

Second symposium on the definition and management of anaphylaxis: Summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium

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There is no universal agreement on the definition of *anaphylaxis* or the criteria for diagnosis. In July 2005, the National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network convened a second meeting on anaphylaxis, which included representatives from 16 different organizations or government bodies, including representatives from North America, Europe, and Australia, to continue working toward a universally accepted definition of anaphylaxis, establish clinical criteria that would accurately

identify cases of anaphylaxis with high precision, further review the evidence on the most appropriate management of anaphylaxis, and outline the research needs in this area. (J Allergy Clin Immunol 2006;117:391-7.)

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Even though anaphylaxis was first described around 100 years ago and is one of the most alarming disorders encountered in medicine, there is no universal agreement on its definition or criteria for diagnosis. Furthermore, this lack of specific criteria for diagnosing anaphylaxis has greatly hampered research into the epidemiology, pathophysiology, and management of this disorder; led to confusion on the part of first responders, emergency personnel, primary care physicians, and patients; and resulted in a failure to diagnose and treat anaphylaxis in a consistent manner.¹⁻³

In an attempt to resolve these problems, the National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) convened a meeting in April 2004 to address these deficiencies.⁴ This 2-day symposium brought together experts and representatives from 13 professional, governmental, and lay organizations to address the issue of defining and managing anaphylaxis. Organizations represented included the American Academy of Allergy, Asthma and Immunology; the American Academy of Emergency Physicians; the American Academy of Family Physicians; the American Academy of Pediatrics; the American College of Allergy, Asthma and Immunology; the American College of Emergency Physicians; the

Abbreviations used

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

American Society of Anesthesiologists; the Centers for Disease Control and Prevention; the Food Allergy Initiative; the International Life Sciences Institute; the National Association of EMS Physicians; the Society for Academic Emergency Medicine; and the US Food and Drug Administration. Clinical criteria were proposed that emphasized the need for heightened suspicion of anaphylaxis in patients with a previous history of allergic reactions to a specific allergen and a known exposure, as well as in patients in whom there is no known history of allergic reactions.

Recently, the Joint Task Force of the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology published an updated practice parameter on the diagnosis and management of anaphylaxis.⁵ In this report the Task Force defined anaphylaxis as “as a condition caused by an IgE-mediated reaction” and noted that such reactions “are often life-threatening and almost always unanticipated.” The purpose of the practice parameter was to provide “the practicing physician with an evidence-based approach to the diagnosis and management of anaphylactic reactions.” In July 2005, the NIAID and FAAN convened a second meeting, which included representatives from the previous organizations and the European Academy of Allergy and Clinical Immunology, the Australasian Society of Clinical Immunology and Allergy, and the Australasian College for Emergency Medicine, to begin the process of facilitating an international agreement. The purpose of this second NIAID/FAAN Symposium was to continue working toward a universally accepted definition of anaphylaxis, establish clinical criteria that would accurately identify cases of anaphylaxis with high precision, further review the evidence on the most appropriate management of anaphylaxis, and outline the research needs in this area.

DEFINITION OF ANAPHYLAXIS AND CRITERIA FOR DIAGNOSIS

Anaphylaxis is a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance. Participants at the symposium agreed that a brief, broad definition of anaphylaxis that reflected its course and potential severity would be most useful to both the medical and lay community and recommended the following: “Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death.”

To identify individuals experiencing such a reaction, criteria proposed at the first symposium were revised,⁴ as outlined in Table I. Participants at the second symposium agreed that the diagnostic criteria must provide the

