

31 Prevention and Treatment of Anaphylaxis

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ANAPHYLAXIS AND ALLERGEN IMMUNOTHERAPY

Definitions

Anaphylaxis is not a reportable disease and both its morbidity and mortality are probably underestimated. A variety of statistics on the epidemiology of anaphylaxis are published (Table 1) (1–10). There is no universally accepted clinical definition of anaphylaxis (11,12). The traditional nomenclature for anaphylaxis reserves the term *anaphylactic* for IgE-dependent reactions and the term *anaphylactoid* for IgE-independent events, which are clinically indistinguishable. The World Allergy Organization, which is an international umbrella organization whose members represent 74 national and regional professional societies dedicated to allergy and clinical immunology, recommends the replacement of this terminology with *immunologic* (IgE mediated and non-IgE mediated, e.g., IgG and immune complex complement mediated) and *nonimmunologic* anaphylaxis and the term “anaphylaxis” refers to both (11). Anaphylaxis was defined by the National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network (Chantilly, Virginia, U.S.). It is considered likely to be present if any one of three criteria is satisfied within minutes to hours: (i) acute onset of illness with involvement of skin, mucosal surface, or both, *and* at least one of the following: respiratory compromise, hypotension, or end organ dysfunction; (ii) two or more of the following occur rapidly after exposure to a *likely* allergen: involvement of skin or mucosal surface, respiratory compromise, hypotension, or persistent gastrointestinal symptoms; (iii) hypotension develops after exposure to a *known* allergen for that patient: age-specific low blood pressure or decline of systolic blood pressure of greater than 30% compared to baseline (12). In clinical practice, however, waiting until the development of multiorgan symptoms is risky since the ultimate severity of an anaphylactic reaction is difficult to predict from the outset.

Signs and symptoms of anaphylaxis vary, but cutaneous features (urticaria, angioedema, erythema) are the most common overall (13). Reactions may be immediate and uniphasic, or they may be delayed in onset, biphasic (recurrent), or protracted (discussed below). Respiratory compromise and cardiovascular collapse cause most fatalities (13,14). An analysis of 202 anaphylaxis fatalities occurring in the United Kingdom from 1992 to 2001 ascertained that the interval between initial onset of food anaphylaxis symptoms and fatal cardiopulmonary arrest averaged 25 to 35 minutes, which was longer than for insect stings (10–15 minutes) or for drugs (mean, 5 minutes in hospital; 10–20 minutes prehospital) (14).

Subcutaneous Allergen Immunotherapy and Anaphylaxis

Three studies suggest that fatalities from subcutaneous allergen immunotherapy (SCIT) occur at a rate of approximately 1/2,500,000 injections (8,15,16). However, the physicians in these surveys included only members of the American Academy of Allergy Asthma and Immunology. Therefore, the prevalence of fatalities resulting from SCIT in the hands of physicians who are not specially trained to practice allergy and immunology remains unknown. These three studies evaluated 104 fatalities from immunotherapy and skin testing between 1945 and 2001. Most of the fatalities occurred from reactions that took place within 30 minutes of the injection. Subjects with asthma or with high levels of allergen-specific IgE were more likely to die from anaphylaxis. Subjects who were symptomatic, especially with asthma, at the time of the injection or who were in their “allergy season” were also at increased risk. Some errors in vial selection, especially when advancing to the next vial, and mistakes in dosage or administration also were important in these deaths.

Table 1 Epidemiology of Anaphylaxis

Statistic	Value	Reference
Incidence	30/100,000 person-yr	1
Risk/person in United States	1–3% per person	1, 2
	1.24–16.74%	3
Risk in hospitalized patients	1/2700	4
Hospital fatalities	154/10 ⁶ patients	5
Mortality rate	1%	2
Food anaphylaxis fatalities	150/yr	6
Peanuts or tree nuts	94% fatalities in registry	7
Fatal reactions to β -lactam antibiotics	400–800/yr	4
Fatalities from allergen immunotherapy	1/2,500,000 injections	8
Systemic reactions to Hymenoptera stings	0.4–4%	9
Prevalence of idiopathic anaphylaxis	34,000 subjects	10

Near-fatal reactions (NFRs) to SCIT also have been examined retrospectively. Of 646 survey allergist-immunologist respondents, 273 reported NFR. The investigators defined an NFR as respiratory compromise, hypotension, or both, requiring emergency epinephrine. Hypotension was reported in 80% and respiratory failure occurred in 10% of NFRs, exclusively in asthmatic subjects. Epinephrine was delayed or not administered in 6% of these cases (17).

Lüderitz-Püchel et al. (18) analyzed 28 of 48 SCIT-related fatalities reported to the Paul Ehrlich Institute from Germany and other countries from 1977 to 1994. Three additional subjects experienced hypoxic brain injury following anaphylaxis. In 23 of the 28 fatalities investigated, the authors could not exclude medical errors and/or inadequate information provided to the subjects as contributory factors to fatal anaphylaxis. Errors include mistakes in dosage and administration of allergen vaccines and failure to adhere to the recommended 30-minute period of observation following injection.

