

Anaphylaxis epidemic: Fact or fiction?

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Key word: *Anaphylaxis*

Epidemiologic studies have confirmed a steady increase in the rate of occurrence of asthma, allergic rhinitis, and eczema in recent decades.^{1,2} The magnitude of this increase is so great that the term “epidemic” is correctly used to describe it. The rate of occurrence of anaphylaxis has also reportedly increased during this time, but the magnitude of this increase is more difficult to ascertain with certainty, and it might or might not warrant the designation “epidemic.”¹⁻⁶

Until the mid 20th century, anaphylaxis was reported rarely and sporadically. In the 1950s and 1960s, the first small case series of individuals with anaphylaxis from medications, diagnostic agents, insect venoms, and foods was published, followed in the 1970s by the first case series of individuals with idiopathic anaphylaxis. The first case series of individuals with exercise-induced anaphylaxis and the first case series of those with natural rubber latex-induced anaphylaxis were not reported until the 1980s.⁷

In this issue of the *Journal*, in a retrospective population-based study, Decker et al⁸ report the incidence of anaphylaxis from 1990 to 2000 in Olmstead County, Minnesota, as 49.8/100,000 person-years. They note that during this decade, the incidence varied from year to year, with a low of 20 per 100,000 person-years in 1993 to a high of 70 per 100,000 person-years in 1998, and that although there was no steady increase, the incidence of 49.8 per 100,000 person-years is more than double the incidence reported from 1983 to 1987 in Olmstead County by Yocum et al.⁹ Both of these studies used the resources of the Rochester Epidemiology Project.^{8,9} Recent publications from other areas of the United States and from around the world also suggest an increase in the rate of occurrence of anaphylaxis¹⁻⁶; for example, in the United Kingdom hospitalization for anaphylaxis has recently increased by 700%.^{2,3}

It is difficult to determine whether there truly is an anaphylaxis epidemic. The presentation of anaphylaxis is often enigmatic,

with variable target organ involvement and expression of symptoms. The clinical diagnosis can sometimes be difficult to make because many of the symptoms are subjective and many of the signs are nonspecific. Both overdiagnosis and underdiagnosis occur and have the potential to affect diagnostic coding and epidemiologic studies. It is therefore possible that the dramatic increase in the rate of occurrence of anaphylaxis reported recently is, at least in part, an artifact attributable either to diagnostic issues, including the recently broadened definition of anaphylaxis, or to coding issues.^{10,11} We will examine each of these possibilities in turn.

ANAPHYLAXIS DEFINITION AND CLINICAL CRITERIA FOR DIAGNOSIS

In the past, low blood pressure or shock were often prominent components of the definition of anaphylaxis; however, a new broader definition has recently evolved.^{10,11} The modern definition does not mandate that reduced blood pressure or shock need to be present; indeed, evidence suggests that initial signs and symptoms in patients dying of anaphylaxis are more likely to involve respiratory distress than circulatory collapse, particularly in fatal food-induced anaphylaxis.¹²⁻¹⁶

Anaphylaxis is now briefly defined as “a serious allergic reaction that is rapid in onset and may cause death.”¹¹ It is considered to be highly likely when any 1 of the following 3 clinical criteria are fulfilled:

1. acute onset of illness within minutes to hours, with involvement of the skin or mucosal tissue and at least 1 of the following: respiratory compromise, reduced blood pressure, or associated symptoms of end-organ dysfunction;
2. two or more of the following that occur rapidly (minutes to hours) after exposure to a likely allergen for that patient: skin or mucosal tissue involvement, respiratory compromise, reduced blood pressure or associated symptoms, or gastrointestinal symptoms; or
3. reduced blood pressure that occurs within minutes to hours after exposure to a known allergen for that patient.

