

Evaluation of National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network criteria for the diagnosis of anaphylaxis in emergency department patients

Ronna L. Campbell, MD, PhD,^a John B. Hagan, MD,^b Veena Manivannan, MBBS,^a Wyatt W. Decker, MD,^a Abhijit R. Kanthala, MBBS,^a Maria Fernanda Bellolio, MD, MS,^a Vernon D. Smith, MD,^a and James T. C. Li, MD, PhD^b Rochester, Minn

Background: Diagnostic criteria were proposed at the Second Symposium on the Definition and Management of Anaphylaxis convened by the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN). Validation is needed before these criteria can be widely adapted into clinical practice.

Objective: Our aim was to retrospectively assess the diagnostic accuracy of the NIAID/FAAN criteria for the diagnosis of anaphylaxis in emergency department (ED) patients.

Methods: A retrospective cohort study of ED patients presenting from April to October 2008 was conducted. Patients given a diagnosis of an allergic reaction or anaphylaxis and a subset of patients with related diagnoses were included. Electronic medical records were reviewed and data were abstracted to determine whether the NIAID/FAAN criteria were met. Records were also independently reviewed in a blinded fashion by 2 experienced attending allergists. Final diagnosis by allergists was considered the reference standard.

Results: Of 214 patients, 86 (40.2%) met the NIAID/FAAN criteria for anaphylaxis. Allergists gave 61 (28.5%) patients diagnoses of anaphylaxis, 59 (96.7%) of whom satisfied the NIAID/FAAN criteria. The interrater agreement between allergists was substantial ($\kappa = 0.77$). The test characteristics of the NIAID/FAAN criteria were as follows: sensitivity, 96.7% (95% CI, 88.8% to 99.1%); specificity, 82.4% (95% CI, 75.5% to 87.6%); positive predictive value, 68.6% (95% CI, 58.2% to 77.4%); negative predictive value, 98.4% (95% CI, 94.5% to 99.6%); positive likelihood ratio, 5.48; and negative likelihood ratio, 0.04.

Conclusions: These results suggest that the NIAID/FAAN criteria are highly sensitive but less specific and are likely to be

useful in the ED for the diagnosis of anaphylaxis. (J Allergy Clin Immunol 2011;■■■:■■■-■■■.)

Key words: Anaphylaxis, diagnostic criteria, test characteristics

Anaphylaxis has a wide spectrum of clinical manifestations, and there are no universally accepted diagnostic criteria. Failure to detect an anaphylactic episode places patients at future risk of potentially life-threatening allergen exposure. Furthermore, the results and reproducibility of epidemiologic, diagnostic, and therapeutic studies depend on establishing reliable and valid diagnostic criteria. Anaphylactic reactions are most commonly diagnosed and managed in the emergency department (ED).^{1,2} The lack of universally accepted diagnostic criteria for anaphylaxis has often resulted in the failure to recognize anaphylaxis and its inconsistent management in the ED.³⁻⁵

Diagnostic criteria have been proposed by the participants of the Second Symposium on the Definition and Management of Anaphylaxis (Fig 1).⁶ The content validity was established by a multinational and multidisciplinary expert panel. Definitions were proposed to “establish clinical criteria that would accurately identify cases of anaphylaxis with high precision.”⁶ However, these criteria have not been evaluated by comparison with an allergist’s diagnosis. Validation is essential before these criteria can be widely adapted into clinical practice. This will lead to better recognition, diagnosis, and management of patients with anaphylaxis.

We hypothesized that the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria for the diagnosis of anaphylaxis would be highly sensitive and specific for the diagnosis of anaphylaxis in ED patients presenting with suspected allergic reactions. Although prospective studies are needed to definitively establish the validity of the NIAID/FAAN criteria, we sought to retrospectively assess the accuracy using electronic medical records review of patients who presented to the ED with possible allergic reactions.

METHODS

Design and setting

We conducted a retrospective cohort study of patients who presented to Saint Marys Hospital ED. Saint Marys Hospital is a 1265-bed tertiary referral hospital. The ED is a 51-bed facility that provides care for approximately

From ^athe Department of Emergency Medicine and ^bthe Division of Allergic Diseases, Mayo Clinic.