Stewart and Lockey (19) reviewed 38 studies for systemic reactions associated with SCIT. The percentage of subjects experiencing one or more systemic reactions ranged from 0.8% to 46.7% for conventional dose schedules (mean 12.92%, SD 10.8%). Systemic reactions per injection during conventional build up schedules occurred in 0.05% to 3.2% of subjects (mean 0.5%, SD 0.87%). All but one study reported rates per injection of 0.6% or less. The 23 studies in which rush or accelerated schedules were used were also reviewed. The percentage of subjects experiencing one or more systemic reactions during the maintenance phase of rush or accelerated SCIT ranged from 0% to 21.1% (mean 4.77%, SD 6.47%). However, the number of systemic reactions was higher during buildup when the interval between injections was reduced ("rush" or "semirush" protocols). Subjects experiencing one or more systemic reaction ranged from 0% to 66.7% with these accelerated schedules (mean 21.33%, SD 17.86%). These accelerated protocols were associated with rates of systemic reactions per injection ranging from 0% to 6.4% (mean 2.36%, SD 1.7%).

MECHANISMS OF ANAPHYLAXIS

Chemical Mediators of Anaphylaxis

The chemical mediators that cause anaphylaxis are preformed and released from granules (histamine, tryptase, glycosidases, and granulocyte chemotactic factors) or are generated from membrane lipids (prostaglandin D₂, leukotrienes, and platelet-activating factor) by the activated mast cell and basophil (13). The development and severity of anaphylaxis also depend on the responsiveness of cells targeted by these mediators. IL-4 and IL-13 are cytokines important in the initial generation of antibody and inflammatory cell responses to anaphylaxis. No comparable studies have been conducted in humans, but anaphylactic effects in the mouse depend on IL-4R α -dependent IL-4/IL-13 activation of the transcription factor, signal transducer and activator of transcription 6 (STAT-6) (20).

Eosinophils may be proinflammatory (e.g., release of cytotoxic granule-associated proteins) or anti-inflammatory (e.g., metabolism of vasoactive mediators) (21,22). A guinea pig anaphylaxis model suggests that eosinophils already present in chronically inflamed airways

may participate in the immediate phase response to allergen exposure as well as the role traditionally expected in the late-phase allergic response (23). Potential implications for human anaphylaxis have not been determined.

Histamine is only one of the mast cell mediators released in anaphylaxis, but its systemic effects have been studied more than other mediators. In one study, investigators infused histamine into normal volunteers at doses ranging from 0.05 to 1.0 $\mu\text{g/kg/min}$ over 30 minutes to determine the plasma levels required to elicit symptoms of anaphylaxis (24). A mean plasma level of 1.61 ± 0.30 ng/mL induced a 30% increase in heart rate; a level of 2.39 ± 0.52 ng/mL induced flushing and headache; and a level of 2.45 ± 0.13 ng/mL induced a 30% increase in pulse pressure. Pretreatment with an H_2 -antagonist (cimetidine) did not alter these reactions. However, pretreatment with the H_1 antagonist, hydroxyzine hydrochloride, increased the level of histamine necessary to increase the heart rate by 30%. Combining the H_1 and H_2 antihistamines significantly raised the level at which histamine elicited all responses. On the basis of these results, the authors concluded that flushing, hypotension, and headache associated with histamine infusion are mediated by both H_1 and H_2 receptors, whereas tachycardia, pruritus, rhinorrhea, and bronchospasm are associated only with H_1 receptors.

H_3 receptors have been implicated in a canine model of anaphylaxis (25). These inhibitory presynaptic receptors modulate endogenous release of norepinephrine from sympathetic fibers that innervate the cardiovascular system. Pretreatment of study animals with thioperamide maleate, an H_3 receptor antagonist, is associated with a higher heart rate and greater left ventricular systolic function compared with a nontreatment group or the other treatment arms involving receptor blockade for H_1 , H_2 , cyclooxygenase, and leukotriene pathways (25). Potential implications for human subjects have not been studied.

Tryptase is concentrated selectively in the secretory granules of human mast cells and released when these cells degranulate. It can activate complement, coagulation pathways, and the kallikrein-kinin contact system with the potential clinical consequences of hypotension, angioedema, clotting, and clot lysis (disseminated intravascular coagulation) (22). Release of β -tryptase (mature tryptase) stored in mast cell secretory granules is more specific for activation than α -protryptase, which is an inactive monomer that is secreted constitutively at rest. Tryptase levels generally correlate with the clinical severity of anaphylaxis (26). However, a dichotomy may exist in the magnitude of tryptase elevations for those individuals experiencing anaphylaxis after parenteral exposure (e.g., injection, insect sting) versus oral exposure (e.g., food ingestion). In an analysis of anaphylaxis fatalities, the parenterally exposed subjects had higher serum levels of tryptase and lower levels of antigen-specific IgE, whereas those who succumbed after oral exposure had low tryptase levels and comparatively higher levels of antigen-specific IgE (27). This difference may be related to the mast cell phenotype first encountered by the culprit antigen. Tryptase- and chymase-containing mast cells (MC_{TC}) are threefold more common in connective tissue than tryptase-containing mast cells (MC_{T}). The latter predominate in the mucosa of the lung and small intestine (27).