ROLE OF LABORATORY TESTS IN DIAGNOSIS

The clinical diagnosis of anaphylaxis is not necessarily corroborated by an increased serum or plasma total tryptase concentration or an increased plasma histamine concentration,¹⁷ and these tests are not routinely performed in anaphylaxis. In the study of Decker et al,⁸ a serum total tryptase level was obtained in only 14 of the 211 patients and was increased in only 5 of these 14 patients (Decker et al, personal communication). Total tryptase and histamine tests have clinically relevant limitations. They are nonspecific markers for anaphylaxis and can be increased in other diseases; plasma histamine concentrations can even be increased if the blood sample is improperly

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Disclosure of potential conflict of interest: F. E. R. Simons received grant support from the Canadian Institutes of Health Research and serves on the advisory boards for Dey, Intelliject, and ALK-Abelló. H. A. Sampson is a consultant for and shareholder in Allertein Therapeutics, LLC; received grant support from the Food Allergy Initiative, the National Institutes of Health, and the National Institute of Allergy and Infectious Diseases; is a consultant/scientific advisor for the Food Allergy Initiative; and is President of the American Academy of Allergy, Asthma & Immunology.

Received for publication October 2, 2008; accepted for publication October 2, 2008.

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J Allergy Clin Immunol 2008;122:1166-8.

0091-6749/\$34.00

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doi:10.1016/j.jaci.2008.10.019

TABLE I. Is anaphylaxis overdiagnosed?

Reasons for potential overdiagnosis of anaphylaxis
Subjective symptoms only*
Nonspecific signs†
Diagnostic error‡
Hyperventilation
Anxiety
Panic attack (difficulty breathing)
Vasovagal episode (faint)
Munchausen syndrome or Munchausen syndrome by proxy (in a child)
Scombroidosis
Anisakiasis

*Overinterpretation of symptoms can occur in highly atopic or highly anxious patients.

†Taken individually, most of the signs of anaphylaxis are nonspecific; it is the symptom patterns in the context of exposure to trigger and the chronology of events that leads to the diagnosis.

‡Anaphylaxis is diagnosed, but the correct diagnosis (eg, one of the entities listed) is missed.

collected or handled. More importantly, serum total tryptase concentrations, the test most widely available in clinical laboratories, are seldom increased in patients with food-induced anaphylaxis, and in most age groups except for the elderly, food is by far the most common trigger of anaphylaxis. Development of laboratory tests with improved sensitivity and specificity that will confirm the clinical diagnosis of an anaphylactic episode in real time is currently the goal of several research groups.¹⁸⁻²¹

IS ANAPHYLAXIS OVERDIAGNOSED?

If the definition of anaphylaxis used to make the diagnosis in an individual patient or used in an epidemiologic study is not stringent enough, anaphylaxis might be overdiagnosed, and this might contribute to the increased incidence reported during the past few years.^{1-6,8} It is unlikely that this happened in studies in which all the International Classification of Diseases, 9th Revision (ICD-9), codes and most of the ICD-10 codes used to identify admissions to the hospital for anaphylaxis included the word “shock.” In some other studies, such as that reported here by Decker et al,⁸ a broader definition of anaphylaxis has been used, and therefore persons with a history of subjective and nonspecific symptoms such as tingling of the lips, axillae, hands, or feet, or subjective respiratory symptoms, such as throat tightness or dyspnea, might be given diagnoses of anaphylaxis and included. However, without a history of antecedent exposure to a likely allergen for that patient, which is not usually available for all patients in epidemiologic studies, such symptoms or signs might or might not indicate anaphylaxis and might allow inclusion of persons with panic attacks, hyperventilation, or presyncope (Table I).

Decker et al⁸ report that about 15% of their cases lacked an identifiable trigger after allergen skin tests and measurement of allergen-specific IgE levels and that no allergy tests were performed in an additional 10% of their patients. Although they use the same definition as that used in the earlier Olmstead County study by Yocum et al,⁹ they also reviewed a sample of records with less specific “allergy” codes, which was not done in the

TABLE II. Is anaphylaxis underdiagnosed?

Reasons for potential underdiagnosis of anaphylaxis
First episode
Trigger not apparent, hidden, or not previously recognized
Idiopathic anaphylaxis
Failure to recognize (by patient or caregiver) because of:
Cognitive, visual or auditory impairment
Neurologic, psychiatric, or psychologic problems*
Use of medications, including sedating H ₁ -antihistamines or recreational drugs, or use of ethanol
Failure to diagnose (by health care professional) because of:
Absence of skin symptoms and signs
Patient not undressed or fully examined
Vulnerable person: infant, elderly
Patient who cannot describe subjective symptoms because of being:
Aphonic or dysphonic
Dyspneic
Unconscious
Reporting of serious or fatal anaphylactic events is not mandatory

*For example, depression, attention deficit hyperactivity disorder, and behavioral issues.

earlier study, and found about 25% of their final 211 cases by reviewing these less specific “allergy” codes.

