

Anaphylaxis

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Anaphylaxis occurs commonly in community settings. The rate of occurrence is increasing, especially in young people. Understanding potential triggers, mechanisms, and patient-specific risk factors for severity and fatality is the key to performing appropriate risk assessment in those who have previously experienced an acute anaphylactic episode. The diagnosis of anaphylaxis is based primarily on clinical criteria and is valid even if the results of laboratory tests, such as serum total tryptase levels, are within normal limits. Positive skin test results or increased serum specific IgE levels to potential triggering allergens confirm sensitization but do not confirm the diagnosis of anaphylaxis because asymptomatic sensitization is common in the general population. Important patient-related risk factors for severity and fatality include age, concomitant diseases, and concurrent medications, as well as other less well-defined factors, such as defects in mediator degradation pathways, fever, acute infection, menses, emotional stress, and disruption of routine. Prevention of anaphylaxis depends primarily on optimal management of patient-related risk factors, strict avoidance of confirmed relevant allergen or other triggers, and, where indicated, immunomodulation (eg, subcutaneous venom immunotherapy to prevent Hymenoptera sting-triggered anaphylaxis, an underused, potentially curative treatment). The benefits and risks of immunomodulation to prevent food-triggered anaphylaxis are still being defined. Epinephrine (adrenaline) is the medication of first choice in the treatment of anaphylaxis. All patients at risk for recurrence in the community should be equipped with 1 or more epinephrine autoinjectors; a written, personalized anaphylaxis emergency action plan; and up-to-date medical identification. Improvements in the design of epinephrine autoinjectors will help to optimize ease of use and safety. Randomized controlled trials of pharmacologic agents, such as antihistamines and glucocorticoids, are needed to strengthen the evidence base for treatment of acute anaphylactic episodes. (*J Allergy Clin Immunol* 2010;125:S161-81.)

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Abbreviations used

CNS: Central nervous system
COPD: Chronic obstructive pulmonary disease
CVD: Cardiovascular disease
NSAID: Nonsteroidal anti-inflammatory drug
OSCS: Oversulfated chondroitin sulfate
Siglec: Sialic acid-binding immunoglobulin-like lectin

This chapter focuses mainly on anaphylaxis in community settings. It provides an overview of epidemiology, pathogenesis, clinical diagnosis, confirmation of the triggers, and long-term management, including prevention of recurrences and emergency preparedness. It highlights recent advances published since the review of anaphylaxis published in the 2008 Mini-Primer.¹

Anaphylaxis is currently defined as a serious allergic reaction that is rapid in onset and might cause death.² The diagnosis is considered to be highly likely when any one of 3 clinical criteria is fulfilled (Table I)²; the presence of reduced blood pressure or shock is not necessarily required. The terms anaphylactoid or pseudoanaphylaxis are no longer recommended for use.

EPIDEMIOLOGY

The lifetime prevalence of anaphylaxis from all triggers is estimated to be 0.05% to 2%.³ The rate of occurrence appears to be increasing, especially in young people.⁴⁻¹⁴ Accurate community-based population estimates are difficult to obtain because of underdiagnosis, underreporting, and miscoding, as well as use of different definitions of anaphylaxis and different methods of case ascertainment in the different populations studied.¹⁵⁻¹⁷ Representative studies of anaphylaxis from all triggers in the general population are summarized in Table II.³⁻¹²

It is likely that anaphylaxis is underdiagnosed, especially if it is a patient's first episode, if there is a hidden or previously unrecognized trigger, or if symptoms are mild, transient, or both.¹⁵ Patients might not be able to describe their symptoms if awareness, cognition, and judgment are impaired or if they are dyspneic or becoming unconscious. The presence of itching, flushing, hives, and/or angioedema is helpful in making the diagnosis; however, skin and mucosal symptoms and signs are absent or unrecognized in 10% to 20% of all anaphylactic episodes. Hypotension sometimes goes undocumented, especially in infants and young children.¹⁵

Underreporting and miscoding of anaphylaxis remain important issues.¹⁵ Only 1% of emergency department visits for acute systemic allergic reactions receive the diagnosis of anaphylaxis; many are called acute allergic reactions, or acute hypersensitivity reactions.^{16,17} In a recent nationally representative probability sample from hospital emergency departments in the United States, 57% of likely episodes of anaphylaxis to food did not receive an emergency department diagnosis of anaphylaxis.¹³

Death from anaphylaxis is considered rare^{8,14,18-23}; however, underreporting of fatalities likely occurs for a variety of reasons.

TABLE I. Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, and swollen lips-tongue-uvula) AND at least 1 of the following:
 - A. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - B. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
 - A. Involvement of the skin–mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
 - B. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - C. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
 - D. Persistent gastrointestinal symptoms (eg, cramping abdominal pain, vomiting)
3. Reduced BP after exposure to a known allergen for that patient (minutes to several hours):
 - A. Infants and children: low systolic BP (age-specific) or greater than 30% decrease in systolic BP*
 - B. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Adapted from reference 2.

BP, Blood pressure; PEF, peak expiratory flow.

*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years. Normal heart rate ranges from 80 to 140 beats/min at age 1 to 2 years, from 80 to 120 beats/min at age 3 years, and from 70 to 115 beats/min after age 3 years. Infants and young children are more likely to have respiratory compromise than hypotension or shock.

These include incomplete clinical information, including lack of a history of concomitant diseases, concurrent medications, and drug or alcohol abuse, and absence of a detailed death scene investigation (eg, interview of witnesses).²² Initial symptoms and signs in fatal episodes of anaphylaxis commonly include respiratory distress rather than circulatory collapse.²¹ The autopsy findings might be nonspecific, and laboratory test results might be within normal limits; however, this cannot be used to exclude the diagnosis of anaphylaxis.²⁰⁻²²

PATHOGENESIS

Triggers of anaphylaxis

Triggers of anaphylaxis in the community are listed in Table III.²⁴⁻⁶⁹ In many countries the most common food triggers are peanut, tree nuts, shellfish, fish, milk, egg, and sesame²⁴⁻²⁶; however, there are important geographic variations, and in some countries other foods, such as chestnut, rice, buckwheat, or chickpea, predominate.²⁷ Any food can potentially trigger anaphylaxis, including previously unrecognized triggers, such as quinoa,²⁸ dragon fruit,²⁹ or some fresh red meats containing carbohydrates.³⁰ Food triggers can be hidden (eg, substituted foods, cross-reacting foods, and cross-contacting foods).²⁶ Food triggers also include additives, such as spices, vegetable gums, and colorants (eg, carmine [cochineal])³¹; contaminants, such as dust mites³²; and parasites, such as the live seafish nematode *Anisakis simplex*.³³

Medication-triggered anaphylaxis can occur in patients of any age; however, it is particularly common in middle-aged and older adults. Antibiotics, especially β -lactam antibiotics, and nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, ibuprofen, and other agents, are often implicated, as are chemotherapeutic agents.^{24,25,34-40} Newly recognized medication triggers include loperamide³⁷; contaminants in medications, such as oversulfated chondroitin sulfate (OSCS)-contaminated heparin³⁸; seemingly innocuous substances, such as vitamins and supplements containing folic acid³⁹; and herbal treatments.⁴⁰ Perioperative medications,⁴¹ iodinated contrast media⁴² and medical dyes are becoming increasingly relevant triggers in community settings. Biological agents that trigger anaphylaxis include monoclonal antibodies (mAbs), such as cetuximab, infliximab, and omalizumab,⁴³⁻⁴⁵ and allergens used in immunotherapy.^{46,47} Vaccines to prevent infectious diseases seldom trigger anaphylaxis. If

they do, the culprit is seldom the immunizing agent itself.⁴⁸⁻⁵¹ Rather, it is likely to be a protein excipient, such as gelatin or egg, or rarely another excipient, such as dextran.^{48,51}

Venom from stinging insects (Order Hymenoptera, family Apidae [eg, honeybees]; family Vespidae [eg, yellow jackets, yellow hornets, white-faced hornets, and paper wasps]; and family Formicidae [eg, ants])⁵²⁻⁵⁴ or, less commonly, saliva from biting insects (flies, mosquitoes, ticks, kissing bugs, and caterpillars) can trigger anaphylaxis.⁵⁴⁻⁵⁷

In health care settings ongoing efforts to prevent anaphylaxis from natural rubber latex have been relatively successful; however, in the community anaphylaxis is still occasionally reported after direct exposure to latex-containing gloves, condoms, rubber-handled racquets, balloons, latex-padded play pits, infant pacifiers, and bottle nipples. It also potentially occurs after ingestion of foods that cross-react with latex, such as banana, kiwi, papaya, avocado, potato, and tomato.⁵⁸

Occupational allergens,²⁵ seminal fluid,⁵⁹ and, rarely, inhaled allergens, such as animal dander⁶⁰ or grass pollen, can also trigger anaphylaxis; some systemic absorption of these allergens likely occurs.

In addition, nonimmune perturbations of mast cells and basophils might lead to anaphylaxis. This potentially occurs after exercise^{61,62} and/or exposure to cold air or water, heat, sunlight/UV radiation, insect venom constituents,^{52,53} radiocontrast media,^{34,42} ethanol, and some medications, including opioids, COX-1 inhibitors, and vancomycin.^{24,25,34} In patients with exercise-induced anaphylaxis, food is a common cotrigger⁶¹; it is hypothesized that in these patients, food-sensitized immune cells are relatively innocuous until they are redistributed into the systemic circulation from gut-associated deposits during exertion.⁶²

Idiopathic anaphylaxis is diagnosed when no triggers can be identified based on history, skin tests are negative, and serum specific IgE levels are absent or undetectable. Before this diagnosis is made, however, the possibility of a hidden or previously unrecognized trigger should be ruled out,^{24,28-30,32,33,37-40,57} and the patients should be evaluated for mastocytosis and clonal mast cell disorders.⁶³⁻⁶⁷

Mechanisms

The underlying pathogenesis of human anaphylaxis commonly involves an immunologic mechanism in which IgE is synthesized