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Corresponding author: Ronna L. Campbell, MD, PhD, Department of Emergency Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905. E-mail: campbell.ronna@mayo.edu.

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Abbreviations used

ED: Emergency department

NIAID/FAAN: National Institute of Allergy and Infectious Diseases/
Food Allergy and Anaphylaxis Network

80,000 patients each year, the vast majority of whom come from Olmsted and the 6 adjacent counties in southeastern Minnesota. On average, 20% of ED patients are children. The study was approved by the Mayo Clinic Institutional Review Board.

Participants

We included all ED patients who provided research authorization and were given a diagnosis of allergic reactions or anaphylaxis by the emergency care provider from April 2008 through October 2008. In addition, we included 5 patients selected by using a random number generator (Research Randomizer, Geoffrey C. Urbaniak and Scott Plous) each from patients given diagnoses of hives, medication reaction, and bee stings during this time period.

Variables

Electronic medical records were reviewed by a research fellow, and data were verified in 25% of cases by an ED physician. Data collected to determine whether the NIAID/FAAN criteria for anaphylaxis were met included inciting allergen, timing of symptom onset, presenting signs and symptoms, and allergic history using a standardized data abstraction form.

The signs and symptoms that were considered positive for meeting the various organ-system components of the criteria were as follows:

1. *involvement of the skin-mucosal tissue*: generalized hives, pruritus, angioedema, and flushing;
2. *respiratory compromise*: dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, cough, voice change, cyanosis, and hypoxemia;
3. *reduced blood pressure or associated symptoms*: hypotonia, collapse, presyncope, sudden weakness, syncope, or incontinence; and
4. *persistent gastrointestinal symptoms*: crampy abdominal pain, nausea, vomiting, or diarrhea.

The electronic medical records (including the ED records and any related follow-up or test records) were compiled. Individual copies of each medical record were reviewed independently by 2 experienced American Board of Allergy and Immunology–certified allergists who were blind to the results regarding fulfillment of NIAID/FAAN criteria. Any diagnostic disagreements between the allergists were subsequently resolved through discussion. The final consensus diagnosis by the 2 allergists was considered the reference standard for the diagnosis of anaphylaxis.

Statistical methods

Data analysis was performed by using descriptive statistics with JMP 8 software. Ninety-five percent CIs and *P* values are provided, where appropriate. Interrater reliability was measured with the κ statistic. In the 2×2 table, in which no events were observed, we corrected by adding a fixed value (+0.5) to all cells to avoid computational errors by dividing by a zero count.^{7,8}

RESULTS

Two hundred twenty-two patients met the inclusion criteria. Of these, 214 patients provided research consent and constituted the study sample. The median age of the study population was 36 years (interquartile range, 17.8–56.0 years). Of the 214 included patients, 119 (55.6%) were female subjects, and 53 (24.8%) were children (age, <18 years). A comparison of patients' demographics and suspected causes between patients who met the NIAID/

FAAN criteria and patients who were given a diagnosis of anaphylaxis by allergists is shown in Table I.

Eighty-six (40.2%) subjects met the NIAID/FAAN criteria for anaphylaxis. ED physicians gave 55 (25.7%) patients diagnoses of anaphylaxis, 15 (27.3%) of whom were not considered to have anaphylaxis by the allergists. Allergists gave 61 (28.5%) patients diagnoses of anaphylaxis, 59 (96.7%) of whom satisfied at least 1 of the NIAID/FAAN criteria for anaphylaxis. Twenty-one (34.4%) of these 61 patients (34.4%) had an alternate ED diagnosis. The remaining 2 (3.3%) did not meet the NIAID/FAAN criteria. Of these, 1 patient was 19 years old and presented with diffuse urticaria and fullness of the throat. The symptoms were attributed to immunotherapy. The other patient was 47 years old and presented with diffuse urticaria and oral edema caused by a wasp sting.

The interrater agreement between the allergists was substantial, with an overall concordance of 90.65% ($\kappa = 0.77$, Table II). The frequencies of presenting signs and symptoms are shown in Table III. The test characteristics of the collective NIAID/FAAN criteria and individual criteria are shown in Table IV. Table V shows the 2×2 table relating patients who met the NIAID/FAAN criteria and patients who were given a diagnosis of anaphylaxis by allergists.