IS ANAPHYLAXIS UNDERDIAGNOSED?

Despite the previous comments, it is also possible that anaphylaxis has been underrecognized and underdiagnosed in recent epidemiologic studies,^{2-5,8} as it is in real life.⁷ Lack of recognition and diagnosis of anaphylaxis potentially occurs in a variety of clinical situations and for a variety of reasons (Table II). It can be difficult to recognize and diagnose if it is the first episode, if symptoms are mild or fleeting, or if the trigger is not apparent, hidden, or previously unrecognized. An allergen trigger might be novel in one geographic location, age group, or occupational setting but not in others. Idiopathic anaphylaxis with no obvious trigger can also be difficult to diagnose. Individuals might fail to recognize an anaphylaxis episode, either in themselves or in someone for whom they are responsible, because of certain medical conditions or ingestion of medications or chemicals that impair awareness, cognition, and judgment (Table II).^{7,22,23}

Dyspneic patients and those slipping into shock might not be able to describe their symptoms. Skin symptoms, such as pruritus, and signs, such as flushing and hives, which are extremely helpful in the diagnosis, are absent or unrecognized in 10% to 20% of all anaphylaxis episodes and are commonly missed if patients cannot describe pruritus or are not undressed and fully examined during an episode. Hypotension sometimes goes undocumented, especially in infants and young children²⁴ or if epinephrine (adrenaline) is injected before the initial blood pressure measurement is made.

Some health care professionals still think that shock is an essential component of the definition of anaphylaxis and do not make the diagnosis in the absence of reduced blood pressure.^{10,11,25,26} Many of the signs that are strongly associated with hypotension and hypoxia in anaphylaxis are nonspecific, such as confusion, collapse, unconsciousness, incontinence, sweating, presyncope, nausea, vomiting, dyspnea, stridor, and wheezing.²⁶ Even in death, anaphylaxis is underdiagnosed.^{6,15,16}

ISSUES WITH ICD-9 AND ICD-10 CODING FOR ANAPHYLAXIS

Patients with multiple-organ system involvement after exposure to a known allergen are often given diagnoses of an allergic reaction or an acute allergic reaction when the correct diagnosis is in fact anaphylaxis. A study of the emergency department management of food-induced acute allergic reactions found that among 678 patients identified based on ICD-9 codes, 51% should actually have been classified as having anaphylaxis. A similar study of insect sting-induced acute allergic reactions found that 31% of the 617 patients should actually have been classified as having anaphylaxis.^{27,28} The study of Decker et al⁸ found that 25% of the anaphylaxis cases identified had received less specific "allergy" codes.

Even if anaphylaxis is recognized and accurately diagnosed, failure to agree on how to code acute allergic reactions likely contributes to the problem of underdiagnosis. The new ICD-10 codes were put in place for anaphylaxis in 2003, but despite this, anaphylaxis coding remains rare, and only 1% of emergency department visits for acute allergic reactions receive this designation.²⁹

SUMMARY

If one compares the average annual incidence of anaphylaxis in the 5 years from 1993 through 1997 in the Decker et al⁸ study (48/100,000 person-years) with the 5 years from 1983 to 1987 in the Yocum et al⁹ study (21/100,000 person-years), the rate of occurrence has more than doubled. Correcting for the 25% of cases identified in the Decker et al⁸ study because of the broader search methods used compared with the Yocum et al⁹ study, there is still a 71% increase in the average annual incidence of anaphylaxis in the subsequent decade (36/100,000 person-years), clearly indicating an increase in the rate of occurrence in this geographic area. Based on this new evidence⁸ and that previously published,²⁻⁶ we therefore conclude that the term "epidemic" can correctly be applied to anaphylaxis, as it is to asthma, allergic rhinitis, and eczema.

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