TABLE II. Epidemiology of anaphylaxis in the general population: All triggers

Author	Date	Description of study	Key findings	Comments
Yocum et al ⁴	1999	Rochester Epidemiology Project, linked indexed medical records of the general population of Olmstead County, MN	During the years 1983-1987, the average annual incidence rate was 21/100,000 person-years, and the most common triggers were foods, medications, and insect stings.	Anaphylaxis frequently was not recognized by patients or physicians.
Simons et al ⁵	2002	Dispensing data for all injectable epinephrine formulations over 5 consecutive years in a general population of 1.15 million in which all dispensings are recorded	Of this defined general population, 0.95% had injectable epinephrine dispensed for out-of-hospital treatment.	Dispensing rates were highest in those <17 years of age (1.44%) and lowest in those ≥65 years of age (0.32%). There was a male predominance to age 15 years and a female predominance after age 15 years.
Bohlke et al ⁶	2004	Large health maintenance organization in the United States, 1991-1997; cases identified from automated database using ICD-9 codes 995.0, 995.6, 995.4, and 999.4 plus medical records review	The incidence rate was 10.5 anaphylactic episodes per 100,000 person-years.	After review of the sample using the additional ICD-9 codes 708.0, 708.9, 995.1, 995.3, and 695.1, the incidence rate was estimated at 68.4 cases/100,000 person-years.
Helbling et al ⁷	2004	Investigated anaphylaxis with circulatory symptoms during a 3-year period, 1996-1998, in Bern, Switzerland (population, 940,000); allergy clinic medical records were reviewed, and emergency departments were contacted to identify additional cases.	Two hundred twenty-six people had 246 episodes of life-threatening anaphylaxis with cardiovascular symptoms, for an incidence rate of 7.9-9.6/100,000 person-years.	There were 3 deaths, resulting in a case fatality rate of 0.0001%.
Lieberman et al ³	2006	Panel convened to review major epidemiologic studies of anaphylaxis	There was a frequency estimate of 50 to 2,000 episodes/100,000 person-years or a lifetime prevalence of 0.05% to 2%.	The largest number of incident cases were found in children and adolescents.
Poulos et al ⁸	2007	Data on hospital admissions for anaphylaxis were extracted for the periods 1993-1994 to 2004-2005, respectively.	There was a continuous increase by 8.8% per year in the incidence rate of ED visits/hospitalizations for anaphylaxis and a steep increase in hospitalizations for food-triggered anaphylaxis in children <5 years of age.	In children, hospitalizations for food-induced anaphylaxis were an increasing concern.
Camargo et al ⁹	2007	State-by-state dispensing data (filled prescriptions, including refills) for epinephrine autoinjectors in 2004 in the United States	State-by-state variation: average was 5.71 EpiPens per 1,000 persons (range from 2.7 in Hawaii to 11.8 in Massachusetts).	Regional variation was also noted: the rate was significantly higher in northern states (except Alaska) than in southern states.
Decker et al ¹⁰	2008	Population-based incidence study from 1990-2000 in the Rochester Epidemiology Project (see Yocum et al study above in this table)	Overall age- and sex-adjusted incidence rate of 49.8/100,000 persons; the annual incidence rate increased from 1990 to 2000.	Age-specific rates were highest for ages 0-19 years (70/100,000 person-years).
Lin et al ¹¹	2008	Characterization of anaphylaxis hospitalizations in New York state in patients <20 years of age	During the study period, 1990-2006, the anaphylaxis hospitalization rate increased by more than 4-fold.	There was overall bimodal age distribution, with peaks in the very young and in teens.
Sheikh et al ¹²	2008	Recorded incidence and lifetime prevalence of anaphylaxis in England were investigated by using QRESEARCH, a national aggregated primary health care database containing the records of >9 million patients.	Age/sex standardized incidence of anaphylaxis was 6.7/100,000 person-years in 2001 and increased by 19% to 7.9/100,000 person-years in 2005; lifetime age/sex standardized prevalence of anaphylaxis was 50/100,000 in 2001 and increased by 51% to 71.5/100,000 in 2005.	Adrenaline prescribing increased by 97% over this time.

This table summarizes selected publications during the past decade in which the rate of occurrence of anaphylaxis from all triggers in the general population was estimated. These estimates vary because of different definitions of anaphylaxis, different methods of case ascertainment, and the different populations studied.

ED, Emergency department; ICD-9, International Classification of Diseases–Ninth Revision.

in response to allergen exposure and becomes fixed to high-affinity receptors for IgE (FcεRI receptors) on the surface membranes of mast cells and basophils (Fig 1).^{1,2,24,25,69-72} Aggregation of receptor-bound IgE molecules occurs on re-exposure to the allergen and results in cell activation and mediator

release.⁷⁰⁻⁷² IgE also contributes to the intensity of anaphylaxis by enhancing the expression of FcεRI on mast cells and basophils.⁷⁰⁻⁷²

Rarely, other immunologic mechanisms that do not involve IgE are implicated in human anaphylaxis.⁷³ IgG-mediated

TABLE III. Mechanisms and triggers of anaphylaxis in the community

Immunologic mechanisms (IgE dependent)
Foods, such as peanut, tree nut, shellfish, fish, milk, egg, sesame, and food additives*
Medications, such as β -lactam antibiotics and NSAIDs, and biological agents†
Venoms, such as stinging insects (Hymenoptera)
Natural rubber latex
Occupational allergens
Seminal fluid (prostate-specific antigen)
Inhalants, such as horse, hamster, and other animal danders and grass pollen (rare)
Radiocontrast media‡
Immunologic mechanisms (IgE independent, formerly classified as anaphylactoid reactions)
Dextran, such as high-molecular-weight iron dextran†
Infliximab†
Radiocontrast media‡
Nonimmunologic mechanisms
Physical factors, such as exercise,§ cold, heat, and sunlight/UV radiation
Ethanol
Medications, such as opioids†
Idiopathic anaphylaxis
Consider the possibility of hidden or previously unrecognized allergens
Consider the possibility of mastocytosis/clonal mast cell disorder

Adapted from references 24-69.

*Food additives include spices, vegetable gums, colorants (carmine/cochineal), monosodium glutamate, sulfites, papain, and contaminants.

†Medications can potentially trigger anaphylaxis through an IgE-dependent immunologic mechanism, an IgE-independent immunologic mechanism, or direct mast cell stimulation. Biological agents include mAbs (eg, cetuximab and omalizumab), allergens, vaccines, and hormones (eg, progesterone).

‡Radiocontrast media potentially trigger anaphylaxis through an IgE-dependent immunologic mechanism or through activation of complement.

§With or without a food or medication cotrigger.

||Includes foods, biting insect saliva, other venoms, medications, and biological agents. Save food or food label, insect or other relevant material, and save patient serum sample for customized *in vitro* tests, such as measurement of allergen-specific IgE (see the text for further details).

anaphylaxis has been reported due to high molecular weight iron dextran or infusion of chimeric, humanized, or human therapeutic mAbs, such as infliximab.^{44,51} Complement-mediated anaphylaxis occurs in association with hemodialysis, OPCS-contaminated heparin,³⁸ protamine neutralization of heparin, liposomal drugs, or polyethylene glycols. Direct activation of the innate immune system might also contribute to triggering anaphylaxis.⁷⁴

In addition, as noted previously, nonimmune activation of mast cells and basophils occurs.^{24,25,34}

A trigger can lead to anaphylaxis through more than 1 mechanism; for example, radiocontrast media can trigger anaphylaxis through an immunologic IgE-dependent mechanism and through direct mast cell activation.^{34,42} OPCS-contaminated heparin triggers anaphylaxis through activation of the complement system, leading to generation of kallikrein, bradykinin, and the complement protein-derived anaphylatoxins C3a and C5a; in addition, factor XII and the coagulation system are involved.^{38,75}

Regardless of the immunologic or nonimmunologic triggering mechanisms and regardless of whether Fc ϵ RI or other receptors, such as G protein-coupled receptors or Toll-like receptors, are activated, mast cells and basophils play an important role in initiating and amplifying the acute allergic response. After IgE/Fc ϵ RI binding and receptor aggregation, multiple tyrosine kinases, including Lyn, Syk, and Fyn, are activated and exert both positive and negative regulation on the signal transduction cascade.^{70,71,76} Calcium influx is the essential proximal intracellular event leading to mast cell degranulation and is controlled by both positive and negative regulation through calcium channels.^{70,77} Mast cells and basophils release preformed chemical mediators of inflammation, including histamine, tryptase, carboxypeptidase A, and proteoglycans.^{68,70,71,78,79} They also release newly generated mediators, such as leukotrienes, prostaglandins,

and platelet-activating factor, and cytokines, such as IL-6, IL-33, and TNF- α , which is a late-phase mediator, as well as a preformed mediator.^{68,70,71,80-84} Sphingosine-1-phosphate is now recognized as a circulating mediator in anaphylaxis, and in addition, it acts as a signaling component within the mast cell.⁸⁵ Once activated, the mast cell response is regulated by the balance of positive and negative intracellular molecular events that extend beyond the traditional kinases and phosphatases.

New discoveries in mast cell biology have the potential to improve the diagnostic and therapeutic approach to human anaphylaxis. For example, stem cell factor and its receptor Kit are fundamentally important in IgE/antigen-induced mast cell activation, and concurrent inhibition of Kit- and Fc ϵ RI-mediated signaling achieves coordinated suppression of human mast cell activation.⁸⁶ An orally effective compound has been identified that binds to Syk, downregulates the interaction of Syk with some of its macromolecular substrates, and inhibits Fc ϵ RI-induced mast cell degranulation *in vitro* and anaphylaxis *in vivo*.⁸⁷ Inhibitory sialic acid-binding immunoglobulin-like lectins (Siglecs) are expressed on human mast cells, on which Siglec-8 engagement results in inhibition of Fc ϵ RI-dependent mediator release without apoptosis.⁸⁸ Anti-IgE antibody potentially plays a therapeutic role by depleting free IgE, with consequent downregulation of Fc ϵ RI on mast cells and basophils and deflation of the intracellular activation signal triggered by IgE/Fc ϵ RI aggregation.⁸⁹ Basophil involvement in anaphylaxis will likely be further elucidated in the future because a monoclonal antibody directed against pro-major basic protein 1 has been identified.⁹⁰ The opening of the endothelial barrier through endothelial G_q/G₁₁-mediated signaling has been identified as a critically important process leading to symptoms of anaphylaxis in many body organ systems.⁹¹

There are few studies of the role of genetic factors in human anaphylaxis. Investigations in this area might improve our

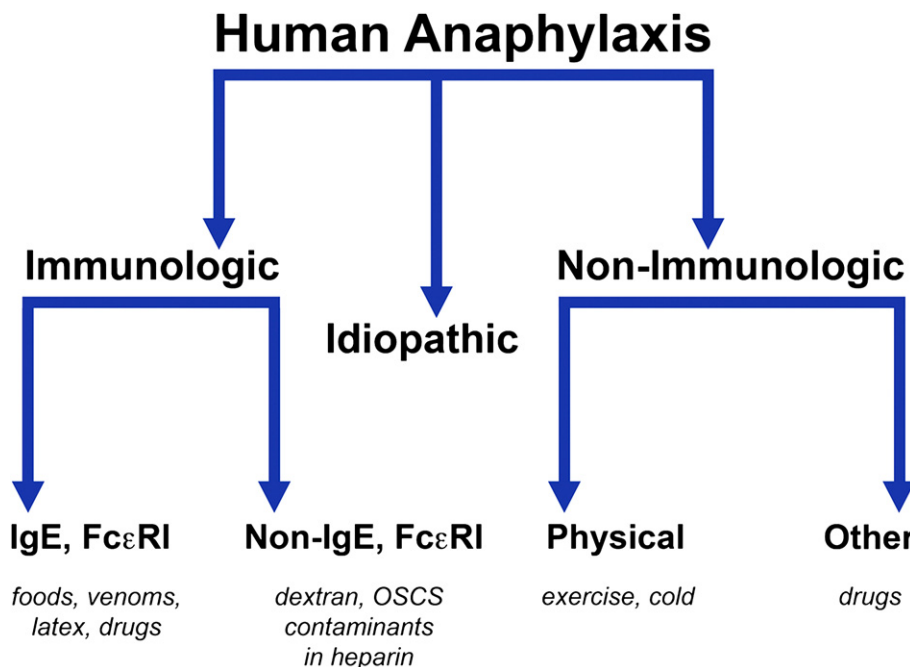


FIG 1. Mechanisms underlying human anaphylaxis. Anaphylaxis is commonly mediated through an immune IgE-dependent mechanism. Rarely, it occurs through another immune mechanism. Uncommonly, it occurs through direct (nonimmune) activation of mast cells. Idiopathic anaphylaxis, currently a diagnosis of exclusion, presents opportunities for identification of previously unrecognized triggers, elucidation of pathophysiologic mechanisms, and identification of patients with mastocytosis or clonal mast cell disorders.⁶⁹

understanding of why anaphylaxis occurs in only a minority of persons who are sensitized to an antigen and why episodes vary greatly in severity from mild with spontaneous remission to severe and fatal.^{92,93}