emergency responder or treating physician with a relatively simple and rapid means to make the diagnosis of anaphylaxis. It was acknowledged that no criteria will provide 100% sensitivity and specificity, but it was believed that the criteria proposed are likely to capture more than 95% of cases of anaphylaxis. Because the majority of anaphylactic reactions include skin symptoms,⁵⁻¹⁰ which are noted in more than 80% of cases when carefully assessed, it was judged that at least 80% of anaphylactic reactions should be identified by criterion 1, even when the allergic status of the patient and potential cause of the reaction might be unknown. However, cutaneous symptoms might be absent in up to 20% of anaphylactic reactions in children with food allergy or insect sting allergy.¹¹⁻¹³ Consequently, in patients with a known allergic history and possible exposure, criterion 2 would provide ample evidence that an anaphylactic reaction was occurring. Gastrointestinal symptoms were included as a pertinent target response because they have been associated with severe outcomes in various anaphylactic reactions.⁹ Finally, criterion 3 should identify the rare patients who experience an acute hypotensive episode after exposure to a known allergen, as described by Pumphrey and Stanworth.¹⁴ Although participants believed that these criteria should accurately identify anaphylactic reactions in more than 95% of cases, it was agreed that these criteria need to be subjected to a prospective multicenter clinical survey to establish their utility and determine whether there is need for further refinement.

MANAGEMENT OF ANAPHYLAXIS

As with the treatment of any critically ill patient, the treatment of anaphylaxis begins with a rapid assessment and maintenance of airway, breathing, and circulation. When a patient fulfills any of the 3 criteria of anaphylaxis outlined above, the patient should receive epinephrine immediately because epinephrine is the treatment of choice in anaphylaxis. There undoubtedly will be patients who present with symptoms not yet fulfilling the criteria of anaphylaxis yet in whom it would be appropriate to initiate therapy with epinephrine, such as a patient with a history of near-fatal anaphylaxis to peanut who ingested peanut and within minutes is experiencing urticaria and generalized flushing. Subsequent interventions are determined on the basis of the clinical course and response to epinephrine. In general, participants at the Second NIAID/FAAN Anaphylaxis Symposium support the therapeutic approach outlined in recently published guidelines.⁵ A summary of these guidelines is provided below, along with a more detailed discussion of the recommended route of parenteral epinephrine, positioning during treatment of anaphylaxis, and suggested observation periods after treatment of an anaphylactic episode.

Epinephrine

Epinephrine is the treatment of choice for anaphylaxis.⁵ Aqueous epinephrine, 0.01 mg/kg (maximum dose,

TABLE I. Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any one 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 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 $(70 \text{ mm Hg} + [2 \times \text{age}])$ from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

0.5 mg) administered intramuscularly every 5 to 15 minutes as necessary, is the recommended dosage for controlling symptoms and maintaining blood pressure.^{15,16} The 5-minute interval between injections can be liberalized to permit more frequent injections if deemed necessary by the clinician.

Intramuscular versus subcutaneous epinephrine. A study in children not experiencing anaphylaxis demonstrated more rapid absorption and higher plasma epinephrine levels when epinephrine was administered intramuscularly in the anterior-lateral thigh with an autoinjector when compared with values after subcutaneous administration.¹⁷ Similarly, in adults not experiencing anaphylaxis, peak plasma epinephrine concentrations were attained more quickly and were higher after intramuscular epinephrine was injected into the thigh than after epinephrine was injected intramuscularly or subcutaneously into the upper arm (deltoid).¹⁸ Similar results were obtained with both an ampule of epinephrine or a spring-loaded (eg, EpiPen [Dey, Napa, Calif]) automatic epinephrine device.^{17,18} Epinephrine injected intramuscularly into the deltoid or subcutaneously over the deltoid did not result in a significant increase of plasma epinephrine levels over endogenous epinephrine levels. It should be noted that studies of the route of injection have not been performed in patients experiencing anaphylaxis. On the basis of this evidence, the participants of the NIAID/FAAN Symposium concluded that intramuscular administration of injectable epinephrine in the anterior lateral thigh is preferred over subcutaneous injection. However, as noted below, intravenous epinephrine might be preferred in some cases if an intravenous line is in place (eg, during surgery).

