

Symposium on the Definition and Management of Anaphylaxis: Summary report

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Abbreviations used

ED: Emergency department
EIA: Exercise-induced anaphylaxis
FAAN: Food Allergy and Anaphylaxis Network
FDA: Food and Drug Administration
NIAID: National Institute of Allergy and Infectious Diseases

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The phenomenon of anaphylaxis was first described in the scientific literature about 100 years ago by Portier and Richet,¹ who reported that their attempts to immunize dogs against the sting of jellyfish with *Actinia* extract instead brought about an acute anaphylactic episode.^{1,2} In the extreme or classic form, anaphylaxis typically involves the cutaneous, respiratory, cardiovascular, and gastrointestinal systems, target organs all heavily populated with mast cells. Although medical practitioners can readily recognize such typical forms of anaphylaxis, its presentation is often more enigmatic, with variable target organ involvement and expression of symptoms. A perusal of various textbooks and reviews on the topic indicates that there is no consensus on exactly how to define anaphylaxis, and consequently, there is considerable disagreement about its prevalence, diagnosis, and management. In April 2004, the National Institute of Allergy and Infectious Diseases (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) cosponsored a multidisciplinary Symposium on the Definition and Management of Anaphylaxis to bring together experts from various disciplines that deal with anaphylaxis. The goal was to review current knowledge and to discuss a definition, treatment strategies, and research objectives.

This 2-day meeting brought together experts and representatives of 12 other professional, governmental, and lay organizations. Organizations represented at the NIAID/FAAN Symposium included the American Academy of Allergy, Asthma and Immunology; 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 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 (FDA). The meeting provided an opportunity for attendees to exchange information, gain a better perspective of how anaphylaxis is recognized and treated, find commonalities between the various specialties' approaches, and identify future research needs. The information presented in this article serves as a basis for future development of a clinical definition of anaphylaxis and a management strategy, and for expansion of a research agenda.

In 1998, a Joint Task Force on Practice Parameters³ defined *anaphylaxis* as an "immediate systemic reaction caused by rapid, IgE-mediated immune release of potent mediators from tissue mast cells and peripheral basophils." The most common etiologies of anaphylactic reactions include allergic responses to food, medications, *Hymenoptera* stings, and latex. Mechanistically, anaphylactic reactions are distinguished from *anaphylactoid reactions*, which "mimic signs and symptoms of anaphylaxis, but are caused by non-IgE-mediated release of potent mediators from mast cells and basophils." Although they provide a mechanistic concept of anaphylaxis, these definitions are of marginal utility to the physician, emergency personnel, and other health care personnel faced with the diagnosis and treatment of a patient presenting with any of a variable constellation of signs and symptoms of this disorder.

One of the major challenges in the study of anaphylaxis is the lack of a widely accepted standard working definition.⁴⁻⁶ In general, published studies use definitions that incorporate various signs and symptoms of anaphylaxis and specific intervals between allergen exposure and the clinical reaction, but specific elements of the definitions vary.⁶⁻¹² One of the major consequences of this lack of standard definition is the failure to diagnose anaphylaxis consistently, as pointed out in several studies.^{6,8,13} In a review of 19,122 emergency department (ED) visits,⁸ 17 cases of anaphylaxis were identified, but only 4 had been appropriately diagnosed and coded. This lack of a consistent definition contributes to the wide variation in the management of anaphylaxis seen in North American EDs.¹⁴

EPIDEMIOLOGY AND INTERNATIONAL CLASSIFICATION OF DISEASES CODING

Study of the epidemiology of anaphylaxis has been hampered by lack of an agreed-on definition and a lack of required reporting of either fatal or serious events. A failure to agree on how severe a reaction must be to code it *anaphylaxis* as opposed to an *allergic reaction* and to appreciate the variable presentation of anaphylaxis contributes to the problem. Very few population-based studies

have been attempted, so the actual incidence of anaphylaxis remains uncertain. Estimates of the incidence range from 10 to 20/100,000 population per year.^{6,12,15} In 2003, the new codes of the International Classification of Diseases, Tenth Revision, were put in place to describe fatal anaphylactic reactions, such as "anaphylactic shock due to adverse food reaction" (T78.0) and "anaphylactic shock, unspecified" (T78.2). However, data presented at the symposium indicated that these codes are underused. Until there are universally accepted diagnostic criteria, standardized coding, and reporting of anaphylaxis, the true incidence and lifetime prevalence of anaphylaxis will remain unknown.