Patient-specific risk factors for severity and fatality

Patients might be at increased risk of anaphylaxis severity and fatality because of age, concomitant disease, concurrent medications, and other factors that are still being delineated (Table IV).^{24,25,64-69,93-108}

In infants anaphylaxis is sometimes hard to recognize because they cannot describe their symptoms, and many of the signs of anaphylaxis in infancy, such as flushing and dysphonia after a crying spell, spitting up or loose stools after feeding, and loss of sphincter control, are ubiquitous in the healthy state.⁹⁴ Teenagers and young adults are at increased risk of anaphylaxis triggered by foods and possibly other agents because of inconsistent behaviors with regard to avoiding their confirmed relevant triggers and carrying epinephrine autoinjectors.⁹⁵ During pregnancy, anaphylaxis places the mother and especially the baby at high risk of fatality or permanent central nervous system (CNS) damage. During the first, second, and third trimesters, potential triggers of anaphylaxis are similar to those in nonpregnant women. During labor and delivery, the most common triggers are penicillins and other β -lactam antibiotics given as prophylaxis against neonatal group B streptococcal infection.⁹⁶ Elderly adults are at increased risk of fatality in anaphylaxis because of concomitant diseases, such as chronic obstructive pulmonary disease (COPD), and cardiovascular diseases (CVDs) and the medications used to treat them.^{21,97-99}

In patients of any age, diseases that impede prompt recognition of triggers or symptoms potentially place patients at increased risk of anaphylaxis.^{24,25,69,93} These include impaired vision or hearing, neurologic disorders, psychiatric disorders (including depression), autism spectrum disorder, developmental delay,^{24,69} and use of medications, such as first-generation H₁-antihistamines (eg, diphenhydramine and chlorpheniramine), antidepressants, or CNS-active chemicals, such as ethanol or recreational drugs.^{24,69}

Concomitant diseases, such as asthma or other chronic respiratory diseases, especially if severe or uncontrolled,^{21,24,25,69} and also CVDs⁹⁷⁻⁹⁹ and mastocytosis or clonal mast cell disorders,^{64-67,100-103} are associated with increased risk of life-threatening or fatal anaphylaxis. Severe allergic rhinitis and severe eczema increase the risk of life-threatening anaphylaxis to some foods.¹⁰⁵ Concurrent medications, such as β -blockers and angiotensin-converting enzyme inhibitors increase the severity of anaphylaxis, and β -blockers potentially make anaphylaxis more difficult to treat.^{24,25,98,99,103,105}

In some patients severe or fatal anaphylactic episodes might be associated with defects in mediator degradation pathways and intracellular signaling pathways, as reflected, for example, in increased baseline serum tryptase levels (which are strongly associated with insect sting-triggered anaphylaxis),^{67,103} increased baseline plasma histamine levels,¹⁰⁴ low serum angiotensin-converting enzyme activity,¹⁰⁵ and reduced platelet-activating factor acetylhydrolase activity.⁸⁰

Other concomitant factors reported to increase the risk of an anaphylactic episode include exercise; exposure to extremes of temperature or humidity or high pollen counts; foreign travel or other disruption of routine; feeling unwell; fever; acute infection,

TABLE IV. Patient factors that increase risk of anaphylaxis severity and fatality

Age*	
Infants:	Underrecognition, underdiagnosis; no appropriate epinephrine auto-injector dose
Adolescents and young adults:	↑ Risk-taking behavior
Pregnancy:	During labor and delivery, antibiotic prophylaxis against neonatal group B streptococcal infection is a common trigger
Elderly:	↑ Risk of fatality from medication and venom-triggered anaphylaxis
Comorbidities*	
Asthma and other respiratory diseases,	especially if severe or uncontrolled
CVDs, including hypertension	
Mastocytosis† and clonal mast cell disorders‡	
Allergic rhinitis and eczema‡	
Depression and other psychiatric diseases	(might impair recognition of symptoms)
Thyroid disease	(some patients with idiopathic anaphylaxis)
Concurrent medication/chemical use*	
Potentially affect recognition of anaphylaxis	
Sedatives/hypnotics/antidepressants/ethanol/recreational drugs	
Potentially increase anaphylaxis severity	
β-Blockers and ACE inhibitors	
Other factors*	
Exercise	
Acute infection, such as upper respiratory tract infection	
Menses	
Emotional stress	
Occupation, such as beekeeping	
Priming effect of recent previous anaphylactic episode	
Increased baseline plasma histamine levels (hyperhistaminemia)	
Increased baseline serum tryptase levels	
Reduced level of PAF AH activity, leading to increased PAF levels	
Reduced level of ACE activity, leading to increased bradykinin levels	

Adapted from references 68, 69, and 94-108.

ACE, Angiotensin-converting enzyme; AH, acetylhydrolase; PAF, platelet-activating factor.

*In some patients several factors might need to be present concurrently for risk to be increased, such as an elderly person plus cardiovascular disease plus β-blocker medication.

†In others concurrent triggers might be needed, such as food plus exercise.

‡Suggested by increased baseline total tryptase levels.

‡Atopic diseases are a risk factor for anaphylaxis triggered by food, exercise, and latex but not for anaphylaxis triggered by insect stings, β-lactam antibiotics, or insulin.

such as an upper respiratory tract infection; emotional stress; menses (premenstrual and ovulatory phases); and/or ingestion of NSAIDs or ethanol.^{20,32,61,62,106-108}

ASSESSMENT OF PATIENTS WITH A HISTORY OF ANAPHYLAXIS

Ideally, patients with a history of an acute anaphylactic episode should be referred to an allergy/immunology specialist with training and experience in risk assessment in anaphylaxis, including confirmation of the diagnosis, verification of the triggers, and evaluation of comorbidities and concurrent medications.

Clinical diagnosis of anaphylaxis

When patients are seen after an acute anaphylactic episode, the history of the episode should be confirmed and relevant emergency medical services and emergency department records should be reviewed.^{24,25,68,69,93} The history should focus on recall of exposure to potential triggering agents or events, the minutes or hours elapsed between exposure and symptom onset, and the evolution of symptoms and signs. Involvement of body organ systems varies among patients and even in the same patient from one episode to another; however, review of anaphylaxis case series reveals some general patterns. Skin involvement is reported in 80% to 90% of episodes, respiratory tract involvement in up to 70%, gastrointestinal tract involvement in up to 45%, cardiovascular system involvement in up to 45%, and CNS involvement in up to 15% (Table V).^{24,25,69,93}

The differential diagnosis of anaphylaxis includes common entities, such as acute generalized hives, acute asthma, syncope, panic attack, aspiration of a foreign body, and cardiovascular or neurologic events.^{24,25} Postprandial syndromes, such as pollen-food syndrome and scombroidosis, also need to be considered, as do excess endogenous histamine syndromes, such as mastocytosis; flush syndromes, including perimenopausal flushing; nonorganic diseases, such as vocal cord dysfunction; and other diagnostic entities, some of which are rarely encountered (Table VI).^{24-26,32,33,63-68,109,110} The differential diagnosis is age related to some extent. In infants foreign body aspiration, congenital malformations of the respiratory or gastrointestinal tracts, and apparent life-threatening event/sudden infant death syndrome need to be considered.⁹⁴ In middle-aged and elderly adults myocardial infarction, pulmonary embolus, and stroke are important considerations.^{21,25,97}

Laboratory tests at the time of the acute anaphylactic episode

In some patients the clinical diagnosis of anaphylaxis can be confirmed by means of a blood test; for example, an increased plasma histamine level or serum total tryptase level. These tests are not specific for anaphylaxis (Table VII).^{24,25,68,78,79}

Plasma histamine levels should optimally be measured 15 to 60 minutes after onset of symptoms of anaphylaxis. Special handling of the blood sample is required. Histamine and its metabolite, N-methylhistamine, can also be measured in a 24-hour urine sample.⁶⁸ Serum total tryptase levels should optimally be

TABLE V. Symptoms and signs of anaphylaxis

Cutaneous/subcutaneous/mucosal tissue
Flushing, pruritus, hives (urticaria), swelling, morbilliform rash, pilo erection
Periorbital pruritus, erythema and swelling, conjunctival erythema, tearing
Pruritus and swelling of lips, tongue, uvula/palate
Pruritus in the external auditory canals
Pruritus of genitalia, palms, soles
Respiratory
Nose: pruritus, congestion, rhinorrhea, sneezing
Larynx: pruritus and tightness in the throat, dysphonia and hoarseness, dry staccato cough, stridor, dysphagia
Lung: shortness of breath, chest tightness, deep cough, wheezing/bronchospasm (decreased peak expiratory flow)
Cyanosis
Gastrointestinal
Nausea, cramping abdominal pain, vomiting (stringy mucus), diarrhea
Cardiovascular
Chest pain, palpitations, tachycardia, bradycardia, or other dysrhythmia
Feeling faint, altered mental status, hypotension, loss of sphincter control, shock, cardiac arrest
CNS
Aura of impending doom, uneasiness, throbbing headache, dizziness, confusion, tunnel vision; in infants and children, sudden behavioral changes, such as irritability, cessation of play, and clinging to parent
Other
Metallic taste in the mouth
Dysphagia
Uterine contractions in postpubertal female patients

Adapted from references 24, 25, 93, and 94. Sudden onset of symptoms and signs is characteristic of anaphylaxis.

measured from 15 minutes to 3 hours after onset of symptoms. No special handling of the blood sample is required. The total tryptase level is typically increased in patients with anaphylaxis triggered by an injected medication or an insect sting and in those with hypotension and shock but is less likely to be increased in those with anaphylaxis triggered by food or in those who are normotensive.^{68,78} Serial measurements of serum total tryptase and comparison with baseline levels obtained after the acute episode or available in stored serum might be more helpful than measurement at a single point in time.^{68,78}

