

9. Anaphylaxis

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Anaphylaxis is an acute-onset, potentially fatal systemic allergic reaction. It is usually triggered by an agent such as an insect sting, food, or medication, through a mechanism involving IgE and the high-affinity IgE receptor on mast cells or basophils. Less commonly, it is triggered through other immunologic mechanisms, or through nonimmunologic mechanisms. It often occurs in community settings. Anaphylaxis episodes range in severity from those that are mild and resolve spontaneously to those that are fatal within minutes. The clinical diagnosis is based on a meticulous history and physical examination, sometimes, but not necessarily, supported by a laboratory test such as an elevated serum total tryptase level. Sensitization to allergen triggers suggested by the history needs to be confirmed by skin testing and measurement of allergen-specific IgE. In some sensitized individuals, additional tests are needed to assess the risk of future anaphylaxis episodes. Prompt injection of epinephrine is life-saving. H₁-antihistamines and inhaled β_2 -adrenergic agonists cannot be depended on to prevent fatality. Long-term risk reduction is an integral part of management. (J Allergy Clin Immunol 2008;121:S402-7.)

Key words: Anaphylaxis, allergic reaction, mast cell, basophil, IgE, Fc ϵ RI, histamine, tryptase, food allergy, venom allergy, medication allergy, epinephrine, adrenaline, H₁-antihistamine

Anaphylaxis is an acute-onset, potentially fatal systemic allergic reaction. Anaphylactic and anaphylactoid reactions do not need to be distinguished with regard to diagnosis and acute treatment. The term *anaphylactoid* is no longer recommended for use.¹ Nevertheless, it remains critically important to understand the effector mechanisms involved in the pathogenesis of anaphylaxis in order to develop optimal risk reduction strategies and prevent recurrence² (Fig 1, A and B).

The true rate of occurrence of anaphylaxis from all triggers is unknown,³ but it appears to be increasing. Lifetime prevalence is estimated as 0.05% to 2%. In prospective studies, underreporting likely occurs, because anaphylaxis may be underdiagnosed in individuals who present with mild or partially treated episodes. In retrospective studies involving chart reviews from emergency departments or clinics, International Classification of Diseases,

Abbreviations used

CNS: Central nervous system

PAF: Platelet-activating factor

Ninth Revision codes for the diagnosis and clinical manifestations of anaphylaxis fail to capture all individuals with the disease.⁴

Epidemiologic studies suggest that anaphylaxis now occurs more commonly in community settings than in health care settings. The rate of occurrence is increased in individuals living in good socioeconomic circumstances. The largest number of incident cases is among children and adolescents.³ Until age 15 years, there is a predilection for males, but after age 15 years, there is a predilection for females. Different trigger factors predominate in different age groups; for example, fatalities from food-induced anaphylaxis peak in adolescents and young adults,^{5,6} and fatalities from anaphylaxis triggered by insect stings, diagnostic agents, and medications predominate in middle-aged and older adults.⁷ There are few studies of the role of genetic factors in anaphylaxis.²

PATHOGENESIS

In many individuals with anaphylaxis, IgE plays a pivotal role. Synthesized in response to allergen exposure, it becomes fixed to Fc ϵ RI on the surface membranes of mast cells and basophils. Aggregation of receptor-bound IgE molecules on re-exposure to the allergen results in cell activation, mediator release, and the immediate hypersensitivity response. IgE also contributes to the intensity of anaphylaxis through mechanisms that go beyond sensitizing, priming, activation, and mediator release; for example, it enhances expression of Fc ϵ RI on mast cells and basophils.^{2,8-10}

Other potential immunologic mechanisms in anaphylaxis include involvement of immune aggregates, IgG, IgM, platelets, and T cells; shift in eicosanoid metabolism toward leukotriene formation; and activation of the complement or coagulation systems.² In some individuals described as having idiopathic anaphylaxis, Fc ϵ RI receptors may be aggregated through autoimmune mechanisms. Nonimmunologic factors, which activate mast cells by mechanisms not yet fully understood, include exercise, cold air or water exposure, radiation, ethanol, insect venom constituents, radiocontrast media, and medications such as opioids and vancomycin.² A few triggers—for example, insect venoms, radiocontrast media, and some medications—potentially act through more than 1 mechanism² (Fig 1, A).