IMMUNOLOGY OF ANAPHYLAXIS

Aggregation of FcεRI by allergen-driven cross-linking of receptor-bound IgE activates mast cells and basophils to release mediators that induce the pathophysiologic features of the anaphylactic response.¹⁶ Initial sensitization occurs through a highly coordinated series of steps involving a variety of cell types and mediators,¹⁷ which is affected by environmental exposure and complex genetic factors. Consequently, even identical twins raised together may lack complete clinical concordance (eg, peanut allergy: monozygotic twins, 64%, compared with dizygotic twins, 7%),¹⁸ thereby highlighting the inaccuracy of making genetic predictions for any one individual, but recognizing the significant genetic component to allergic disease.

An important immunologic feature of allergy is the fact that not all sensitized subjects exhibit clinical reactivity. Although the quantity of circulating IgE antibodies to both food and airborne allergens appears to correlate directly with the probability of clinical reactivity,¹⁹⁻²¹ the exact series of events that occur between contact with an allergen by a sensitized individual, and sufficient activation of mast cells, basophils, and possibly other cells to induce an anaphylactic reaction, remains to be elucidated. When mast cells/basophils are activated, several well-characterized mediators are released (eg, histamine and tryptase). Unfortunately, tryptase is not found to be elevated consistently in the blood of patients presenting with anaphylaxis,²² especially in food allergy,²³ and histamine is elevated only briefly at the outset of the reaction and is unstable to routine handling. Therefore, additional biomarkers need to be identified that are both present during most or all anaphylactic reactions and easily and rapidly measured.

PATHOPHYSIOLOGY OF ANAPHYLAXIS

Allergic reactions begin when an allergen crosses an epithelial and/or endothelial barrier and then interacts with cell-bound IgE antibodies. The integrity of natural barriers such as the skin or the gastrointestinal tract must be breached, and these allergens must then gain access to the reactive, sensitized cells in tissues (mast cells) or blood

(basophils). The release of cellular mediators then leads to end-organ responses in the skin, respiratory tract, cardiovascular system, and/or gastrointestinal tract and possibly the nervous system (Table I). The onset of severe symptoms is dependent on the causative factor. In one series, the median time to cardiac or respiratory arrest was 30 minutes for food, 15 minutes for insect venom, and 5 minutes for medications or contrast reagents.²⁴ Anaphylactic reactions are not necessarily uniphasic; additional patterns of reactions include delayed onset, protracted or persistent reactions, and biphasic reactions wherein the initial reaction is followed by a relatively symptom-free period and then the symptoms recur, often in severe form and more refractory to therapy.^{23,25} The exact cells and mediators involved in each of these patterns have not been completely defined. Exercise, certain medications (eg, nonsteroidal anti-inflammatory drugs), anesthesia, and alcohol may affect the severity of the response to allergen. Furthermore, fatal reactions are more likely to occur in individuals with asthma,^{23,26,27} possibly more so when the asthma is poorly controlled. An important physiologic consequence of anaphylaxis is the marked hypovolemia that may occur and the resulting empty ventricle syndrome in patients who remain in an upright position.²⁸ A better understanding of the molecular interactions in the airway of individuals with asthma and of the cardiovascular physiology in anaphylactic reactions would aid in the treatment of subjects experiencing these events.

ANAPHYLAXIS BY MAJOR CAUSATIVE AGENTS

Although the immunobiology and pathophysiology of anaphylaxis are basically the same regardless of the provoking factor, different allergens lead to subtle differences in the response.

