

Anaphylaxis: Recent advances in assessment and treatment

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Activity Objectives

1. To review the epidemiology and pathogenesis of anaphylaxis.
2. To discuss the clinical diagnosis of an acute anaphylaxis episode and the laboratory tests that might support the diagnosis.
3. To list the ways of confirming the trigger for an anaphylaxis episode (history, allergen skin tests, allergen-specific IgE levels, and challenge tests).
4. To describe long-term preventive measures for patients with a history of anaphylaxis.
5. To state the critical steps in the first-aid treatment of anaphylaxis in the community.

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The incidence rate of anaphylaxis is increasing, particularly during the first 2 decades of life. Common triggers include foods, medications, and insect stings. Clinical diagnosis is based on a meticulous history of an exposure or event preceding characteristic symptoms and signs, sometimes but not always supported by a laboratory test such as an elevated serum total tryptase level. Physician-initiated investigation of patients with anaphylaxis whose symptoms and signs are atypical sometimes leads to important insights into previously unrecognized triggers and mechanisms. In idiopathic anaphylaxis, in which no trigger can be confirmed by means of skin testing or measurement of specific IgE, the possibility of mastocytosis or a clonal mast cell disorder must be considered in addition to the possibility of a previously unrecognized trigger. Long-term risk reduction in patients with anaphylaxis focuses on optimal management of relevant comorbidities such as asthma and other respiratory diseases, cardiovascular disease, and

mastocytosis or a clonal mast cell disorder; avoidance of the relevant confirmed allergen trigger; and relevant immunomodulation such as medication desensitization, venom immunotherapy, and possibly in the future, immunotherapy with food. Emergency preparedness for recurrence of anaphylaxis in community settings includes having epinephrine (adrenaline) autoinjectors available, knowing when and how to use them, and having a written, personalized anaphylaxis emergency action plan and up-to-date medical identification. Randomized controlled trials of the pharmacologic interventions used in an acute anaphylaxis episode are needed. (*J Allergy Clin Immunol* 2009;124:625-36.)

Key words: *Anaphylaxis, systemic allergic reaction, food allergy, medication allergy, insect venom allergy, epinephrine, adrenaline*

This review highlights recent advances in basic, translational, and clinical science that are leading to better understanding of anaphylaxis, particularly in the areas of epidemiology, pathogenesis, risk assessment, and long-term risk reduction in the community.¹

Anaphylaxis, as defined by an international multidisciplinary group of experts, is a serious allergic reaction that is rapid in onset and can cause death.² The diagnosis is based on defined clinical criteria. Hypotension and shock are not necessarily present. The term “anaphylactoid” is no longer recommended for use.

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Abbreviations used

CNS: Central nervous system

OSCS: Oversulfated chondroitin sulfate

EPIDEMIOLOGY

The true rate of occurrence of anaphylaxis from all triggers in the general population is unknown.^{3,4} Community-based population estimates are difficult to evaluate because of under-diagnosis and under-reporting, as well as miscoding and the use of a variety of case definitions and measures of occurrence.⁴⁻⁶ Despite this, it is clear that anaphylaxis is not rare and that the rate of occurrence is increasing, especially in the first 2 decades of life.⁷⁻⁹ In a retrospective, population-based study using the resources of the Rochester Epidemiology Project, the incidence rate of anaphylaxis was reported to double from 21 per 100,000 person-years in the 1980s to 49.8 per 100,000 person-years in the 1990s.⁷ The highest incidence rate, 70 per 100,000 person-years, was found in those 0 to 19 years of age. Similar results have been reported in other studies.^{8,9} Before the age of 15 years, there is a predilection for males, but after the age of 15 years, there is a predilection for females. In children, adolescents, and young adults, foods are the most common trigger. In middle-aged and older adults, medications and stinging insect venoms are important considerations, as is idiopathic anaphylaxis.³

Death from anaphylaxis is considered rare¹⁰⁻¹⁴; however, underreporting of fatal anaphylaxis likely occurs because of incomplete clinical information, absence of a detailed death scene investigation, lack of specific autopsy findings, lack of laboratory tests with optimal specificity and sensitivity to confirm the diagnosis, and miscoding.^{5,6}

PATHOGENESIS

An understanding of potential triggers, mechanisms, and patient-specific risk factors in anaphylaxis is the key to performing an appropriate risk assessment in someone who has previously experienced an acute anaphylaxis episode (Fig 1).^{1,3,15,16}

Triggers

The number of potential anaphylaxis triggers is infinite. The most common food triggers are peanut, tree nuts, shellfish, fish, milk, and egg.^{1,3,10-12} Hidden food triggers include substituted foods, cross-reacting foods, cross-contacting foods, food contaminants (eg, storage mites), food additives (eg, the orange-red dye carmine [cochineal]), and food parasites (eg, the live nematode *Anisakis simplex*).¹⁶ Newly recognized food triggers include quinoa, fish gelatin, and seal and whale meat eaten by indigenous peoples.¹⁷⁻¹⁹

Medication triggers include β -lactam and other antibiotics; aspirin, ibuprofen, and other analgesics²⁰; and newly recognized agents such as oversulfated chondroitin sulfate (OSCS)-contaminated heparin,²¹ as well as seemingly innocuous substances such as folic acid contained in vitamins and supplements.²² Biologic agents that trigger anaphylaxis include mAbs such as cetuximab,²³ infliximab,²⁴ and omalizumab²⁵; allergens used in immunotherapy²⁶; and, rarely, vaccines to prevent infectious diseases.²⁷

Venom from a stinging insect (order Hymenoptera)²⁸ or, less commonly, saliva from a biting insect (eg, order Diptera [flies and mosquitoes] or Hemiptera [kissing bugs]) can induce anaphylaxis.^{28,29} Other triggers include natural rubber latex, occupational allergens, and, less commonly, seminal fluid prostate-specific antigen,³⁰ or inhalant allergens such as horse, hamster, or other animal dander and grass pollen.^{1,3,16} Nonimmunologic triggers include exercise,³¹ cold air or water,³² heat, radiation, ethanol, and some medications such as opioids.^{1,3,16}

Physician-initiated investigation of patients with anaphylaxis who have atypical symptoms and signs or atypical chronology of symptoms and signs sometimes leads to important insights into previously unrecognized triggers and mechanisms, as in the following examples. Anaphylaxis triggered by red meat that occurs 4 to 6 hours after ingestion is due to the oligosaccharide galactose α -1,3 galactose rather than to a protein.³³ Anaphylaxis triggered by cetuximab often occurs after the first infusion because of pre-existing antibodies to galactose α -1,3 galactose.²³ Anaphylaxis triggered by omalizumab sometimes has a delayed onset and a protracted course involving gradual escalation of symptoms over several hours.²⁵ Anaphylaxis triggered by heparin contaminated by OSCS is associated with an atypical symptom pattern in which abdominal pain, nausea, hypotension, and shortness of breath predominate and skin signs are infrequent.^{21,34}