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

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A

ANAPHYLAXIS PATHOGENESIS

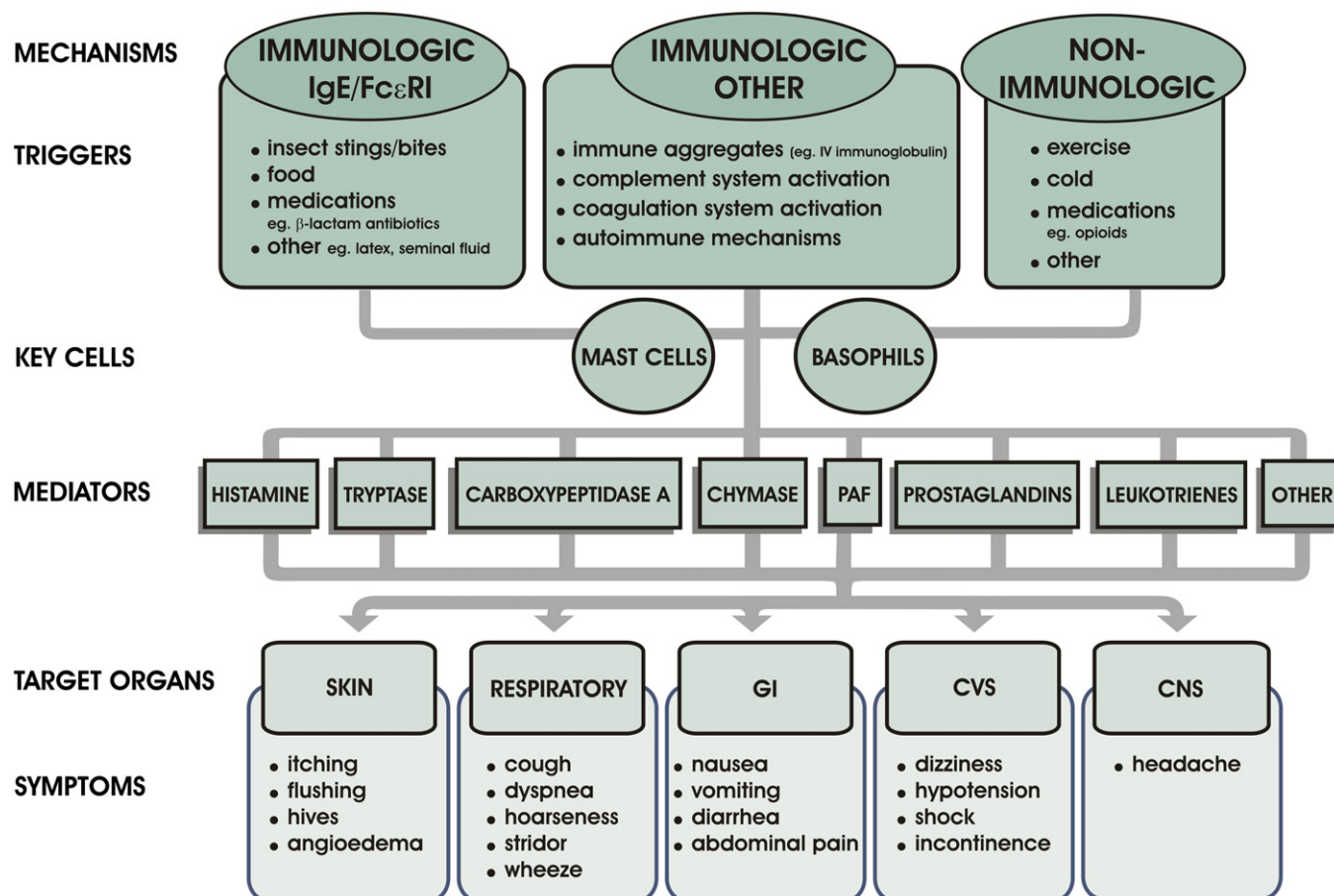


FIG 1A. Summary of the pathogenesis of anaphylaxis. Other potential triggers include occupational allergens, inhalants such as horse dander or grass pollen, allergen immunotherapy, vaccines to prevent infectious diseases, hormones, colorants, and enzymes. Some triggers may act through more than 1 mechanism. Individuals with anaphylaxis, by definition, usually have involvement of 2 or more body systems concurrently; the occasional exceptions are those with isolated hypotension after exposure to a known trigger.