Table VI shows the suspected alternate diagnosis in patients who met the NIAID/FAAN criteria but were not considered to have anaphylaxis after the allergists' review.

DISCUSSION

One of the primary goals of developing the NIAID/FAAN criteria was to provide the emergency responder or treating physician with a relatively simple and rapid means of making the diagnosis of anaphylaxis.⁹ The members of the Second Symposium on the Definition and Management of Anaphylaxis hypothesized that the proposed criteria were likely to capture more than 95% of the cases of anaphylaxis.

In this sample the NIAID/FAAN criteria identified more than 95% of the patients who were given a diagnosis of anaphylaxis. Patients who did not meet the criteria were unlikely to have anaphylaxis, as evidenced by the low negative likelihood ratio. Although there were 5 patients who met criterion 3 (ie, reduced blood pressure after exposure to a known allergen for that patient), all of these patients also had involvement of the skin or mucosa, and 4 of them had respiratory symptoms; therefore they also met criterion 1 and criterion 2. Furthermore, criterion 3 was provided by the consensus group largely to accommodate anaphylaxis occurring in an intraoperative setting. Thus it is not surprising that it was infrequently invoked by itself in the ED setting.

Despite the high sensitivity, the NIAID/FAAN criteria did not identify all patients who were given a diagnosis of anaphylaxis. There were 2 patients who did not meet the criteria and yet were given a diagnosis of anaphylaxis. The first patient had urticaria and throat fullness after receiving immunotherapy. A sensation of throat fullness might be indicative of laryngeal edema, which would be considered a respiratory symptom. The NIAID/FAAN criteria do not include throat fullness as a respiratory symptom. Throat fullness or tightness is a common complaint among ED patients presenting with anaphylaxis, but the clinical significance of this subjective symptom is difficult to assess.¹ Performing nasopharyngoscopy in the evaluation of patients complaining of throat fullness could potentially aid in a more accurate classification of this symptom.

Anaphylaxis is highly likely when any one of the following 3 criteria is 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 ONE 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

PEF, Peak expiratory flow; BP, blood pressure.

*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 x age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Modified from Sampson, et al.⁶ Used with permission.

FIG 1. NIAID/FAAN clinical criteria for the diagnosis of anaphylaxis.

TABLE I. Patients' demographics and suspected causes in patients who met the NIAID/FAAN criteria and in patients who were given a diagnosis of anaphylaxis by allergists

	Overall (n = 214), no. (%)	Patients who met NIAID/FAAN criteria (n = 86), no. (%)	Patients who were given diagnosis anaphylaxis by allergists (n = 61), no. (%)
Female sex	119 (55.6)	50 (58.1)	30 (49.2)
Age (y)			
Median	36	34	34
Interquartile range	17.8-56	12.8-50.3	12.5-49.5
Suspected cause			
Food	52 (24.3)	33 (38.4)	29 (47.5)
Medication	56 (26.2)	23 (26.7)	11 (18.0)
Venom	34 (15.9)	11 (12.8)	12 (19.7)
Contrast	5 (2.3)	2 (2.3)	2 (3.3)
Immunotherapy	2 (0.9)	1 (1.2)	2 (3.3)
Latex	1 (0.5)	1 (1.2)	0
Vaccine	2 (0.9)	0	0
Other	17 (7.9)	2 (2.3)	0
Unknown	45 (21.0)	13 (15.1)	5 (8.2)

The second patient had diffuse urticaria and oral edema after a wasp sting. These symptoms represent a generalized reaction to venom from a stinging insect and thus could be considered a precursor to anaphylactic reactions or potentially anaphylaxis with only mucocutaneous symptoms.¹⁰ The NIAID/FAAN criteria do not allow for the earlier possibility because oropharyngeal edema is considered to be of cutaneous origin.