Mechanisms

Most triggers lead to anaphylaxis through a mechanism that involves cross-linking of IgE and aggregation of Fc ϵ RI on mast cells and basophils.^{15,16,35,36} In human anaphylaxis other immunologic mechanisms that do not involve IgE are less commonly implicated and less definitively proven. These include IgG-antigen complexes, activation of the complement and coagulation systems, and possibly other mechanisms such as cytotoxicity, T-cell activation, neuropeptide (substance P) release, or autoimmunity.^{16,34-36} There is indirect evidence that in response to injection of high-dose antigen, human anaphylaxis can occur through IgG-antigen complexes, macrophages, and platelet-activating factor; specific IgG responses have been reported to murine immunoglobulin determinants on infliximab and to dextran contained in vaccines or in high-molecular-weight iron dextran formulations.^{24,37,38} A well-documented example of complement and coagulation system involvement is OSCS-contaminated heparin-triggered anaphylaxis, in which activation of the complement system leads to generation of kallikrein and bradykinin, as well as the anaphylatoxins C3a and C5a, and the coagulation system is involved through Factor XII.^{21,34} Nonimmune perturbations of mast cells and basophils caused by exercise or exposure to cold air or cold water can also lead to anaphylaxis. In the same patient more than 1 mechanism might contribute to an anaphylaxis episode.^{16,21,34}

Regardless of the initiating trigger and mechanism, cellular events involving activation of tyrosine kinases and calcium influx in mast cells and basophils result in rapid release of granule-associated preformed mediators such as histamine, tryptase, carboxypeptidase A3, chymase, and proteoglycans.^{16,35,39} Downstream activation of phospholipase A₂, COXs, and lipoxygenases leads to production of arachidonic acid metabolites,

MECHANISMS AND TRIGGERS

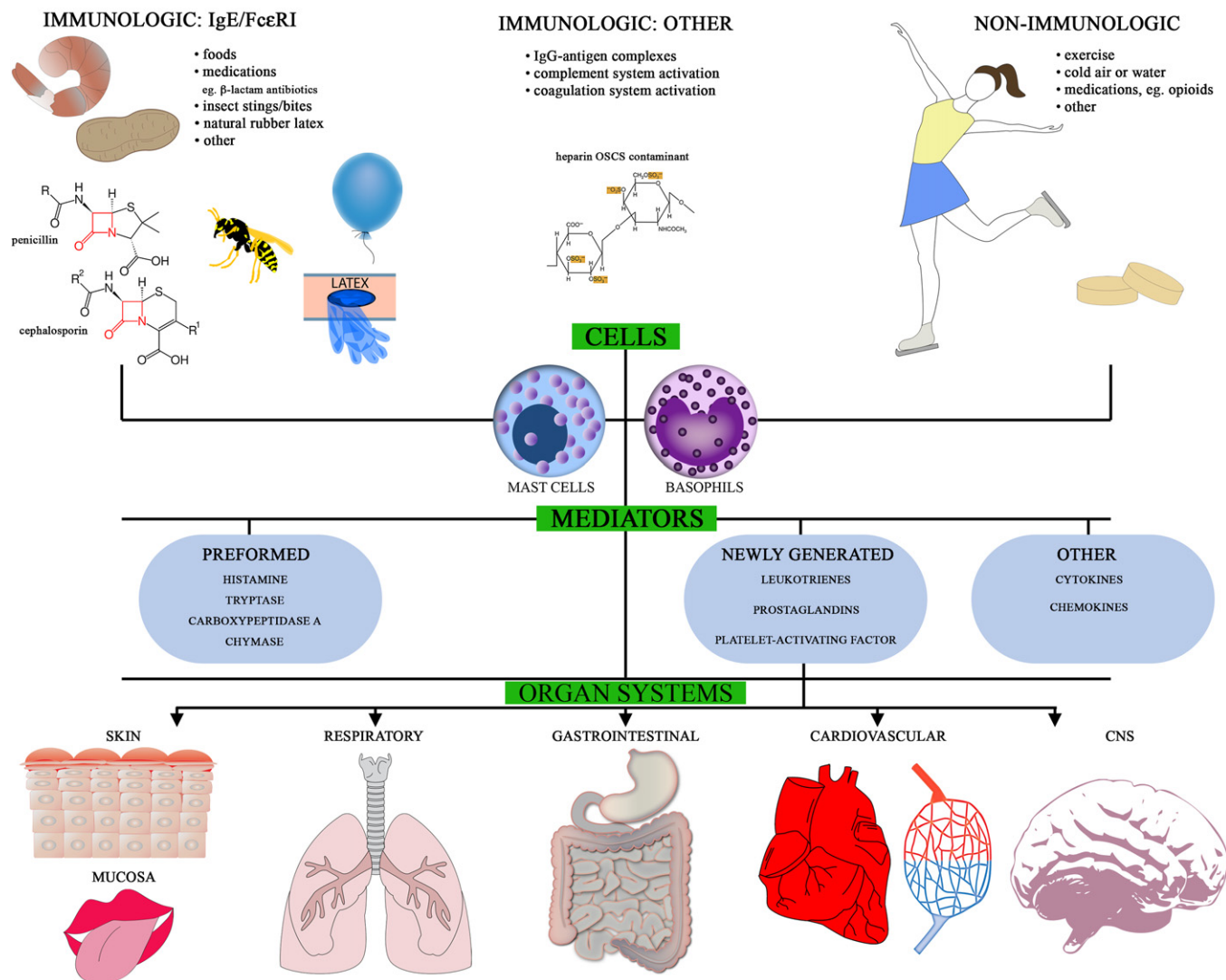


FIG 1. Pathogenesis of anaphylaxis: mechanisms and triggers, cells, mediators, and organ systems. Human anaphylaxis usually occurs through a mechanism that involves cross-linking of IgE and aggregation of high-affinity receptors for IgE on mast cells and basophils. Common triggers include foods such as shrimp and peanut; medications such as penicillins, cephalosporins, and other β -lactam antibiotics; insect stings; and natural rubber latex. Other immunologic mechanisms that do not involve IgE are less commonly implicated and less definitively proven; however, humans experience IgG-antigen complex-mediated anaphylaxis (not shown) and anaphylaxis involving complement system activation and coagulation system activation, as exemplified by OSCS-contaminated heparin-triggered anaphylaxis. Nonimmunologic triggers include exercise, cold air, and some medications such as opioids. On activation, mast cells and basophils release more than 100 chemical mediators of anaphylaxis, only a few of which are listed. The diagnosis of anaphylaxis is based on a history of exposure to a triggering agent or event, the time elapsed between exposure and symptom onset, and the evolution of signs and symptoms over minutes or hours, usually in 2 or more body organ systems. Adapted from Simons.¹⁵