initiating and amplifying the acute allergic response.^{2,8-15} They release mediators of inflammation, including histamine, proteases such as tryptase, mast cell carboxypeptidase A3 and chymase, lipids such as platelet-activating factor (PAF), prostaglandins (PGD₂), and leukotrienes (LTC₄), as well as chemokines, and cytokines (Fig 1, A). 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.¹⁰ 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 important in IgE/antigen-induced mast cell degranulation and cytokine production.¹¹ Inhibitory sialic acid-binding immunoglobulin-like lectins (Siglecs) are extensively expressed on human mast cells.¹² Sphingosine kinases are reported to be determinants of mast cell responsiveness.¹³ In the future, basophil

involvement might be more readily characterized, thanks to identification of a mAb directed against an intermediate form of pro-major basic protein 1.¹⁴ Anti-IgE antibody might play a therapeutic role by depleting free IgE, with consequent downregulation of FcεRI receptors on mast cells and basophils and deflation of the intracellular activation signal triggered by IgE/FcεRI aggregation.¹⁵

Animal models provide information that is potentially relevant to human anaphylaxis. For example, in murine anaphylaxis, 2 main immunologic pathways have been described: (1) a classic pathway involving a small amount of antigen, FcεRI on mast cells and basophils and release of histamine, leukotrienes, serotonin, and PAF; and (2) a pathway involving a relatively large amount of antigen, IgG-antigen complex-induced activation of macrophages by cross-linking of FcγRIII, and release of mediators, predominantly PAF.¹⁶

DIAGNOSIS

Diagnosis of anaphylaxis depends primarily on a meticulous clinical history: ascertaining exposure to potential triggering agents or events, time elapsed between exposure and symptom onset, and evolution of the episode over minutes or hours. Among individuals recognized as having anaphylaxis, target organs include skin (90% of episodes), respiratory tract (70%), gastrointestinal tract (30% to 45%), cardiovascular system (10% to 45%), and central nervous system (CNS; 10% to 15%; Fig 1, A). Diagnosis is impeded when symptoms are not recognized, and when skin signs are absent. As reflected in the clinical criteria supporting the new anaphylaxis definition, many individuals with anaphylaxis never develop hypotension or shock,^{1,5-7} and respiratory tract obstruction is often the predominant cause of death.^{6,7} The differential diagnosis of anaphylaxis is age-dependent.^{2,17}

Laboratory tests available to support the clinical diagnosis of anaphylaxis include plasma histamine levels and serum or plasma total tryptase levels, which do not necessarily correlate with each other, in part because of the different time courses of their appearance in, and disappearance from, the circulation. Histamine should be measured in blood samples obtained within 15 to 60 minutes of onset; tryptase, in samples obtained within 15 to 180 minutes. Even in optimally timed samples, histamine and tryptase levels may be within normal limits; in particular, tryptase levels are seldom elevated in food-triggered anaphylaxis, in which basophil involvement possibly predominates over mast cell involvement. Measurement of serial tryptase levels, or of baseline levels in postevent serum or stored serum, might be helpful. In the future, more widespread availability of measurement of additional mast cell and basophil activation markers such as mature β -tryptase, mast cell carboxypeptidase A3, chymase, and PAF, or a panel of such markers, might be useful.^{2,18,19} (Fig 1, A).

The specific trigger implicated by the history of an anaphylaxis episode needs to be confirmed, so that it can be avoided and future episodes can be prevented.^{17,20} In individuals with IgE-dependent anaphylaxis, positive allergen skin tests and elevated quantitative allergen-specific IgE levels indicate sensitization, which is a risk factor for anaphylaxis, but they are not diagnostic of anaphylaxis.^{2,8} Sensitization to novel triggers suggested by the history, for which there are no commercially available test antigens, can be identified through development of customized *in vitro* tests.²

Individuals with *Hymenoptera* sting-triggered anaphylaxis should be evaluated by an allergy/immunology specialist, because of the complexities involved in assessment and the high potential for cure when appropriate treatment is instituted.^{17,20-22} Positive intradermal tests to venom and/or elevated venom-specific IgE levels occur in as many as 25% of adults in the general population, most of whom do not develop anaphylaxis after an insect sting. Positive tests therefore do not necessarily predict the risk of, or the severity of, future venom-triggered anaphylaxis episodes, and it is critically important that they be interpreted in the context of the clinical history. Measurement of upregulation of basophil surface activation markers such as CD63 and CD203c after stimulation with venom is used in the clinical evaluation of these individuals in some countries, but remains a research tool in North America.²³ Cross-reacting compounds among venoms (such as hyaluronidases), and cross-reacting carbohydrate derivatives between venom and nonvenom allergens, may account for some positive tests. Clinical risk of anaphylaxis is

increased by factors such as stinging insect species, recent stings leading to mast cell or basophil priming, concurrent disease such as asthma, COPD, or mastocytosis, and concurrent use of medications such as nonselective β -blockers.^{7,24-27}

