SUPPLEMENT ARTICLE

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Recognition and First-Line Treatment of Anaphylaxis

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ABSTRACT

The International Classification of Diseases (ICD)-9 included a code only for anaphylactic shock. The improved ICD-10 coding defines the different symptoms and types of anaphylaxis and includes coding for anaphylaxis without shock. This new coding is consistent with the efforts of the National Institute of Allergy and Infectious Diseases (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN), who convened a panel to formulate a definition of and the diagnostic criteria for anaphylaxis. Anaphylaxis is a serious reaction that has a rapid onset and may cause death. It is a systemic immunoglobulin E-mediated reaction resulting from the sudden release of multiple mediators from mast cells and basophils. Foods are the most common triggers for anaphylactic reactions, followed by drugs, insect stings, and idiopathic anaphylaxis (anaphylaxis of unknown cause). If the NIAID/FAAN criteria are met and anaphylaxis is diagnosed, epinephrine administration is mandatory. Delays in epinephrine administration have been associated with fatalities. Patients should have ready access to >1 epinephrine autoinjector in the outpatient setting. An individualized emergency action plan should be developed for each patient at risk for anaphylaxis.
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KEYWORDS: Allergy; Anaphylaxis; Emergency action plan; Epinephrine; Epinephrine autoinjectors; Patient education

In 2005, the National Institute of Allergy and Infectious Diseases (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) convened a panel to come to a consensus on a definition for anaphylaxis.[1] (Note: As of November 12, 2012, FAAN merged with the Food Allergy Initiative under the name Food Allergy Research & Education [FARE].) For the general public, they defined anaphylaxis as a serious reaction that has rapid onset and may cause death. For health care professionals, anaphylaxis was characterized as a systemic reaction resulting from the sudden release of multiple mediators from mast cells and basophils, often life threatening, and usually unexpected. The World Allergy Organization (WAO) has divided anaphylaxis into *immunologic* (further divided into immunoglobulin E [IgE]-mediated and non-IgE-mediated), *nonimmunologic*, and *idiopathic* causes.[2] If the cause is nonimmunologic, a reaction may occur on the first exposure to an allergen. An alternative terminology refers to IgE-mediated reactions as *anaphylactic*, with all other reactions designated as *anaphylactoid*. These 2 classification methods are compared in **Figure 1**.[2,3]

DIAGNOSTIC CRITERIA FOR ANAPHYLAXIS

The NIAID/FAAN definition of anaphylaxis has been translated into clinical diagnostic criteria.[1] **Figure 2** should be consulted for details, but criteria include an acute onset of illness (minutes to hours) and involvement of the dermatologic, respiratory, cardiovascular, or gastrointestinal systems. The number of criteria required to be met depends on whether an allergen exposure is unknown, likely, or

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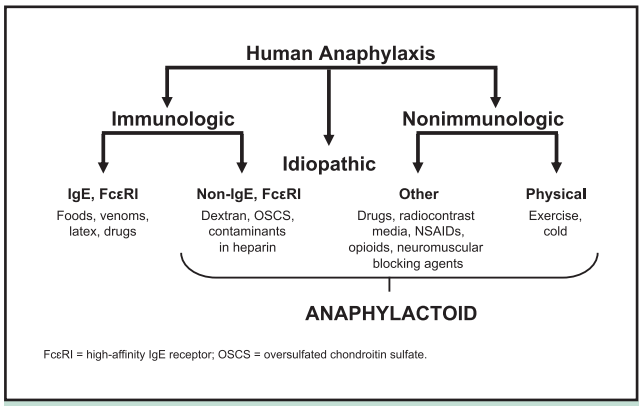

Figure 1 Classification of human anaphylaxis, comparing the immunologic/nonimmunologic/idiopathic scheme proposed by the World Allergy Organization and the anaphylaxis/anaphylactoid terminology. (Adapted with permission from *J Allergy Clin Immunol* © 2006 Elsevier.[3])

known. The NIAID/FAAN criteria were validated specifically in the emergency department (ED), with a sensitivity of 96.7% and a specificity of 82.4%, suggesting a highly sensitive set of parameters with lower specificity.[4] Thus, these criteria likely will be useful in the ED setting for the diagnosis of anaphylaxis. When these criteria are met and a subsequent diagnosis of anaphylaxis is made, it is mandatory to administer epinephrine.[1,5,6]

However, exceptions to these criteria, which are often overlooked by the reader, are addressed in the text of the consensus article.[1] For example, a child who is known to be allergic to peanuts initially may present only with cutaneous manifestations and therefore not meet the criteria for anaphylaxis, yet this child should be treated with epinephrine regardless.