Other biomarkers reported to be useful in confirming an acute episode of anaphylaxis include serum mature β -tryptase; mast cell carboxypeptidase A3; chymase; platelet-activating factor; bradykinin; C-reactive protein; cytokines, such as IL-2, IL-6, IL-10, IL-33, and TNF-receptor I; and urinary cysteinyl leukotriene E4 and 9- α -11- β prostaglandin F₂.^{68,72,80-84} Many studies of these potential biomarkers have included appropriate control groups, such as patients with severe acute asthma, but some have not. Biomarkers are released at different times after activation of mast cells and basophils, and patients experiencing anaphylaxis in community settings arrive in emergency departments at different time intervals after symptom onset; therefore measurement of a panel of different biomarkers might be useful.⁶⁸

Confirmation of the triggers of anaphylaxis

An important aspect of risk assessment in patients who have experienced anaphylaxis in the community is confirmation of the trigger or triggers identified through a detailed history of antecedent exposures, so that the relevant specific trigger or triggers can be avoided and recurrences of anaphylaxis can be prevented (Table VIII).^{24-26,34,52,58,61,68,69,93,111} Skin tests should be performed with validated instruments, techniques, and recording systems, preferably at least 3 to 4 weeks after the anaphylactic episode, to allow time for rearming of skin mast cells and recovery

of mast cell releasability.⁶⁸ Measurement of allergen-specific IgE levels by using a quantitative method can be performed at any time during or after the acute anaphylactic episode; however, if the blood sample is obtained during or shortly after the episode from patients who have received intravenous fluid resuscitation, levels can be falsely undetectable or low because of the dilutional effect on circulating IgE. Negative tests for sensitization to a trigger in a patient with a convincing history of anaphylaxis from that trigger should be repeated weeks or months later. It is important to note that both positive skin tests and increased specific IgE levels indicate sensitization to the allergens tested but are not diagnostic of anaphylaxis or any other disease.^{24-26,34,52,58,68,69}

If indicated, incremental challenge/provocation tests should be conducted in appropriately equipped health care facilities by professionals trained and experienced in patient selection, timing of the challenge, use of challenge protocols, and diagnosing and treating anaphylaxis. Before a challenge is performed, the potential risks and benefits should be discussed with the patient (or, for children, the caregivers) and documented in the medical record.^{68,111}

Assessment of patients with food-triggered anaphylaxis. Skin prick tests with foods that elicit a wheal of 3 mm larger than that caused by the negative control (eg. saline) are considered positive. Commercially available food allergen extracts do not contain standardized allergens. Some food allergens, such as fruits and vegetables, are labile and degrade in glycerinated extracts during manufacture and storage; therefore skin prick tests with these allergens are often performed with fresh foods. Intradermal tests to foods are contraindicated because of lack of specificity (false-positive tests) and their potential for triggering anaphylaxis.^{26,68,112} An exception to this might be use of intradermal tests to assess sensitization to fresh meat containing the carbohydrate galactose- α -1,3-galactose.³⁰

In food-sensitized patients specific IgE levels have predictive values for positive (failed) or negative (passed) food challenge

TABLE VI. Differential diagnosis of anaphylaxis

Common entities	Nonorganic disease
Acute generalized hives	Vocal cord dysfunction
Acute asthma	Munchausen syndrome
Syncope (faint, vasovagal episode)	
Panic attack	
Aspiration of a foreign body	Shock
Cardiovascular event (myocardial infarction, pulmonary embolus)	Hypovolemic Cardiogenic
Neurologic event (seizure, stroke)	Distributive (eg, spinal cord injury) Septic (might involve all of the above)
Postprandial syndromes	Other
Pollen-food syndrome*	Nonallergic angioedema
Scombroidosis†	Red Man syndrome (vancomycin)
Monosodium glutamate	Urticarial vasculitis
Sulfites	Hyper-IgE urticaria syndrome Progesterone anaphylaxis Pheochromocytoma Idiopathic systemic capillary leak syndrome
Excess endogenous histamine	
Mastocytosis/clonal mast cell disorders‡	
Basophilic leukemia	
Flush syndromes	
Perimenopause	
Carcinoid	
Autonomic epilepsy	
Medullary carcinoma thyroid	

Adapted from references 24-26, 63-68, 109, and 110.

*Pollen-food allergy syndrome, also termed oral allergy syndrome, is elicited by a variety of plant proteins, especially pathogen-related proteins that comprise a large number of class 2 allergenic proteins found in various fruits and vegetables. These plant proteins cross-react with airborne allergens. Typical symptoms include pruritus, tingling, and angioedema of the lips, tongue, palate, throat, and ears after eating raw, but not cooked, fruits and vegetables.

†This disease is due to histamine poisoning from fish, such as tuna, mackerel, saury, mahi-mahi, anchovies, and herring, that are stored at increased temperatures (30°C), at which bacteria such as *Morganella morganii* and *Klebsiella pneumoniae* produce histamine and *cis*-urocanic acid. Symptoms occur from minutes to hours after ingestion of the fish and last for hours. They include flush (especially of the face and neck), angioedema, nausea, vomiting, diarrhea, and hypotension. An important clue to the diagnosis is that more than 1 person eating the fish is usually affected. Skin prick tests to fish are negative, and fish-specific IgE levels are absent or undetectable.

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

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

tests. Allergen-specific IgE levels with greater than 95% predictive risk values of a positive (failed) food challenge result have been identified by using the ImmunoCAP (Phadia, Uppsala, Sweden). These levels are defined for cow's milk (≥ 15 kU/L), egg (≥ 7 kU/L), peanut (≥ 14 kU/L), tree nuts (≥ 15 kU/L), and fish (≥ 20 kU/L); in infants lower values have been established for milk (≥ 5 kU/L) and egg (≥ 2 kU/L).²⁶ Predictive values for allergen-specific IgE levels potentially differ from one immunoassay to another, and this can affect management decisions.^{26,68,113}

A positive skin test, an increased serum IgE level, or both to a specific food document sensitization to that food. Such tests are not diagnostic of anaphylaxis because sensitization to 1 or more food allergens is common in the general population of healthy

people who have no history of anaphylaxis. For example, 60% of young people have a positive skin prick test to 1 or more foods, yet most of those with positive tests have never experienced anaphylaxis from a food.¹¹⁴ In addition, although positive skin tests and increased allergen-specific IgE levels correlate with an increased probability of clinical reactivity to specific foods, the results of these tests do not necessarily correlate with the risk of future anaphylactic episodes or with the severity of such episodes.^{26,68}

Oral food challenge testing was extensively reviewed in the *Journal* in 2009.¹¹¹ Patients with a convincing history of anaphylaxis to a specific food and evidence of sensitization to that food should not undergo oral food challenge tests because of their high risk of anaphylaxis from such tests. Others, such as those with an equivocal history, low or moderate evidence of sensitization, or both, might benefit from a physician-monitored incremental oral food challenge. A positive (failed) challenge provides a sound basis for continued avoidance of the food. A negative (passed) challenge allows introduction or reintroduction of the specific food into the patient's diet.¹¹¹

Unproved or disproved diagnostic methods, such as electrodermal skin testing and kinesiology, remain in use for assessment of patients with food allergy.¹¹⁵

In the future, *in vitro* tests that will distinguish reliably between sensitization without risk of clinical reactivity versus sensitization with risk of clinical reactivity might be available. These include measurement of allergen-specific basophil reactivity,¹¹⁶ assessment of sensitization by using recombinant allergens,¹¹⁷ peptide microassay-based immunoassays to map IgE and IgG₄ binding to sequential allergen epitopes,¹¹⁷⁻¹¹⁹ or assessment of allergen-specific cytokine or chemokine production.⁶⁸

Assessment of medication- or biological agent-triggered anaphylaxis. Any medication or biological agent can potentially trigger anaphylaxis. For most agents, the antigenic determinants have not been characterized or validated; indeed, the relevant immunogenic prodrugs, haptens, metabolites, and unidentified degradation products or contaminants are often unknown.^{34,38,68} For most medications, with the exception of some β -lactam antibiotics, appropriate reagents are not commercially available for use in skin tests, measurement of medication-specific IgE levels, or other *in vitro* tests.^{34,68} Customized tests and physician-monitored challenge/provocation tests performed in specialized centers therefore play a central role in assessment of patients with a history of anaphylaxis triggered by a medication.^{34,68,120-122}

For assessment of anaphylaxis triggered by vaccines to prevent allergic diseases, skin prick tests should be performed not only with the immunizing agent but also with the relevant excipients in the culprit vaccine, such as gelatin in measles vaccines or egg in some influenza vaccines and in yellow fever vaccine.^{48,68}

Assessment of stinging insect-triggered anaphylaxis. Standardized Hymenoptera venoms, such as honeybee, yellow jacket, yellow hornet, white-faced hornet, and paper wasp, are available for skin testing. Skin prick tests, if negative, should be followed by intradermal tests.⁵²⁻⁵⁴ Use of dialyzed venoms in skin tests is reported to improve the identification of venom-sensitized patients.¹²³ For fire ant-triggered anaphylaxis, whole-body extracts are used as skin test reagents.^{34,55} Measurements of venom-specific IgE levels and fire ant whole-body extract-specific

TABLE VII. Laboratory tests: Acute anaphylactic episode

Histamine*
Obtain blood sample within 15 minutes to 1 hour of symptom onset* (use wide-bore needle, keep sample cold (at 4 degrees C), centrifuge it promptly, and freeze plasma promptly).
Twenty-four-hour urine histamine and N-methylhistamine measurements might also be helpful.
Total tryptase* (pro, pro', and mature forms of α/β -tryptases)
Obtain blood sample within 15 minutes to 3 hours of symptom onset.
Consider comparing the levels measured during the acute episode with a baseline level.†
If higher during the acute episode than in baseline serum, the diagnosis of anaphylaxis is confirmed.‡
If within normal limits during the acute episode, the diagnosis of anaphylaxis cannot be excluded.
Total tryptase level can be measured in postmortem serum.§
Additional laboratory tests

Adapted from references 24, 25, 68, 78, 79 and 81.

*Increases of histamine and tryptase levels are not specific for anaphylaxis. For example, histamine levels are increased in patients with scombroid poisoning and tryptase levels are increased in patients with myocardial infarction, trauma, amniotic fluid embolus, and sudden infant death syndrome.

†Obtained 24 hours after resolution of the acute event or on stored serum, if available (levels are stable for ≥ 1 year if stored at -20 degrees C).

‡If greater than 11.4 ng/mL in both acute and baseline sera, the diagnosis of mastocytosis or clonal mast cell disorder should be considered.

§Blood samples should be obtained from femoral vessels and not the heart; the level needs to be correlated with the clinical history because, as noted above, increased levels are also found in other clinical situations, such as myocardial infarction, trauma, amniotic fluid embolism, and sudden infant death syndrome.

||When sorting out the differential diagnosis of anaphylaxis, the detailed clinical history and physical examination might suggest the need for additional laboratory tests to confirm or rule out diseases such as mastocytosis, basophilic leukemia, carcinoid (serum serotonin level and urinary 5 hydroxyindoleacetic acid), medullary carcinoma of the thyroid/ vasoactive polypeptide-secreting gastrointestinal tumor (substance P and vasointestinal polypeptide), pheochromocytoma (free metanephrine in plasma and urinary vanillylmandelic acid), hereditary angioedema (C4 and C1 esterase inhibitor), or diagnostic imaging to confirm or rule out hydatid cysts. Investigation of the complement cascade (C4a, C5a, and C3a), the contact system (bradykinin, high-molecular-weight kininogen, kallikrein-C1-inhibitor complexes, and factor XIIa-C1-inhibitor complexes), and coagulation pathway (factors V, VIII, and fibrinogen), although usually not performed, might support the clinical diagnosis of anaphylaxis; however, these tests also appear to lack specificity.