Food-induced anaphylaxis is commonly triggered by cow's milk, egg, peanut, tree nuts, finned fish, shellfish, wheat, soy, or sesame; however, any food may be implicated, including other seeds, fruits, vegetables, gums, and spices. Selection of foods for skin prick testing or *in vitro* testing should be guided by the history, because sensitization to food occurs in as many as 60% of individuals in the general population, most of whom do not develop anaphylaxis from foods. Intradermal tests to foods are contraindicated. Few commercial food allergens are standardized. Testing with fresh foods is often performed. Identification of food-specific IgE levels with greater than 95% predictive risk values for clinical reactivity (positive challenge) has been an important advance (ImmunoCap; Phadia AB, 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).^{2,28,29}

Individuals with a convincing history of anaphylaxis to a specific food, and evidence of sensitization (positive skin prick test or elevated specific IgE level) to that food, need no further testing. Others might require a physician-monitored incremental oral food challenge, conducted in an appropriately staffed and equipped healthcare facility, in order to predict clinical reactivity. Challenges are time-consuming and not without risk. Additional approaches to distinguishing between sensitization and clinical risk are therefore being developed. Determination of specific IgE-binding epitopes on an allergen such as peanut or milk potentially provides increased ability to determine the risk of, and the severity of, a future reaction. For example, individuals with IgE antibodies binding to stable linear epitopes are more likely to have severe-persistent allergy, whereas those with IgE binding to conformational epitopes dependent on protein folding are more likely to have mild-transient allergy. Other approaches being tested include measurement of the rate of change of the allergen-specific IgE level, the ratio of allergen-specific IgE to total IgE, and upregulation of basophil surface activation markers after stimulation with food antigen.^{2,28,29}

Any medication can trigger anaphylaxis, including those used in the treatment of allergic diseases, omalizumab and other mAbs (rituximab, trastuzumab, alemtuzumab), and chemotherapy drugs (platins, taxenes). For most medications, antigenic determinants have not been characterized or validated; indeed, the relevant immunogens, including haptens, metabolites, and unidentified degradation products, are unknown. If IgE is involved in the pathogenesis—for example, in β -lactam antibiotic-triggered anaphylaxis—skin tests and medication-specific IgE levels are helpful. Tests involving measurement of upregulation of basophil activation marker expression after stimulation with medication are in clinical use in some countries. Physician-monitored challenge tests performed in specialized centers remain the gold standard in assessment.^{2,20,30,31}

MANAGEMENT

When anaphylaxis occurs in a healthcare facility, rapid assessment of airway, breathing, circulation, and orientation is mandatory; in addition, the skin should be examined and body weight