Drug-induced anaphylaxis (medications, biologics, vaccines)

For the correct diagnosis of drug-induced anaphylaxis, accurate historical information is needed, such as when the inciting agent was given, the interval to reaction, medications the patient had received previously (to determine previous sensitization), and the patient's response to therapy. Objective data such as records from the ED or referring physician may help in making the correct diagnosis. If drug immunogens are known (eg, penicillin or large-molecular-weight proteins such as insulin), both *in vivo* and *in vitro* tests may be useful in identifying relevant allergens. Unfortunately, validated tests for IgE-mediated reactions are unavailable for most drugs and biologics. The identification of relevant immunogenic determinants and the development of valid diagnostic agents are urgently needed. Patients who have had drug-induced anaphylactic reactions should be instructed to discuss their reactions with their doctor, and a causative agent/trigger should be identified by skin testing when

possible.²⁹ Likewise, physicians should take a careful history of patients to evaluate the likelihood of potential drug-induced anaphylaxis before prescribing or administering medications.

Anesthetic-induced anaphylaxis

Anaphylaxis to anesthesia is a rare, serious adverse reaction. The incidence of anesthetic-induced anaphylaxis varies between 1:3500 and 1:20,000, and the mortality rate is reported to be approximately 4%, with an additional 2% surviving with severe brain damage.³⁰⁻³² The early signs are often unrecognized, and cardiovascular collapse is often the sole presentation, occurring in about 50% of cases. Bronchospasm and hypotension also may be the sole presenting features, making the diagnosis quite difficult, because these clinical conditions are more common under anesthesia and may have many different causes. In addition, the diagnosis may be missed altogether, resulting in serious implications for future anesthetics. Neuromuscular blocking drugs have been reported as the most common trigger.^{31,33,34} Some reactions are caused by the direct activation of mast cells, whereas others appear to be IgE-mediated. Data regarding the utility of skin testing are controversial because of the possibility of false-positive results.³⁵ Prevention of these reactions will require further studies as well as guidelines on the utility of skin testing.

Insect sting-induced anaphylaxis

Onset of anaphylaxis to insect stings is generally rapid, and fatal insect stings tend to be more rapid in onset, with 96% of fatal reactions beginning within 30 minutes of the sting.³⁶ Consequently there is a need to emphasize rapid treatment with epinephrine (often self-administered) for these reactions in susceptible subjects rather than taking a wait-and-see approach, and to strongly encourage follow-up evaluation and expert counseling. This is the only form of anaphylaxis for which immunotherapy is currently available to prevent reactions to subsequent stings.³⁷ It is important to recognize that cutaneous symptoms may be absent in as many as 20% of cases of anaphylaxis,³⁸ with urticaria absent in more than 30% of cases. Currently, most fatal reactions cannot be prevented because they occur on the first sting reaction, and diagnostic skin tests are not useful for screening because they are positive in 25% of adults.³⁹ The lack of an anaphylactic response to a sting in individuals who are highly sensitized or even recently reactive requires future investigation to reveal the mechanism that prevents such individuals from reacting.

Food-induced anaphylaxis

Food-induced anaphylaxis is the most common single cause of anaphylaxis treated in EDs in the United States, especially in the younger population.⁴⁰ The majority of reactions are not fatal. There are no known laboratory parameters that predict the severity of food-induced reactions, although there may be a correlation between the number of IgE-binding sites (epitopes) recognized by a

TABLE I. Clinical signs and symptoms of anaphylaxis

Cutaneous/subcutaneous/mucosal tissue
Flushing, pruritus, hives (urticaria), angioedema, morbilliform rash, pilor erection
Pruritus of lips, tongue, and palate; edema of lips, tongue, and uvula
Periorbital pruritus, erythema and edema, conjunctival erythema, tearing
Respiratory
Laryngeal: pruritus and tightness in the throat, dysphagia, dysphonia and hoarseness, dry staccato cough, stridor, sensation of pruritus in the external auditory canals
Lung: shortness of breath, dyspnea, chest tightness, deep cough and wheezing/bronchospasm (decreased peak expiratory flow)
Nose: pruritus, congestion, rhinorrhea, sneezing
Cardiovascular
Hypotension
Feeling of faintness (near-syncope), syncope, altered mental status
Chest pain, dysrhythmia
Gastrointestinal
Nausea, crampy abdominal pain, vomiting (stringy mucus), diarrhea
Other
Uterine contractions in women, and aura of doom

patient's IgE antibodies on a food protein (epitope diversity) and the likelihood of a severe reaction.⁴¹ However, currently there is no way to identify who will have a severe reaction or to predict when it will occur. In general, reactions worsen with the development of asthma and as children get older. Early use of epinephrine is important and can prevent progression to severe reactions.⁴²