Intravenous epinephrine. Intravenous epinephrine is an option for patients with severe hypotension or cardiac arrest unresponsive to intramuscular doses of epinephrine and fluid resuscitation. Although there is no precisely established dosage or regimen for intravenous epinephrine in anaphylaxis, 5- to 10- μg intravenous bolus (0.2 $\mu\text{g}/\text{kg}$) doses for hypotension and 0.1 to 0.5 mg administered intravenously in the presence of cardiovascular collapse

have been suggested.¹⁹ A recent single-center trial described successful initial management with intravenous epinephrine infusions for anaphylaxis with hypotension, suggesting that this might be a viable strategy.^{10,20} Detailed procedures for the preparation and administration of epinephrine infusions have been published.⁵ It is important to recognize the potential for lethal arrhythmias when administering intravenous epinephrine, and therefore continuous cardiac monitoring is recommended. Continuous low-dose epinephrine infusions might represent the safest and most effective form of intravenous delivery because the dose can be titrated to the desired effect and can avoid the potential for accidental administration of large boluses of epinephrine.

Oxygen and adrenergic agonists

High-flow oxygen (through a nonrebreather mask or endotracheal tube) should be administered to patients experiencing respiratory symptoms or hypoxemia. Those who are hemodynamically unstable might benefit from oxygen as well. Inhaled β_2 -agonists, such as albuterol, might be useful for bronchospasm refractory to epinephrine.⁵

Positioning of the patient

Patients in anaphylactic shock (ie, those with anaphylaxis and signs of critical organ hypoperfusion) should be placed in a recumbent position with the lower extremities elevated unless precluded by shortness of breath or vomiting. These recommendations are based on evidence that passive leg raise can increase stroke volume and cardiac output by shifting fluid centrally in patients in shock.²¹ Furthermore, observations of victims of fatal anaphylactic shock suggest that postural changes, such as moving to a more upright position or being prevented from taking a supine posture, might have contributed to the fatal outcome.²²

Fluid resuscitation

Patients who remain hypotensive despite epinephrine should have aggressive fluid resuscitation. Large volumes

TABLE II. Biphasic reactions

| Study | Frequency of biphasic reactions | No. of biphasic reactions/total no. of patients in study | Time from initial to biphasic reaction (h) |
|------------------------------------|---------------------------------|--|--|
| Brazil and MacNamara ³³ | 18% | 6/34 | 4.5-29.5 |
| Douglas et al ³¹ | 6% | 6/103 | 1-72 |
| Lee and Greenes ³⁴ | 6% | 6/105 | 5.6-47.6 |
| Starks and Sullivan ²⁹ | 20% | 5/25 | 1-8 |
| Brady et al ³² | 3% | 2/67 | 24-28 |
| Smit et al ⁸ | 5% | 15/282 | 1-23 |

Adapted from Smit et al.⁸

of crystalloid might be needed in the first 5 to 10 minutes; in severe reactions with hypotension, up to 35% of the blood volume might extravasate in the first 10 minutes, and vasodilatation can cause pooling, with even more reduction in the effective blood volume and thus distributive shock.²³ The volume given must be tailored to the clinical situation; persistent hypotension requires a more aggressive approach with multiple fluid boluses (10-20 mL/kg under pressure), including colloid, as well as crystalloid, whereas a largely respiratory reaction or one that responds promptly to initial treatment requires less aggressive fluid management.

Vasopressors

Potent vasopressors, such as noradrenaline, vasopressin, or metaraminol, might be required to overcome vasodilatation if epinephrine and fluid resuscitation have failed to maintain a systolic blood pressure of greater than 90 mm Hg.²⁰ Recent case reports and animal studies have demonstrated that vasopressin is useful when treating hemorrhagic and septic shock. The effect of vasopressin on systemic anaphylaxis has not been investigated, except in clinical case reports. Vasopressin increases blood pressure because of vasoconstriction through the V1 receptor.²⁴

H₁- and H₂-antihistamines

Antihistamines (H₁- and H₂-antagonists) are slower in onset of action than epinephrine, have little effect on blood pressure, and should be considered a second-line treatment for anaphylaxis. Antihistamines are useful for the symptomatic treatment of urticaria-angioedema and pruritus. Diphenhydramine, administered intravenously or intramuscularly (or orally for mild symptoms), can be given at 25 to 50 mg for adults and 1 mg/kg (up to 50 mg) for children. Treatment with a combination of H₁- and H₂-antagonists has been reported to be more effective in attenuating the cutaneous manifestations of anaphylaxis than treatment with H₁-antagonists alone.^{25,26} Ranitidine and cimetidine have been most studied, but no controlled studies have demonstrated superiority of one H₂-antagonist over another.