CLINICAL MANIFESTATIONS OF ANAPHYLAXIS

Anaphylaxis affects many different organ systems. Mucocutaneous manifestations are most common, followed by the respiratory, cardiovascular, gastrointestinal, and other systems. **Table 1** presents the frequency of occurrence of the signs and symptoms of anaphylaxis.[7] The differential diagnosis of anaphylaxis includes many possibilities, but the most prominent include septic shock, vasovagal reaction, cardiogenic shock, and hypovolemic shock.

Anaphylactic reactions have 3 basic patterns: uniphasic, biphasic, and protracted reactions. A uniphasic reaction occurs as an isolated reaction producing signs and symptoms typically within 30 minutes of exposure to an offending stimulus and resolving spontaneously or with treatment, usually within 1-2 hours.[5,6] In a biphasic response, the initial reaction is followed by a second wave of symptoms after resolution (spontaneously or with treatment) of the first phase.[5,6] Most biphasic reactions occur within 8 hours of the patient's first symptoms. Up to 20% of patients experience a biphasic reaction; thus, it is particularly important that patients be observed in the ED or elsewhere after an episode. The preferred duration of the observation period has not been established, but 6-8 hours (or more) after an event is reasonable. A protracted anaphylactic reaction is a severe reaction that may last for a prolonged period of time (eg, 24-32 hours), and may include protracted shock and respiratory distress despite aggressive and appropriate therapy.[6,8]

EPIDEMIOLOGY OF ANAPHYLAXIS

The epidemiology of anaphylaxis is difficult to assess, in part, because of a lack of universally accepted definitions or criteria for diagnosis and no requirement to report fatal

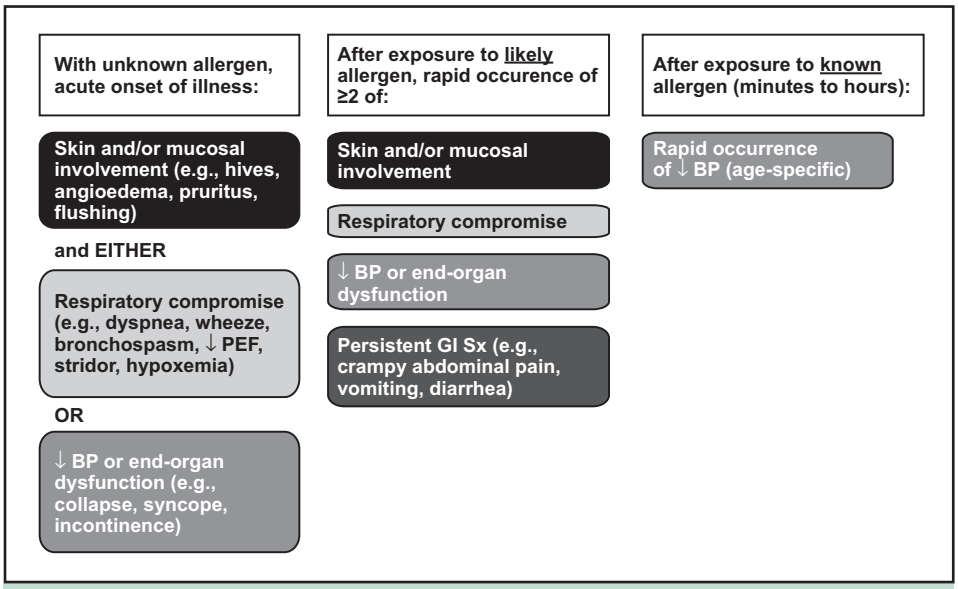

Figure 2 Clinical criteria for the diagnosis of anaphylaxis.[1]

