

Anaphylaxis: Diagnostic criteria and epidemiology

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ABSTRACT

Evaluation of anaphylaxis is a common reason for emergency department referral to an allergist. Establishing unified diagnostic criteria has been an evolving process with the most recent definition proposed by the Second Symposium on the Definition and Management of Anaphylaxis convened by the National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network. Proper identification of these patients in the emergency department allows for the opportunity to dispense potentially life-saving epinephrine autoinjectors, provide education, and allergist referral. Future epidemiological studies are likely to be impacted as the definition of anaphylaxis becomes more unified.

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A history of anaphylaxis is one of the many reasons patients are referred to an allergist. The diagnosis of anaphylaxis is commonly made or suspected during an emergency department visit, because this is where patients most frequently undergo the initial evaluation of severe allergic reactions.^{1,2} The correct diagnosis has implications for future prevention and proper treatment in these patients. Historically, this has been a challenge, at least in part because of the lack of universally agreed on diagnostic criteria for anaphylaxis and the evolving definition of anaphylaxis.

HISTORY OF THE DEFINITION OF ANAPHYLAXIS

The first Joint Task Force of Practice Parameter on anaphylaxis was published in 1998. In this document, anaphylaxis was defined as “an immediate systemic reaction caused by rapid, IgE-mediated immune release of potent mediators from tissue mast cells and peripheral blood basophils” and anaphylactoid reactions as “immediate systemic reactions that mimic anaphylaxis but are not caused by IgE-mediated immune responses.”³ In this document, clinical anaphylaxis was defined as a generalized reaction that included “pruritus, urticaria, angioedema, hypotension, wheezing, bronchospasm, nausea, vomiting, abdominal pain, di-

arrhea, uterine contractions, and cardiac effects.”³ These symptoms were stated as occurring “singly or in various combinations.”³

The first “Symposium on the Definition and Management of Anaphylaxis,” convened by the National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network (NIAID/FAAN), occurred in 2004.⁴ This symposium acknowledged the need for a more consistent clinical definition of anaphylaxis to improve the recognition and management of anaphylaxis. In this document,⁴ the authors put forth a preliminary proposal of clinical criteria for anaphylaxis involving three separate criteria. The second “Symposium on the Definition and Management of Anaphylaxis” convened by the NIAID/FAAN in 2005 modified the original criteria to establish the current clinical criteria.⁵

CURRENT DIAGNOSTIC CRITERIA AND DEFINITION

The participants of the “Second Symposium on the Definition and Management of Anaphylaxis” defined anaphylaxis as “a serious allergic reaction that is rapid in onset and may cause death.”⁵ The initially proposed clinical criteria were revised to identify patients who were likely experiencing an anaphylactic reaction in the acute setting to optimize recognition and appropriate management (Fig. 1). Recognition of frequently seen symptoms of anaphylaxis, such as flushing, provides opportunity to administer appropriate therapy early in the course. These clinical criteria have also been accepted by the World Allergy Organization and were included in the “Guidelines for the Assessment and Management of Anaphylaxis” and the 2010 Joint Task Force Practice Parameter on anaphylaxis.^{6,7} In