Corticosteroids

The effectiveness of corticosteroids in anaphylaxis has never been determined in placebo-controlled trials. However, their usefulness in other allergic diseases has

led to their incorporation into anaphylaxis management. Because the onset of action is slow, steroids are not useful in the acute management stage. It has been suggested that their use might prevent a protracted or biphasic reaction, although there is no evidence to prove this.^{11,27} If given, the dosing of intravenous corticosteroids should be equivalent to 1.0 to 2.0 mg/kg per dose of methylprednisolone every 6 hours. Oral administration of prednisone, 1.0 mg/kg, up to 50 mg might be sufficient for milder attacks.

Glucagon for persistent hypotension in patients taking β -blockers

Although there are no epidemiologic studies that demonstrate increased frequency of anaphylaxis in patients receiving β -blockers, there are multiple reported cases of increased severity or treatment-refractory anaphylaxis in these patients.²⁸ Theoretically, there are multiple mechanisms by which β -blockade could blunt the response to epinephrine. If administration of epinephrine in these patients is ineffective, administration of glucagon can be attempted. Glucagon is thought to reverse refractory hypotension and bronchospasm by activating adenylate cyclase independent of the β -receptor; however, the occurrence and importance of this mechanism of action in anaphylaxis is unproved. The recommended dosage for glucagon is 1 to 5 mg (20-30 μ g/kg [maximum dose, 1 mg] in children) administered intravenously over 5 minutes and followed by an infusion (5-15 μ g/min) titrated to clinical response. Airway protection must be ensured because glucagon frequently causes emesis.

Observation

After the treatment of an anaphylactic reaction, an observation period should be considered for all patients because the reaction might recur as the effect of epinephrine wears off (intramuscular epinephrine results in increased serum levels for an hour or more) and because of the risk of a biphasic reaction. The occurrence of biphasic reactions has been established in the literature and appears to occur in 1% to 20% of anaphylactic reactions (as depicted in Table II).^{8,11,27,29-34} In a study evaluating patients with fatal or near-fatal food reactions, approximately 20% of patients experienced a biphasic reaction, indicating that biphasic reactions might be more likely in patients who present initially with severe symptoms.¹¹ The reported time intervals between the initial reaction

and the onset of the second phase ranged from 1 to 72 hours.^{11,27,30-34} Unfortunately, no reliable clinical predictors have been identified to enable the identification of patients at increased risk of a biphasic reaction, although some studies have suggested that patients requiring higher doses of epinephrine to control initial symptoms or delayed administration of epinephrine might be associated with increased risk of a biphasic reaction.^{11,15,33,34} Generally, the same organ systems are involved in the initial and secondary reaction. However, in the study by Smit et al,⁸ 3 patients with initially stable vital signs returned with abnormal vital signs (2 with hypotension and 1 with dyspnea and decreased oxygen saturation). On the basis of the evidence to date, the participants attending the NIAID/FAAN Symposium recommended that observation periods be individualized on the basis of the severity of the initial reaction, reliability of the patient, and access to care. A reasonable length of time to consider observing the postanaphylactic patient is 4 to 6 hours in most patients, with prolonged observation times or hospital admission for patients with severe or refractory symptoms. More caution should be used in patients with reactive airway disease because most fatalities associated with anaphylaxis occur in these patients.