B

ANAPHYLAXIS MANAGEMENT

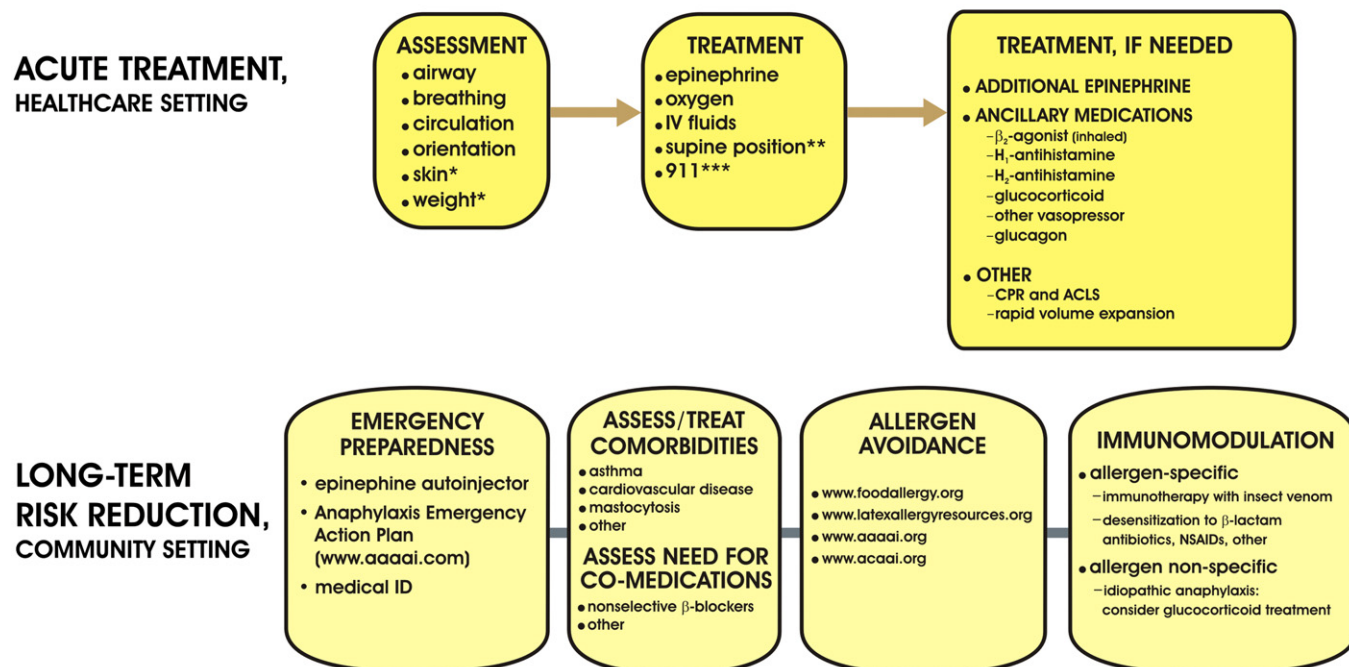


FIG 1B. Summary of anaphylaxis management. Acute treatment is the same regardless of the mechanism or trigger involved in anaphylaxis. In contrast, for long-term risk reduction, avoidance measures and immunomodulation are trigger-specific; currently, immunomodulation is available only for a minority of individuals with anaphylaxis. All at-risk individuals need to have comorbidities and comedications assessed, to be taught the importance of emergency preparedness, and to be instructed in the use of self-injectable epinephrine.

*The skin should be inspected, and weight estimation is important, especially in infants and children, and also in overweight and obese teens and adults, in order to calculate an optimal dose of epinephrine and other medications needed in treatment and resuscitation. **Supine position, as tolerated, to prevent empty ventricle syndrome. ***Call 911/emergency medical services for anaphylaxis occurring in community healthcare facilities such as medical, dental, or infusion clinics, where optimal backup might not be available for resuscitation. *ACLS*, Advanced cardiac life support; *CPR*, cardiopulmonary resuscitation; *CVS*, cardiovascular; *GI*, gastrointestinal; *ID*, identification (eg, bracelet, wallet card); *IV*, intravenous.

(mass) should be estimated. This should be followed by prompt intramuscular injection of epinephrine, administration of supplemental oxygen, establishment of an airway, placing the individual in the supine position, and insertion of 1 or more large-bore intravenous lines for fluid replacement and infusion of epinephrine and additional medications, if needed^{17,20} (Fig 1, B). Pharmacologic interventions in anaphylaxis have changed little during the past 6 decades.

Long-term risk reduction measures include accurate risk assessment, optimal management of comorbidities, and relevant specific preventive treatment such as avoidance of confirmed triggers and/or immunomodulation. At-risk individuals should be equipped with self-injectable epinephrine, a personalized Anaphylaxis Emergency Action Plan, and medical identification¹⁷ (Fig 1, B).

Comorbidities such as vision or hearing impairment, CNS diseases, and use of prescription, nonprescription, and recreational drugs or ethanol potentially impede recognition of anaphylaxis triggers and symptoms. Comorbidities such as asthma,

COPD, ischemic heart disease, and mastocytosis (symptomatic or asymptomatic) potentially affect recognition and treatment, and should be optimally managed. The relative benefits and risks of medications such as nonselective β -blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers that potentially impede the response to treatment should be reviewed^{2,5-7,17,20,25-27} (Fig 1, B).