Twenty-seven (31.4%) patients who met the NIAID/FAAN criteria for anaphylaxis were not given a diagnosis of anaphylaxis

TABLE II. Two-by-two table relating diagnoses by the 2 allergists

Diagnosis of anaphylaxis by allergist 1				
Diagnosis of anaphylaxis by allergist 2	Count	Yes	No	
	Column %			
Yes	Row %	49	14	63
		89.09	8.81	
		77.78	22.22	
No		6	145	151
		10.91	91.19	
		3.97	96.03	
		55	159	214

by the board-certified allergists. The specificity of the NIAID/FAAN criteria using criterion 1, 2, or 3 was 82.4%. In the diagnosis of anaphylaxis, high sensitivity is preferred over optimal specificity to maximize the number of anaphylaxis cases detected in the ED setting. The significance of failing to recognize and diagnose anaphylaxis lies in the missed opportunity to prevent potential future fatal episodes. A study of fatal anaphylaxis found that of 139 fatalities, only 22% of patients with food allergy and 18% of patients with venom allergy who had a fatal anaphylactic episode had a previous history of severe allergic reactions.¹¹ A similar study of fatal and near-fatal anaphylaxis found that the previous allergic event had required urgent hospital intervention in one third of fatal reactions and one sixth of near-fatal reactions.¹² Even in cases in which the criteria are met but the diagnosis is uncertain, follow-up with an allergist might be important to confirm or refute the diagnosis, to perform allergy testing (if indicated), and to facilitate patient education.

TABLE III. Frequency of organ system involvement and presenting signs and symptoms in patients who did or did not meet the NIAID/FAAN criteria

	Patients who met NIAID/FAAN criteria, n = 86 (%)	Patients who did not meet NIAID/FAAN criteria, n = 128 (%)
Skin and/or mucosal tissue	86 (100)	87 (68.0)
Generalized hives	52 (60.5)	37 (28.9)
Pruritus	36 (41.9)	60 (46.9)
Angioedema	38 (44.2)	31 (24.2)
Flushing/diaphoresis	26 (30.2)	7 (5.5)
Respiratory compromise	77 (89.5)	13 (10.2)
Dyspnea	62 (72.1)	10 (7.8)
Wheeze/bronchospasm/reduced PEF	21 (24.4)	5 (3.9)
Stridor	2 (2.3)	0
Cough	10 (11.6)	2 (1.6)
Voice change	20 (23.3)	2 (1.6)
Cyanosis/hypoxemia	2 (2.3)	0
Reduced BP or associated end-organ dysfunction involvement	21 (24.4)	3 (2.3)
Hypotension	11 (12.8)	1 (0.8)
Hypotonia/collapse/presyncope/sudden weakness	17 (19.8)	3 (2.3)
Syncope	2 (2.3)	0
Incontinence	0	0
Gastrointestinal symptoms	31 (36.1)	7 (5.5)
Crampy abdominal pain	8 (9.3)	2 (1.6)
Nausea	17 (19.8)	3 (2.3)
Vomiting	14 (16.3)	2 (1.6)
Diarrhea	4 (4.7)	3 (2.3)

BP, Blood pressure; PEF, peak expiratory flow.

TABLE IV. Test characteristics of NIAID/FAAN criteria for the diagnosis of anaphylaxis compared with the reference standard of allergist's diagnosis

Test characteristics	Criterion 1, 2, or 3	Criterion 1	Criterion 2	Criterion 3
Patients meeting criterion (n)	86	79	71	5
Patients given diagnosis of anaphylaxis (n)	59	53	53	5
Sensitivity, % (95% CI)	96.7 (88.8-99.1)	86.9 (76.2-93.2)	86.9 (76.2-93.2)	8.9 (4.0-18.5)
Specificity, % (95% CI)	82.4 (75.5-87.6)	83.0 (76.3-88.1)	88.2 (82.2-92.4)	99.7 (97.0-100)
Positive predictive value, % (95% CI)	68.6 (58.2-77.4)	67.1 (56.1-76.4)	74.6 (63.4-83.3)	91.7 (51.7-99.1)
Negative predictive value, % (95% CI)	98.4 (94.5-99.6)	94.1 (88.7-97.0)	94.4 (89.3-97.1)	73.1 (66.7-78.6)
Likelihood ratio of a positive test result	5.48	5.1	7.39	27.32
Likelihood ratio of a negative test result	0.04	0.16	0.15	0.91

TABLE V. Two-by-two table relating patients who met the NIAID/FAAN criteria and patients with allergists' diagnosis of anaphylaxis

