Current perspectives

Anaphylaxis, killer allergy: Long-term management in the community

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Traditionally, physicians are trained to diagnose and treat anaphylaxis as an acute emergency in a health care setting. In addition to this crucial and time-honored role, we should be cognizant of our wider responsibility to (1) provide a risk assessment for individuals with anaphylaxis, (2) prevent future anaphylaxis episodes by developing long-term personalized risk reduction strategies for affected individuals, and (3) emphasize anaphylaxis education. Risk assessment should include verification of the trigger factor or factors for the anaphylaxis episode by obtaining a comprehensive history and performing relevant investigations, including allergen skin tests and measurement of allergen-specific IgE in serum. In addition, the potential effect of comorbidities and concurrently administered medications on the recognition and emergency treatment of subsequent episodes should be determined. Risk reduction strategies should be personalized to include information about avoidance of specific triggers and initiation of relevant specific preventive treatment (eg, venom immunotherapy). At-risk individuals should be coached in the use of self-injectable epinephrine and equipped with an anaphylaxis emergency action plan and with accurate medical identification. Anaphylaxis education should be provided for these individuals, their families and caregivers, health care professionals, and the general public. Further development of an optimal diagnostic test for anaphylaxis and of tests and algorithms to predict future risk and prevent fatality are urgently needed. (J Allergy Clin Immunol 2006;117:367-77.)

Key words: *Acute systemic allergic reaction, adrenaline, anaphylaxis, antihistamine, epinephrine, food allergy, histamine, insect sting allergy, latex allergy, tryptase*

Progress is being made toward a universally accepted definition of anaphylaxis as ''a serious allergic reaction that is rapid in onset and may cause death.''[1] Although the true prevalence of anaphylaxis is unknown,[2] it is not as rare as generally believed[2,3]; rather, it appears to be underrecognized and undertreated.[4]

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Anaphylaxis is a disease of modern times. The reported death of the Pharoah Menes from a wasp sting was likely a myth.[5] Sporadic case reports of anaphylaxis were published in the 17th, 18th, and 19th centuries. During the early decades of the 20th century, anaphylaxis occurred mainly in health care settings, and the main trigger was injection of biologic agents such as diphtheria antitoxin. In the 1950s and 1960s, the first case series of individuals with anaphylaxis from medications, diagnostic agents, insect venoms, and foods were published,[6] followed in the 1970s by the first case series of individuals with idiopathic anaphylaxis and in the 1980s by the first case series of individuals with anaphylaxis triggered by exercise, and anaphylaxis triggered by natural rubber latex (Fig 1).

Recognition and treatment of anaphylaxis in medical settings remains critically important, as does vigilance in preventing anaphylaxis triggered by diagnostic and therapeutic agents.[7] There is, however, increasing awareness that anaphylaxis now occurs frequently in community settings where no health care professionals are present and where it is most commonly triggered by food, insect venom, or medication and less commonly by allergens, such as natural rubber latex, or physical factors, such as exercise (Table I).[8-21]

Individuals with anaphylaxis occurring in the community often recover spontaneously and might never be seen by a health care professional. Even if they are treated in an emergency department, an urgent care facility, or a primary care physician's office, the majority are not referred to a specialist for long-term management.[11,13,14] Most of the published information on anaphylaxis emphasizes the physician's traditional and crucial role in the diagnosis and treatment of the acute event.[12,22,23] In this review we will focus on the important additional role played by allergy-immunology specialists involving risk assessment of individuals with anaphylaxis, long-term individualized risk reduction to prevent and treat future episodes, and anaphylaxis education. This dual role encompasses the physician's traditional role, yet extends well beyond it (Fig 2).

RISK ASSESSMENT

In the long-term management of anaphylaxis, risk assessment includes confirmation of the diagnosis by

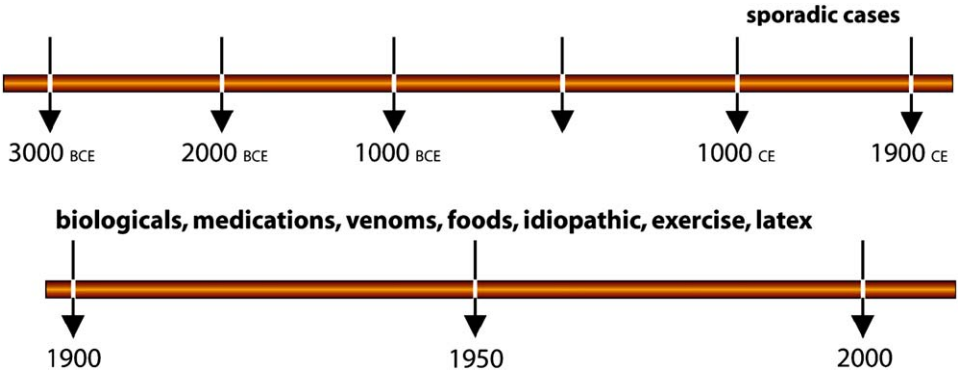

FIG 1. Timelines showing that anaphylaxis is a modern disease. The first case series of individuals with anaphylaxis from medications, insect venoms, and foods were published in the 1950s and 1960s, followed in the 1970s by case series of individuals with idiopathic anaphylaxis and in the 1980s by case series of anaphylaxis triggered by exercise and natural rubber latex. Note that the scale of the timelines differs. *BCE*, Before Common Era; *CE*, Common Era.