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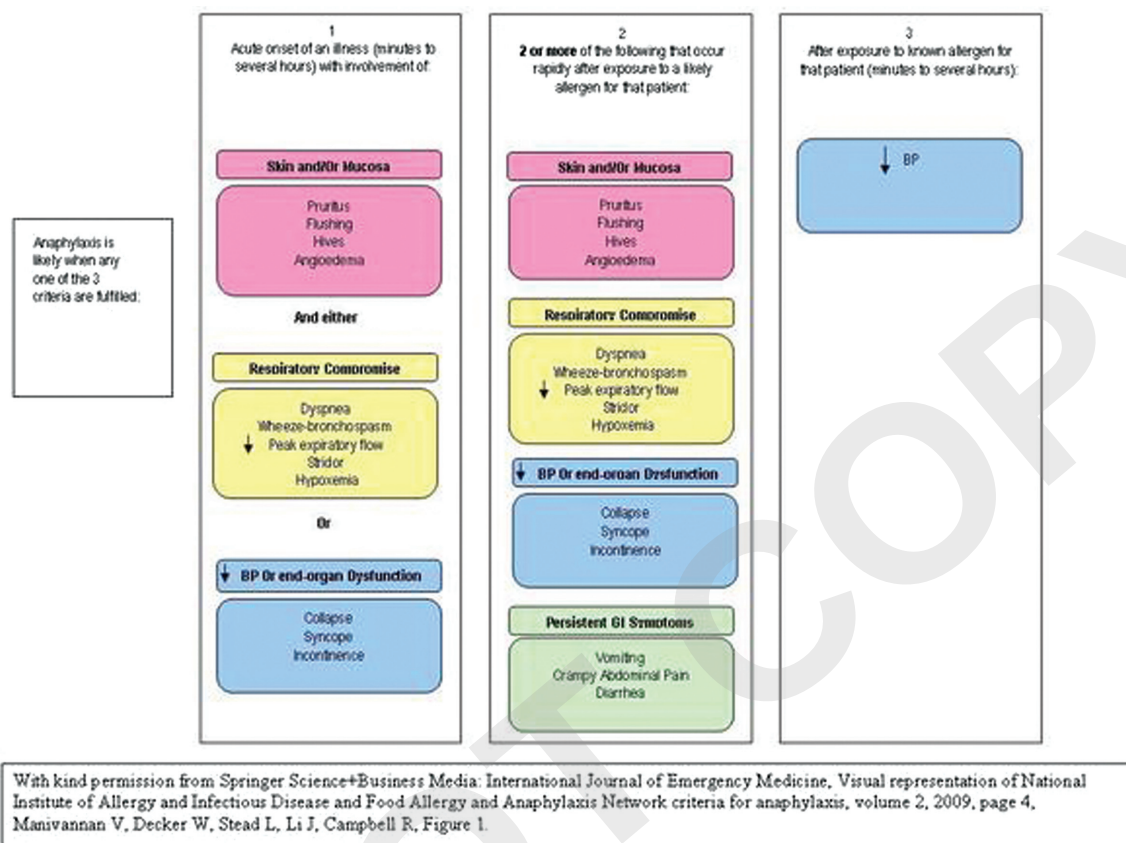


Figure 1. National Institutes of Health Food Allergy and Anaphylaxis Network criteria for anaphylaxis.

addition, biphasic reactions can occur in up to 20% of patients and can occur from 1–78 hours after the initial event. However, most biphasic reactions occur within ~8 hours.⁸

In addition, there has been a movement away from defining reactions that are IgE mediated as anaphylactic and non-IgE mediated as anaphylactoid. Rather, regardless of initiating mechanism, all reactions consistent with anaphylaxis are deemed to be “anaphylactic reactions.”⁹

A recent study was conducted to evaluate the accuracy of the NIAID/FAAN criteria proposed at the “Second Symposium on the Definition and Management of Anaphylaxis” in emergency department patients.¹⁰ The NIAID/FAAN criteria were compared with a reference standard of the diagnosis made by two independent board-certified allergists. Electronic medical records from patients diagnosed with allergic reaction, anaphylaxis, or a sample of related diagnoses were reviewed from April to October 2008. A total of 214 patients were identified. Of these, 86 (40.2%) met the NIAID/FAAN criteria for anaphylaxis, and 61 (28.5%) of these patients were given a diagnosis of anaphylaxis by allergists. Of these 61 patients, 59 met NIAID/FAAN criteria. Therefore, the sensitivity of the NIAID/FAAN criteria was high (96.7%), but

specificity was somewhat lower (82.4%). The negative predictive value was also high (98.4%), indicating that patients who do not meet the NIAID/FAAN criteria are very unlikely to have anaphylaxis. The positive predictive value was 68.6%, meaning that of 100 patients meeting NIAID/FAAN criteria, 69 would have anaphylaxis. Thus, although the NIAID/FAAN criteria are likely to be a useful tool for identification of patients with possible anaphylaxis in the emergency department, they can not replace clinical judgment.¹¹

EVALUATION OF ANAPHYLAXIS

To identify triggers of anaphylaxis, it is important to elicit a careful history of exposures and activities performed by the patient in the hours leading up to the suspected reaction (Table 1). Some of these triggers for anaphylaxis include food, medications, insect stings, and latex exposure. In addition, important historical information to elicit should include medication ingestion (prescription, nonprescription, supplements, etc.), food ingestion (consider scombroid reaction associated with fish), exercise, ethanol, insect sting versus bite, atopic status, environmental conditions (temperature and location), and, in women, menstrual cycle.^{6,7}

Table 1 Causes of anaphylaxis

Foods

North America—Cow's milk, egg, peanut, tree nut, shellfish, and fish
Galactose α -1,3 galactose
Europe—Fruits
Middle East—Sesame
Asia—Buckwheat, chickpea, and rice