Levels of total tryptase peak 60 to 90 minutes after the onset of anaphylaxis and can persist as long as five hours after the onset of symptoms (22). The estimated positive predictive value of tryptase elevations in 259 subjects with anesthesia-associated anaphylaxis is 92.6%, and the estimated negative predictive value of normal tryptase levels is 54.3% (28). Serial tryptase measurements might improve diagnostic sensitivity, but further investigation is needed (12).

Elevations of histamine and tryptase may not correlate clinically. In an emergency department study evaluating subjects who presented with acute allergic reactions, elevated histamine was observed in 42 of 97 subjects, but only 20 exhibited increased tryptase levels (29). Serum histamine levels also correlate with the severity and persistence of cardiopulmonary manifestations, but not with urticaria (29,30).

Nitric oxide (NO), a potent autacoid vasodilator formerly known as endothelium-derived relaxing factor, appears to be involved in the complex interaction of regulatory and counterregulatory mediators in mast cell activation, including anaphylaxis (31,32). L-Arginine is converted to NO as histamine binds to H_1 receptors during phospholipase C-dependent calcium mobilization. Physiologically, NO participates in the homeostatic control of vascular tone and regional blood pressure. Experiments with NO inhibitors in mice, rabbits, and dogs demonstrate that NO promotes bronchodilation, coronary artery vasodilation, and decreases histamine release. However, its net effects in anaphylaxis appear to be detrimental vascular smooth muscle relaxation and enhanced vascular permeability (33).

Metabolites of arachidonic acid include products of lipoxygenase and cyclooxygenase pathways. Of note, leukotriene B₄ is a chemotactic agent and thus can solicit other cells to participate in anaphylaxis. These cells theoretically contribute to biphasic (recurrent) anaphylaxis and to protracted reactions. Other effects of arachidonic acid metabolites may reflect mast cell degranulation, since elevations occur in tryptase and histamine. These effects include bronchospasm, hypotension, and skin erythema (22).

Inflammatory mediators also activate the contact system. These consist of kininogenase, kallikrein, and tryptase. Release of these mediators may induce formation of bradykinin as well as the activation of factor XII. This, in turn, may produce clotting, clot lysis, and subsequent activation of complement. In contrast, some mediators may have a salutary effect that limits anaphylaxis. For example, chymase may activate angiotensin II, which can modulate hypotension. Heparin inhibits clotting, kallikrein, and plasmin, opposes complement formation, and modulates tryptase activity (22).

There are other inflammatory pathways that participate in anaphylactic episodes. These may be extremely important in the prolongation and amplification of anaphylaxis. Much of the supporting evidence derives from data obtained during experimental insect sting challenges. During severe episodes of anaphylaxis, there is concomitant activation of complement, coagulation pathways, and the contact (kallikrein-kinin) system. Decreases in C4 and C3, as well as the formation of C3a, have been observed in anaphylaxis. Demonstrable evidence for coagulation pathway activation during severe anaphylaxis includes decreases in factor V, factor VIII, and fibrinogen, and fatal disseminated intravascular coagulation in some instances (14,30). Of 202 anaphylaxis fatalities analyzed retrospectively over a 10-year period in the United Kingdom, seven (8%) were attributable to disseminated intravascular coagulation (14). Successful treatment with tranexamic acid is reported (34). Contact system recruitment is indicated by decreased high molecular weight kininogen and the formation of kallikrein-C1 inhibitor and factor XIIIa-C1 inhibitor complexes. Kallikrein activation not only results in the formation of bradykinin but also activates factor XII. Factor XII alone can lead to clotting and clot lysis via plasmin formation, and plasmin can also activate complement (22).

Effects on the Cardiovascular System

Anaphylaxis can be associated with myocardial ischemia, conduction defects, atrial and ventricular arrhythmias, and T-wave abnormalities (35). Whether such changes are related to direct mediator effects on the myocardium, exacerbation of preexisting myocardial insufficiency by the hemodynamic stress of anaphylaxis, or from either exogenous or endogenous epinephrine is unclear (30,35-37).

Histamine exerts its pathophysiologic effects during anaphylaxis via both H₁ and H₂ receptors. H₁ receptors mediate coronary artery vasoconstriction and increase vascular permeability, whereas H₂ receptors increase atrial and ventricular inotropy, atrial chronotropy, and coronary artery vasodilation. The interaction of H₁ and H₂ receptor stimulation appears to mediate decreased diastolic pressure and increased pulse pressure (38). Animal studies suggest a possible modulatory role for H₃ receptors (25). Platelet-activating factor (PAF) also decreases coronary blood flow, delays atrioventricular conduction, and has negative inotropic effects on the heart (35).