TABLE I. Anaphylaxis in the community

Allergen triggers (IgE-dependent immunologic mechanism)
Foods, especially peanut, tree nut, seafood, fin fish, milk, egg
Insect (Hymenoptera) venoms
Natural rubber latex
Medications (eg, β-lactam antibiotics)
Biologic materials, including allergens, vaccines, and hormones (eg, progesterone)
Food additives, including spices, insect-derived colorants (eg, carmine), and vegetable gums
Inhalants (eg, horse dander)
Seminal fluid
Occupational allergens
Novel or unusual allergens (examples*)
Foods: vegetables, fruits, lupin flour, mites, bird's nest soup
Biting insect saliva: mosquitoes, pigeon ticks, triatomid bugs, green ants
Venoms: jellyfish, scorpions, snakes
Medications and biologic agents: Botox, bee products, herbal formulations
Nonallergen triggers (IgE-independent, formerly classified as anaphylactoid, reactions)
Physical factors (eg, exercise†, cold, heat, sunlight/UV radiation
Medications (eg, opiates)
Ethanol
Idiopathic anaphylaxis

*See references 8 and 15 through 21.
†With or without a food or medication co-trigger.

retaking the history of the acute episode and reviewing the results of laboratory tests, if any, obtained at the time; evaluation of comorbidities and concurrently administered medications; and verification of the trigger factor or factors.

Confirmation of the diagnosis

The diagnosis of anaphylaxis is based on a detailed description of the episode, including antecedent activities and response to treatment.[22,23] It is a clinical diagnosis based on pattern recognition and probability. Anaphylaxis is a dynamic continuum, usually characterized by a definable exposure to a potential trigger and by rapid onset, evolution, and resolution of symptoms within minutes to hours.[12,22] The patterns of target organ involvement are variable. Expression of up to 40 potential symptoms and signs might differ among individuals, and in the same individual from one episode to another. Spontaneous recovery occurs frequently, likely because of endogenous compensatory mechanisms such as increased epinephrine and angiotensin II secretion.[24]

Anaphylaxis episodes might be underreported for a variety of reasons. Individuals might be experiencing their first episode or having their first known exposure to the trigger and might not recognize what is happening to them, especially when symptoms come and go rapidly. If they are very young, dyspneic, or in shock, they might not be able to describe their symptoms. Skin symptoms, such as itching, and signs, such as flushing and urticaria, which are extremely helpful in the diagnosis, are absent or unrecognized in 10% or more of all episodes and might be missed if an individual cannot describe itching or is not fully examined during the episode, for example, when anaphylaxis occurs in a public place such as a restaurant.[9,23] Hypotension sometimes goes undocumented, especially in infants and young children or when the initial blood pressure measurement is obtained after epinephrine administration. The reluctance of some health care professionals to diagnose anaphylaxis in the absence of shock also leads to underrecognition.[4] Individuals might fail to recognize an anaphylaxis episode, either in themselves or in those for whom they care, because of neurologic, psychiatric,[25] or psychologic problems or ingestion of medications or chemicals that impair cognition and judgment (Table II). Signs that are strongly associated with hypotension and hypoxia in anaphylaxis, such as confusion, collapse, unconsciousness, incontinence, sweating, presyncope, nausea, vomiting, dyspnea, stridor, and wheeze,[11] although unlikely to be missed, are nonspecific. Anaphylaxis in a known asthmatic individual might go