including prostaglandins and leukotrienes,⁴⁰ and synthesis of platelet-activating factor⁴¹. In addition, an array of cytokines and chemokines are synthesized and released, including IL-6, the newly recognized IL-33⁴² and TNF- α , which is both a late-phase mediator and a preformed mediator.³⁵ The opening of the endothelial barrier through endothelial G_q/G_{11} -mediated signaling has been identified as a critically important process

leading to anaphylaxis symptoms in many body organ systems.⁴³

In murine models of anaphylaxis, differences in genetic backgrounds have a profound effect on signaling pathways, activation of mast cells, and progression to anaphylaxis.^{37,44} In human anaphylaxis, studies of the role of genetic factors are few; however, pursuing investigations in this area might help us to understand

why anaphylaxis only occurs in a minority of those who are sensitized to an antigen, and why it ranges in severity from a benign self-limiting event to a catastrophic fatal event.^{16,41,45}

Patient-specific risk factors

Age-related factors might increase risks in patients with anaphylaxis. The disease can be hard to recognize in infants, who cannot describe their symptoms and in whom some anaphylaxis signs such as flushing and dysphonia after a crying spell, spitting up or loose stools after feeding, and incontinence also occur ubiquitously in the healthy state.⁴⁶ Teenagers and young adults are at increased risk of food-triggered anaphylaxis because of inconsistent behaviors with regard to avoiding their confirmed food trigger or triggers and carrying their epinephrine autoinjectors.⁴⁷ Anaphylaxis is uncommon during pregnancy; however, when it does occur, the mother and especially the baby are at high risk of fatality or permanent central nervous system (CNS) impairment. During the first, second, and third trimesters, potential triggers are similar to those seen in nonpregnant women. During labor and delivery, penicillins and other β -lactam antibiotics given as prophylaxis against infant group B streptococcal infection are now the most common triggers.⁴⁸ The elderly are at increased risk of fatality caused by anaphylaxis for a variety of reasons, including concomitant diseases, especially chronic obstructive pulmonary disease and cardiovascular disease, and use of concurrent medications such as β -adrenergic blockers.^{3,13,16,45,49,50}

Diseases that place patients at increased risk for anaphylaxis episodes and for fatality include those that impede prompt recognition of triggers or symptoms such as vision or hearing impairment, neurologic disorders, psychiatric disorders, autism spectrum disorder, and developmental delay.¹ Severe concomitant allergic rhinitis and eczema, and especially asthma,⁴⁵ as well as chronic obstructive pulmonary disease¹³ and other respiratory diseases, cardiovascular diseases,⁴⁹ and mastocytosis and clonal mast cell disorders,⁵¹⁻⁵⁴ are associated with an increased risk of severe, life-threatening, or fatal anaphylaxis.

Some concurrent medications, including any CNS-active medication such as diphenhydramine, chlorpheniramine, and other first-generation H_1 -antihistamines, or any CNS-active chemical such as ethanol or a recreational drug, can interfere with recognition of anaphylaxis.^{1,16} Other concurrent medications such as β -adrenergic blockers and angiotensin-converting enzyme inhibitors used in the management of cardiovascular diseases potentially make anaphylaxis more difficult to treat.^{45,49,50}

Various other concomitant factors, most of which have not been systematically studied, are also reported to increase the risk of an anaphylaxis episode. These include exercise, exposure to extremes of temperature or humidity, disrupted routine, feeling unwell, acute infection (eg, upper respiratory tract infection), emotional stress, menses (premenstrual and ovulatory phase), and ingestion of ethanol or medications such as aspirin or other nonsteroidal anti-inflammatory medications.^{1,12,16,31,32}

RISK ASSESSMENT: DIAGNOSIS OF ANAPHYLAXIS

Anaphylaxis is unpredictable and can occur in anyone, anywhere, at any time. It is underrecognized by patients and underdiagnosed by health care professionals.⁶

TABLE I. Differential diagnosis of anaphylaxis

Common entities	Nonorganic disease
Acute generalized hives	Vocal cord dysfunction
Acute asthma	Munchausen syndrome§
Syncope (fainting)	Other forms of shock
Panic attack	Hypovolemic
Aspiration of a foreign body	Cardiogenic
	Distributive
Restaurant syndromes	Septic (might involve all of the above)
Monosodium glutamate	Other (eg, spinal cord injury)
Sulfites	
Scombroidosis*	
Excess endogenous histamine	Miscellaneous
Mastocytosis/clonal mast cell disorder†	Nonallergic angioedema
	Urticarial vasculitis
Basophilic leukemia	Hyper-IgE, urticaria syndrome
Hydatid cyst‡	Progesterone anaphylaxis
	Pheochromocytoma
Flush syndromes	Red man syndrome
Perimenopause	Capillary leak syndrome
Carcinoid	Cardiovascular (myocardial infarction)
Autonomic epilepsy	Neurologic events (seizure, cerebrovascular event)
Thyroid medullary carcinoma	

Adapted from Lieberman.³

*Histamine poisoning from fish (eg, tuna) stored at increased temperatures; more than 1 person eating the fish is usually affected.

†Anaphylaxis might be the first manifestation of mastocytosis or a clonal mast cell disorder.

‡Ruptured or unruptured; defined geographic distribution includes Mediterranean areas.

§Nonorganic diseases also include Munchausen syndrome by proxy in a child or other dependent, globus hystericus, and undifferentiated somatoform anaphylaxis.