Latex-induced anaphylaxis

Latex is the second leading cause of anaphylaxis during the perioperative period. Although the incidence of latex anaphylaxis has increased over the period of the last 20 years, it now appears to have reached a plateau largely because of increased awareness of the problem, a decreased use of latex products, and new labeling warnings about the presence of latex in medical products enforced by the FDA.⁴³ A surveillance system is needed to track cases of latex-induced anaphylaxis and latex allergy. To determine how many people are affected with latex allergy, an FDA-approved reagent for skin testing is essential to reduce the wide variation in reported sensitization. Latex anaphylaxis is largely preventable by instituting latex-safe protocols, which include substituting latex-free gloves when latex is not essential, and substituting low-powder, low-protein gloves when latex is essential.⁴⁴

Exercise-induced anaphylaxis

Exercise can lead to typical anaphylaxis.⁴⁵ A variety of activities can lead to exercise-induced anaphylaxis (EIA), including jogging, walking, tennis, and dancing. EIA is unpredictable and often difficult to diagnose. It has been suggested that as many as 50% of cases of EIA may be associated with the ingestion of a food, ie, food-associated EIA.⁴⁶ In such cases, delaying exercise for about 5 hours after eating will prevent reactions. The pathogenesis and true incidence of EIA remain unknown.

Idiopathic anaphylaxis

The diagnosis of idiopathic anaphylaxis is a diagnosis of exclusion.⁴⁷ The exact incidence of idiopathic anaphy-

laxis is unknown, but several studies estimate that nearly 20% of cases of anaphylaxis are idiopathic. There are no clinically distinguishing features (although 33% of cases are nocturnal), and it may be fatal. Management often consists of prophylactic corticosteroid and antihistamine therapy.⁴⁸

DIAGNOSIS AND MANAGEMENT

As demonstrated by the diverse organizations that participated in the NIAID/FAAN symposium, anaphylaxis is seen by different types of clinicians in a variety of clinical settings. This presents a formidable challenge to the creation of a disease definition that will fit all settings. Regardless of setting, however, epinephrine is the medication of choice for treating anaphylaxis.

Prehospital

Anaphylaxis is a rare condition in the prehospital setting, accounting for about 0.5% of ambulance runs, and about 10% of these cases receive epinephrine.⁴⁹ There are significant variations in emergency medical services protocols regarding the definition and treatment of anaphylaxis.⁴⁹ The inconsistencies in case definitions, documentation, and diagnostic and treatment protocols limit the utility of the data in this area. Currently it is within the scope of practice for paramedics to use epinephrine to treat anaphylaxis. There are insufficient data to support or refute the benefits and/or safety of basic emergency medical services responders using self-injectable epinephrine for the treatment of anaphylaxis. More research is needed to determine whether the use of self-injectable epinephrine by Basic Life Support personnel for treating anaphylaxis is warranted.

ED

Anaphylaxis is a relatively infrequent diagnosis in the ED compared with allergic reactions, eg, 1 in 439 encounters in one series.⁵⁰ Anaphylaxis is typically

defined as an allergic reaction with multiorgan involvement, respiratory insufficiency, and hemodynamic compromise. The ED treatment guidelines for anaphylaxis are similar to those recommended in the allergy and immunology literature, which includes ensuring a patent airway, establishing intravenous access, administering subcutaneous/intramuscular/intravenous epinephrine, and making appropriate referral to prevent future reactions.