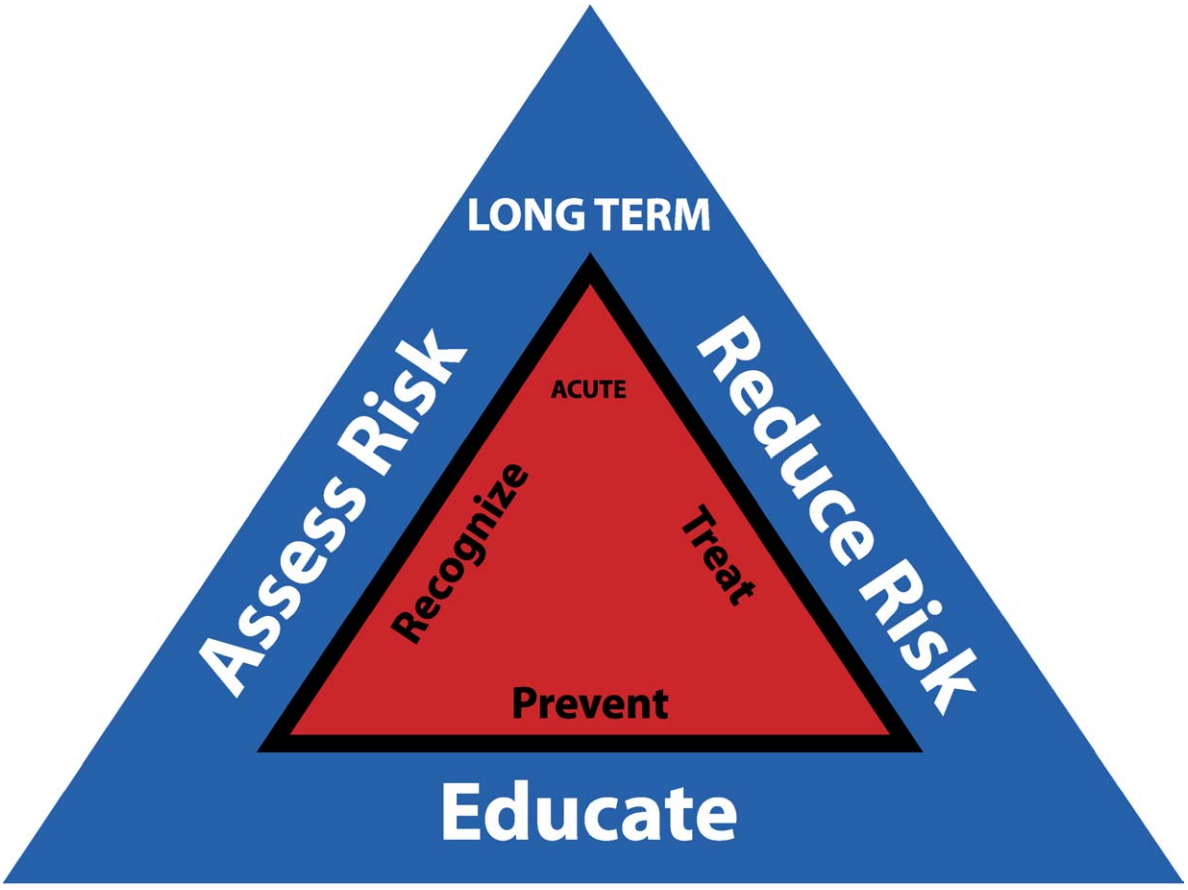

FIG 2. The dual role of the allergy-immunology specialist in anaphylaxis. In addition to their crucial traditional role (ie, diagnosis, treatment, and prevention of anaphylaxis as an acute emergency in a health care setting), allergy-immunology specialists have the responsibility to provide comprehensive risk assessment of individuals with a history of anaphylaxis, develop long-term personalized risk reduction strategies for these individuals, and promulgate anaphylaxis education.

unrecognized when the focus is solely on acute respiratory symptoms, with failure to note accompanying symptoms, such as itching, hives, or dizziness suggestive of impending shock.

The differential diagnosis of anaphylaxis is well delineated in textbooks. It includes more than 40 other diseases, including flush syndromes (eg, carcinoid), restaurant syndromes (eg, scombroidosis), histamine excess syndromes (eg, systemic mastocytosis), and other diseases (eg, pheochromocytoma).[22] In the community, however, diagnostic dilemmas for individuals with anaphylaxis, their caregivers, and non–health care professionals usually involve common problems, such as acute asthma, acute generalized hives, fainting, or anxiety–panic attacks. Age-related considerations are also a concern, such as sudden respiratory distress caused by choking and inhalation of a foreign body in a young child, and sudden collapse caused by a myocardial infarction or stroke in a middle-aged or elderly person.

Laboratory tests for diagnosis

The clinical diagnosis of anaphylaxis can sometimes be supported by documentation of increased plasma histamine or serum tryptase concentrations.[26,27] Although histamine levels are more likely to be increased than tryptase levels are in individuals with symptoms and signs of anaphylaxis, it is not practical to measure histamine levels because they need to be obtained within 1 hour of symptom onset and are not stable during routine handling. The widely available laboratory test for total serum tryptase level measures constitutively secreted α-tryptase in addition to β-tryptase, a better marker of mast cell activation. Even when obtained in a timely manner within 1 to 6 hours of the onset of a clinically documented anaphylaxis episode, serum tryptase levels might be within normal limits.[26,27] Serial measurements increase the sensitivity and specificity of the test.[27] Biomarkers with greater specificity and sensitivity, such as mast cell carboxypeptidase, are being investigated.[28]

Comorbidities and concurrent medications

Persistent asthma, especially if not optimally controlled, is an important risk factor for death from anaphylaxis.[29,30] Other comorbidities and characteristics, such as acute infection or psychologic stress, although not adequately studied in the context of anaphylaxis, might