Clinical diagnosis

Diagnosis depends on pattern recognition and is primarily based on the clinical history of exposure to a potential triggering agent or event, the time elapsed between exposure and symptom onset, and the evolution of symptoms and signs over minutes or hours. The target organs involved include the skin (80% to 90% of episodes), respiratory tract (70% of episodes), gastrointestinal tract (30% to 45% of episodes), heart and vasculature (10% to 45% of episodes), and CNS (10% to 15% of episodes).^{1-3,16}

There is increasing awareness of the importance of the heart as a target organ in anaphylaxis. In the healthy human heart, mast cells are present throughout the myocardium and in the intima of the coronary arteries. In patients with coronary artery disease, mast cells are found in atherosclerotic lesions and contribute to atherogenesis.³⁶ Histamine, leukotriene C_4 , and prostaglandin D_2 released from mast cells lead to coronary artery spasm. For these reasons, anaphylaxis can unmask subclinical coronary artery disease. Myocardial infarction, arrhythmias, or both can occur during an anaphylaxis episode, even if epinephrine is not injected.^{16,49}

The differential diagnosis of anaphylaxis consists of a long list of diseases (Table I). Common diagnostic dilemmas involve acute generalized hives, acute asthma, syncope, and panic attack. The differential diagnosis is, to some extent, age-dependent. For example, in infants it includes foreign body aspiration, congenital malformations of the respiratory and gastrointestinal tracts, and apparent life-threatening event/sudden infant death syndrome.⁴⁶ In middle-aged and older adults, acute myocardial infarction and cerebrovascular events are important considerations.^{1,3,16,49}

Laboratory tests

There are more than 100 biomarkers of mast cell and basophil activation. Currently, histamine and total tryptase (pro, pro', and mature forms of α - and β -tryptases) are the only ones measured in clinical laboratories.^{16,39} These tests have limitations, including suboptimal specificity and sensitivity, when used to confirm the diagnosis of an acute anaphylaxis episode.

Plasma histamine levels are increased for only 15 to 60 minutes after symptom onset. Special handling of the blood sample is required; for example, obtaining it through a wide-bore needle, keeping it cold at all times, centrifuging it immediately, and freezing the plasma promptly. Histamine and its metabolite, N-methylhistamine, can also be measured in a 24-hour urine sample.¹⁶

Plasma or serum total tryptase levels are increased from 15 minutes to 3 hours after symptom onset. No special handling of the blood sample is required. An increased tryptase level is useful for confirming the clinical diagnosis when anaphylaxis is triggered by an injected agent such as a medication or stinging insect venom, and when signs include hypotension or shock. Tryptase levels are seldom increased when anaphylaxis is triggered by food^{10,55} or when hypotension or shock is absent.¹⁶ Serial measurements of total tryptase levels, including measurement in a "remission sample" taken after complete resolution of the event, might be more helpful than a single measurement.¹⁶

Other mast cell activation products have potential utility as confirmatory laboratory tests in an anaphylaxis episode. These include measurement of plasma or serum levels of mature β -tryptase,³⁹ mast cell carboxypeptidase A3,¹⁶ chymase,¹⁶ platelet-activating factor,⁴¹ and cytokines,⁴² as well as measurement of urinary levels of cysteinyl leukotriene E₄ and 9- α ,11- β -prostaglandin F₂.⁴⁰ Different biomarkers are released at different times from activated mast cells and basophils, and patients present at different times after symptom onset; therefore, measurement of a panel of biomarkers is likely to be more helpful than measurement of only 1 biomarker.¹⁶ Despite recent advances in this area, the goal of developing rapid, sensitive, and specific laboratory tests that can be used at point of care to confirm the clinical diagnosis of anaphylaxis remains elusive.

RISK ASSESSMENT: CONFIRMATION OF THE ANAPHYLAXIS TRIGGER

In each patient with a history of anaphylaxis, it is important to identify and confirm the trigger and the effector mechanism, because most long-term preventive measures are trigger- and mechanism-specific.

History, skin tests, and allergen-specific IgE levels

A meticulous history of the acute anaphylaxis episode is needed to guide selection of allergens for skin testing and also to provide the basis for interpretation of the skin tests, which are optimally performed at least 3 to 4 weeks after the episode.¹⁶ Standardized allergens are commercially available for Hymenoptera venom but not for other anaphylaxis triggers such as foods, medications, biologic agents, fire ant venom, biting insect saliva, and natural rubber latex, necessitating use of alternatives such as fresh foods, the medications or biologic agents themselves, and insect whole-body extracts.^{16,28,29} Use of validated skin test

instruments, validated skin test techniques (eg, restricting the use of intradermal/intracutaneous tests to investigation of some medication allergies and insect venom allergy), and standardized systems for recording skin test results all contribute to improved risk assessment.¹⁶

Measurement of allergen-specific IgE levels in serum is helpful in patients who have experienced anaphylaxis. For example, in those with food triggers, specific IgE levels measured with a quantitative system such as the ImmunoCap (Pharmacia Diagnostics, Uppsala, Sweden), correlate with clinical reactivity and have predictive value for positive (passed) or negative (failed) food challenges.⁵⁶ Allergen-specific IgE levels obtained by using different assays are not equivalent, and this can potentially affect management decisions.⁵⁷

A positive skin test response, an increased serum IgE level, or both, to a specific allergen document sensitization to that allergen; however, these tests are not diagnostic of anaphylaxis because sensitization to 1 or more allergens is common in the general population of healthy persons who have no history of anaphylaxis. For example, 50% to 60% of young people have a positive skin prick test response to 1 or more foods, yet most of those with positive tests have never experienced anaphylaxis from a food.⁵⁸ Similarly, up to 26% of adults have a positive intradermal test or an increased specific IgE level to 1 or more stinging insect venoms, yet most of those with positive tests have never experienced anaphylaxis from an insect sting.⁵⁹ In addition, although positive skin tests to allergen and increased allergen-specific IgE levels are risk factors for anaphylaxis, the degree of positivity of these tests does not necessarily predict the severity of, or risk of fatality in, a future anaphylaxis episode.^{16,56}

Challenge tests and beyond

In some patients, physician-monitored incremental challenge tests are needed to ascertain the clinical relevance of positive allergen skin tests and increased allergen-specific IgE levels. Challenge tests should be conducted only in appropriately equipped health care facilities staffed by health care professionals who are trained and experienced in selecting patients, performing challenges, and diagnosing and treating anaphylaxis. The potential risk versus the potential benefit to the individual patient should be carefully considered before any challenge test is performed.^{16,20,56,60}

Oral food challenge testing is commonly conducted by allergy/immunology specialists and has been reviewed in depth in the *Journal* earlier this year.⁶⁰ A negative oral food challenge allows introduction or reintroduction of the food into the patient's diet, whereas a positive oral food challenge provides a sound basis for continued avoidance of that food.⁶⁰

In anaphylaxis triggered by a medication, the allergen might not be the medication per se, but rather, a metabolite or an unidentified breakdown product. Except for β -lactam antibiotics and a few other medications, such allergens are generally not available for skin testing or *in vitro* testing. Physician-monitored challenge (provocation) tests therefore play a unique role in the diagnosis of medication allergy and indeed are the gold standard tests for many medications.²⁰ In the study of stinging insect allergy, challenges are used only in research.¹⁶