Table 1 Signs and Symptoms of Anaphylaxis

Signs and Symptoms	Frequency (%)
Urticaria, angioedema	88
Dyspnea, wheeze	47
Dizziness, syncope, hypotension	33
Nausea, vomiting, diarrhea, cramping abdominal pain	30
Flush	46
Upper airway edema	56
Headache	15
Rhinitis	16
Substernal pain	6
Pruritus without rash	5
Seizure	2

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or serious anaphylactic events, likely resulting in its underdiagnosis.[1,4,5] As described previously, the NIAID/FAAN diagnostic criteria have been validated in the ED and may prove useful for emergency health care professionals in assessing and diagnosing anaphylaxis and thus lead to increased reporting of anaphylactic events.[4]

The American College of Allergy, Asthma and Immunology convened a round table of physicians interested in the epidemiology of anaphylaxis in 2006 to estimate its incidence.[9] The round table discussion led to an improved estimation of the frequency of anaphylaxis: approximately 50 to 2000 episodes per 100,000 persons, or a lifetime prevalence of 0.05% to 2.0%. The incidence of anaphylaxis was approximately 1% when calculations were based on epinephrine outpatient dispensing data, with patients aged <17 years (1.44%) having a slightly higher incidence than older age groups (0.9% for individuals aged 17-64 years and 0.32% for those aged 65 years or older).[10]

The prevalence of anaphylaxis has been increasing, as is allergy in general.[11-15] For example, Lin and colleagues[11] evaluated hospitalizations for patients with allergic diseases (ie, anaphylaxis, angioedema, urticaria, or unspecified allergy) as the primary diagnosis from 1990 to 2006 in New York State (**Figure 3**). They found that for those aged <20 years, the anaphylaxis hospitalization rate had increased >4-fold during this time period.

Geographic location may influence the incidence of anaphylaxis. Sheikh and Alves[16] found that rural areas had higher rates of anaphylaxis than urban environs in a study of emergency admissions to hospitals in England between 1991 and 1995.[16] Sheehan et al[17] also reported that the incidence of food-induced anaphylaxis was nearly double in the northern US than in southern areas. A north-south gradient in the US also has been observed for the dispensing of epinephrine autoinjectors, with increased dispensing in the north.[18] Australian data also have shown an association between distance from the equator and risk of anaphylaxis (ie, greater risk with more southern latitudes in the Southern Hemisphere).[19] These observations imply a protective role for exposure to sunlight and possibly increased vitamin D levels.[19] In addition to geography, other risk factors for anaphylaxis include atopy, asthma, female gender, and higher socioeconomic status.[20,21]

COMMON TRIGGERS OF ANAPHYLAXIS

Foods (35%) represent the most common triggers for allergic reactions, followed by drugs and biologics (20%), insect stings (20%), exercise (5%), and vaccines (3%).[22] Idiopathic or unknown causes account for approximately

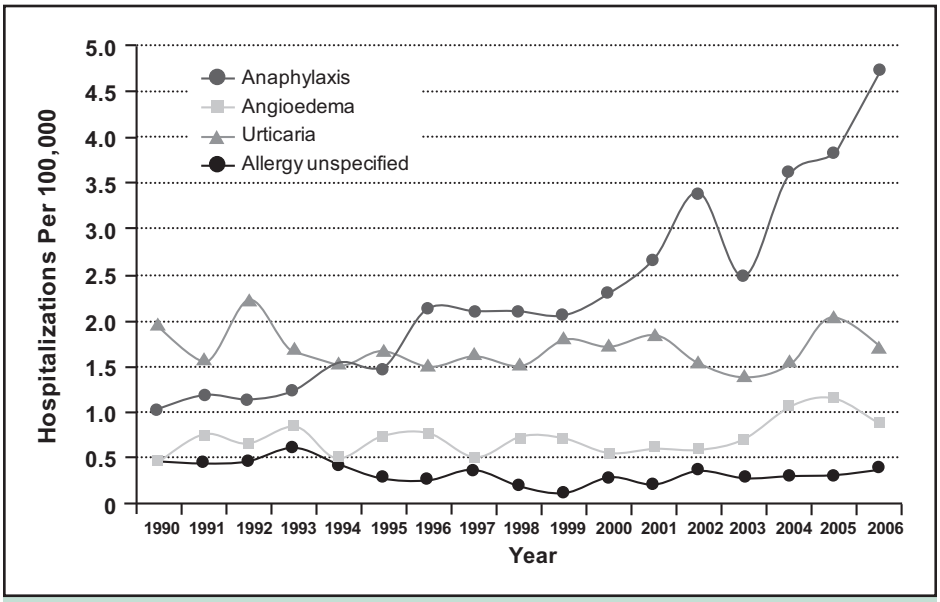

Figure 3 Increasing anaphylaxis hospitalizations in New York State (1990-2006). (Reprinted with permission from *Ann Allergy Asthma Immunol* © 2008 Elsevier.[11])