Outpatient follow-up and management

Patients who have experienced anaphylaxis from exposures that might be encountered in nonmedical settings should carry self-injectable epinephrine for use if anaphylaxis develops.^{5,11} As noted above, there has been no universally accepted definition of anaphylaxis. Therefore the clinical criteria suggested above might be helpful in determining who should be prescribed self-injectable epinephrine. Until there are universally accepted criteria for the diagnosis of anaphylaxis, the indications for the prescription of self-injectable epinephrine will continue to be problematic. Currently, there is a consensus that patients experiencing respiratory or cardiovascular symptoms after exposure to a known allergen in the community should receive self-injectable epinephrine. Beyond this consensus, it is unclear who should be given a prescription for self-injectable epinephrine. However, limiting prescriptions of self-injectable epinephrine to this criteria in patients with peanut and other nut allergy, for example, would fail to cover up to 80% of patients experiencing a fatal anaphylactic reaction.³⁵ Patients who are prescribed self-injectable epinephrine should also have an emergency action plan detailing its use and the follow-up management. The complexities of prescribing self-injectable epinephrine and providing an accompanying emergency action plan have been described recently by Sicherer and Simons,³⁶ and the ethical dilemmas have been discussed by Hu et al.³⁷

Before discharge from an emergency facility, all patients experiencing an anaphylactic reaction should receive information about how to avoid the precipitating allergen (if known). Other issues to consider include alerting patients about national organizations providing important information and educational materials (eg, the

Food Allergy and Anaphylaxis Network, www.foodallergy.org), as well as being advised to obtain prompt follow-up with an allergist and notify their primary care physician. At present, these 3 steps (ie, self-injectable epinephrine prescription, patient education, and follow-up evaluation) are infrequently performed in North American emergency departments.^{38,39} Because emergency departments are the treatment setting for most anaphylaxis visits,¹ this represents an important and as yet untapped opportunity to improve patient care.

RESEARCH NEEDS

The investigation of anaphylaxis has been impeded by the lack of universally accepted diagnostic criteria and the absence of reliable laboratory biomarkers to confirm the clinical impression. This in turn has thwarted efforts to ascertain the incidence and outcome of anaphylaxis in various populations, to determine the most effective forms of therapy, to identify patients at risk for life-threatening anaphylaxis, and to elucidate the basic immunologic and pathogenic mechanisms responsible for the variable course of anaphylaxis in different individuals. A multicenter prospective study of the diagnostic criteria proposed herein is needed to determine whether they allow the clinician and investigator to identify accurately patients with anaphylaxis regardless of cause. Assuming that these criteria prove to be adequately sensitive and specific for diagnosing anaphylaxis, studies determining the incidence, cause, clinical features, natural course, and outcome of anaphylaxis are needed to provide the clinician with evidence-based features of this disorder that will enable more effective prevention and therapeutic interventions. Clinical trials can be facilitated by the formation of an anaphylaxis consortium.

It was believed that the measurement of certain mast cell–derived mediators, such as histamine and tryptase, would provide confirmatory evidence of an anaphylactic reaction. However, in a series of 97 patients presenting to an emergency department and given diagnoses of anaphylaxis, only 42% were found to have increased plasma histamine levels, and 21% were determined to have increased plasma tryptase levels.²⁶ One small study demonstrated that serial estimations of plasma tryptase levels might improve sensitivity (36% to 73%).⁴⁰ Sensitive and specific biomarkers of anaphylaxis and evolving anaphylaxis are needed that will establish the presence of the disorder when sufficient historical information is not available or symptoms are atypical. New proteomic approaches, metabolomic approaches, or both might prove useful in identifying relevant biomarkers. Biomarker assays could be useful to confirm the diagnosis when in doubt, which can have important follow-up implications. If available at the bedside, they could even assist in the identification of patients at risk of persistent or delayed-phase reactions. However, given the emergency and fulminant nature of this disease, such approaches are unlikely to be useful for guiding immediate resuscitative

interventions. Laboratory trials can be facilitated by the formation of an anaphylaxis registry with close collaboration between different centers and across specialties.