Raper and Fisher (36) described two previously healthy subjects who developed profound myocardial depression during anaphylaxis. Echocardiography, nuclear imaging, and hemodynamic measurements confirmed the presence of myocardial dysfunction. Intra-aortic balloon counterpulsation supplemented anaphylaxis treatment to provide hemodynamic support. Balloon counterpulsation was required for up to 72 hours because of persistent myocardial depression, even though other clinical signs of anaphylaxis had resolved. Both subjects recovered with no subsequent evidence of myocardial dysfunction. Thus, the heart may be a primary target for anaphylaxis, even in subjects with no preexisting cardiovascular disease.

Increased vascular permeability during anaphylaxis can shift up to 35% of intravascular volume to the extravascular space within 10 minutes (39). Intrinsic compensatory responses to anaphylaxis, e.g., endogenous catecholamines, angiotensin II, and endothelins, also influence the extent of clinical manifestations and, when adequate, may be lifesaving independent of medical intervention. These compensatory responses, however, produce variable effects on peripheral vascular resistance. Some subjects experience abnormal elevation of the peripheral

vascular resistance (maximal vasoconstriction), yet shock persists due to reduced intravascular volume, while others have decreased systemic vascular resistance despite elevated levels of catecholamines (13). These differences have important clinical implications since the latter scenario may respond favorably to therapeutic doses of vasoconstrictor agents, while the former is vasoconstrictor unresponsive and requires large-volume fluid resuscitation.

In a retrospective review of prehospital anaphylactic fatalities in the United Kingdom, the postural history was known for ten individuals (40). Four of the ten fatalities were associated with the assumption of an upright or sitting posture. Postmortem findings were consistent with pulseless electrical activity (PEA) and an "empty heart" attributed to reduced venous return from vasodilation and concomitant volume redistribution.

Since IgE attached to mast cells can trigger mast cell degranulation and mast cells accumulate at sites of coronary atherosclerotic plaques, some investigators suggest that anaphylaxis promotes plaque rupture, thus risking myocardial ischemia (41,42). Stimulation of the H₁ histamine receptor may also produce coronary artery vasospasm (42-44). Calcitonin gene-related peptide (CGRP) released during anaphylaxis may help to counteract coronary artery vasoconstriction during anaphylaxis (45,46). CGRP, a sensory neurotransmitter widely distributed in cardiovascular tissues, relaxes vascular smooth muscle and has cardioprotective effects in animal models of anaphylaxis (47).

While tachycardia is the rule, bradycardia may occur during anaphylaxis, so bradycardia may not be as useful to separate anaphylaxis from a vasodepressor reaction as previously thought. Relative bradycardia, initial tachycardia followed by a reduction in heart rate despite worsening hypotension, is reported in experimentally induced insect sting anaphylaxis (30,48,49).

Two distinct phases of physiologic response occur in mammals subjected to hypovolemia. The initial response is a baroreceptor-mediated sympathoexcitatory phase comprised of an overall increase in cardiac sympathetic drive and concomitant withdrawal of resting vagal drive, which together produce tachycardia and peripheral vasoconstriction (50). When the effective blood volume falls by 20% to 30%, a second phase follows characterized by withdrawal of the vasoconstrictor drive, relative or absolute bradycardia, increased vasopressin, further catecholamine release as the adrenal axis becomes more active, and hypotension (50,51). Hypotension in this hypovolemic scenario is independent of the bradycardia since it persists after atropine reverses bradycardia.

Conduction defects and sympatholytic medications may also produce bradycardia (13). Excessive venous pooling with decreased venous return, also present in vasodepressor reactions, may activate tension-sensitive sensory receptors in the inferoposterior portions of the left ventricle, resulting in a cardioinhibitory (Bezold-Jarisch) reflex that stimulates the vagus nerve and causes bradycardia (22).

Hemodynamic collapse may occur immediately with no cutaneous or respiratory symptoms (52,53). Of 27 subjects with anaphylaxis in Scandinavia who received prehospital treatment, there were two fatalities, 23 hospitalizations, and two subjects were discharged home after emergency department evaluation. Of subjects with cardiovascular collapse and/or respiratory failure, 70% had cutaneous symptoms, whereas 30% had gastrointestinal manifestations and 85% neurologic deficits (52).

AGENTS OF ANAPHYLAXIS

No evaluation can conclusively prove causation of anaphylaxis without directly challenging the subject with the suspected agent. Direct challenge is generally contraindicated due to safety concerns in subjects who have experienced potentially life-threatening anaphylaxis. Cause and effect may often be demonstrated historically in subjects who experience recurrent, objective findings of anaphylaxis on inadvertent reexposure to the offending agent. Specific diagnostic testing, where appropriate, may confirm the presence of specific IgE and/or the degranulation of mast cells and basophils.