TABLE II. Comorbidities and concurrent medications relevant to anaphylaxis

Comorbidities	
Might interfere with recognition of trigger or symptoms	**Might affect treatment**
Impairment of vision or hearing	Asthma
Neurologic disease	Cardiovascular disease
Psychiatric disease (eg, depression, ADHD)	Lack of coordination or strength (inability to self-inject epinephrine)
Developmental delay	
Behavior problem	
Substance abuse	
Concurrently administered medications	
Might interfere with recognition of trigger or symptoms	**Might affect treatment**
Sedatives (eg, sedating H_1-antihistamines)	β-Adrenergic blockers*
Hypnotics	α-Adrenergic blockers*
Ethanol	Angiotensin-converting enzyme inhibitors†
Recreational drugs	Angiotensin II receptor blockers†
	Tricyclic antidepressants‡
	Monoamine oxidase inhibitors‡
	ADHD§ medications (eg, amphetamines, methylphenidate)

ADHD, Attention deficit–hyperactivity disorder.
*Regardless of route of administration; potentially decrease epinephrine efficacy by blocking effects at adrenergic receptors.
†Potential interference with endogenous compensatory responses.
‡Potential increase in adverse effects of epinephrine because of prevention of epinephrine uptake at adrenergic receptors.
§Side effects are similar to those of epinephrine; amphetamines and methylphenidate release intracellular stores of epinephrine and also block monoamine oxidase, preventing epinephrine uptake at adrenergic receptors.

also increase the risk.[31] When anaphylaxis occurs in the community in the absence of a health care professional, any problem that interferes with an individual's ability to recognize triggers and early symptoms (eg, visual or auditory impairment, depression, or substance abuse) places that individual at increased risk (Table II).

In addition, many commonly used central nervous system–active medications and chemicals potentially affect recognition of anaphylaxis triggers and symptoms. These include sedating H_1-antihistamines,[32] ethanol, and recreational drugs. Concurrent administration of other medications such as orally or topically administered β-adrenergic blockers, angiotensin-converting enzyme inhibitors, and, to a lesser extent, angiotensin II blockers, potentially interferes with the response to treatment (Table II).[33-35]

Verification of the trigger or triggers

Individuals with anaphylaxis need access to appropriately trained specialist physicians who will take the time needed to sort out the history of the episode and provide the context for interpretation of skin tests and measurement of allergen-specific IgE levels in serum, preferably by means of a quantitative test, such as the CAP System FEIA (Pharmacia Upjohn Diagnostics, Uppsala, Sweden) and other tests.[15,36-44] Less obvious or less common triggers might be overlooked, even by physicians. For example, anaphylaxis after a meal or snack might have been triggered by a trace amount of food, such as a cross-contaminating food, or (potentially) by a hormonally or genetically modified food, or by a substituted food, a hidden food ingredient, or a food additive. A concomitant trigger, such as exercise, might be involved.[23,36] Even an obvious trigger, such as a painful insect sting that is usually self-reported reliably, needs to be confirmed (Table I).[37-39]

Standardized extracts are preferred for skin testing; however, they are not commercially available for many allergens relevant to anaphylaxis, including foods (leading to the practice of skin testing with fresh foods), biting insect saliva, or natural rubber latex. The recombinant food, insect saliva, and latex allergens being developed will therefore be useful.[15,36,40]

Although a positive skin test response and increased IgE levels to a specific allergen document sensitization to the allergen, they do not necessarily prove that the allergen is the causative trigger for symptoms. Many individuals with positive skin test responses and increased serum IgE levels specific to foods are able to ingest these foods without developing symptoms. Moreover, although individuals with strongly positive skin test responses and high levels of allergen-specific IgE in serum generally have an increased probability of clinical reactivity, these tests do not necessarily predict the severity and risk of fatality in future anaphylaxis episodes. Up to 25% of all adults have positive skin test responses to insect venom or venoms, yet only a small percentage of these individuals experience anaphylaxis after a sting; conversely, an individual can experience anaphylaxis caused by an insect sting and have negative venom skin test responses and absent or undetectable venom-specific IgE concentrations in serum.[37-39] Additional tests, such as measurement of allergen-specific activation of basophils, are being developed.[39]

For some anaphylaxis triggers, such as some medications,[41] physician-monitored incremental challenges conducted in an appropriately equipped and staffed health care facility are helpful, although they are time consuming, costly, and not without risk. Moreover, to confirm the absence of, and avoid overdiagnosis of, clinical food allergy, some mildly sensitized individuals with no history of a recent allergic reaction might require carefully supervised incremental double-blind or open food challenges to distinguish between sensitization associated with clinical tolerance and sensitization associated with risk of anaphylaxis.[36,42-44] Serial measurement of allergen-specific IgE levels in serum and mathematic modeling of the rate of change in the levels in relation to the individual's age might help to predict loss of clinical reactivity over time.[45] Promising research involves development of peptide microarray immunoassays to determine food allergen