As outlined in the previous symposium,⁴ most anaphylactic reactions are due to IgE-mediated hypersensitivity reactions resulting from cross-linking of allergen-specific IgE molecules on the surface of tissue mast cells and possibly basophils. However, this mechanism alone does not explain the severity of the allergic manifestations, the variability in target organ responses among individuals or within the same individual, the differences in threshold doses of allergen necessary to provoke anaphylactic responses, the variable responses to therapy, the induction of biphasic or protracted anaphylactic reactions, or the eventual outcome of the reaction. A recent study suggested that the diversity of IgE allergenic epitope recognition might play a role in the severity of allergic responses,⁴¹ but this represents a fraction of the potential variables occurring between the time an allergen enters the body and the end result of an anaphylactic reaction. For example, it might be informative to perform genomic and functional studies of polymorphisms or gain-of-function mutations in various mediator, cytokine, and chemokine receptors; the Kit receptor; elements of intracellular signaling pathways; or other factors that might influence either the activation or function of the effector cells of anaphylaxis or the responses of the structural cells in the target organs affected in this disorder.

In addition, investigation is required into the pathophysiologic mechanisms and appropriate treatment of reactions fulfilling the diagnostic criteria listed for anaphylaxis but that do not involve an IgE-mediated mechanism, commonly referred to as *anaphylactoid* or *pseudoallergic reactions*. Furthermore, studies have suggested a role for the nervous system in eliciting the full symptom complex of anaphylaxis,⁴² and this is an area that warrants further investigation. Well-characterized animal models would clearly facilitate efforts to understand the basic pathophysiology occurring during anaphylaxis; to determine the interactions between various cell types; to elucidate effects of mediators, cytokines, and chemokines released during an anaphylactic response; and to delineate better therapeutic strategies. Recently, animal models that appear reflective of anaphylaxis in human subjects have been established in mice,⁴³ dogs,⁴⁴ and pigs,⁴⁵ but better models are needed.

During the NIAID/FAAN Symposium and in the recently published practice parameter on anaphylaxis,⁵ therapeutic strategies for the management of anaphylaxis were suggested largely on the basis of "clinical experience." In fact, there is a major need to evaluate the most appropriate therapeutic measures and medications for the treatment of anaphylaxis. Although virtually all authorities agree that epinephrine is the drug of choice for the treatment of acute anaphylaxis, there are limited data on the appropriate dose, timing, route, or frequency of administration. H₁- and H₂-antihistamines, corticosteroids, or both are commonly used in the treatment of anaphylaxis, but there are virtually no data demonstrating their

functional role or effectiveness. Prospective controlled trials to establish the appropriate dosing of these medications and the role of other therapeutic interventions, such as the optimal type and rate of fluid replacement, and the use of vasopressors, glucagon, nebulized albuterol or epinephrine, leukotriene inhibitors, and cytokine antagonists (eg, anti-TNF) also are warranted. Ideally, therapeutic measures could be studied in appropriate animal models before initiating clinical trials. Before any clinical studies, clinically useful severity scoring and outcome measurement tools need to be validated.

There is also a need for outcomes research in well-characterized patients. Little information is available on the benefits and risks of providing epinephrine auto-injectors, antihistamines, corticosteroids, and written medical instructions to patients with food and insect venom allergy and their caregivers (eg, parents and school, day care, and restaurant personnel) and first-line emergency personnel. Studies of long-term sequelae, adherence to follow-up referral, subsequent reactions, and quality of life in patients experiencing anaphylactic reactions also are lacking. As outcome data are becoming available, evaluation of the most effective means of disseminating information about the prevention and management of anaphylaxis to patients, primary care physicians, first responders, and emergency department personnel should help alleviate the tremendous disparities in therapeutic approaches seen in the United States and around the world.

A number of studies from around the world suggest that anaphylactic reactions commonly occur both inside and out of the hospital environment.^{46,47} In light of the general increase in IgE-dependent allergic disorders in the developed world over the past several decades, there is an urgent need to understand better the basic immunology and pathophysiology of anaphylaxis and to optimize therapy on the basis of well-controlled clinical trials. In addition, the characterization of clinical features and discovery of biomarkers that would identify patients at risk for anaphylaxis or for biphasic or prolonged severe reactions would greatly enhance the care of these patients, decrease patient and family anxieties, and reduce the risk of unfavorable outcomes. The universal acceptance of specific clinical criteria to identify anaphylaxis, as proposed here, will facilitate and expedite research in this critical area.

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