Virtually any agent capable of activating mast cells or basophils may potentially precipitate anaphylaxis. Table 2 lists common causes of anaphylaxis classified by pathophysiologic mechanism. Idiopathic anaphylaxis may be one of the most common since this diagnosis accounts for approximately one-third of cases in most retrospective studies of

Table 2 Representative Agents That Cause Anaphylaxis

IgE dependent
Foods
Medications
Insect venoms
IgE independent
Nonspecific degranulation of mast cells and basophils
Opioids
Muscle relaxants
Idiopathic
Exercise
Cold, heat
Disturbance of arachidonic acid metabolism
Nonsteroidal anti-inflammatory drugs
Complement activation/activation of contact system
Radiocontrast media
ACE inhibitors
Protamine (possibly)

Source: Modified from Ref. 13.

anaphylaxis (1,22,54). Of 601 subjects evaluated over two decades in a university-affiliated practice, 356 (59%) were thought to have idiopathic anaphylaxis (55). This series excluded anaphylaxis due to SCIT and insect stings. Idiopathic anaphylaxis remains a diagnosis of exclusion.

The most common identifiable causes of anaphylaxis are foods, medications, insect stings, and allergen immunotherapy injections (Figs. 1 and 2) (1,19,22,54). Anaphylaxis to peanuts and/or tree nuts causes the greatest concern because of its life-threatening severity, especially in subjects with asthma, and the propensity for lifelong allergic sensitivity to these foods. Of added importance, investigators report that the majority (52%) of peanut-allergic children experience life-threatening symptoms with subsequent reactions, even if atopic dermatitis previously is the only adverse clinical manifestation (56). A quantitative radioallergosorbent test (RAST) for food-specific IgE can be diagnostic. For example, subjects with peanut-specific IgE levels of at least 15 kU/L as measured by one reference laboratory have at least a 95% chance of allergic manifestations, possibly anaphylaxis, if they eat peanuts (57). Thus, a diagnostic food challenge is not indicated in such individuals and might be hazardous.

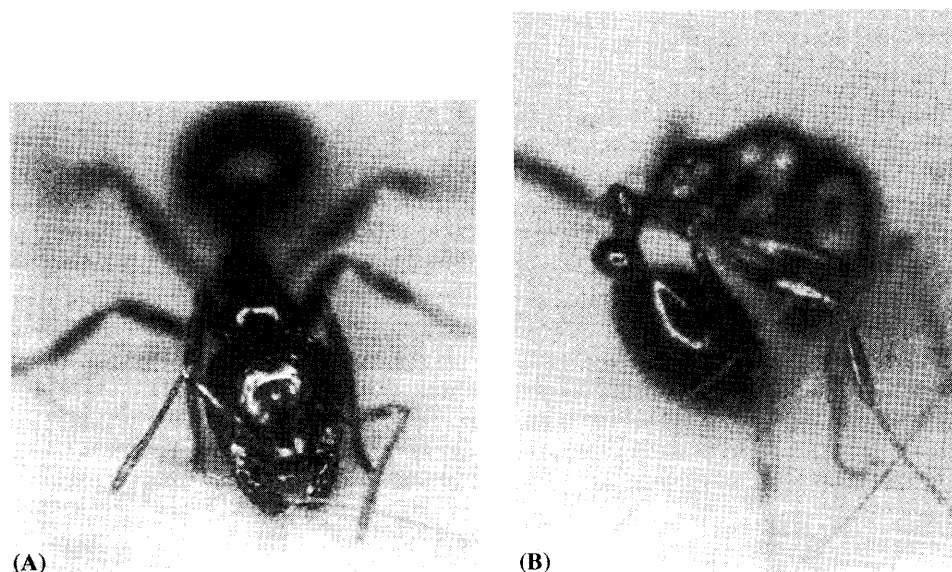


Figure 1 Imported fire ant attaches itself with its mandibles (A) and then stings about this anchor point in a circular pattern (B).

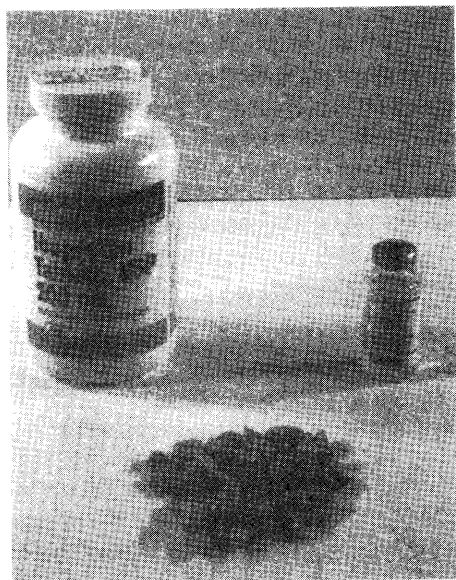


Figure 2 Nonsteroidal anti-inflammatory drugs, penicillin, and peanuts are examples of agents that cause anaphylaxis.