In the future, the need for time-consuming, potentially risky challenge tests might diminish because *in vitro* tests to distinguish reliably between sensitization without risk of clinical

reactivity versus sensitization with risk of clinical reactivity are being developed and validated.¹⁶ These include assessment of the allergen-induced basophil activation markers CD63 and CD203c,⁶¹ use of dialyzed or recombinant allergens,^{16,62} and assessment of allergen-specific cytokine or chemokine production.¹⁶ In addition, peptide microarray-based immunoassays to map IgE and IgG4 binding to sequential allergen epitopes potentially differentiate between clinically reactive and tolerant patients.^{56,63}

Before making the diagnosis of idiopathic anaphylaxis, physicians should consider the possibility of a hidden or previously unrecognized trigger and should also measure the patient's baseline serum total tryptase level, which reflects the increased burden of mast cells in all forms of mastocytosis.³⁹ It has been suggested that if the total tryptase level is greater than 11.4 ng/mL (the new upper limit of normal), further investigations such as examination for cutaneous mastocytosis, are indicated, and if it is greater than 20 ng/mL, a bone marrow biopsy is indicated, even if cutaneous manifestations are absent.⁵⁴

LONG-TERM RISK REDUCTION: PREVENTIVE MEASURES

Long-term preventive measures to reduce the risk of fatality in patients with anaphylaxis include optimal management of relevant comorbidities such as asthma, cardiovascular disease, and mastocytosis, and awareness of other concomitant factors as described in the "Patient-specific risk factors" section, as well as trigger avoidance and immunomodulation (Fig 2).^{1,3,15}

Avoidance of specific triggers

Avoidance of a confirmed relevant anaphylaxis trigger is the basis of all long-term risk reduction measures in patients with anaphylaxis.^{1-3,20,56} Clear and consistent information about confirmed relevant triggers and how to avoid them should be provided. For some allergens, lifelong vigilant trigger avoidance is necessary. Complete avoidance of exposure to a trigger such as a food is easy to recommend but often difficult to implement because of food substitution or lurking cross-reacting, cross-contacting, or contaminating allergens.⁶⁴ The ensuing lifestyle changes potentially disrupt activities and lead to anxiety and decreased quality of life for those at risk of anaphylaxis and their families.⁶⁵

For anaphylaxis triggered by a medication, avoidance is critically important. An alternative medication, preferably a non-cross-reacting agent from a different therapeutic class but sometimes an agent from the same class, can often be substituted effectively and safely.²⁰

Preventive strategies for exercise-induced anaphylaxis should focus on avoidance of relevant co-triggers such as foods, medications, cold air or cold water exposure, or other concomitant factors. Premedication and warm-up are less effective in prevention of exercise-induced anaphylaxis than they are in the prevention of exercise-induced bronchospasm.^{1,3,31}

Immunomodulation

Oral desensitization to a specific food such as milk, egg, or peanut can be achieved as documented in randomized controlled trials in carefully selected, physician-monitored monitored patients⁶⁶⁻⁷⁰ and is accompanied by long-term humoral and cellular

changes.⁷⁰ Adverse effects, sometimes requiring administration of epinephrine, occur during oral desensitization, especially during the initial dose escalation.⁷¹ The benefit/risk ratio appears to be acceptable in most patients studied to date, and further investigations are ongoing.^{56,66}

Interventions that are not specific for a particular food allergen also appear promising. Subcutaneous injections of anti-IgE antibody, although not curative, potentially provide an increased margin of protection against inadvertently ingested foods (and other allergens) for many patients at risk of anaphylaxis.⁷² Food Allergy Herbal Formula-2, which potentially prevents food-induced anaphylaxis and leads to true immunologic tolerance, is now being studied in humans.⁷³

For anaphylaxis triggered by a medication, if it is not possible to substitute an alternative drug, physician-supervised desensitization strategies with the offending agent are effective and safe, particularly for β -lactam or other antibiotics, aspirin or other nonsteroidal anti-inflammatory drugs, and chemotherapy agents. Desensitization lasts as long as the medication is regularly administered; however, immunologic tolerance does not occur, and if the medication is discontinued for a time, symptoms recur when it is restarted.^{20,74}

Long-lasting protection against anaphylaxis triggered by stinging insect venom(s) can be achieved in most patients who receive a 3- to 5-year course of subcutaneous injections of the relevant venoms,^{28,75} as documented in randomized placebo-controlled trials. Venom immunotherapy can be safely administered to all patients at risk, including those with mastocytosis or a clonal mast cell disorder who are at particularly high risk for anaphylaxis and a fatal reaction after an insect sting and also during venom immunotherapy.⁷⁶ Anti-IgE antibody has been used to control reactions to venom immunotherapy in patients with indolent systemic mastocytosis.⁷⁷ For prevention of anaphylaxis from fire ant stings or insect bites, subcutaneous injections of the relevant whole-body extract are used.²⁸

Patients with frequent episodes of idiopathic anaphylaxis (≥ 6 per year or ≥ 2 per 2 months) should receive prophylaxis with 60 to 100 mg of prednisone each morning for 1 week, then 60 mg on alternate mornings for 3 weeks, followed by gradual tapering of the dose over 2 months,⁷⁸ in addition to an H₁-antihistamine such as 10 mg/day cetirizine. The recommendation for this prophylaxis regimen is based on expert opinion and consensus. Anti-IgE antibody injections might be helpful.⁷⁹ Randomized controlled trials of these approaches are needed.

LONG-TERM RISK REDUCTION: EMERGENCY PREPAREDNESS

Anaphylaxis sometimes recurs despite relevant avoidance measures and immunomodulation. When this happens, it is impossible to predict whether the patient will die within minutes, respond to treatment, or recover spontaneously because of endogenous compensatory mechanisms such as secretion of epinephrine, angiotensin II, and endothelin I.¹⁶ Therefore, those at risk, and their caregivers and friends should be prepared to recognize and treat unanticipated recurrences of anaphylaxis in the community. Emergency preparedness focuses on carrying 1 or more epinephrine autoinjectors and having an anaphylaxis emergency action plan.^{1,80} The management of acute anaphylaxis in a health care facility is reviewed in depth elsewhere.^{81,82}

