists. The interrater agreement between the allergist-immunologists was substantial ($\kappa = 0.7$), with an overall concordance rate of 86.2% (150 of 174). The NIAID/FAAN criteria for anaphylaxis were met by 91 patients (52.3%) (Figure 3). The allergist-immunologists gave 61 patients (35.1%) diagnoses of anaphylaxis, 58 (95.1%) of whom satisfied at least 1 of the NIAID/FAAN criteria for anaphylaxis. The test characteristics of the NIAID/FAAN criteria overall and individual criteria (1, 2, or 3) are presented in Table II. Test characteristics of the NIAID/FAAN criteria were as follows: sensitivity, 95.1% (95% CI, 85.4%-98.7%); specificity, 70.8% (95% CI, 61.4%-78.8%); positive predictive value, 63.7% (95% CI, 52.9%-73.4%); negative predictive value, 96.4% (95% CI, 89.1%-99.1%); positive LR, 3.26; and negative LR, 0.07.

The univariable associations of the individual features of the NIAID/FAAN criteria with the consensus diagnosis of anaphylaxis by the 2 allergist-immunologists are presented in Table III. Table IV presents the suspected alternate diagnoses in the 33 patients who met the NIAID/FAAN criteria but were not considered to have anaphylaxis after the allergist-immunologists' review. The most common alternate diagnoses were anxiety and medication reactions.

DISCUSSION

Anaphylaxis can present with a wide range of signs and symptoms; currently, serum markers that are both sensitive and specific are not available for confirmation of the diagnosis. The development of clinical diagnostic criteria by the members of the Second Symposium on the Definition and Management of Anaphylaxis was a substantial contribution to the advancement of anaphylaxis clinical care and research.[6] The criteria have been endorsed by major allergy organizations worldwide during the past decade[11,12] and are used broadly in anaphylaxis research. Validation of the clinical criteria is essential for better assessing their accuracy.

In this study of 174 prospectively enrolled ED patients with signs or symptoms of a possible allergic reaction or anaphylaxis, the NIAID/FAAN criteria were 95% sensitive and 71% specific compared with the evaluation of expert allergist-immunologists. To our knowledge, this is the first study to prospectively evaluate the NIAID/FAAN clinical

TABLE III. Univariable associations with consensus diagnosis of anaphylaxis by 2 allergist-immunologists

Feature	Anaphylaxis*		OR (95% CI)	*P* value
	No (n = 113)	Yes (n = 61)		
Acute onset of symptoms†	81 (72)	61 (100)	49.07 (2.82-853.61)	.008
Exposure to likely allergen	98 (87)	58 (95)	2.96 (0.82-10.66)	.10
Exposure to known allergen	27 (24)	25 (41)	2.21 (1.13-4.32)	.02
Flushing, diaphoresis, warmth	64 (57)	51 (84)	3.91 (1.80-8.46)	<.001
Pruritus	76 (67)	37 (61)	0.75 (0.39-1.43)	.38
Diffuse urticaria	57 (50)	24 (39)	0.64 (0.34-1.20)	.16
Lip angioedema	45 (40)	30 (49)	1.46 (0.78-2.74)	.24
Tongue angioedema	26 (23)	24 (39)	2.17 (1.11-4.26)	.03
Uvula angioedema	26 (23)	29 (48)	3.03 (1.56-5.91)	.001
Emesis	6 (5)	9 (15)	3.09 (1.04-9.13)	.04
Abdominal cramping, pain	13 (12)	18 (30)	3.22 (1.45-7.15)	.004
Dyspnea, difficulty breathing	44 (39)	46 (75)	4.81 (2.40-9.63)	<.001
Wheezing, bronchospasm	21 (19)	30 (49)	4.24 (2.13-8.46)	<.001
Stridor	2 (2)	1 (2)	0.93 (0.08-10.42)	.95
Decreased PEF‡	0	0	NE	NE
Hypoxemia	3 (3)	6 (10)	4.00 (0.96-16.60)	.06
Hypotension, decreased BP	1 (1)	6 (10)	12.22 (1.44-103.99)	.02
Syncope	2 (2)	9 (15)	9.61 (2.00-46.04)	.005
Incontinence	2 (2)	2 (3)	1.88 (0.26-13.70)	.53

BP, Blood pressure; *NE*, not estimated; *OR*, odds ratio; *PEF*, peak expiratory flow.
*Values are no. of patients (%).
†OR, 95% CI, and *P* value estimated using Firth's penalized maximum likelihood.
‡PEF was measured in 24 patients, and none had an abnormal result.

TABLE IV. Suspected diagnosis in patients who met NIAID/FAAN criteria but were not given a diagnosis of anaphylaxis

Suspected alternate diagnosis	No. of patients (n = 33)
Anxiety	7
Non-NSAID medication reaction	6
Indeterminate reaction	5
Food allergy	3
Bee sting with localized reaction	2
Acute urticaria	2
NSAID drug reaction	1
Environmental allergy (cat)	1
Acute pruritus	1
COPD exacerbation	1
Chronic urticaria and angioedema exacerbation	1
Asthma exacerbation	1
Angioedema secondary to radiation therapy	1
Migraine with vomiting	1

COPD, Chronic obstructive pulmonary disease; *NSAID*, nonsteroidal anti-inflammatory drug.

criteria. In our previous retrospective validation of the criteria,[9] we found them to be 97% sensitive and 82% specific. Our current study results, demonstrating similar sensitivity and lower specificity, probably represent a more accurate characterization of the clinical performance of the criteria. The most likely reason for the lower specificity observed in this study than in our retrospective study was that more symptoms were reported and documented in the prospective study during the completion of the patient questionnaire than were documented in the medical record, which thus led to more patients meeting the NIAID/FAAN criteria than would have if the medical record alone was used.