MANIFESTATIONS AND DIFFERENTIAL DIAGNOSIS

Clinical Manifestations of Anaphylaxis

The broad spectrum of possible clinical presentations may complicate the diagnosis of anaphylaxis. Special attention should be directed toward assessment of both upper and lower airways, respiratory and pulse rates, blood pressure, tissue perfusion, and appearance of the skin. Measurement of peak expiratory flow rate and pulse oximetry may also be useful, where appropriate.

Anaphylaxis is associated with the following signs and symptoms, alone or in combination: diffuse erythema, pruritus, and urticaria; angioedema; bronchospasm; laryngeal edema; hyperperistalsis; uterine cramps; hypotension; or cardiac arrhythmias. Urticaria and angioedema are the most common manifestations (55,58,59). Anaphylaxis, however, occurs as part of a clinical continuum. It can begin with relatively minor symptoms such as itchy palms, eyes, nose, or skin and rapidly progress to a life-threatening respiratory and cardiovascular reaction. Cutaneous findings may be delayed or absent in rapidly progressive anaphylaxis. The next most common manifestations of anaphylaxis are respiratory symptoms, followed by dizziness, syncope, and gastrointestinal symptoms. The more rapid anaphylaxis occurs after exposure to an offending stimulus, the more likely the reaction is to be severe and potentially life-threatening (15,60).

Differential Diagnosis for Anaphylaxis

Several systemic disorders share clinical features with anaphylaxis, with the vasodepressor (vasovagal) reaction probably the condition most commonly confused with anaphylaxis. In vasodepressor reactions, however, urticaria is absent, the heart rate is typically bradycardic, bronchospasm or dyspnea is usually absent, the blood pressure may be normal or depressed, and the skin is usually cool and pale. Tachycardia is the rule in anaphylaxis, but it may be absent in subjects with hypovolemia (after initial tachycardia), conduction defects, increased vagal tone due to a cardioinhibitory (Bezold-Jarisch) reflex, or in those who take sympatholytic medications. Myocardial dysfunction may cause sudden hemodynamic collapse with or without an arrhythmia. A pulmonary embolism may produce tachycardia, dyspnea, tachypnea, and chest discomfort that can be pleuritic. Systemic mastocytosis, a disease characterized by mast cell proliferation in multiple organs, usually features urticaria pigmentosa (brownish macules that transform into wheals on stroking) and recurrent episodes of pruritus, flushing, tachycardia, abdominal pain, diarrhea, syncope, or headache. Pancreatic polypeptide syndromes may produce flushing and diarrhea. Other diagnostic considerations for children, in particular, include foreign body aspiration, acute poisoning, and a seizure disorder.

Signs and symptoms frequently observed in anaphylaxis may occur by themselves in other disorders. Subjects with hereditary angioedema, for example, experience episodes of nonpruritic, typically painless edema of the extremities with or without laryngeal edema and abdominal discomfort due to visceral involvement. Factitious anaphylaxis is characterized by repeated, self-induced episodes of anaphylaxis. Anaphylaxis alternatively may be surreptitiously inflicted upon a susceptible subject, an example of Munchausen syndrome by proxy. Undifferentiated somatoform idiopathic anaphylaxis likewise is a psychiatric disorder in which subjects report symptoms identical to those encountered in idiopathic anaphylaxis, but objective findings are absent, and the subjects meet established diagnostic criteria for this disorder (61).

VARIATIONS ON THE THEME

Exercise-Induced Anaphylaxis

Anaphylaxis associated with exercise occurs as two syndromes of physical allergy: exercise-induced anaphylaxis (EIA) and cholinergic urticaria (58). EIA occurs with prolonged strenuous exercise, frequently in conditioned athletes, such as marathon runners, and is usually accompanied by a short prodrome of cutaneous warmth and generalized pruritus. It may occur only after ingestion of certain foods, such as lettuce or celery, or a medication, such as aspirin, prior to exercise. Clinical manifestations may progress to generalized erythema and urticaria, nausea and diarrhea, upper or lower airway obstruction, hypotension, and possibly syncope as exercise continues (58). Prophylaxis with antihistamines, a corticosteroid, or cromolyn sodium does not consistently prevent EIA. Episodes occur sporadically, which distinguishes EIA from other forms of physical urticaria in which exercise provocation invariably produces symptoms (58). Some individuals may demonstrate symptoms during a controlled exercise challenge but the test is often negative, despite a classic clinical history (58). Subjects with EIA should be taught how to administer epinephrine and preferably should exercise with a partner educated about EIA and how to treat it.

Exercise avoidance remains the best treatment since the natural history of the syndrome is not fully understood. Shadick et al. (62) surveyed 365 subjects with EIA over an average of 10.6 years (62). Of survey respondents, 47% had fewer episodes and 46% had stabilized since diagnosis. Forty-one percent reported no episodes in the year preceding the survey. Successful respondents apparently had moderated their exercise programs and avoided provocative factors (62).