TABLE VIII. Confirmation of a potential trigger for an anaphylactic episode

Allergen skin tests
Percutaneous (prick or puncture)*
Intradermal (intracutaneous) for selected allergens such as insect venoms and β -lactam antibiotics†
Allergen-specific serum IgE levels
Quantitative ELISAs‡
Allergen challenge tests§
Most commonly performed with foods or medications
Other challenge tests
Exercise
Cold
Heat
Sunlight
Work up of patients with idiopathic anaphylaxis (in whom detailed history of antecedent events/exposures does not yield any clues about triggers and skin test results and allergen-specific IgE measurements are negative)
Search for a previously unrecognized trigger
Measure serum baseline total tryptase levels (normal value, <11.4 ng/mL)
Inspect skin closely for evidence of urticaria pigmentosa
Consider bone marrow biopsy (perform c-Kit mutational analysis in addition to usual stains for identification of spindle-shaped mast cells in clusters)

Adapted from references 24-26, 34, 52, 58, 61, 67, 100-102, and 111.

*Allergens for skin testing should be selected on the basis of the history. Standardized extracts are available only for some Hymenoptera venoms and some inhalant allergens. Patients should discontinue H₁-antihistamines 7 days before skin testing. Many people in the general population are sensitized to allergens (eg, 60% of teens to food and as many as 28.5% of adults to venom).

†Intradermal tests are generally contraindicated in food allergy because of the high likelihood of false-positive results and the possibility of triggering anaphylaxis.

‡Available commercially for foods, insect venoms, and latex but not for most medications or biological agents. Refer to predictive values, where available, for foods such as peanut, tree nuts, fish, milk, and egg.

§Open, single-blind, or double-blind depending on clinical history and allergen. "First do no harm": challenge *only* if assessment (clinical history, skin tests, and/or measurement of allergen-specific IgE levels) indicate that the patient is at low risk for anaphylaxis. Perform *only* under medical supervision in a hospital or other health care facility.

||Assessment of cotriggers, such as a food, medication, or cold exposure, is needed.

IgE levels are commercially available. Some patients with a history of Hymenoptera sting-triggered anaphylaxis have negative skin test responses to insect venoms but increased specific IgE levels to venoms and *vice versa*.^{52,124} Challenge/provocation tests with stinging and biting insects are potentially dangerous and are used only in research.^{52-57,68,125}

Positive intradermal tests to stinging insect venoms, increased venom-specific IgE levels, or both occur in up to 28.5% of the general adult population, most of whom do not have systemic symptoms after an insect sting.^{52-54,68} It is therefore critically important that the test results be interpreted in the context of the clinical history. Cross-reacting carbohydrate derivatives between venom allergens and plant

or other nonvenom allergens might account for many of these positive test results. In some centers additional tests used to assist in interpretation of positive test results include consideration of total IgE levels as well as venom-specific IgE levels,¹²⁵ and measurement of basophil activation markers, such as CD63 or CD203c after incubation with different concentrations of venom.^{53,68,125}

Conversely, venom skin tests might be negative and venom-specific IgE levels might be absent or undetectable in patients with a convincing history of insect sting-triggered anaphylaxis. Negative tests might be due to rare IgE- or non-IgE-mediated reactions to a protein or peptide constituent¹²⁷ such as melittin in honeybee venom or mastoparan in vespid venom; variability of intradermal testing; anergy in patients tested within a few weeks of the sting; decrease in the immune response to venom over time in patients stung many years before testing; or increased patient vulnerability to anaphylaxis. As noted previously, risk of severe or fatal anaphylaxis increases with older age; concurrent diseases, including CVDs; and concurrent use of medications, such as β -blockers or angiotensin-converting enzyme inhibitors,^{52,53,97,103} as well as in patients with mastocytosis, clonal mast cell disorders, or increased baseline tryptase levels.^{52,53,72,100-103} If the baseline total tryptase level is greater than 11.4 ng/mL (the new upper limit of normal), meticulous examination for cutaneous mastocytosis is indicated, and if the level is greater than 20 ng/mL, a bone marrow biopsy is indicated, even if cutaneous manifestations are absent.⁶⁷ Also, in some patients clinical risk of anaphylaxis is increased by factors such as a recent sting; a previous severe systemic reaction to a sting; a sting on the head, neck, or throat; or the entomology of the stinging insect.^{52-54,68,103}

Assessment of anaphylaxis from other triggers. For assessment of anaphylaxis triggered by natural rubber latex, skin prick tests should be performed with commercial latex allergens, where available, or with extracts of rubber products, such as natural rubber latex gloves, where commercial allergens are not available. Consideration should be given to testing with foods that cross-react with latex, such as banana, kiwi, papaya, avocado, potato, and tomato.^{58,68} Latex-specific IgE antibodies can also be measured.

For assessment of exercise-triggered anaphylaxis, skin tests should be performed with potential food allergen cotriggers.⁶¹ An exercise intensity threshold can be defined in an exercise challenge test to diagnose food-dependent exercise-induced anaphylaxis.¹²⁸

Assessment of idiopathic anaphylaxis. When a meticulous history of antecedent exposures and events does not yield any clues about potential triggers and when allergen skin tests are negative and specific IgE measurements are absent or undetectable to selected common allergens, patients are said to have idiopathic anaphylaxis. Before making this diagnosis, physicians should consider the possibility of a hidden or previously unrecognized trigger. Sensitization to a novel trigger for which there is no commercially available test allergen can be identified through a history of the event and confirmed by objective tests. These potentially include skin testing the patient and 1 or more controls with crude extracts of the suspected culprit allergen (although there is no quality assurance that such extracts contain the relevant allergenic components) and/or development of customized, sensitive, specific ELISAs and other *in vitro* tests, including gel electrophoresis and IgE immunoblotting, for identification of specific IgE to the suspect allergen.^{63,68,69}

The serum total tryptase level should be measured in all patients with idiopathic anaphylaxis.^{63-68,78,100-103} This important screening test for mastocytosis reflects the increased burden of mast cells in all forms of this disease.⁷⁸

MANAGEMENT OF PATIENTS AT RISK FOR ANAPHYLAXIS IN COMMUNITY SETTINGS

Long-term preventive measures include optimal management of relevant comorbidities, such as asthma, other chronic respiratory diseases, CVDs, and mastocytosis and clonal mast cell disorders.^{63-67,97-102} These measures also include discussion of the relative benefits and risks of concurrent medications (eg, β -blockers, angiotensin-converting enzyme inhibitors, and others that are widely and effectively used in the management of CVDs) with the patient and his or her cardiologist and documentation of the rationale for treatment decisions in the patient's medical record.^{97-99,103}

With the exception of venom immunotherapy for patients with insect sting-triggered anaphylaxis, current recommendations for prevention of anaphylaxis and emergency preparedness for treatment of anaphylaxis in the community are based on expert opinion and consensus rather than on randomized, double-blind, placebo-controlled trials. Preventive strategies for anaphylaxis in community settings that involve trigger avoidance and immunomodulation are summarized in Table IX.^{1,2,24-26,34,52,54,58,69,93,129-153} Follow-up at regular intervals is an important aspect of long-term risk reduction.

Long-term risk reduction: Prevention of anaphylaxis

Anaphylaxis triggered by food. Written personalized information about avoidance of confirmed relevant food triggers, including lists of common hidden sources of the food or foods and high-risk situations, such as buffet and catered meals and unlabeled desserts, baked goods, and candies, should be provided. Patients should be directed to resources that provide up-to-date, consistent information about avoidance of the specific food or foods (Table IX).^{26,129} Food avoidance measures potentially decrease quality of life for those at risk of anaphylaxis and for their caregivers^{130,131} because of lifestyle changes that disrupt activities, uncertainty about ambiguities in advisory labeling,¹³² and anxiety about the risk of accidental exposures.^{26,133} Strict avoidance of many foods potentially leads to nutritional deficiencies.²⁶ Some patients at risk for anaphylaxis to foods, or their caregivers, turn to complementary and alternative medicine for relief.¹¹⁵

Allergen-specific oral immunotherapy is currently a research procedure for prevention of anaphylaxis triggered by food. Clinical trials with foods such as milk, egg, or peanut have been conducted in carefully selected patients in appropriately equipped food allergy research centers by physicians and other health care professionals who have experience in performing food challenges, administering oral immunotherapy, and diagnosing and treating anaphylaxis.^{108,112,134-141} A few of the studies have had a double-blind, placebo-controlled design.¹³⁷ Adverse effects have been common with some oral immunotherapy dosing regimens, especially on the initial dose escalation day and on subsequent dose build-up days.¹⁴¹

In some of these studies, clinical desensitization to a food has been accompanied by long-term, food-specific humoral and cellular changes,^{138,140} including decreased titrated skin prick tests, decreased basophil activation, decreased IgE levels, and increased IgG₄, IL-10, IFN- γ , and TNF- α levels.¹⁴⁰ Studies in progress will resolve the issue as to whether oral immunotherapy for food-triggered anaphylaxis leads not only to clinical desensitization but also to true immunologic tolerance in which patients

TABLE IX. Preventive strategies for anaphylaxis in community settings

Allergen-specific trigger avoidance based on history of exposure and confirmation of sensitization (strength of recommendation = C)
Foods,* including additives and contaminants
Medications and biological agents†
Insect stings and bites
Natural rubber latex*
Inhalants
Seminal fluid
Occupational allergens
Other
Nonimmunologic triggers: avoid relevant exposure (strength of recommendation = C)
Exercise-induced anaphylaxis‡
Cold air or water
Heat
Sunlight/UV radiation
Medications, such as opioids
Ethanol
Immunomodulation
Food: Currently, oral immunotherapy is a research procedure supervised by physicians in specialized food allergy centers (strength of recommendation pending).
Insect venoms: allergen-specific immunotherapy (strength of recommendation = A)
Medications†: desensitization (strength of recommendation = B)
Seminal fluid: desensitization (strength of recommendation = C)
Idiopathic anaphylaxis (for frequent episodes only; strength of recommendation = C)
Oral glucocorticoid, such as prednisone; H ₁ -antihistamine, such as cetirizine (used for prophylaxis)

Adapted from reference 153 and others; see text for details.

*These Web sites consistently provide accurate up-to-date information: the Food Allergy and Anaphylaxis Network (www.foodallergy.org); the American Latex Allergy Association (www.latexallergyresources.org); the American Academy of Allergy, Asthma & Immunology (www.aaaai.org); and the American College of Allergy, Asthma & Immunology (www.acaai.org).

†Avoid the medications suspected of triggering anaphylaxis and substitute a non-cross-reacting medication, preferably from a different therapeutic class. If this is not possible, desensitization should be performed (eg, for β -lactam antibiotics, NSAIDs, and chemotherapy drugs).