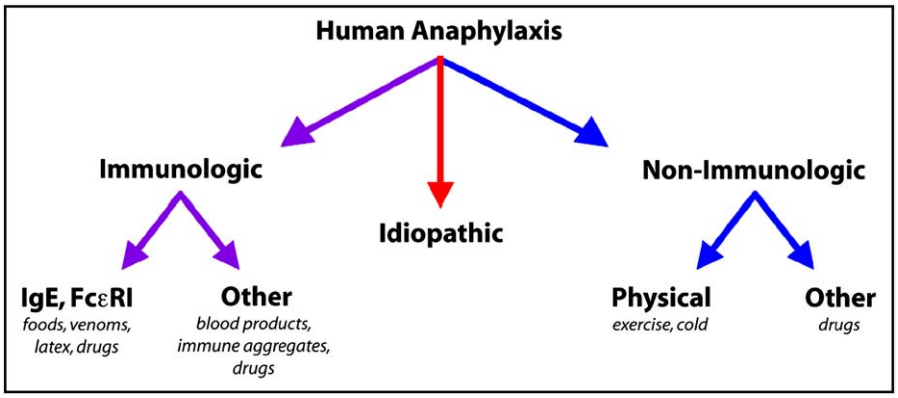

FIG 3. Mechanisms underlying human anaphylaxis. Anaphylaxis might be immune mediated or might occur through direct (nonimmune) perturbation of mast cells. Idiopathic anaphylaxis, currently a diagnosis of exclusion, presents opportunities for elucidation of pathophysiologic mechanisms.

epitopes bound by an individual's serum. Individuals with IgE directed at sequential epitopes tend to have persistent risk of symptoms.[36] The greater the number of epitopes recognized, the greater the likelihood of a severe allergic reaction.[46] Continued development of practical tests that will distinguish reliably between sensitized clinically tolerant individuals and sensitized individuals at risk for anaphylaxis are needed,[46,47] as is the development of tests and algorithms that will predict an individual's future risk for anaphylaxis and risk of fatality.

Novel triggers

From time to time, novel or unusual anaphylaxis triggers are reported (Table I).[15-20] Documentation of anaphylaxis from a previously unrecognized trigger is facilitated by actions taken at the time of the acute event and by subsequent investigations (Table I). These include (1) obtaining comprehensive information about the episode, including antecedent activities, symptoms and signs, and response to treatment; (2) measuring serum tryptase levels in a timely manner; (3) saving the suspected trigger allergen (eg, leftover food or vomited food, stinging or biting insect, or medication) and gathering as much information as possible about the allergen (including, if relevant, package label, and manufacturer's name and coordinates); and (4) obtaining sera for measurement of allergen-specific IgE levels, immunoblotting, and other tests. Some allergy-immunology laboratories have the capability of developing customized sensitive and specific *in vitro* tests, such as ELISAs, to detect the presence of specific IgE to novel suspected allergens.[16-20,39] An allergen might be novel in one population but not in another, depending on geographic location, age, and occupation,[21,48,49] and the clinical importance of an allergen might increase over time (eg, allergic reactions to sesame are increasing in the "developed" world).[49]

Mechanisms of anaphylaxis

In many individuals, anaphylaxis has a well-defined underlying immunologic mechanism, often involving IgE, FcεRI receptors, mast cells, basophils, and release of cytokines, chemokines, and chemical mediators of inflammation such as histamine and tryptase (Fig 3). In some individuals, other immunologic mechanisms might be involved, such as cytotoxic events involving IgM or IgG, immune aggregates, shift in eicosanoid metabolism toward leukotriene formation, or activation of the complement, kalikrein-kinin, or coagulation systems or of platelets or T cells.[12,22,31] It might be worthwhile to study the expression of the anaphylatoxin receptors C3aR and C5aR in anaphylaxis, given their increased expression in fatal asthma.[50] Nonimmunologic perturbation of mast cells by physical factors such as exercise or cold exposure, or by medications such as opiates, might also occur (Table I).[12,22,31] Allergy-immunology specialists should be alert for opportunities to investigate mechanisms in anaphylaxis, for example in individuals with idiopathic anaphylaxis, currently a diagnosis of exclusion,[12,22] the possibility of novel mechanisms, as well as novel triggers or occult underlying disease such as mastocytosis, should be considered.[51-53] Genetic factors might play a role in determining susceptibility to anaphylaxis, a largely unexplored area to date.[54,55]

Much has been learned, and remains to be learned, from animal models with regard to the immunopathophysiology of anaphylaxis, despite species differences in the primary organs and systems involved. In murine models 2 main immunologic pathways have been described: a pathway involving IgE FcεRI receptors, mast cells, histamine, leukotrienes, serotonin, and platelet-activating factor and a pathway involving IgG, FcγRIII, macrophages, and platelet-activating factor.[56]