Cholinergic Urticaria

Cholinergic urticaria, also called "heat urticaria," is caused by increased core body temperature due to fever, stress, environmental factors, or exercise. Skin lesions frequently appear as 2- to 4-mm pruritic wheals ("microhives") surrounded by marked erythema. Systemic manifestations, similar to those described for EIA, may also occur but are unusual. Subjects with this syndrome might develop wheals at the site where methacholine is injected or generalized urticaria when the body is warmed, as with a plastic occlusive suit (58).

Idiopathic Anaphylaxis

Idiopathic anaphylaxis is a syndrome of repeated anaphylactic episodes for which no cause can be determined (63). It may occur in children as well as adults (59,61) and fatalities are rare (61). Within one year, almost all subjects enter a period of prolonged remission or have infrequent and less severe episodes (59). Failure to respond to prednisone should prompt consideration of another diagnosis (59). (See sect. on "Special Management Problems" for management of idiopathic anaphylaxis.)

Serial histories and diagnostic tests for foods, spices, and vegetable gums have occasionally identified the culprit agent in subjects previously presumed to have idiopathic anaphylaxis (22). The usefulness of prick skin testing for reactions to food allergens was tested in 102 subjects presumed to have idiopathic anaphylaxis (64). One-third had positive tests to one or more foods from a battery of 79 food allergens. Five subjects experienced anaphylaxis after eating a food implicated by a positive skin test. Two subjects stopped having reactions after they eliminated the implicated food from their diet, but they refused subsequent

confirmatory oral food challenge. The 10 allergens that provoked anaphylaxis in these seven subjects were aniseed, cashew, celery, flaxseed, hops, mustard, mushroom, shrimp, sunflower, and walnut. The authors conclude that skin testing with selected foods may be useful to identify food allergens that cause anaphylaxis, since 7% of subjects in the reference group previously presumed to have idiopathic anaphylaxis had food-induced anaphylaxis.

Anaphylaxis Attributed to Endogenous Progesterone

A syndrome of recurrent anaphylaxis apparently triggered or exacerbated by progesterone has been described in five female subjects (65,66). Four of these subjects reported attacks that exacerbated during pregnancy, lessened during lactation, and increased when lactation ceased. Three of the five subjects experienced remission when treated with a luteinizing hormone-releasing hormone (LHRH) analogue, which apparently antagonized LHRH and inhibited progesterone. Immediate skin test reactions to intradermal injection of 40 to 2000 μ g of medroxyprogesterone were present in responders to LHRH analogue therapy. Systemic reactions characterized by urticaria and hypotension developed in two subjects after 100 μ g of LHRH was administered intravenously during the luteal phase of their menstrual cycles. The authors postulated that progesterone, in some undefined way, facilitates mast cell mediator release. The three subjects whose anaphylactic symptoms were dramatically reduced by LHRH analogue therapy subsequently underwent oophorectomy with long-lasting reduction in their symptoms. One subject, however, continued to require combined H₁ and H₂ antihistamine therapy to control attacks.

Recurrent and Persistent Anaphylaxis

The reported incidence of biphasic (recurrent) anaphylaxis varies from less than 1% to a maximum of 23%. Additionally, the reported time of onset of the late phase may vary from 1 to 72 hours. Potential risk factors include severity of the initial phase, delayed or suboptimal doses of epinephrine during initial treatment, laryngeal edema or hypotension during the initial phase, delayed symptomatic onset after antigen exposure (often a food or insect sting), or prior history of biphasic anaphylaxis. It is unclear whether systemic corticosteroids administered in the initial phase can prevent or lessen late-phase reactions (67,68).

Persistent anaphylaxis, anaphylaxis which may last from 5 to 32 hours, occurred in 7 of 25 subjects (28%) in the Stark and Sullivan (69) report with two fatalities. Of 13 subjects analyzed in a report on fatal or near-fatal anaphylaxis to foods, 3 (23%) similarly experienced persistent anaphylaxis (70). Retrospective data from other investigators, however, suggest that persistent anaphylaxis is uncommon.

Neither biphasic nor persistent anaphylaxis can be predicted from the severity of the initial phase of an anaphylactic reaction since they have occurred after what were perceived initially to be mild episodes. Since life-threatening manifestations of anaphylaxis may recur, it may be necessary to monitor selected subjects up to 24 hours after their apparent recovery from the initial phase.

MANAGEMENT OF ANAPHYLAXIS

General

Practice parameters (71) and consensus emergency management guidelines (72,73) concerning anaphylaxis and its management are available. However, physicians and other healthcare professionals may not follow them. In a standardized clinical anaphylaxis scenario, as defined by U.K. Resuscitation Council guidelines, 5% of senior house officers would use the proper dose and/or route of administration for epinephrine as outlined in the published guidelines (74). Other reports examining treatment patterns for anaphylaxis in the emergency departments of civilian (75) and military hospitals (76) indicate that epinephrine is administered during anaphylaxis to 16% and 50% of patients, respectively, according to consensus guidelines.