However, there is considerable controversy about the choice of treatment for acute allergic reactions not including respiratory and/or hemodynamic compromise. A recent multicenter study showed that typical ED treatment includes antihistamines, steroids, epinephrine, or some combination of these agents.¹⁴ There was wide variability in emergency physicians' treatment of allergic reactions (and of more severe allergic reactions that might be considered anaphylaxis), with treatment appearing to be symptom-based. Epinephrine probably is underused, and when it is used, it is often given by the subcutaneous route, which may not be optimal in the overwhelming majority of cases.^{51,52} Steroids are used in the emergency management of anaphylaxis and are prescribed by about 50% of the physicians on discharge,¹⁴ although there is no evidence to support this treatment.

The few available studies suggest that anaphylaxis is probably underrecognized and undertreated in both the prehospital setting and the ED.^{8,14} A simple clinical definition of anaphylaxis and further education of ED personnel and those in the prehospital setting are needed to increase the recognition and standardize the treatment of anaphylaxis. Simulation-based training of anaphylaxis and other medical emergencies with full-scale simulators has shown promise in improving the performance of health care professionals in dealing with medical crises.⁵³ The treatment plan for anaphylaxis should be effective, simple, and swift. This is particularly important in patients with a history of anaphylaxis and an identifiable anaphylactic trigger who are not yet *in extremis*. Treatment of anaphylaxis should include epinephrine. Oral H₁-antihistamines may not be effective in more severe allergic reactions because they are relatively slow to act and principally relieve cutaneous symptoms, rather than the cardiorespiratory problems that make anaphylaxis a life-threatening emergency.

Allergist office

When a patient presents after an anaphylactic reaction, the main objective of the allergist is to ascertain the etiology of the reaction and then to educate the patient in appropriate measures to avoid future reactions. In addition, the allergist must educate patients to recognize early signs and symptoms of anaphylaxis, and equip them with the medications and training to deal with future reactions. For example, patients with food or insect sting allergy should be given self-injectable epinephrine and a written emergency plan to implement in case of a future reaction. An H₁-antihistamine may relieve flushing, pruritus, urticaria, and rhinorrhea in anaphylaxis; a rapidly ab-

sorbed H₁-antihistamine is preferable (eg, cetirizine 1.0 ± 0.5 hours diphenhydramine 1.7 ± 1.0 hours to peak plasma level after a single oral dose).⁴⁹ MedicAlert bracelets (MedicAlert Foundation International, Turlock, Calif) are frequently recommended.

Primary care office

The main goal of primary care physicians is to identify patients at increased risk for an anaphylactic reaction. Patients with a history suggestive of a previous systemic reaction should be identified, potential causes should be explored, avoidance of allergens that may provoke anaphylaxis should be discussed, and patients should be educated on the necessity and proper use of injectable epinephrine. A high index of suspicion should exist about any patient—particularly an atopic patient—describing a systemic reaction that includes any of the features of anaphylaxis. Better guidelines are needed regarding diagnostic criteria, appropriate testing, and prevention strategies for food allergy. In addition, better parameters are necessary for when to refer patients to an allergy specialist for follow-up care of suspected allergic/anaphylactic reactions.

Patient perspective

The lack of consensus on the definition of anaphylaxis has contributed to a diffuse and poorly coordinated approach to patient education and care. Depending on who has made the diagnosis, patients may receive conflicting information. Once the family returns home and begins to implement avoidance strategies and to prepare for a potential reaction, long lists of questions typically arise. Childhood food allergy has been shown to have a significant effect on parental quality of life.⁵⁴ Patients and their families need clear, consistent, and comprehensive written instructions for avoiding, recognizing, and treating anaphylactic reactions. They need effective educational resources to learn how to manage their allergy and properly balance fear with caution, and how to educate others such as school staff and childcare providers.

Epinephrine in the first aid treatment of anaphylaxis

Epinephrine is the medication of choice for treating an anaphylactic episode, and the World Health Organization classifies it as an essential drug. Although it has a relatively narrow therapeutic/toxic window (benefit/risk ratio), it remains the drug of choice for the first aid treatment of anaphylaxis. Epinephrine is widely dispensed yet underused by patients and treating physicians.¹⁴ The recommended dose of epinephrine is 0.01 mg/kg intramuscular to as much as 0.3 mg, and it may be repeated within 5 minutes if symptoms worsen or severe symptoms persist. The lateral aspect of the thigh appears to be the optimal location for administration.⁵⁵ Currently there are 2 doses of self-injectable epinephrine on the US market—EpiPen Jr (0.15 mg) and EpiPen (0.3 mg) (both Dey, Inc, Napa, Calif)—but additional fixed doses are needed.