LONG-TERM RISK REDUCTION

Long-term risk reduction includes optimal management of relevant comorbidities (eg, asthma or cardiovascular disease), avoidance of confirmed triggers, and specific preventive treatment where relevant, as well as providing at-risk individuals with a personalized anaphylaxis

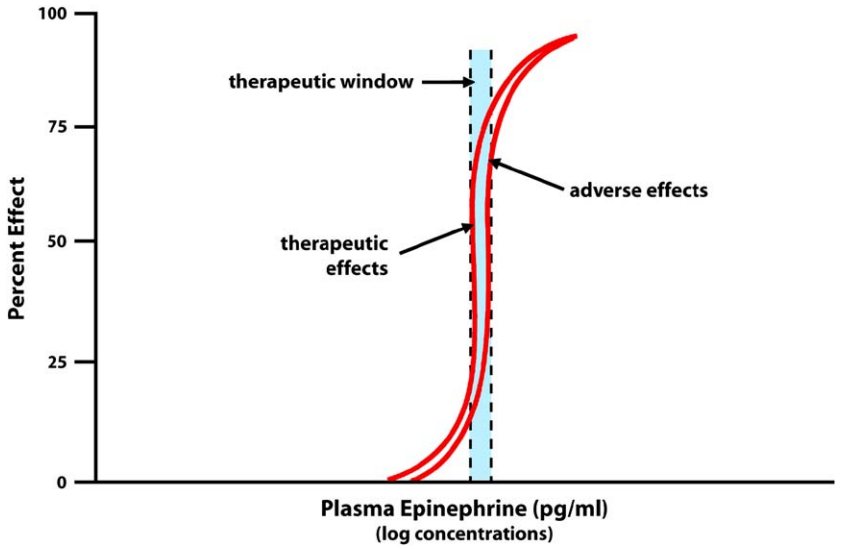

FIG 4. The narrow therapeutic window of epinephrine. The life-saving pharmacologic effects of epinephrine, including vasoconstriction, decreased mucosal edema, bronchodilation, and decreased release of histamine, tryptase, and other mediators of inflammation, cannot be divorced from pharmacologic effects such as pallor, anxiety, tremor, and palpitations, which are perceived as adverse effects. Serious adverse effects are rare. The therapeutic range of plasma concentrations associated with successful anaphylaxis treatment is unknown.

emergency action plan and medical identification, and coaching them in the use of self-injectable epinephrine.

Avoidance of specific triggers

The natural history of anaphylaxis differs, depending on the trigger; however, for many triggers, lifelong avoidance is necessary.[57] Written and specific information on trigger avoidance should be provided and reviewed at regular intervals with those at risk and their caregivers,[38,57] who should be directed to Web site resources that consistently provide accurate information. These include the Food Allergy and Anaphylaxis Network (www.foodallergy.org); the American Latex Allergy Association (www.latexallergyresources.org); the American Academy of Allergy, Asthma and Immunology (www.aaaai.org); and the American College of Allergy, Asthma and Immunology (www.acaai.org). Complete avoidance of exposure to a confirmed trigger (eg, a food, a stinging or biting insect, or natural rubber latex) for prevention of anaphylaxis is easier said than done. For processed foods in particular, labeling might be absent, hard to read because of small print, or hard to comprehend because of multisyllabic chemical terms. The constant vigilance and subsequent lifestyle changes required every day, year round, might have a profound negative effect on the quality of life for the individual with anaphylaxis and his or her family.[57-59] Referral to a licensed nutritionist might be helpful for individuals with multiple dietary restrictions caused by confirmed food allergies.

Preventive treatment, including trigger-specific treatment

Prevention strategies for anaphylaxis triggered by exercise include avoidance of relevant food or medication co-triggers (or, if no specific co-trigger is identified, avoidance of ingesting anything at all) within 4 hours of strenuous exercise, along with precautions such as discontinuing exercise at the earliest hint of symptom development, never exercising alone, and always carrying self-injectable epinephrine. Warm-up and premedication are less effective than they are in prevention of exercise-induced bronchospasm.[23]

For idiopathic anaphylaxis, a personalized prophylactic medication regimen should include one or more of the following: an oral corticosteroid, H_1-antihistamine, H_2-antihistamine, or leukotriene modifier.[23]

Anaphylaxis from insect stings can be almost entirely prevented by use of allergen-specific immunotherapy initiated by an allergy-immunology specialist,[37,38,60] and protection is long lasting.[60] Desensitization strategies are effective for seminal fluid–induced anaphylaxis and for anaphylaxis triggered by some medications, including β-lactam antibiotics, and acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs.[23]

In the future, novel preventive immunomodulatory strategies will be available for long-term risk reduction in anaphylaxis.[36,57,61-63] These might include allergen-specific treatment, such as engineered recombinant proteins in which substitution of a critical amino acid within the IgE-binding epitopes reduces IgE binding and prevents IgE-mediated reactions,[61] or nonspecific treatment, such as use of anti-CD63 antibodies.[62] Proof of principle of one allergen-nonspecific approach, the efficacy of regular injections of anti-IgE antibody to prevent anaphylaxis, has already been obtained in humans with peanut allergy,[63] and eventually, this might provide many individuals with an increased margin of protection against exposure to trace amounts of various allergens to which they are sensitized.