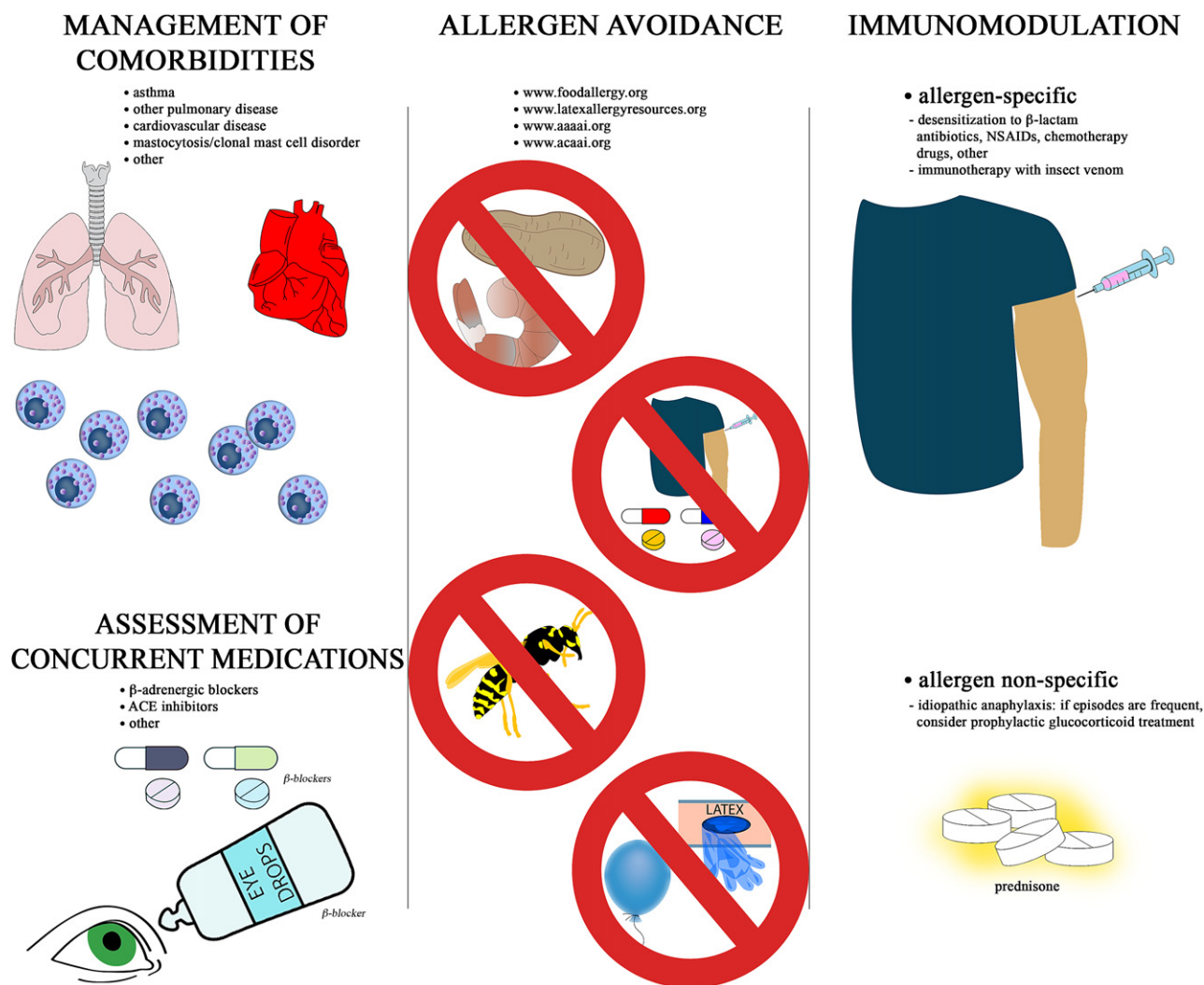


FIG 2. Prevention of anaphylaxis in community settings. Patient-specific risk factors should be appropriately assessed. Optimal management of comorbidities such as asthma, cardiovascular disease, and mastocytosis/clonal mast cell disorder is critically important. The benefits and risks of concurrent medications, especially β -adrenergic blockers, should be assessed, discussed, and documented. Other preventive strategies are trigger specific. Vigilant avoidance of confirmed relevant triggers is fundamental. The Web sites listed provide up-to-date, consistent patient information about allergen avoidance. Currently, immunomodulation is only used to prevent anaphylaxis from a few triggers. In patients with medication-triggered anaphylaxis in whom an alternative agent cannot be substituted effectively and safely, physician-monitored desensitization is useful. In most patients with stinging insect-triggered anaphylaxis, a 3- to 5-year course of subcutaneous venom immunotherapy is life-saving. For patients with frequent episodes of idiopathic anaphylaxis, a 3-month trial of prophylactic treatment with an oral glucocorticoid and a nonsedating H_1 -antihistamine is recommended (see text for details). In the future, oral immunotherapy might be used to prevent food-triggered anaphylaxis, and anti-IgE antibody might be used to prevent anaphylaxis from a variety of triggers, as well as idiopathic anaphylaxis. Adapted from Simons.¹⁵

Self-injectable epinephrine

The World Health Organization lists epinephrine (adrenaline) as an essential medication for the treatment of anaphylaxis, and all published national anaphylaxis guidelines recommend epinephrine as the treatment of first choice in an acute episode (Table II).^{1-3,83} There is no absolute contraindication to epinephrine injections in patients with anaphylaxis.^{1-3,15,80-82,84-86}

Epinephrine's life-saving α_1 -adrenergic vasoconstrictor effects prevent and relieve upper airway obstruction caused by mucosal edema and prevent and relieve shock (Fig 3).⁸⁵ The

recommended epinephrine dose in acute anaphylaxis is 0.01 mg/kg, to a maximum adult dose of 0.5 mg, injected intramuscularly in the midanterolateral thigh to achieve peak plasma and tissue concentrations rapidly.^{1-3,15,80-82,84-86} This dose is lower than the initial epinephrine dose used in cardiopulmonary resuscitation. Failure to inject it promptly before a patient with anaphylaxis experiences acute cardiorespiratory failure and shock potentially increases the risk of death¹⁰⁻¹³ and potentially increases the risk of biphasic anaphylaxis in which initial symptoms resolve, only to recur 1 to 72 hours later despite no further exposure to the trigger.⁸⁷

TABLE II. Rationale for epinephrine as the first-aid treatment of choice for anaphylaxis in the community

Medication	Epinephrine	β_2 -Adrenergic agonists	H ₁ -antihistamines	Glucocorticoids
Route	IM injection	Inhalation	Oral	Oral
Grade of recommendation for anaphylaxis treatment	B (adults/children) C (infants)	C	C	C
Pharmacologic effects	At α_1 -receptor: ↑ vasoconstriction ↑ vascular resistance ↑ blood pressure ↓ mucosal edema (larynx) At β_1 -receptor: ↑ heart rate ↑ cardiac contraction force At β_2 -receptor: ↓ mediator release ↑ bronchodilation ↑ vasodilation	At β_2 -receptor: ↑ bronchodilation	At H ₁ -receptor: ↓ itch (skin, mucus membranes) ↓ flush ↓ hives ↓ sneezing ↓ rhinorrhea	Used in anaphylaxis to prevent biphasic or protracted symptoms (late-phase symptoms)
Potential adverse effects (usual doses)	Anxiety, pallor, tremor, palpitations, dizziness, headache	Tremor, tachycardia, dizziness, jitteriness	First-generation drugs cause sedation and impair cognitive function	Unlikely to occur during a 1- to 3-day course
Comment	Treatment of first choice No absolute contraindication to its use	Ancillary treatment to epinephrine	Ancillary treatment to epinephrine, not life-saving; slow onset of action	Systematic review of evidence is pending