TABLE II. Examples of clinical criteria for anaphylaxis: A preliminary proposal for further discussion

Anaphylaxis is likely when any 1 of the 3 criteria are fulfilled

- (1) Acute onset of an illness (minutes to hours) with involvement of
Skin/mucosal tissue (eg, hives, generalized itch/flush, swollen lips/tongue/uvula)
AND
Airway compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced PEF)
OR
Reduced BP or associated symptoms (eg, hypotonia, syncope)
- (2) Two or more of the following after exposure to known allergen for that patient (minutes to hours)
History of severe allergic reaction
Skin/mucosal tissue (eg, hives, generalized itch/flush, swollen lips/tongue/uvula)
Airway compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced PEF)
Reduced BP or associated symptoms (eg, hypotonia, syncope)
In suspected food allergy: gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
- (3) Hypotension after exposure to known allergen for that patient (minutes to hours)
Infants and children: low systolic BP (age-specific) or >30% drop in systolic BP*
Adults: systolic BP <100 mm Hg or >30% drop from their baseline

Caution: These criteria describe so-called *classic* cases of anaphylaxis. Other presentations may also indicate anaphylaxis (eg, early presentation, generalized flushing; isolated presentation, sudden hypotension only in a patient without evidence of allergen exposure; classic presentation but with a nonallergenic cause, such as exercise). Conversely, clinicians need to remember the potential for false-positive symptoms or signs (eg, difficulty breathing from panic, faintness from vasovagal episode).

BP, Blood pressure; PEF, peak expiratory flow.

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

In true cases of anaphylaxis, epinephrine must be injected promptly, but even then as many as 10% of cases may not be reversible.²⁷ Treatment should include intramuscular epinephrine. Use of intravenous epinephrine should be reserved for the most extreme conditions, such as in cases under anesthesia, because virtually all adverse outcomes caused by epinephrine result from its intravenous administration.²⁴ The more advanced the anaphylactic reaction (eg, development of hypotension), the less likely epinephrine is to reverse the reaction.⁵⁶ In spite of the evidence to support the benefits of epinephrine, patients/caregivers are reluctant to inject epinephrine.⁵⁷ Reasons for not using the epinephrine include failure to recognize symptoms of anaphylaxis, rationalization that the reaction initially seemed to be mild, a health care facility was close by, spontaneous recovery occurred after the previous episode, reliance on oral antihistamine, concerns about adverse effects of epinephrine, or fear of the pain caused by the injection. New formulations are under development, including sublingual⁵⁸ and new formulations of inhaled epinephrine, but currently available epinephrine formulations from a metered dose inhaler are unlikely to be useful in the treatment of nonrespiratory symptoms of anaphylaxis.⁵⁹

DISCUSSION

It is time to develop a universal and, ideally, international definition of anaphylaxis, because the current lack of agreement on what constitutes anaphylaxis has led to confusion on the part of first responders, emergency personnel, primary care physicians, and patients; has resulted in suboptimal diagnosis, treatment, and education

of affected patients; and has hampered research efforts. It was apparent to those at the NIAID/FAAN symposium that the definition could not be mechanistically based, but that a specified constellation of readily identifiable signs and symptoms is necessary to make the definition clinically useful. Whether anaphylaxis is the result of IgE-mediated or non-IgE-mediated mechanisms is of little consequence in the immediate treatment of an anaphylactic/anaphylactoid reaction but is of considerable importance when counseling a patient about the potential for future reactions and how to avoid them.