‡Avoid relevant cotriggers, such as food, medication, cold air, or cold water.

remain desensitized even if the food is not eaten on a regular basis.^{112,134,135}

Future directions in specific immunotherapy to food and other allergens that trigger anaphylaxis might include allergen administration through the sublingual route, “engineered” recombinant protein allergens, a mixture of major recombinant allergens, CpG-oligonucleotide-conjugated allergens, peptides or polymers of major allergens, and other novel approaches.¹¹²

Immunomodulatory approaches that are not specific for a particular food allergen are also being studied. Food Allergy Herbal Formula-2, a well-characterized mixture of Chinese herbs that prevents food-induced anaphylaxis and leads to long-lasting immunologic tolerance in a murine model, has now entered clinical trials.¹⁴² Subcutaneous injections of anti-IgE antibody potentially provide an increased margin of protection against food and other allergen triggers of anaphylaxis for many, although not all, patients at risk (Table IX).¹⁴³

Medication- or biological agent-triggered anaphylaxis. For anaphylaxis triggered by a medication or a biological agent, avoidance is critically important. An alternative non-cross-reacting agent, preferably from a different therapeutic class but sometimes from the same class, can often be substituted effectively and safely.³⁴ Where this is not possible, desensitization with the offending agent is indicated.^{34,144} Standardized 12-step desensitization protocols in which antigens are introduced in an incremental manner over several hours have been published for some agents, such as β -lactam antibiotics or other antibiotics, aspirin or other NSAIDs, insulin, and chemotherapeutic agents, including taxanes and platins, as well as mAbs.¹⁴⁴ Once achieved, desensitization is maintained through regular administration of

the medication. Immunologic tolerance does not occur, and if the medication is discontinued, symptoms can recur when it is restarted.¹⁴⁴ Desensitization should be conducted in an appropriately equipped health care facility staffed by health care professionals who are trained and experienced in using desensitization protocols and in the recognition and treatment of breakthrough symptoms, including those of anaphylaxis.^{34,144} The cellular and molecular mechanisms underlying temporary desensitization without immunologic tolerance are not yet fully understood.¹⁴⁴

In patients with a history of vaccine- or vaccine component-triggered anaphylaxis who have negative skin tests to the vaccine and its components, it is highly unlikely that IgE antibody is present. The vaccine can therefore be administered in the usual manner; however, it is prudent to observe such patients for 1 hour afterward instead of the customary 30 minutes. In patients with a positive history and positive skin tests, a suitable alternative vaccine is sometimes available; for example, egg-free seasonal influenza vaccine and egg-free pandemic A/H1N1 vaccine grown in mammalian cell culture systems are now available in some countries. If a suitable alternative vaccine is not available, the culprit vaccine should be administered in an appropriately equipped and staffed health care facility by using a graded-dose protocol (Table IX).⁴⁸

Stinging insect-triggered anaphylaxis. For anaphylaxis triggered by stinging insects, avoidance of exposure involves several approaches. Yellow jacket, hornet, or wasp nests or fire ant mounds in the vicinity of the patient’s home should be professionally exterminated. Awareness of high-risk outdoor work or leisure activities, such as gardening, camping, picnicking, or barbecuing,

is important. When outdoors, appropriate protective clothing, including shoes and socks, should be worn. Personal insect repellents, such as DEET, are not effective in preventing insect stings in contrast to their efficacy in preventing insect bites.⁵⁴

In most patients with Hymenoptera venom-triggered anaphylaxis, a 3- to 5-year course of subcutaneous injections of the relevant standardized insect venom or venoms significantly reduces the risk of anaphylaxis from a subsequent sting and provides long-lasting protection.^{52-54,124} This potentially curative treatment is underused.⁵³ In children a 98% protection rate can be achieved, and the effect lasts for decades after venom injections are discontinued.^{52,145} Use of purified extracts potentially reduces large local reactions during venom immunotherapy.¹⁴⁶ Venom immunotherapy can be safely administered to all those at risk, including high-risk patients with mastocytosis or clonal mast cell disorders, although a slow rate of dose escalation is often necessary in such patients.^{147,148} Anti-IgE antibody is reported to be useful in controlling reactions to venom immunotherapy in patients with mastocytosis.¹⁴⁹ For prevention of anaphylaxis from fire ant stings^{54,55} or from insect bites,^{54,57} subcutaneous injections of the relevant whole-body extracts are used.

In adults venom immunotherapy significantly reduces sting-induced cutaneous systemic reactions and is therefore indicated for patients with sting-induced generalized urticaria and no other systemic symptoms.^{52,124} It also reduces large local reactions to stings and might be considered for at-risk patients who cannot totally avoid insect exposure, such as beekeepers, and/or those who experience frequent or severe large local reactions.¹⁵⁰ In children, venom immunotherapy is not indicated either for sting-induced generalized urticaria without other systemic symptoms or for large local reactions (Table IX).¹⁴⁵

Anaphylaxis induced by other triggers. Avoidance of the relevant specific confirmed trigger is the key to prevention of anaphylaxis recurrence, such as avoidance of natural rubber latex⁵⁸ or occupational allergens.^{1,2,24,25,69} Desensitization provides short-term immunomodulation for patients at risk of anaphylaxis to seminal fluid.⁵⁹ In the future, regular subcutaneous injections of anti-IgE antibody might be indicated for patients with anaphylaxis triggered by various allergen triggers. For anaphylaxis induced by some nonimmune triggers, such as cold, heat, sunlight/UV radiation, or ethanol, avoidance of the trigger is the key to prevention of recurrences (Table IX).²⁵

Exercise-triggered anaphylaxis. Strategies for prevention of exercise-induced anaphylaxis include strict avoidance of relevant cotriggers, such as food, medication, or ethanol ingestion and cold air or cold water exposure, and awareness of other potential concomitant risk factors, such as acute infection, emotional stress, menses (premenstrual and ovulatory phases), extremes of temperature and humidity, and high pollen counts. Additional precautions include never exercising alone, discontinuing exertion immediately when the first symptom of anaphylaxis is noted, always carrying 1 or more epinephrine autoinjectors, and carrying a cell (mobile) phone for calling 911/emergency medical services during activities such as long-distance running or cross-country skiing. Premedication and warm-up are not effective in preventing exercise-induced anaphylaxis (Table IX).^{24,25,61}

Idiopathic anaphylaxis. Immunomodulation with pharmacologic agents is often recommended for patients with frequent episodes of idiopathic anaphylaxis, which is defined as more than 6 per year or more than 2 per 2 months. One example of a

prophylaxis regimen involves 60 to 100 mg of prednisone each morning for 1 week, followed by 60 mg on alternate mornings for 3 weeks and then gradual tapering of the dose over 2 months, in addition to an H₁-antihistamine, such as 10 mg of cetirizine daily.⁶³ Anti-IgE antibody injections have been reported to be helpful in patients with idiopathic anaphylaxis and in anaphylaxis with no apparent trigger that occurs in patients with mastocytosis. (Table IX)^{151,152}

Long-term risk reduction: Emergency preparedness for anaphylaxis recurrences in the community

Those at risk for anaphylaxis in the community and their caregivers should be prepared to recognize episodes that occur despite best efforts to avoid the relevant trigger and other preventive measures and to provide prompt life-saving first-aid treatment of such episodes.^{2,24-26,34,52,54,69,93,153} Emergency preparedness involves carrying 1 or more epinephrine autoinjectors, having an anaphylaxis emergency action plan, and wearing appropriate medical identification.^{1,2,24-26,54,69,153}

Epinephrine (adrenaline): the medication of choice. For treatment of an anaphylaxis recurrence in the community, injection of epinephrine is the first-aid medication of choice, as recommended in all anaphylaxis guidelines. The rationale for this is summarized in Table X.^{24,154,156-162} Most guidelines recommend injecting epinephrine from an autoinjector intramuscularly in the midanterolateral aspect of the thigh. The first aid dose of epinephrine is 0.01 mg/kg of a 1 mg/mL (1:1,000) dilution to a maximum dose of 0.5 mg in an adult or 0.3 mg in a child. This dose can be repeated every 5 to 15 minutes, as needed.^{154,155,163-165} Patients should not suddenly sit or stand after receiving an epinephrine injection because this can lead to the empty inferior vena cava/empty ventricle syndrome and sudden death.¹⁶⁶

In patients with anaphylaxis, epinephrine has potent life-saving α_1 -adrenergic vasoconstrictor effects on the small arterioles and precapillary sphincters in most body organ systems.¹⁵⁶ It decreases mucosal edema, thereby preventing and relieving upper airway obstruction, and it also prevents and relieves hypotension and shock (Table X).¹⁵⁶⁻¹⁶⁰ In addition, its β_1 -adrenergic effects lead to increased force and rate of cardiac contractions, and its β_2 effects lead to increased bronchodilation and decreased release of mediators, such as histamine and tryptase, from mast cells and basophils.¹⁵⁶

Prompt injection is important. In most countries the highest epinephrine dose currently available in an autoinjector is 0.3 mg. This dose is low compared with the initial adult dose of 1 mg epinephrine used in cardiopulmonary resuscitation and is unlikely to be effective if anaphylaxis has progressed to the point at which cardiopulmonary resuscitation is needed. Delayed injection of epinephrine is associated with fatal anaphylaxis¹⁸⁻²¹ and also contributes to the increased likelihood of biphasic anaphylaxis, which is defined as symptom recurrence 1 to 72 hours (usually within 8 hours) after resolution of the initial symptoms despite no further exposure to the trigger.¹⁶⁷⁻¹⁶⁹

The best way of providing first-aid treatment with epinephrine (adrenaline) for anaphylaxis in the community is by using an autoinjector; however, currently available autoinjectors have a number of limitations. Only 2 fixed epinephrine doses, 0.15 mg and 0.3 mg, are available in autoinjector formulations in most countries (EpiPen, Dey, LP, Napa, Calif; Twinject, Shionogi & Co, Ltd, Osaka, Japan; Anapen, Lincoln Medical, Salisbury, Wiltshire, United Kingdom). The 0.15 mg dose is too high for

TABLE X. Epinephrine (adrenaline): Medication of first choice for anaphylaxis

Strength of recommendation	B-C
Pharmacologic effects when given by injection (oral administration is ineffective because of rapid metabolism in the GI tract)	At α_1 -receptor ↑ Vasoconstriction/↑ vascular resistance in most body organ systems ↑ Blood pressure ↓ Mucosal edema (larynx)
	At β_1 -receptor ↑ Heart rate ↑ Cardiac contraction force
	At β_2 -receptor ↓ Mediator release ↑ Bronchodilation ↑ Vasodilation
Practical aspects	↓ Mucosal edema and relieves upper airway obstruction ↓ Wheezing ↓ Hives ↑ Blood pressure and prevents and relieves hypotension and shock
Potential adverse effects (after usual dose of 0.01 mg/kg to a maximum of 0.5 mg [adults] IM)*	Anxiety, pallor, tremor, palpitations, dizziness, and headache; these symptoms indicate that an appropriate pharmacologic dose has been injected.
Potential adverse effects (after overdose, such as IV bolus dose, overly rapid IV infusion, or erroneous administration of a concentrated epinephrine solution 1:1,000 [1 mg/mL] by the IV route)†	Pulmonary edema, hypertension, angina, myocardial infarction, ventricular arrhythmias; note that the latter 3 adverse effects also potentially occur in untreated anaphylaxis when subclinical coronary artery disease is unmasked, because the heart itself is a potential target organ in anaphylaxis.‡
Comment: why the intramuscular route is preferred	Epinephrine has a vasodilator effect in skeletal muscle.‡ Skeletal muscle is well vascularized. After intramuscular injection into the vastus lateralis, absorption is rapid, and epinephrine reaches the central circulation rapidly. Rapid absorption is critical in anaphylaxis in which the median time to respiratory or cardiac arrest is 15 minutes (venom) to 30 minutes (food).