The rationale for intramuscular injection is that striated muscle is well vascularized, facilitating rapid systemic absorption and prompt achievement of peak epinephrine pharmacologic effects. In contrast, subcutaneous tissue consisting mostly of poorly vascularized adipose tissue is an excellent repository for slow absorption of injected substances (as used to advantage in subcutaneous immunotherapy with allergens), and time to peak epinephrine pharmacologic effects is variable. Grade of recommendation for use of a medication refers only to its use in the treatment of anaphylaxis. Inhaled β_2 -adrenergic agonists and inhaled glucocorticoids receive grade A recommendations for use in asthma; H₁-antihistamines receive a grade A recommendation for use in allergic rhinoconjunctivitis and urticaria.

Adapted from Simons.⁸⁰

IM, Intramuscular.

The epinephrine autoinjectors currently available for first-aid use have several intrinsic limitations. Only 2 fixed doses of epinephrine, 0.15 mg and 0.3 mg, are available in autoinjector formulations. The 0.15-mg dose is too high for infants and young children weighing less than 15 kg. The 0.3-mg dose is too low for some children and for most teens and adults, especially those who are overweight or obese. In addition, many auto-injectors have a needle length of 1.43 cm. Based on computed tomographic scans of the distance from the skin to the surface of the vastus lateralis muscle in the thigh, this is too short to penetrate the subcutaneous tissue and achieve intramuscular injection in many children,⁸⁸ let alone in overweight or obese teens and adults.⁸⁹ The ability to use autoinjectors is not intuitive, and even health care professionals need to be trained to use them correctly and safely.^{90,91}

Failure to inject epinephrine promptly in patients with anaphylaxis occurs because of a lack of recognition of signs and symptoms, delayed diagnosis, perception that the episode is mild, preference for using an oral H₁-antihistamine, and lack of availability or affordability of an epinephrine autoinjector.^{92,93} Concerns about adverse effects, especially potential myocardial infarction and cardiac arrhythmias, need to be weighed against the cardiac risks of untreated anaphylaxis, including the unmasking of subclinical coronary artery disease (see the "Clinical diagnosis" section).^{16,49} Mild transient pharmacologic effects of epinephrine such as pallor, tremor, anxiety, palpitations, headache, and dizziness, are common and indicate that a therapeutic dose has been given.⁸⁵ More serious adverse effects such as pulmonary edema, are usually attributable to an overdose and have been reported after an intravenous bolus dose, an overly rapid intravenous infusion, or intravenous

infusion of an inappropriately high epinephrine dose such as a concentrated 1:1,000 (1 mg/mL) solution instead of a dilute 1:10,000 (0.1 mg/mL) solution.⁸¹

On rare occasions, epinephrine appears to be ineffective in anaphylaxis. Lack of efficacy might be due to a delay in epinephrine injection, suboptimal route or site of injection, injection of too low a dose on a mg/kg basis, or inadvertent injection of a low dose because the epinephrine solution is past the expiry date.^{85,92} Lack of efficacy might also be due to an error in diagnosis, extremely rapid progression of anaphylaxis, or the empty vena cava/empty ventricle syndrome, in which patients in shock suddenly sit, stand, or are placed upright, the vena cava empties within seconds, and epinephrine is prevented from circulating in the body.¹²

Other medications play an ancillary role in the treatment of anaphylaxis in the community. H₁-antihistamines relieve itch and hives, but they do not relieve airway obstruction or shock. β_2 -Adrenergic agonists relieve bronchospasm, but they do not relieve upper airway obstruction or shock. Glucocorticoids might prevent protracted or biphasic symptoms, but they do not provide rapid relief of upper or lower airway obstruction, shock, or other symptoms of anaphylaxis^{1-3,80-82,94} (Table II).

Future directions in pharmacologic treatment of anaphylaxis

Current research efforts to improve acceptability of epinephrine formulations include production of epinephrine autoinjectors that deliver a 0.5-mg dose, have a needle length of 2.54 cm, and have added safety features to eliminate needle exposure after

epinephrine (adrenaline) effects

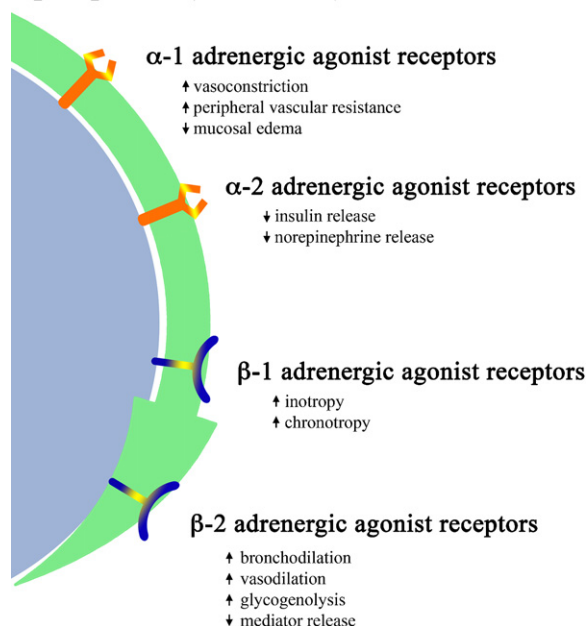


FIG 3. The effects of epinephrine (adrenaline). Through the α_1 -adrenergic receptor, epinephrine leads to vasoconstriction, increased peripheral vascular resistance, and decreased mucosal edema. These actions are unique among the medications used for the treatment of anaphylaxis in the community. They lead to prevention and relief of obstruction to airflow in the larynx, as well as the lower airways, and prevention and relief of hypotension and shock. The pharmacologic effects of epinephrine are biphasic; for example, at low doses, it potentially leads to vasodilation and increased mediator release. Adapted from Simons.⁸⁵

epinephrine injection. In addition, compact, lightweight, and easy-to-use autoinjectors are being designed, and noninjectable epinephrine formulations for administration through the sublingual or transdermal routes are in development.^{91,95}