All parties attending the NIAID/FAAN symposium agreed on the signs and symptoms that may be seen in an anaphylactic reaction, as listed in Table I. Viewing anaphylaxis as a continuum, or in degrees of severity, circumvents the problem of defining a point at which an acute allergic reaction becomes anaphylaxis. A previous proposal, based on retrospectively collected data on 1149 systemic hypersensitivity reactions presenting to an ED over a 9-year period, suggested grading reactions into 3 categories; mild, moderate, and severe.⁵ Logistic regression analyses of the associations between various signs and symptoms and the progression to hypoxia and hypotension were used to construct a grading scale. Confusion, fainting, unconsciousness, and incontinence were strongly associated with hypotension and hypoxia and were used to define a severe reaction. Moderate reactions were defined by the presence of diaphoresis, vomiting, lightheadedness, dyspnea, stridor, wheezing, chest and/or throat tightness, nausea, and abdominal pain: these signs and symptoms were more weakly associated with hypotension and hypoxia. Reactions limited to the skin (eg, flushing, urticaria, erythema, and angioedema) were considered mild reactions and were not associated

with hypoxia or hypotension (ie, not anaphylaxis). This report also emphasized the association of gastrointestinal symptoms with anaphylaxis and the direct association of age with increasing severity in drug-induced and insect sting-induced anaphylactic reactions. However, the retrospective nature of this study produces obvious limitations, and the results have not been validated.

A prospective study to ascertain which symptoms of anaphylaxis best correlate with major outcomes (eg, hypoxia, hypotension, neurological sequelae) could prove invaluable. Although viewing anaphylaxis as a continuum or in degrees of severity may provide a more useful standard for prescribing therapy and for classifying reactions for epidemiological studies, some participants at the conference thought that a simpler definition, striving for high sensitivity and low false positivity, was desirable. For some participants, the primary concern was that a simple clinical definition could not include all subjects with anaphylaxis (ie, that it would have less than 100% sensitivity). For others, the more sensitive definitions came with an unacceptably high number of false-positive results (ie, the risk of calling nonallergic problems anaphylaxis). Table II represents one approach that provides a compromise between these 2 viewpoints.

The criteria proposed emphasize the need for heightened suspicion in patients with a previous history of severe allergic reactions to a specific allergen and a known exposure. It also would prompt physicians dealing with a limited patient history to consider treatment for suspected anaphylaxis on the basis of readily available clinical criteria. Patients who satisfy 1 of the 3 criteria in Table II are likely to have anaphylaxis. Cases of anaphylaxis falling outside the criteria depicted in Table II will occur, as exemplified by examples listed under "Caution." Ultimately it is imperative that clinical criteria for diagnosing anaphylaxis be analyzed and validated in prospective studies and that they are demonstrated to be effective and user-friendly.

In the past 100 years, great strides have been made in our understanding of the immunology and pathophysiology of anaphylaxis. The constellation of potential symptoms seen in anaphylactic reactions and many of the etiologic agents have been well described. However, the variable clinical nature of the anaphylactic response, even in the same individual, indicates that there is still much we do not understand. It remains to be answered why some patients only have mild reactions whereas others suddenly develop fatal reactions, and why some individuals recover spontaneously whereas others die despite rapid heroic measures. In the laboratory, we need to identify biomarkers, including genetic profiles and genomic and proteomic markers, that accurately predict who is at risk to develop anaphylaxis and who has actually had an anaphylactic reaction. Relevant animal models need to be identified to elucidate the molecular, immunologic, and physiologic mechanisms responsible for anaphylaxis and to study more effective means of therapy and prevention. Animal and human studies of preventing severe allergic

reactions by immunotherapy and other immune-based therapies need to be developed. Diagnostic and treatment protocols, including when and by whom medical management should be initiated, must be evidence-based and validated by appropriate clinical studies.

A follow-up meeting is envisioned that will elucidate educational needs and further expand research objectives concerning pathogenesis, diagnosis, treatment, and prevention of anaphylaxis, including both basic and clinical research on diagnosing and treating anaphylaxis, and studies to evaluate the efficacy of various proposed clinical algorithms. Public and provider education also should be a major effort once a clear definition is established. In addition, this effort will need to be extended to the international arena because it will be important to develop a worldwide consensus on key aspects of the definition/classification, nomenclature, diagnosis, and management of anaphylaxis.

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