Written, personalized information about avoidance of the documented trigger (stinging insect, food, medication, or other) should be provided, along with direction to additional up-to-date sources of information (Fig 1, B). Avoidance measures may negatively affect quality of life.¹⁷

In as many as 98% of individuals with anaphylaxis from a *Hymenoptera* sting, an appropriate course of venom immunotherapy dramatically reduces the risk of anaphylaxis from a subsequent sting. Immunotherapy is not indicated in children with mild cutaneous systemic reactions, or in individuals of any age with large local reactions.^{21,22} Agent-specific rapid desensitization provides short-term immunomodulation for individuals at

risk for anaphylaxis from seminal fluid, or from therapeutic agents such as β -lactam antibiotics, fluoroquinolones, vancomycin, acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs, insulin, platins, taxenes, and mAbs.^{20,30,31}

Future directions in allergen-specific immunotherapy might include allergen administration through the sublingual route; "engineered" recombinant proteins; CpG-oligonucleotide conjugated allergens, peptides, or polymers of major allergens; a mixture of major recombinant allergens; and other novel approaches.³² Immunomodulators such as anti-IgE antibody³³ and anti-CD63 antibodies might be helpful, especially for individuals at risk of anaphylaxis from multiple allergens.¹⁷

For prophylaxis of moderate or severe idiopathic anaphylaxis, consideration should be given to prescribing an oral glucocorticoid. Individuals with exercise-triggered anaphylaxis should be advised to avoid exercising alone, and to avoid concurrent triggers such as food, medication, or cold air; if no food cotrigger is identified, they should avoid postprandial exercise entirely.^{17,20,34}

Life-saving long-term risk reduction measures for individuals who have experienced anaphylaxis are summarized in Fig 1, B. A personalized Anaphylaxis Emergency Action Plan (download from www.aaaai.org) should emphasize prompt epinephrine injection followed by transport to the nearest emergency department, because as many as 20% of individuals will experience biphasic or protracted symptoms.^{17,34,35} Medical identification jewelry and wallet cards (available at www.aaaai.org) should list confirmed triggers, relevant comorbidities, and concurrent medications.

Delayed epinephrine injection contributes to fatalities in anaphylaxis.⁵⁻⁷ An initial dose of 0.01 mg/kg intramuscularly achieves high plasma and tissue levels rapidly; however, in many individuals, optimal intramuscular dosing is impossible with currently available epinephrine autoinjectors, either because of their short needle length, or the availability of only 2 premeasured doses (0.15 mg and 0.3 mg).³⁶ Novel epinephrine delivery systems, including a sublingual dosage form, are being developed to address these issues.³⁷ Retrospective studies indicate that 16% to 35% of individuals who inject epinephrine require a second dose. Reluctance to inject epinephrine because of fear of adverse cardiac effects should be tempered by awareness that the heart is a potential target organ in anaphylaxis, and that myocardial ischemia and dysrhythmias can occur even if epinephrine is not given.³⁸ H_1 -antihistamines and inhaled β_2 adrenergic agonists cannot be substituted for epinephrine in anaphylaxis treatment.^{17,34,39,40}

Anaphylaxis education programs and educational materials for at-risk individuals and their caregivers are being developed and validated. Patients with asthma, who may be at increased risk of death from anaphylaxis, have unique educational needs.¹⁷ Anaphylaxis awareness needs to be increased among healthcare professionals, teachers, hospitality/food service industry workers, legislators, and the general public.^{5,6,17,34}

In summary, future progress in risk assessment and risk reduction in anaphylaxis depends on increased understanding of the complex pathogenesis of this potentially fatal disease. Improved laboratory tests are needed to support the clinical diagnosis, and to facilitate accurate risk assessment in allergen-sensitized individuals. Advances in the pharmacologic treatment of anaphylaxis are needed; additional options for administering epinephrine in first-aid treatment are an important step in this direction. Novel allergen-specific and allergen nonspecific immunomodulatory

strategies will eventually be available for long-term risk reduction.