Insect

Stinging—Hymenoptera (Apidae and Vespidae) and Formicidae (ant)
Biting—Kissing bugs, mosquitoes, and ticks

Medications

Antibiotics—Penicillin, cephalosporins, and fluoroquinolones
Antiviral agents
Antifungal agents
NSAIDS
Chemotherapeutics and biological agents
Oversulfated chondroitin sulfate in heparin
Vaccines—Usually secondary to a nonimmunizing component, *i.e.* gelatin and egg

Mast cell disorders

Mast cell activation syndrome
Mastocytosis

Others

Radiocontrast media and fluorescein dye
Perioperative agents
Neuromuscular agents, antimicrobials, latex, opioids, colloid plasma expanders, protamine, chlorhexidine, and blood transfusions
Allergen skin testing and allergen-specific immunotherapy
Natural rubber latex
Seminal fluid
Airborne allergens (rare)
Idiopathic anaphylaxis
Exercise-induced (likely associated with concomitant food intake)

Source: Refs. 6 and 9.

NSAIDs = nonsteroidal anti-inflammatory drugs.

Laboratory testing can be useful to support a diagnosis of anaphylaxis. However, it is not universally available and when available, results are often not timely enough to guide clinical management of an acute reaction. Furthermore, many serum markers have limited sensitivity. Plasma histamine is the first mediator to rise (5–10 minutes) and peak and should be measured within 1 hour of symptoms.⁷ Because of the difficulty in collecting the specimen and sampling conditions needed to accurately measure histamine, it is not often obtained.^{6,7} Serum tryptase peaks 1–1.5 hours after the onset of symptoms and can persist up to 5–6 hours. Commercially available testing reagents measure total tryptase, and serum levels are ideally drawn within 3 hours of symptoms.^{6,7} Urinary metabolites such as *N*-methylhistamine and 11- β -prostaglandin F2 α can also be measured in 24-hour urine collections to evaluate for mast cell mediator release.

Further evaluation of the cause of the anaphylactic episode could involve additional focused diagnostic testing based on the clinical history. This could include skin-prick/intradermal and serum-specific IgE. If testing is initially negative, repeat testing in ~4 weeks should be pursued.^{5,9} Challenge testing could be useful in a closely monitored situation after appropriate informed consent. In patients with a history suspicious for a mast cell disorder, a baseline serum total tryptase should be obtained as well as a possible bone marrow biopsy, to assess for multifocal dense aggregates of abnormal mast cells, aberrant CD25 on mast cells, and assessment for KIT mutation. The KIT abnormality is most commonly associated with the D816V mutation, which leads to a gain of function of the tyrosine kinase portion of KIT, which interacts with stem cell factor, which promotes mast cell proliferation and survival.¹²

Table 2 Research criteria defining anaphylaxis

As at least one symptom of generalized mediator release

Flushing; generalized pruritus; pruritus or paresthesias of lips, axilla, hands, or feet; urticaria; angioedema; lip tingling/paraesthesia; conjunctivitis; or chemosis

At least one additional symptom involving the oral and gastrointestinal tract, or respiratory or cardiovascular system

Oral—Oral mucosal pruritus; intraoral angioedema of buccal mucosa, tongue, palate, or oropharynx; nausea; emesis; dysphagia; abdominal cramps; or diarrhea

Respiratory—Rhinitis, stridor, cough, hoarseness, aphonia, tightness in the throat, dyspnea, wheezing, hypopharyngeal or laryngeal edema, or cyanosis

Cardiovascular—Chest pain, arrhythmia, hypotension, presyncope, syncope, tachycardia, bradycardia, orthostasis, seizures, or shock

Source: Ref. 20.

EPIDEMIOLOGY

Earlier studies on the epidemiology and prevalence of anaphylaxis previously have been plagued by the lack of a consensus definition of anaphylaxis. In 2006, a review article on the epidemiology of anaphylaxis by the American College of Allergy, Asthma, and Immunology Epidemiology of Anaphylaxis Work Group was published. All relevant articles published in English were reviewed. At the time of the review there was no consensus definition of anaphylaxis. Thus, the articles included were based on the individual author's definition of anaphylaxis. The lifetime prevalence of anaphylaxis was estimated to be between 0.05 and 2.0%. In adults, antibiotics, nonsteroidal anti-inflammatory drugs, and insect stings were the most common causes of anaphylaxis. Anaphylaxis was most common in children and food allergy is the most common etiology in children. In the United States, the most common causative foods were peanut (children), shellfish (adults), tree nuts, fish, eggs, milk, soy, and wheat.¹³