ANAPHYLAXIS EMERGENCY ACTION PLAN

NAME: _____ **AGE:** _____

ALLERGY TO: _____

Asthma □ **Yes** ***(high risk for severe reaction)*** □ **No**

Other health problems besides anaphylaxis: _____

_____

Concurrent medications, if any: _____

_____

SYMPTOMS OF ANAPHYLAXIS INCLUDE:

MOUTH	**itching, swelling of lips and/or tongue**
THROAT*	**itching, tightness/closure, hoarseness**
SKIN	**itching, hives, redness, swelling**
GUT	**vomiting, diarrhea, cramps**
LUNG*	**shortness of breath, cough, wheeze**
HEART*	**weak pulse, dizziness, passing out**

Only a few symptoms may be present. Severity of symptoms can change quickly.
****Some symptoms can be life-threatening! ACT FAST!***

WHAT TO DO:

1. INJECT EPINEPHRINE IN THIGH USING (check one): □ **EpiPen Jr (0.15 mg)** □ **Twinject 0.15 mg** □ **EpiPen (0.3 mg)** □ **Twinject 0.3 mg**

Other medication/dose/route: _____

IMPORTANT: ASTHMA PUFFERS AND/OR ANTIHISTAMINES CAN'T BE DEPENDED ON IN ANAPHYLAXIS!

2. CALL 911 or RESCUE SQUAD (BEFORE CALLING CONTACTS)!

3. Emergency contact #1: home _____ **work** _____ **cell** _____

Emergency contact #2: home _____ **work** _____ **cell** _____

Emergency contact #3: home _____ **work** _____ **cell** _____

DO NOT HESITATE TO GIVE EPINEPHRINE!

COMMENTS: _____

_____

_____ _____

Doctor's Signature/Date **Parent's Signature (for individuals under age 18 yrs)/Date**

FIG 5. Anaphylaxis emergency action plan. All individuals at risk for anaphylaxis in the community need an emergency action plan. If the individual at risk is an infant or child, the plan should include their picture in the upper right corner. The plan shown as an example was adapted from reference 75.

FIG 6. Medical identification. All individuals at risk for anaphylaxis in the community need accurate medical identification. The folding wallet card shown as an example was designed with the assistance of the American Academy of Allergy, Asthma and Immunology Anaphylaxis Education Task Force. *Exterior surfaces,* Anaphylaxis can be fatal/anaphylaxis symptoms; *interior surfaces,* personal identification/what to do for a life-threatening reaction.

Self-injectable epinephrine and an emergency action plan for anaphylaxis recurrence

Despite long-term risk reduction measures, anaphylaxis triggers might be inadvertently encountered, and episodes might recur and be subsequently more severe.[64] Physicians should not hesitate to prescribe self-injectable epinephrine for use in community settings, where no health care professional is available to assist in the recognition and treatment of anaphylaxis.[65] All individuals at risk for anaphylaxis in the community and their caregivers should be taught how to use an epinephrine autoinjector.

Epinephrine is characterized by concentration-dependent, bidirectional effects and a narrow therapeutic index (benefit-to-risk ratio, Fig 4). Common transient adverse effects, such as pallor, tremor, anxiety, and palpitations correlate with its pharmacologic activity and are generally not a cause for concern.[66] Serious adverse effects, such as myocardial ischemia, dysrhythmias, and pulmonary edema are usually, although not always, attributable to overdose, particularly to rapid administration of inappropriately high concentrations through the intravenous route. Myocardial ischemia and cardiac arrhythmias can occur in individuals with anaphylaxis who have not received any epinephrine.[12]

Death can occur rapidly and unpredictably in anaphylaxis, and therefore epinephrine should be injected promptly, preferably intramuscularly,[67] to achieve peak concentrations rapidly in plasma and tissues.[12,22,67] The limited range of premeasured fixed doses, 0.15 mg and 0.3 mg, currently available in autoinjectors presents a dilemma for physicians prescribing epinephrine for infants and children[68] and also for large adolescents and adults. Lack of availability of autoinjectors with a needle length adequate to achieve intramuscular injection in obese or overweight individuals, especially women, is also a concern.[69]

In many countries life-saving epinephrine autoinjectors are not available for individuals in need.[70] Existing alternatives cannot be depended on to produce high concentrations of epinephrine rapidly in tissues; these include laypersons' use of a needle and syringe to draw up and measure an epinephrine dose from an ampule[71] or use of a chlorofluorocarbon-containing epinephrine metered-dose inhaler.[72] Novel sublingual dosage forms of epinephrine are being developed specifically for self-administration in the community.[73]