one fifth of remaining cases. Although triggers ultimately may be found for most cases of idiopathic anaphylaxis, there does seem to be an intrinsic disorder, currently unidentified, linked to some allergic reactions.

The 8 foods responsible for >90% of serious allergic reactions in the US are fin fish, shellfish, peanuts, tree nuts, milk, eggs, wheat, and soy.[23] In children, a recent survey suggests the prevalence of food allergies is 8.0%, an increase from previous reports.[12] Among these young patients, 38.7% reported severe reactions and 30.4% had multiple food allergies. Peanuts, milk, and shellfish allergies demonstrated the highest prevalence in the pediatric population. The odds of having a food allergy were related to race, age, income, and geographic location.

Allergy to any specific food may change over time, with a patient growing out of some allergies while developing allergies to new foods. While exposure to food allergens outside the home is a large concern, the household remains the most common site for exposure.[24] Patients and caregivers must remember that the severity of any single reaction does not predict the severity of future episodes, so a minimal or no reaction to food on a single exposure does not guarantee similar safety with subsequent exposure. In another article in this supplement, Dr Ruchi Gupta addresses in depth the special considerations surrounding the treatment of adolescents and young adults.[25]

MANAGING ANAPHYLAXIS

The International Classification of Diseases (ICD)-9 codes included only anaphylactic shock, omitting the majority of anaphylactic reactions that occur in patients who do not experience shock. If not acutely in shock, many patients do not receive epinephrine, although it should be administered to anyone even at risk for progressing to anaphylactic shock (eg, when a patient's sole symptom is hives). ICD-10 coding has improved on this.

The first principle of management is avoidance of allergens. During an acute episode of anaphylaxis, health care professionals usually do not have time to evaluate potential causes, so follow-up is needed with the patient's primary care physician or an allergist to identify the anaphylactic trigger.[6,7] A detailed history of potential exposures to foods, medications, latex, and insects must be taken. Skin testing or careful re-exposure to allergens (in selected cases) may be used by trained allergists. Patients should be alerted to the fact that previous tolerance does not rule out a trigger as the cause of a current event. Patients and caregivers must be educated by physicians and other health care professionals about avoiding food allergens outside of the home and hidden allergens.[7] For example, they should routinely read food labels and request detailed information about food and its preparation in restaurants. Knowledge of "cross-reacting" foods is important (eg, a patient who is allergic to peanuts is at risk of a reaction to lupine flour [both being legumes], and someone allergic to shrimp is at risk of reacting to other crustaceans).

Epinephrine is the only first-line treatment of anaphylaxis; it is the sole effective treatment for an acute reaction.[6,7] Delays in administration have been associated with fatalities.[6] Cardiac or respiratory arrest may develop rapidly, occurring within a median time of 5-30 minutes in one study.[26] Approximately one half of deaths (13/25) in one study occurred within 1 hour after the onset of anaphylaxis.[27] Epinephrine autoinjectors, which are available in 0.15-mg and 0.3-mg strengths, must be carried and readily accessible if an allergic reaction is severe and repeated.

Diphenhydramine is the most common drug given in the ED, even though it takes up to 80 minutes for 50% suppression of histamine flare and only affects the histamine mediator of anaphylaxis.[28] Corticosteroids are the second most commonly administered drug in an emergency situation, but they also work slowly. Epinephrine is the treatment of choice as a first response because it acts on multiple receptors and has a maximal pharmacodynamic effect within 10 minutes of intramuscular (IM) administration into the thigh.[29,30] Multiple groups, including the NIAID, the WAO, the International Collaboration in Asthma and Allergy, and the Joint Task Force on Practice Parameters (representing