Using the second symposium NIAID/FAAN definition of anaphylaxis, foods remained the most common trigger of anaphylaxis in an urban pediatric population from 2004 to 2008, followed by unknown triggers and medications. Of the 213 episodes that were retrospectively determined to meet criteria for anaphylaxis or required epinephrine administration, only 62 were coded as anaphylaxis. The rates of admission for anaphylaxis were lower in patients with early, premergency department, administration of epinephrine. It was also observed that children using Medicaid had less frequent administration of epinephrine before presentation to the emergency department for an episode of anaphylaxis.¹⁴ There has also been some evidence of higher rates of anaphylaxis in the northern United States as opposed to southern states, as well as epinephrine autoinjector prescriptions.^{15,16} In 2005–2006, using ICD-9-CM anaphylaxis codes, an ICD-9-CM-based algorithm, age-adjusted incidence rates of emergency department visits for anaphylaxis in Florida

were reported to be 6.6/100,000 per year from male subjects and 8.7/100,000 per year for female subjects.¹⁷ Hospitalization rates for anaphylaxis have also increased dramatically internationally. In Australia, the rates of hospitalizations for anaphylaxis, using ICD-9-CM data, over a span of 10 years increased by 8.8% per year with even marked increase in children <5 years of age secondary to food ingestion.¹⁸ Overall, food allergy has been shown to be increasing in children in recent years, also with more severe initial presentation including anaphylaxis.¹⁹

Two different studies based on the population of Olmsted County, MN, characterize the evolving epidemiology of anaphylaxis in this population. The first retrospective study by Yocum *et al.*,²⁰ provided a detailed description of clinical criteria used to define anaphylaxis (Table 2). The study analyzed data from 1983 to 1987. Two exceptions that were classified as anaphylaxis include isolated laryngeal edema or immediate shock and syncopal event after injection or medication or radiocontrast. In total there were 154 episodes of anaphylaxis among 133 residents. The authors concluded that anaphylaxis occurrence rate was 30 per 100,000 person-years and the annual incidence rate was 21 per 100,000 person-years (<1% incidence). The peak incidence occurred from July through September, likely accounted for by increase in insect sting. The most frequently suspected allergens were food, medication, or insect sting. Approximately one-half of the cohort had underlying atopic disease. One hundred percent of the cohort had some form of cutaneous manifestation and 69% had respiratory symptoms.²⁰

The second study by Decker *et al.* was also a retrospective population-based incidence study based out of Olmsted County from 1990 to 2000.²¹ The authors used the same definition of anaphylaxis as Yocum *et al.*²⁰ Two hundred eleven cases of anaphylaxis were identified of which 118 were female subjects. Overall age- and sex-adjusted incidence rate was 49.8 per 100,000 person-years, with ages 0–19 years having the

highest incidence. The mean age was 29.3 years, 84.4% were white, and 41.2% of patients did not have a previous history of atopy. Overall, food accounted for 33.2% of reactions, insect sting accounted for 18.5%, medication accounted for 13.7%, contrast agent accounted for 0.5%, others accounted for 9.0%, and 25.1% of cases did not have an identifiable trigger. Again, the peak incidence was July through September. The most common signs and symptoms were mucocutaneous and respiratory. The authors found that the incidence rates significantly increased from 46.9 per 100,000 person-years in 1990 to 58.9 per 100,000 person-years in 2000. Reanalysis of data using the NIAID/FAAN clinical criteria revealed that three of the cases would have been excluded but results were not significantly changed.²¹

CONCLUSIONS

The establishment of clear and clinically relevant guidelines for diagnosis and management of anaphylaxis in emergency department and urgent care settings are important because most patients are initially evaluated in these settings. The NIAID/FAAN criteria at present are internationally the most widely accepted diagnostic clinical criteria and appear to be useful for the identification of patients who might be experiencing anaphylactic reactions. Earlier identification may lead to more rapid epinephrine administration, increased monitoring for potential biphasic reactions, increased prescriptions for epinephrine autoinjectors, and decreased morbidity and mortality. Furthermore, a referral to an allergist would be beneficial for the patient to determine the nature of the agent that triggered his/her anaphylactic reaction, to counsel on decreasing the risk of future reactions, and to re-review epinephrine autoinjector usage and technique. Finally, the evolving definition and diagnostic criteria are likely to impact epidemiological studies of anaphylaxis.

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