Adapted from references 24 and 154-162.

GI, Gastrointestinal; IM, intramuscular; IV, intravenous.

*The epinephrine dose recommended for initial treatment of anaphylaxis is lower than the dose recommended for initial use in cardiopulmonary resuscitation and is unlikely to be effective after cardiac arrest has occurred. Ideally, epinephrine doses should be stated concentrations (ie, milligrams per milliliter) rather than as ratios; however, both methods are in common use.

†Intravenous infusion of epinephrine presents a high risk of harmful side effects. It should be given only by physicians who are trained and experienced in the dose titration of vasopressors (preferably by using an infusion pump) against continuous hemodynamic monitoring.

‡Epinephrine enhances blood flow in coronary arteries because of increased myocardial contractility and increased duration of diastole. This action and the vasodilator effect in skeletal muscle produced by endogenous epinephrine are well-recognized aspects of the fight-or-flight response.

infants and children weighing less than 15 kg. The 0.3 mg dose is too low for children weighing more than 30 kg and for teens and adults. In the United Kingdom a 0.5 mg epinephrine dose is available in the Anapen. Autoinjectors with 1.43 cm needles might not achieve intramuscular injection in some children and adults, as ascertained by using computed tomographic scans of the thigh to measure the distance from the skin to the surface of the vastus lateralis muscle.^{170,171} The force of the injection likely also contributes to intramuscular deposition and rapid absorption of epinephrine.¹⁷²

Health care professionals need to be trained to use epinephrine autoinjectors correctly and safely in order to train and coach those at risk for anaphylaxis and their caregivers in how to use them correctly and safely.¹⁷³ Unintentional injections from epinephrine autoinjectors into fingers, thumbs, and hands by patients self-injecting or by caregivers injecting children or others have been reported to poison control centers with increasing frequency in the past decade. These unintentional injections might not only result in injury but also in partial or complete loss of the epinephrine dose for the person having an anaphylactic episode, the so-called “lost dose hazard.”^{174,175} Epinephrine autoinjectors with

improved design, including needle protection features, are being introduced.

Up to 20% of patients who receive an initial first-aid dose of epinephrine for treatment of anaphylaxis in the community are reported to require a second dose, either because of ongoing symptoms or because of biphasic anaphylaxis.^{167-169,176-178} Most patients with anaphylaxis respond promptly to epinephrine injections; the potential reasons for apparent lack of response in a minority of patients are summarized in Table XI.^{158,166,170,171,175,178-181}

Transient pharmacologic effects of epinephrine, such as pallor, tremor, anxiety, palpitations, headache, and dizziness, that occur within 5 to 10 minutes after injection are usually mild and confirm that a therapeutic epinephrine dose has been given. Serious adverse effects, such as pulmonary edema or hypertension, are usually attributable to epinephrine overdose. Although they can occur after administration by any route, they are most commonly reported after either an intravenous bolus dose, an overly rapid intravenous infusion, or an intravenous injection of a concentrated 1 mg/mL (1:1,000) epinephrine solution instead of the dilute 0.1 mg/mL (1:10,000) epinephrine solution appropriate for intravenous infusion.^{24,154}

TABLE XI. Reasons for apparent lack of response to epinephrine

Physician-related factors
Error in diagnosis*
Empty ventricle syndrome†
Patient-related factors
Rapid anaphylaxis progression
Patient taking a medication that interferes with optimal epinephrine effect, such as an α -adrenergic blocker or β -adrenergic blocker
Epinephrine-related factors
Epinephrine autoinjector not available‡
Epinephrine autoinjector not prescribed by physician
Epinephrine autoinjector not affordable (prescription not picked up)
Injected too late
Dose too low on a milligram per kilogram basis
Dose too low because of injection of epinephrine that is past the expiry date§
Injected using incorrect technique, such as not enough force
Injection route not optimal
Injection site not optimal
Adverse reaction to sodium metabisulfite preservative in the epinephrine solution (rare)

Adapted from references 158, 166, 170, 171, 175, and 178-181.

*For example, if epinephrine is injected for a disease, such as nonallergic angioedema or food protein-induced enterocolitis, that would not be expected to respond well to it.

†Occurs when the epinephrine injected cannot circulate in the body because the patient is suddenly placed upright and the vena cava (and ventricle) empties.

‡In many countries life-saving epinephrine autoinjectors are not available for those at risk of anaphylaxis. Existing alternatives cannot be depended on to produce high tissue concentrations of epinephrine rapidly. These include having a patient or caregiver draw up epinephrine from an ampule, use of a syringe prefilled with epinephrine, or use of an epinephrine metered-dose inhaler.

§The maximum shelf-life of EpiPen and Twinject autoinjectors is 12 to 18 months. The maximum shelf life of AnaPen autoinjectors (available in the United Kingdom) is 18 to 24 months. The maximum shelf life of a syringe prefilled with epinephrine in a physician's office is 3 to 4 months. *In vitro* degradation (breakdown) products of epinephrine are ineffective in patients with anaphylaxis.

||Epinephrine through other routes, such as subcutaneous injection or inhalation from a metered-dose inhaler or nebulizer and compressor is not recommended for the treatment of anaphylaxis because it is more difficult to achieve high plasma and tissue concentrations rapidly when these routes are used.

Traditionally, many physicians have been reluctant to inject epinephrine in middle-aged or older patients with anaphylaxis because of concerns regarding cardiac adverse effects. In fact, the heart is a potential target organ in anaphylaxis. In healthy people mast cells are present throughout the myocardium (between myocardial fibers, around blood vessels, and in the coronary artery intima).^{72,97} In patients with coronary artery disease, the number and density of cardiac mast cells is increased because mast cells are also present in atherosclerotic plaques, where they contribute to atherogenesis.⁹⁷ Histamine, leukotrienes, platelet-activating factor, and other mediators released after mast cell stimulation potentially lead to coronary artery spasm.⁹⁷ Patients with anaphylaxis can present with acute coronary syndrome secondary to either vasospasm or acute plaque rupture and thrombus formation. In patients with coronary artery disease, the use of epinephrine requires caution; however, concerns about its potential adverse effects need to be weighed against the cardiac risks of untreated anaphylaxis and the knowledge that epinephrine injection usually enhances blood flow in the coronary arteries because its β_2 -adrenergic action leads to increased myocardial contractility and increased duration of diastole compared with systole (Table X).^{24,25,97,161,162}

Other medications. More than 40 H_1 -antihistamines are available for use,¹⁸² and many of these medications are recommended for use in anaphylaxis; in some anaphylaxis guidelines, dosage regimens are provided for up to 7 different H_1 -antihistamines. H_1 -antihistamines do not prevent or relieve upper or lower airway obstruction, hypotension or shock.^{182,183} After oral administration, their onset of action ranges from 1 to 3 hours.¹⁸² The rapid improvement in symptoms sometimes attributed to oral H_1 -antihistamines likely reflects spontaneous resolution of the anaphylactic episode. First-generation, potentially sedating H_1 -antihistamines, such as

diphenhydramine, chlorpheniramine, and promethazine, have a poor benefit/risk ratio.^{182,184} When self-administered in patients with anaphylaxis, these medications potentially impair self-recognition of symptoms. When given to a child, they potentially complicate interpretation of CNS symptoms and signs, such as drowsiness. An H_1 -antihistamine might be useful as an adjunctive measure to relieve residual hives that have not disappeared after epinephrine injection (Table XII).^{153,183}

β_2 -Adrenergic agonists do not have a vasoconstrictor effect and do not decrease mucosal edema, prevent or relieve upper airway obstruction, hypotension or shock. They are potentially useful when administered by nebulization as an adjunctive measure to relieve residual bronchospasm that has not disappeared after epinephrine injection (Table XII).¹⁵⁴

Glucocorticoids are traditionally given to prevent and relieve biphasic or protracted anaphylaxis (Table XII).¹⁸⁵

Emergency preparedness in the community: Additional measures. Almost 40% of persons at risk of anaphylaxis in the community reportedly use a written anaphylaxis emergency action plan.¹⁷⁸ Most plans list common symptoms and signs of anaphylaxis and emphasize the importance of using the epinephrine autoinjector promptly and of calling 911 or emergency medical services promptly (download from www.aaaai.org).^{69,186} Plans should be personalized for each at-risk patient by listing comorbidities and concurrent medications, describing the epinephrine autoinjector and dose prescribed for the patient, and providing appropriate contact telephone numbers, such as those of family members.^{69,186} Plans need to be updated and discussed with the patient, and if relevant, his or her caregivers, on a regular basis. Formal evaluation of the clinical efficacy and cost-effectiveness of these plans is needed.¹⁸⁷

TABLE XII. Adjunctive medications for the treatment of anaphylaxis

Medication (example)	H ₁ -antihistamines* (oral, such as cetirizine; IV, such as diphenhydramine)	H ₂ -antihistamines* (ranitidine)	β ₂ -Adrenergic agonists* (salbutamol [albuterol])	Glucocorticoids* (oral, such as prednisone; IV, such as methylprednisolone)
Strength of recommendation*	C	C	C	C
Pharmacologic effects	At H ₁ -receptor ↓ Itch (skin, mucus membranes) ↓ Flush ↓ Hives ↓ Sneezing ↓ Rhinorrhea	At H ₂ -receptor ↓ Gastric acid secretion ↓ Vascular permeability ↓ Hypotension ↓ Flushing ↓ Headache ↓ Tachycardia ↓ Chronotropic and inotropic activity ↓ Mucus production (airway)	At β ₂ -receptor ↑ Bronchodilation	↓ Late-phase allergic response to allergen
Practical aspects	↓ Itch and hives but not life-saving in anaphylaxis	Small additive effect (10% or so) when used in conjunction with an H ₁ -antihistamine for ↓ in vascular permeability, ↓ flushing, and ↓ hypotension	↓ Wheeze, cough, and shortness of breath but do not ↓ upper airway obstruction or relieve hypotension and are not life-saving in anaphylaxis	Effects take several hours; used to prevent biphasic or protracted anaphylaxis; however, there is no evidence from high-quality randomized controlled trials that this occurs.
Potential adverse effects (usual doses)	First-generation drugs cause sedation and impair cognitive function.	Ranitidine: unlikely cimetidine: potentially causes hypotension if infused rapidly	Tremor, tachycardia, dizziness, jitteriness	Unlikely to occur during a short 1- to 3-day course
Potential adverse effects (overdose)	Coma, respiratory depression	Unlikely	Headache, hypokalemia	Unlikely
Comment	Many different H ₁ -antihistamines and different dose regimens are listed as adjunctive medications in anaphylaxis guidelines.	Not mentioned in most anaphylaxis guidelines; an H ₂ -antihistamine should not be used alone in anaphylaxis; if used, it should be given with an H ₁ -antihistamine.	Deliver by nebulization and face mask.	Different glucocorticoids and different dose regimens are used; these medications are unlikely to play a role in the initial minutes to hours of an anaphylactic episode.