REFERENCES

1. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Brannum A, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391-7.
2. Simons FER, Frew AJ, Ansotegui IJ, Bochner BS, Finkelman F, Golden DBK, et al. Risk assessment in anaphylaxis: current and future approaches. *J Allergy Clin Immunol* 2007;120:S2-24.
3. Lieberman P, Camargo CA Jr, Bohlke K, Jick H, Miller RL, Sheikh A, et al. Epidemiology of anaphylaxis: findings of the American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group. *Ann Allergy Asthma Immunol* 2006;97:596-602.
4. Clark S, Gaeta TJ, Kamarthi GS, Camargo CA. ICD-9-CM coding of emergency department visits for food and insect sting allergy. *Ann Epidemiol* 2006;16:696-700.
5. Bock SA, Munoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001-2006. *J Allergy Clin Immunol* 2007;119:1016-8.
6. Pumphrey RSH, Gowland MH. Further fatal allergic reactions to food in the United Kingdom, 1999-2006. *J Allergy Clin Immunol* 2007;119:1018-9.
7. Greenberger PA, Rotskoff BD, Lifshultz B. Fatal anaphylaxis: postmortem findings and associated comorbid diseases. *Ann Allergy Asthma Immunol* 2007;98:252-7.
8. Prussin C, Metcalfe DD. 5. IgE, mast cells, basophils, and eosinophils. *J Allergy Clin Immunol* 2006;117:S450-6.
9. Galli SJ, Kalesnikoff J, Grimbaldston MA, Piliponsky AM, Williams CMM, Tsai M. Mast cells as "tunable" effector and immunoregulatory cells: recent advances. *Annu Rev Immunol* 2005;23:749-86.
10. Rivera J, Gilfillan AM. Molecular regulation of mast cell activation. *J Allergy Clin Immunol* 2006;117:1214-25.
11. Jensen BM, Metcalfe DD, Gilfillan AM. Targeting kit activation: a potential therapeutic approach in the treatment of allergic inflammation. *Inflamm Allergy Drug Targets* 2007;6:57-62.
12. Yokoi H, Myers A, Matsumoto K, Crocker PR, Saito H, Bochner BS. Alteration and acquisition of Siglecs during in vitro maturation of CD34+ progenitors into human mast cells. *Allergy* 2006;61:769-76.
13. Olivera A, Mizugishi K, Tikhonova A, Ciaccia L, Odom S, Proia RL, et al. The sphingosine kinase-sphingosine-1-phosphate axis is a determinant of mast cell function and anaphylaxis. *Immunity* 2007;26:287-97.
14. Plager DA, Weiss EA, Kephart GM, Mocharlam RM, Matsumoto R, Checkel JL, et al. Identification of basophils by a mAb directed against pro-major basic protein 1. *J Allergy Clin Immunol* 2006;117:626-34.
15. Chang TW, Shiung Yu-Y. Anti-IgE as a mast cell-stabilizing therapeutic agent. *J Allergy Clin Immunol* 2006;117:1203-12.
16. Finkelman FD, Rothenberg ME, Brandt EB, Morris SC, Strait RT. Molecular mechanisms of anaphylaxis: lessons from studies with murine models. *J Allergy Clin Immunol* 2005;115:449-57.
17. Simons FER. Anaphylaxis, killer allergy: long-term management in the community. *J Allergy Clin Immunol* 2006;117:367-77.
18. Schwartz LB. Diagnostic value of tryptase in anaphylaxis and mastocytosis. *Immunol Allergy Clin North Am* 2006;26:451-63.
19. Vadas P, Gold M, Perelman B, Liss G, Lack G, Blyth T, et al. Platelet-activating factor, PAF-acetylhydrolase and severe anaphylaxis. *N Engl J Med* 2008;358:28-35.
20. Joint Task Force on Practice Parameters, American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology, Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of anaphylaxis: an updated practice parameter. *J Allergy Clin Immunol* 2005;115:S483-523.
21. Golden DBK. Insect sting allergy and venom immunotherapy: a model and a mystery. *J Allergy Clin Immunol* 2005;115:439-47.
22. Golden DBK, Kagey-Sobotka A, Norman PS, Hamilton RG, Lichtenstein LM. Outcomes of allergy to insect stings in children, with and without venom immunotherapy. *N Engl J Med* 2004;351:668-74.
23. Klein-Tebbe J, Erdmann S, Knol EF, MacGlashan DW Jr, Poulsen LK, Gibbs BF. Diagnostic tests based on human basophils: potentials, pitfalls and perspectives. *Int Arch Allergy Immunol* 2006;141:79-90.
24. Jappe U, Raulf-Heimsoth M, Hoffmann M, Burrow G, Hubsch-Muller C, Enk A. In vitro Hymenoptera venom allergy diagnosis: improved by screening for