Epinephrine should always be prescribed in the context of broader educational interventions, including a written, personalized, and regularly updated anaphylaxis emergency action plan (Fig 5).[74,75] Such plans should list the most common symptoms and signs of anaphylaxis and emphasize prompt epinephrine injection, followed by transportation of the individual to the nearest hospital emergency department,[75] because treatment for biphasic or prolonged anaphylaxis might be required.[76]

Individuals at risk for a recurrent episode of anaphylaxis should be cautioned not to depend on an oral H_1-antihistamine for relief.[32,66] Although H_1-antihistamines relieve itch and hives, in usual doses they do not relieve airway obstruction, gastrointestinal symptoms, or shock, or prevent mediator release from mast cells and basophils. After administration by mouth, H_1-antihistamine absorption and onset of action are slow, taking at least 1 to 2 hours. In many anaphylaxis episodes, the rapid

TABLE III. Key messages in anaphylaxis education*: ANAPHYLAXIS = KILLER ALLERGY

Who is at risk? Anyone, especially those allergic to foods such as peanut, tree nut, seafood, fin fish, milk, or egg, or to insect stings or bites, natural rubber latex, or medications.
When can it happen? Within minutes, anytime the allergic person comes in contact with his or her trigger.
How do we know? Several symptoms occur at the same time, such as itching, hives, flushing, difficulty breathing, vomiting, diarrhea, dizziness, confusion, or shock.
Where can it happen? Anywhere, such as home, restaurant, school, child care or sports facility, summer camp, car, bus, airplane.
What should we do? Inject epinephrine, call 911 or local emergency medical service number, and notify the individual's family (in that order)! Act quickly. Anaphylaxis can be mild, or it can be fatal.
Why is follow-up needed? Anaphylaxis can occur repeatedly. The trigger needs to be confirmed, and long-term preventive strategies need to be implemented.

*For individuals at risk and their caregivers, and for the general public.

improvement attributed to an orally administered H_1-antihistamine is likely due to spontaneous improvement.

All individuals known to be at risk for anaphylaxis should be equipped with accurate medical identification listing their confirmed trigger factor or factors and their relevant comorbidities and concurrent medications. Available options include wallet cards (Fig 6) and medical identification jewelry, with or without an embedded medical record. The jewelry might not be practical for some at-risk individuals because of initial and ongoing expense, lack of durability, and potential for exacerbating atopic dermatitis–eczema or contact dermatitis.[77] Up-to-date information about life-threatening allergies should be accurately documented in an individual's electronic and paper medical records, which should be labeled or flagged to denote high risk. Electronic pagers and alarm systems might be useful in reducing morbidity and mortality from anaphylaxis; however, prospective studies of these devices are needed in this context.

ANAPHYLAXIS EDUCATION

Education of individuals with anaphylaxis and their families and caregivers helps to banish anxiety and fear and instills confidence in their ability to cope, not only by preventing anaphylaxis episodes, but also by recognizing and treating them promptly if they occur. All health care professionals, including all physicians, nurses, emergency medical service technicians, and first responders need regular anaphylaxis education updates. Ideally, advanced cardiac life support instruction should introduce the concepts of prescribing self-injectable epinephrine for individuals who are treated for anaphylaxis occurring in the community, and referring such individuals to appropriate specialists for long-term management.

The first episode of anaphylaxis can be fatal.[30] It is therefore important to increase awareness of anaphylaxis as a killer allergy among teachers, coaches, camp directors, child care providers, food industry workers, and restaurant workers.[78] It is also important to increase awareness among members of the general public (Table III), to provide clear aids to recognition of early signs and symptoms, and to promulgate prompt use of self-injectable epinephrine. Optimally, epinephrine autoinjectors should be available in all public places where anaphylaxis might occur.

Legislators appear to be receptive toward changing public policy and improving medical services for individuals with anaphylaxis. Landmark legislation being implemented in 2006 includes the National Food Allergy Labeling Consumer Protection Act in the United States, which mandates clear food labeling, and an Act to Protect Anaphylactic Pupils (Sabrina's Law) in Ontario, Canada, which mandates establishing minimum standards for managing anaphylaxis in schools.

SUMMARY

There is more to anaphylaxis than the acute and potentially life-threatening emergency itself, critically important as that is. Physicians, particularly allergy-immunology specialists, play a pivotal role in long-term management of anaphylaxis, which encompasses, yet goes beyond, their traditional role in diagnosing and treating the acute event. All individuals with anaphylaxis should be referred to a specialist physician who is knowledgeable about (1) risk assessment, including verification of triggers and assessment of comorbidities and concurrent medications; (2) personalized risk reduction involving prevention and treatment of future episodes; and (3) anaphylaxis education.

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