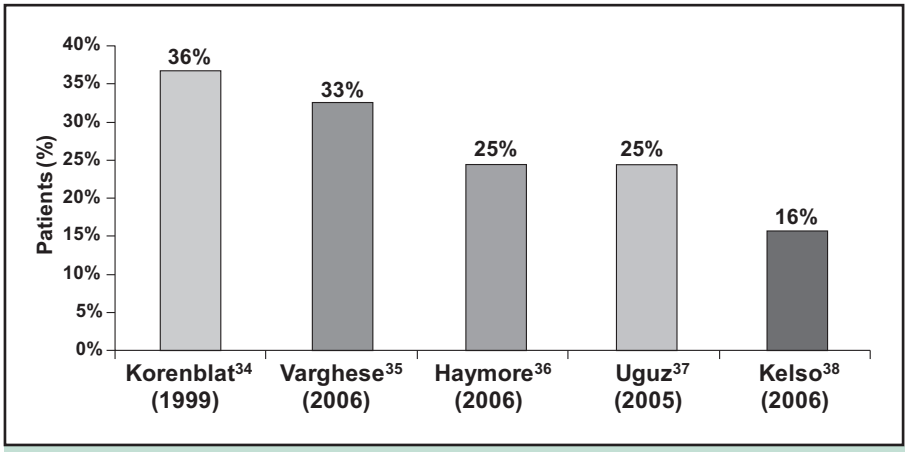

Figure 4 Frequency of need for ≥2 doses of epinephrine, regardless of cause.[34-38]

several professional allergy/asthma organizations) state that epinephrine is an essential treatment for anaphylaxis.[23,31-33]

In 5 studies reviewed, 16% to 36% of patients required more than 1 dose of epinephrine, increasing as the severity of anaphylaxis rose (**Figure 4**).[34-38] For example, Korenblat et al,[34] in a retrospective study of 105 anaphylactic episodes in 88 patients in an outpatient clinic, found that 35.5% of patients required >1 dose of epinephrine. Even 1 in 5 patients with the lowest severity index required >1 dose. Thus, patients must have ready access to more than a single epinephrine autoinjector in the outpatient setting.

As has been noted, failure to administer epinephrine promptly has been linked to fatal anaphylactic reactions.[6] However, even when injected quickly after the onset of symptoms, epinephrine sometimes has failed to be effective, possibly due to rapid progression of anaphylaxis.[30] Another explanation may be delayed absorption of epinephrine.[30] A study in children has shown that the time to maximum plasma concentration (T_{max}) averaged 8 ± 2 minutes with IM EpiPen (n = 8; Mylan Specialty L.P., Basking Ridge, NJ) versus 34 ± 14 minutes with subcutaneous epinephrine (n = 9; $P < .05$),[30] leading the authors to conclude that subcutaneous administration of epinephrine should be reevaluated and IM administration should be used preferentially.

Finally, an individualized emergency action plan should be developed for each patient and is discussed in greater detail later in this supplement, including a template of a plan available online.[39] The American Academy of Allergy, Asthma, and Immunology recommends development of an individualized emergency action plan for any patient at risk for anaphylaxis.[40] It is imperative to stress that health care professionals should not hesitate to administer IM epinephrine when a patient presents with symptoms of anaphylaxis, even if uncertainty about the diagnosis remains. Physicians should train all patients to call 911 immediately at the first signs of anaphylaxis, even after administration of the epinephrine autoinjector. Emergency contacts such as caregivers should be called only after first responders are in transit to the patient experiencing symptoms of anaphylaxis. Asthma inhalers and/or antihistamines should not be the medications of first resort for anaphylaxis.

CONCLUSIONS

Education about anaphylaxis, its triggers, and allergen avoidance is critical for patients and their caregivers. An individualized emergency action plan should be developed for each patient at risk for anaphylaxis. Patients and caregivers should understand that when avoidance of allergens is not possible and anaphylaxis occurs, IM epinephrine delivered into the thigh is the treatment of choice. Epinephrine rapidly antagonizes the pathophysiologic manifestations produced by the multiple mediators that are active in anaphylaxis. The weight-appropriate dose of epinephrine should be administered promptly at the onset of apparent anaphylaxis, and each patient should carry >1 epinephrine autoinjector to manage life-threatening reactions. All patients should receive professional medical attention after an episode.

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