There are no randomized double-blind, placebo-controlled trials of any of these medications in the treatment of acute anaphylaxis episodes. The route of administration of H₁-antihistamines and glucocorticoids depends on the severity of the anaphylaxis episode. Adapted from reference 153.

*For use in anaphylaxis.

Those at risk for anaphylaxis in the community should wear medical identification jewelry that provides worldwide access to a patient registry service 24 hours a day, 365 days of the year, so that health care professionals treating them can obtain relevant information about their triggers, concomitant diseases, and concurrent medications if needed. An anaphylaxis wallet card listing relevant confirmed triggers, concomitant diseases, and concurrent medications is available at www.aaaai.org.^{69,153}

An approach to anaphylaxis education for health care professionals, people at risk of anaphylaxis and their caregivers, and the general public is outlined in Table XIII.^{69,153,188,189} The consistent message in anaphylaxis education should be that anaphylaxis is potentially a killer allergy, not a trivial lifestyle disease, and that prompt treatment is life-saving.^{69,153}

Anaphylaxis education projects are now becoming a priority in some communities. The main goal of these efforts is to teach people to act promptly, recognize anaphylaxis, use an epinephrine

autoinjector correctly and safely, call for help, transfer the patient to a health care facility, and also to recommend follow-up, preferably with an allergy/immunology specialist. Examples of specific education projects are those focusing on anaphylaxis after omalizumab injection in a physician's office,¹⁹⁰ and on follow-up of patients with anaphylaxis who are treated in the emergency department.¹⁹¹ Many patients discharged from an emergency department after anaphylaxis treatment still do not receive a prescription for self-injectable epinephrine or a referral to a specialist physician.¹⁹² Lack of access to epinephrine autoinjectors for children experiencing anaphylaxis in schools remains a concern.^{188,189,193,194}

EMERGENCY MANAGEMENT OF ACUTE ANAPHYLAXIS IN A HEALTH CARE FACILITY

Emergency management of anaphylaxis in a health care facility is reviewed in depth elsewhere.^{154,155,163,164} In any physician's

TABLE XIII. Anaphylaxis education

Health care professionals	
Who:	physicians, nurses, pharmacists, emergency medical technicians, and first responders
What:	definition of anaphylaxis (new); shock not necessarily a criterion for diagnosis
	Common triggers
	Emergency preparedness
	Recognition of evolving symptoms and signs; can be difficult in those unable to describe their symptoms, such as infants, or patients with dysphonia, dyspnea, or shock; severity varies among patients and in the same patient from one episode to another
	Treatment: promptly and simultaneously inject epinephrine, activate 911 or emergency medical services,* and place patient on the back or in position of comfort with lower extremities elevated
When:	at regular intervals
Key messages:	Anaphylaxis can kill rapidly (within 15 minutes after an insect sting and within 30 minutes after ingestion of a food trigger). Inject first-aid dose of epinephrine promptly. Especially, do not hesitate if the patient has trouble breathing, throat tightness, or altered level of consciousness.
People at risk for anaphylaxis	
Who:	those who have experienced anaphylaxis previously and are at risk for recurrences and their families; for teens and young adults, their peers
What:	triggers of anaphylaxis, prevention of episodes (trigger specific), emergency preparedness—recognize symptoms and signs, inject epinephrine; activate emergency medical services,* notify family
	Hands-on epinephrine autoinjector training and coaching
When:	teachable moments in the weeks or months after an anaphylactic episode and then at yearly intervals or more often
Key messages:	Death from anaphylaxis can occur within minutes. Promptly inject epinephrine, activate emergency medical services* Place the patient on the back or in a position of comfort with lower extremities elevated.
General public	
Who:	educators, coaches, camp directors, child care providers, food industry workers, restaurant workers, and transportation workers
What:	Anaphylaxis occurs in infants, children, teens, and adults who appear to be in excellent health until exposed to their trigger. Symptoms that mandate immediate treatment are sudden difficulty breathing, throat tightness, and altered level of consciousness.
When:	at regular intervals, such as the start of academic year for educators; a highly publicized fatal episode of anaphylaxis increases public awareness.
Key messages:	Anaphylaxis is a killer allergy. Promptly inject epinephrine, activate emergency medical services*. Place the patient on the back or in a position of comfort with lower extremities elevated.

Adapted from references 69, 153, 166, 188 and 189.

*Transport of the patient to an emergency department.

TABLE XIV. Reasons for lack of randomized controlled trials in patients with anaphylaxis

Anaphylactic episodes are unpredictable.
Anaphylaxis commonly occurs in community settings (eg, home, restaurant, and school).
Baseline measurements of vital signs and oxygenation are often not available.
Symptoms and signs vary from one person to another and from one episode to another, even in the same person, with regard to time of onset after exposure to trigger (minutes to hours), body organ systems involved, severity, and duration.
Symptoms sometimes resolve spontaneously because of endogenous production of epinephrine, endothelin I, and angiotensin II.
Randomized placebo-controlled trials would be unethical for epinephrine, although randomized placebo-controlled trials of H ₁ -antihistamines, H ₂ -antihistamines, and glucocorticoids might be conducted in the future.
Rarely, even with prompt and optimal treatment and monitoring, anaphylaxis can be fatal.

Adapted from reference 200.

office or clinic where allergen skin tests or allergen challenge/provocation tests are performed or allergen-specific immunotherapy, anti-IgE antibody injections or vaccine injections are given, it is important to develop and rehearse an anaphylaxis management plan, train the staff, and ensure availability of essential medications (within expiry date), as well as essential supplies and equipment.¹⁹⁵

The basic principles of anaphylaxis management in a health care facility include rapid assessment of the patient's airway, breathing, circulation, and orientation/mentation; examination of the skin; and estimation of body weight/mass. Initial treatment involves discontinuing exposure to the trigger, if relevant (eg, discontinuing administration of an intravenous medication or biological agent), and then prompt and simultaneous intramuscular injection of epinephrine in a first-aid dose of 0.01 mg/kg to a maximum adult dose of 0.5 mg, calling for help (either a resuscitation team or 911/emergency medical services, whichever

is appropriate), and placing the patient on the back or in a position of comfort with the lower extremities elevated.^{154,155,166,195} Administration of supplemental oxygen by face mask at a rate of at least 6 to 8 L/min, airway management, and insertion of 1 or more large-bore (no. 14 or 16) needles or intravenous catheters for infusion of large volumes of fluid, such as 0.5 to 1 L of 0.9% (isotonic) saline in 5 to 10 minutes to an adult, should be performed if needed.^{154,155,163,195} Most anaphylaxis guidelines recommend administration of an adjunctive medication such as an H₁-antihistamine, a nebulized β_2 -adrenergic agonist, and a glucocorticoid^{154,155,163-166} and some also recommend an H₂-antihistamine.¹⁶³

It has also been suggested that epinephrine and other vaso-pressors should be administered intravenously only by physicians who are trained, experienced, and equipped to administer these potent medications effectively and safely; that is, to titrate the rate of infusion (preferably by using an infusion pump), according to

the patient's hemodynamic response assessed by means of continuous, noninvasive cardiac and blood pressure monitoring and pulse oximetry.^{154,155} If it is used, intravenous epinephrine should only be given by slow infusion (not a bolus) of a dilute solution, 0.1 mg/mL (1:10,000) that is appropriate for intravenous use, and not the concentrated 1 mg/mL (1:1,000) dilution that is appropriate for intramuscular injection.¹⁵⁴ Physician confusion between dilute and concentrated epinephrine solutions potentially leads to dosing errors and fatality.¹⁹⁶ Existing studies do not permit a conclusion with regard to whether any one vasopressor is superior to another in preventing mortality in critically ill patients with shock.¹⁹⁷ Even in the hands of intensive care specialists, use of intravenous vasopressors might not improve outcomes and might increase fatality rates.^{198,199}

FUTURE DIRECTIONS IN THE PHARMACOLOGIC MANAGEMENT OF ANAPHYLAXIS

Recommendations for the treatment of acute anaphylactic episodes are based on expert opinion rather than on randomized controlled trials in patients experiencing anaphylaxis at the time of the study. The reasons for lack of randomized controlled trials of pharmacologic interventions in anaphylaxis are summarized in Table XIV.²⁰⁰

It is important to note that the evidence base for epinephrine injection in the treatment of anaphylaxis is stronger than the evidence base supporting the use of H₁-antihistamines, H₂-antihistamines, or glucocorticoids in anaphylaxis.^{160,165,183,185} Recommendations for prompt epinephrine injection are based on fatality studies, epidemiologic studies, observational studies, nonrandomized controlled studies in patients actually experiencing anaphylaxis, randomized controlled studies in patients not experiencing anaphylaxis at the time of the study, *in vitro* studies, and studies in animal models.^{157-160,200}

The World Health Organization (www.who.int) and the World Allergy Organization,¹⁵⁹ as well as all anaphylaxis guidelines,^{154,155,163-165} are in universal agreement that epinephrine injection is fundamentally important in anaphylaxis management. Placebo-controlled trials of epinephrine are therefore clearly unethical. Recommendations for the maximum initial dose of epinephrine or the route of injection differ among the guidelines, however, and in the future, it might be possible to conduct randomized trials comparing different first-aid epinephrine doses or different routes of injection.²⁰⁰

In contrast to the consensus about epinephrine, there is no consensus among published anaphylaxis guidelines with regard to the use of H₁-antihistamines, H₂-antihistamines, or glucocorticoids in the treatment of anaphylaxis. Many different H₁-antihistamines in a variety of dose regimens are recommended.¹⁸³ Several different glucocorticoids in a variety of dose regimens are recommended.¹⁸⁵ H₂-antihistamines are not mentioned in most guidelines.¹⁶⁵ In the future, it might therefore be possible to conduct randomized placebo-controlled trials of these medications in acute anaphylaxis episodes.²⁰⁰

If randomized controlled trials are conducted, in addition to the intervention being tested, it will be critically important to take rigorous appropriate precautions to ensure that all patients have prompt, optimal, standard-of-care treatment with epinephrine injections, are placed in the recumbent position or a position of comfort with lower extremities elevated; and have appropriate treatment with supplemental oxygen, airway management, and

high-volume intravenous fluid resuscitation, as well as continuous noninvasive monitoring of heart rate, blood pressure, and oxygenation.^{154,155,163,164,166,190,195}

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