- cross-reactive carbohydrate determinants and reciprocal inhibition. *Allergy* 2006;61:1220-9.
25. Golden DBK, Breisch NL, Hamilton RG, Guralnick MW, Greene A, Craig TJ, et al. Clinical and entomological factors influence the outcome of sting challenge studies. *J Allergy Clin Immunol* 2006;117:670-5.
26. Muller UR, Haeberli G. Use of beta-blockers during immunotherapy for Hymenoptera venom allergy. *J Allergy Clin Immunol* 2005;115:606-10.
27. Stumpf JL, Shehab N, Patel AC. Safety of angiotensin-converting enzyme inhibitors in patients with insect venom allergies. *Ann Pharmacother* 2006;40:699-703.
28. Sicherer SH, Sampson HA. 9. Food allergy. *J Allergy Clin Immunol* 2006;117:S470-5.
29. Sampson HA. Update on food allergy. *J Allergy Clin Immunol* 2004;113:805-19.
30. Greenberger PA. 8. Drug allergy. *J Allergy Clin Immunol* 2006;117:S464-70.
31. Castells M. Desensitization for drug allergy. *Curr Opin Allergy Clin Immunol* 2006;6:476-81.
32. Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy. *J Allergy Clin Immunol* 2007;119:780-91.
33. Leung DYM, Sampson HA, Yunginger JW, Burks AW Jr, Schneider LC, Wortel CH, et al. Effect of anti-IgE therapy in patients with peanut allergy. *N Engl J Med* 2003;348:986-93.
34. Simons FER. Anaphylaxis: evidence-based long-term risk reduction in the community. *Immunol Allergy Clin North Am* 2007;27:231-48.
35. Lieberman P. Biphasic anaphylactic reactions. *Ann Allergy Asthma Immunol* 2005;95:217-26.
36. Simons FER. First-aid treatment of anaphylaxis to food: focus on epinephrine. *J Allergy Clin Immunol* 2004;113:837-44.
37. Rawas-Qalaji MM, Simons FER, Simons KJ. Sublingual epinephrine tablets versus intramuscular injection of epinephrine: dose-equivalence for potential treatment of anaphylaxis. *J Allergy Clin Immunol* 2006;117:398-403.
38. Kounis NG. Kounis syndrome (allergic angina and allergic myocardial infarction): a natural paradigm? *Int J Cardiol* 2006;110:7-14.
39. Sheikh A, ten Broek VM, Brown SGA, Simons FER. H₁-antihistamines for the treatment of anaphylaxis with and without shock. *Cochrane Database Syst Rev* 2007;1:CD006160.
40. Simons FER. Advances in H₁-antihistamines. *N Engl J Med* 2004;351:2203-17.

Anaphylaxis

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Learning objectives: "Anaphylaxis"

1. To describe the pathogenesis of anaphylaxis.
 2. To state the basic principles of diagnosis and risk assessment in anaphylaxis.
 3. To discuss management of acute anaphylaxis and long-term risk reduction in anaphylaxis.
-

CME items

Question 1. Anaphylaxis in human beings commonly occurs through all of the following mechanisms except —

- A. IgE and high-affinity receptors for IgE on mast cells and basophils.
- B. immune aggregates.
- C. autoimmune mechanisms.
- D. delayed hypersensitivity.

Question 2. A serum total tryptase level is measured within 3 hours of onset of anaphylaxis symptoms. Which of the following statements about the result of this test is **not** true?

- A. If elevated, it supports the clinical diagnosis of anaphylaxis.
- B. If within normal limits, it rules out the diagnosis of anaphylaxis.
- C. It is likely to be within normal limits if a food triggered the anaphylaxis episode.
- D. It may or may not correlate with a concurrently measured plasma histamine level.

Question 3. Individuals who are candidates for Hymenoptera venom immunotherapy to prevent future episodes of anaphylaxis to insect stings are identified primarily on the basis of —

- A. a history of a previous sudden acute systemic allergic reaction to an insect sting.
- B. positive intradermal test to Hymenoptera venom.
- C. elevated specific IgE to Hymenoptera venom.
- D. upregulation of basophil surface activation markers (eg, CD63 or CD203c) after Hymenoptera venom stimulation.

Question 4. Which of the following statements does **not** apply to the role of immunomodulation in prevention of subsequent anaphylaxis episodes?

- A. Venom immunotherapy has a long-lasting protective effect in most individuals with Hymenoptera venom-triggered anaphylaxis.
- B. Allergen nonspecific immunotherapy (eg, with omalizumab) is indicated for individuals sensitized to food allergens.
- C. Short-term desensitization is useful for individuals at risk for anaphylaxis from β -lactam antibiotics or nonsteroidal anti-inflammatory drugs.
- D. Oral glucocorticoid treatment should be considered for individuals with moderate to severe idiopathic anaphylaxis.