Despite the high sensitivity, the NIAID/FAAN clinical criteria did not identify all patients who were given a diagnosis of anaphylaxis by the allergist-immunologists—3 patients who did not meet the clinical criteria were given a diagnosis of anaphylaxis. The first patient was stung by a bee and had development of localized swelling, flushing, and sinus tachycardia with normal blood pressures. Tachycardia may precede hypotension during the initial phases of anaphylaxis,[13] but the NIAID/FAAN criteria do not specifically recognize this as an early cardiovascular manifestation.

The second patient had generalized urticaria, lip tingling, and throat tightness. Although throat tightness may be a symptom of angioedema or respiratory compromise, it is not formally included as a cutaneous or respiratory symptom in the NIAID/FAAN criteria. Throat tightness can also be a symptom of anxiety; thus, evaluation with nasopharyngolaryngoscopy in the ED may be helpful in better classifying this symptom.

The third patient had a history of anaphylaxis related to latex products and had acute chest tightness and dizziness after receiving an influenza vaccine that contained latex. Vital signs, including heart rate and blood pressures, were within normal limits. Chest tightness is a broad symptom that could suggest respiratory or cardiovascular compromise. Peak expiratory flow

was not measured in this patient. Because decreased peak expiratory flow is included in the criteria, more frequently measuring peak flow in the ED may help to better assess these patients.

Thirty-three of the 91 patients who met the NIAID/FAAN criteria for anaphylaxis (36.3%) were not given a diagnosis of anaphylaxis by the board-certified allergist-immunologists. The specificity of the NIAID/FAAN criteria overall was 70.8%. For the diagnosis of anaphylaxis, high sensitivity is preferred over specificity to maximize the number of cases of anaphylaxis that are detected in the ED. In a study of 139 fatal cases of anaphylaxis, only 18% of the patients with venom-allergic and 22% of the patients with food-allergic fatalities had a previous severe reaction.[14] Thus, failure to detect a mild anaphylactic episode would miss an opportunity to diagnose anaphylaxis and prevent potential future fatal episodes.

False-positive identification with the NIAID/FAAN criteria is possible, which makes clinical judgment important. If the diagnosis of anaphylaxis is uncertain, the risks and benefits of epinephrine administration must be carefully considered. Currently, there are no absolute contraindications to epinephrine administration.[11,12] Furthermore, intramuscular epinephrine given at appropriate doses to adults and children has also been shown to be safe. In children, adverse effects, including pallor, tremor, and palpitations, are mild and transient as the plasma epinephrine concentrations are achieved.[15] In adults, intramuscular administration of epinephrine to patients with anaphylaxis has been shown to be very safe, with most adverse cardiovascular events being associated with intravenous bolus epinephrine administration.[16]

Anaphylaxis guidelines recommend that patients with anaphylaxis or suspected anaphylaxis be referred to an allergy-immunology specialist.[11] In a previous study examining outcomes of allergy-immunology follow-up after an ED visit for anaphylaxis, 35% of the patients with suspected anaphylaxis in the ED had an alteration in the diagnosis or suspected trigger after allergy-immunology evaluation.[17] Follow-up with an allergist-immunologist can help determine whether anaphylaxis was present, allow for testing if indicated, and provide appropriate additional patient education.

Our study had several limitations. Sensitivity can be falsely increased in cases of referral bias, in which patients with suspected anaphylaxis are more likely to be included in the study and meet the diagnostic standard. In addition, given that there are currently no objective independent tests for anaphylaxis, this study relied on expert opinion as the reference standard. To overcome this limitation, both allergist-immunologists were blinded to each other's conclusions, as well as to whether the NIAID/FAAN criteria were met. However, the allergist-immunologists were familiar with the NIAID/FAAN criteria and, therefore, may have been influenced by them. In our study, there was 16% discordance between the allergists, which highlights the difficulty in diagnosing anaphylaxis and underscores the utility of the NIAID/FAAN criteria in providing an objective alternative to aid in the diagnosis.

Our study is also limited in that it was a single-center study and the majority of our patient population was white, which may limit the study's external validation. Another limitation in terms of external validation is that the predictive value of NIAID/FAAN criteria will be different depending on the prevalence of anaphylaxis in the population. Thus, applying these results to a population with a lower prevalence of anaphylaxis than that in the current study will increase the negative predictive value, which means that a negative NIAID/FAAN criterion is more likely to be a true negative.

Until sensitive and specific serum markers are available for the confirmation of anaphylaxis, clinical criteria will continue to have a central role in the diagnosis of anaphylaxis in the ED. Despite the limitations of the NIAID/FAAN criteria, the high sensitivity of the criteria found in our study suggests that they will encourage a consideration of the diagnosis of anaphylaxis in the ED but cannot replace clinical judgment. The NIAID/FAAN criteria have several strengths that are likely to increase the diagnosis of anaphylaxis in the ED: (1) they underscore that shock does not need to be present for anaphylaxis to be diagnosed; (2) they highlight that patients with relatively mild symptoms may have anaphylaxis (eg, patients with urticaria and vomiting after exposure to a likely trigger); and (3) they emphasize that the absence of mucocutaneous symptoms does not rule out anaphylaxis. The NIAID/FAAN criteria are likely to be a useful tool in improving the diagnosis of anaphylaxis. Similar to identification tools available for sepsis, incorporation of the NIAID/FAAN criteria into an automated medical record detection tool may be an effective and practical strategy for identifying anaphylaxis in the ED. In the future, additional prospective multicenter analyses will be helpful in further validating and refining the criteria.

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