To date, no randomized controlled trials that meet current standards have been conducted for any of the pharmacologic interventions used to treat anaphylaxis.⁹⁶ A systematic review documents that the evidence base for current therapeutic intervention with epinephrine consists of clinical experience, and expert opinion and consensus, observational studies, randomized controlled studies in patients not experiencing anaphylaxis at the time, epidemiologic studies, fatality studies, *in vitro* studies, and studies in animal models.^{80,86,96} No new pharmacologic agents are available for the treatment of an acute anaphylaxis episode.⁹⁶

All published national anaphylaxis guidelines agree that epinephrine is fundamental to acute management, although they do not agree on the initial dose or route of injection of epinephrine.⁸³ Placebo-controlled trials of epinephrine are clearly unethical; however, with appropriate precautions, it might be possible to conduct randomized trials comparing different first-aid epinephrine doses or different routes of administration.⁹⁶

There is no consensus among published national anaphylaxis guidelines with regard to the use of H_1 -antihistamines, H_2 -antihistamines, or glucocorticoids in the treatment of acute anaphylaxis episodes.⁸³ It is therefore reasonable to consider conducting randomized placebo-controlled trials of these medications in patients with anaphylaxis. In such studies, appropriate precautions should be taken to ensure that all patients have

appropriate, prompt, standard-of-care treatment with epinephrine injections, supplemental oxygen and airway management, high-volume intravenous fluids, and continuous monitoring of heart rate, blood pressure, and oxygenation.⁹⁶

Other measures for emergency preparedness

Epinephrine autoinjectors are the cornerstone of emergency preparedness for anaphylaxis in the community. Additional measures include an anaphylaxis emergency action plan, medical identification, and anaphylaxis education.^{1,2,80}

Anaphylaxis emergency action plan. Anaphylaxis emergency action plans are currently used by almost 40% of persons at risk for anaphylaxis in the community, or their caregivers.⁹² Plans (an example can be downloaded from www.aaaai.org) should be written and personalized for each patient. They should aid in the recognition of anaphylaxis by listing the most common symptoms and signs and emphasize the importance of promptly injecting epinephrine and contacting emergency medical services for transportation to a hospital emergency department.² Approximately 20% of patients with anaphylaxis in the community require a second dose of epinephrine because of lack of response to the first dose, or development of a biphasic reaction.^{87,92,97} Some anaphylaxis emergency action plans state that H_1 -antihistamines are not life-saving because they do not prevent or relieve respiratory failure or shock.^{80,94} Although the available evidence to support use of self-management plans is encouraging, their clinical efficacy and cost-effectiveness need to be formally evaluated in randomized controlled trials.⁹⁸

Medical identification. Persons at risk for anaphylaxis in the community should wear accurate and up-to-date medical identification listing their confirmed trigger factors, relevant comorbidities, and concurrent medications. Available options include medical identification jewelry such as Medic-Alert (Turlock, Calif) or Anaphylaxis Wallet Cards (available at www.aaaai.org).^{1,80}

Anaphylaxis education. The current anaphylaxis epidemic is a relatively recent phenomenon.^{4,6-9} It should therefore not be assumed that all health care professionals are aware that anaphylaxis occurs commonly in the community or that they have up-to-date knowledge and skills with regard to teaching patients to recognize and treat it in this setting.^{90,91} The main focus of anaphylaxis education should be on preparedness for an acute anaphylaxis episode by ensuring that those at risk and caregivers can recognize anaphylaxis, demonstrate how to use an epinephrine autoinjector correctly and safely, and understand the importance of calling for help promptly.^{80,81} Specific anaphylaxis education projects developed in the past few years include those focused on anaphylaxis after omalizumab injection in the physician's office,⁹⁹ and on follow-up of patients with anaphylaxis who are treated in an emergency department.¹⁰⁰

SUMMARY

This clinical review has highlighted important recent advances leading to a better understanding of anaphylaxis epidemiology, pathogenesis, risk assessment, and long-term risk reduction in the community. These advances are summarized in the text box "What do we know?" Despite the excellent progress made in the past few years, many crucial questions remain to be answered, as summarized in the text box "What is still needed?"

The assistance of Ms Lori McNiven is gratefully acknowledged.

What do we know?

- The incidence rate of anaphylaxis is increasing, especially in young people.
- Anaphylaxis is commonly triggered by foods, medications and biologic agents, and insect stings.
- Physicians play an important role in documenting previously unrecognized anaphylaxis triggers and mechanisms.
- Most, but not all, anaphylaxis episodes involve cross-linking of IgE and FcεRI; less commonly, other immunologic mechanisms such as the complement and coagulation pathways, or nonimmunologic mechanisms are involved.
- Patient-specific risk factors such as severe asthma, cardiovascular disease, and mastocytosis, as well as some concurrent medications, contribute to the severity of anaphylaxis episodes and to fatal reactions.
- Diagnosis of an acute anaphylaxis episode is based on pattern recognition, specifically characteristic symptoms and signs occurring minutes to hours after a relevant exposure or event.
- Laboratory tests (histamine levels, total tryptase levels, or both) might or might not confirm the clinical diagnosis of anaphylaxis; the history always trumps the test results.
- Many people are sensitized to allergens such as foods or insect stings that potentially trigger anaphylaxis, but only a minority of those sensitized to an allergen develop anaphylaxis from it.
- The evidence base for prevention and treatment of anaphylaxis consists largely of expert opinion and consensus, with the exception of stinging insect venom immunotherapy, which is based on randomized, double-blind, placebo-controlled trials.
- The epinephrine autoinjectors currently available provide life-saving first-aid treatment of anaphylaxis in the community, but they have intrinsic limitations (see text).

What is still needed?

- Improved accuracy in assessment of the rate of occurrence of anaphylaxis (eg, by reducing miscoding of anaphylaxis episodes)
- A cost-effective method of confirming previously unrecognized anaphylaxis triggers.
- Further elucidation of molecular mechanisms in anaphylaxis, including those that do not involve IgE and FcεRI
- Ability to quantify patient-specific risk factors such as asthma, chronic obstructive pulmonary disease, cardiovascular disease (the heart as a target organ), or mastocytosis/clonal mast cell disorders.
- A rapid, specific, sensitive *in vitro* test or panel of tests to confirm the clinical diagnosis of acute anaphylaxis.
- Optimal *in vitro* tests to determine the risk of anaphylaxis in allergen-sensitized patients and reduce the need for challenge tests.
- Additional randomized placebo-controlled trials of oral immunotherapy to prevent food-triggered anaphylaxis.

- Randomized placebo-controlled trials of anti-IgE antibody to prevent anaphylaxis triggered by any allergen and to prevent idiopathic anaphylaxis.
- Randomized placebo-controlled trials of pharmacologic agents such as antihistamines and glucocorticoids in acute anaphylaxis to improve the evidence base for treatment.
- Improved design of epinephrine autoinjectors to optimize ease and safety of use.

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