Patients met NIAID/FAAN criteria	Allergists' diagnosis of anaphylaxis		
	Yes	No	
Yes	59	27	86
No	2	126	128
	61	153	214

The lack of prospectively validated diagnostic criteria for anaphylaxis has likely contributed to the underdiagnosis of anaphylaxis in the ED. True estimates of anaphylaxis in the ED have been difficult to ascertain and have likely resulted in the significant underestimation of the burden of anaphylaxis in the United States.⁵ Several studies have reported that a diagnosis of an

allergic reaction is used by emergency physicians to make a diagnosis of multisystem organ involvement in patients who should have received a diagnosis of anaphylaxis.^{3-5,13} Recent studies on the ED management of food-induced and insect sting-induced acute allergic reactions found that 51% of patients given a diagnosis of allergic reactions caused by food and 31% of patients given a diagnosis of insect sting allergy were, in fact, found to have had anaphylaxis.^{3,4} This is not a new finding because a study by Klein and Yocum¹³ in 1995 found that only 23% of patients with anaphylaxis were given a diagnosis of anaphylaxis by the emergency physician; most were given a diagnosis of an allergic reaction. In our study 65.6% of patients with an allergist's diagnosis of anaphylaxis were also given a diagnosis of anaphylaxis by emergency physicians. This suggests a modest, although potentially clinically important increase in the recognition of anaphylaxis in ED patients.

Our study has several limitations. The reliance on expert opinion for the reference standard could be considered a limitation. There are no objective independent tests for anaphylaxis. We

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

Suspected alternate diagnosis	No. of patients, n = 27	No. of patients with mucocutaneous involvement, no. (%)	No. of patients with respiratory compromise, no. (%)	No. of patients with cardiovascular involvement or end-organ dysfunction, no. (%)	No. of patients with gastrointestinal symptoms, no. (%)
Indeterminate reaction	8	8 (100)	8 (100)	1 (12.5)	2 (25)
Nonsteroidal anti-inflammatory drug reaction	2	2 (100)	2 (100)	0	0
Other medication reaction	8	8 (100)	6 (75)	2 (25)	2 (25)
Allergic reaction	2	2 (100)	2 (100)	0	1 (50)
Asthma exacerbation	2	2 (100)	2 (100)	1 (50)	2 (100)
Anxiety	2	2 (100)	2 (100)	0	0
Carcinoid syndrome	1	1 (100)	1 (100)	1 (100)	0
Postviral syndrome	1	1 (100)	1 (100)	0	0
Oral allergy syndrome	1	1 (100)	1 (100)	1 (100)	1 (100)

sought to overcome this limitation by blinding each allergist to whether the NIAID/FAAN criteria were met, as well as to the other allergist's independent conclusions. The NIAID/FAAN criteria are based on the concept of a multisystem allergic reaction and provide examples of particular signs or symptoms that represent involvement of a particular organ system. Thus the inclusion of additional signs or symptoms could affect the sensitivity and specificity. Additionally, the fact that our cohort is predominantly white might limit the external validity of the study. The fixed zero-cell correction meets the objective of avoiding computational errors; however, it has the undesirable effect of biasing study estimates toward no difference and overestimating variances of study estimates and can introduce directional bias in the treatment effect. Finally, because of the retrospective design, the quality of the data is dependent on the accuracy of the medical record. To decrease the effect of these limitations, patients were enrolled as a consecutive cohort, decreasing the baseline measurement and selection biases. To reduce the random and systematic errors, we enhanced the precision and accuracy of the variables collected using a standardized measurement method and predesigned data abstractions forms.

Our results suggest that the NIAID/FAAN criteria are highly sensitive but less specific. However, prospective validation should be performed with the goal of optimally detecting and quantifying the severity of anaphylaxis in the ED setting. Until prospectively validated clinical criteria or rapidly available sensitive biomarkers are available, anaphylaxis will likely continue to be underrecognized in the ED setting.

Clinical implications: Many patients meeting the NIAID/FAAN criteria have anaphylaxis, although some might not (positive predictive value, 68.6%). However, patients not meeting the criteria are very unlikely to have anaphylaxis (negative predictive value, 98.4%).

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