Clinicians who perform procedures and administer medications should have the appropriate medications and equipment available to treat anaphylaxis. The following equipment and supplies are recommended (71,77,78): (i) stethoscope and sphygmomanometer, (ii) tourniquets, tuberculin syringes, and large-bore needles (e.g., 14-gauge needles),

Table 3 Management of Acute Anaphylaxis

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|------|--|
| I. | Immediate intervention |
| a. | Assessment of airway, breathing, circulation, and adequacy of mentation |
| b. | Administer epinephrine <i>intramuscularly</i> every 5–15 min, in appropriate doses, as necessary, depending on the presenting signs and symptoms of anaphylaxis, to control signs and symptoms and prevent progression to more severe symptoms such as respiratory distress, hypotension, shock, and unconsciousness |
| c. | Place patient in recumbent position and elevate lower extremities |
| II. | Possibly appropriate subsequent measures depending on response to epinephrine |
| a. | Establish and maintain airway |
| b. | Administer oxygen |
| c. | Establish venous access |
| d. | Normal saline IV for fluid replacement |
| III. | Specific measures to consider after epinephrine injections, where appropriate |
| a. | Consider epinephrine infusion |
| b. | Consider H ₁ and H ₂ antihistamines |
| c. | Consider nebulized β_2 agonist (e.g., albuterol) for bronchospasm resistant to epinephrine |
| d. | Consider systemic corticosteroids |
| e. | Consider vasopressor (e.g., dopamine) |
| f. | Consider glucagon for patient taking β -blocker |
| g. | Consider atropine for symptomatic bradycardia |
| h. | Consider transportation to an emergency department or an intensive care facility |
| i. | For cardiopulmonary arrest during anaphylaxis, high-dose epinephrine and prolonged resuscitation efforts are encouraged, if necessary. (See reference for specific details.) |
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Source: Adapted from Ref. 71.

(iii) injectable aqueous epinephrine 1:1000, (iv) equipment for administering oxygen, (v) oral airway, (vi) equipment for administering intravenous fluids, (vii) injectable H₁ and H₂ antihistamines (e.g., diphenhydramine and ranitidine), (viii) corticosteroids for intravenous injection, and (ix) a vasopressor (e.g., dopamine). Depending on the clinical setting, glucagon, an automated electronic defibrillator (AED), and a one-way valve face mask with an oxygen inlet port [e.g., Pocket-Mask[®] (Laerdal Medical Corporation, Gatesville, Texas, U.S.) or similar device] might be desirable. The emergency kit should be up-to-date and complete. Everyone directly involved in patient care should be able to locate necessary supplies, rapidly assemble fluids for intravenous administration, and be aware of treatment guidelines for anaphylaxis.

A sequential approach to management is outlined in Table 3. The judicious use of epinephrine, maintenance of adequate oxygenation, and maintaining an effective circulatory volume are the most important considerations. Assessment and maintenance of airway, breathing, circulation, and mentation are essential initial management steps. Altered mentation may reflect underlying hypoxia. Measurement of pulse oximetry and peak expiratory flow rate, where appropriate, may be useful to guide therapy. Patients should be monitored continuously to facilitate prompt detection of new clinical findings or treatment complications. A patient should be transferred to an emergency facility depending on the clinical severity of the reaction, response to treatment, and the likelihood that other complications will occur.

Anaphylactic shock, a form of distributive shock, may shift significant fluid volume from the central to the peripheral vascular compartment, potentially resulting in inadequate venous return to the heart (39,40). Thus, the recumbent position is strongly recommended, essential in the hypotensive subject, and provides autotransfusion (or preservation) of approximately 1 to 2 L of fluid into the central vascular compartment (79).

Systemic absorption of an agent must be minimized by stopping intravenous infusion of offending medications or other biologic agents. Severe laryngeal edema may develop within 30 to 180 minutes (72). Therefore, an endotracheal tube should be inserted as soon as possible if laryngeal edema does not promptly reverse following parenteral administration of

epinephrine. H_1 and H_2 antagonists, a corticosteroid, and volume expanders can be infused once intravenous access is established.

Epinephrine

How to Use Epinephrine

Epinephrine is the treatment of choice for anaphylaxis (12,71-73,80,81). It should be given as soon as any signs or symptoms of anaphylaxis appear. Data are limited concerning the frequency with which two or more doses (reports range from 16-36%) of epinephrine are utilized to treat anaphylaxis (82-84). Fatalities from anaphylaxis can result from delayed administration or inadequate doses of epinephrine and from severe respiratory and/or cardiovascular complications (14,71). Even with ideal treatment, patients still die from anaphylaxis (7,14,70,85-87). It is important to note that *there are no absolute contraindications for epinephrine administration to treat anaphylaxis* (71). All subsequent therapeutic interventions depend on the initial response to this medication and toxicity from or inadequate response to epinephrine indicates that additional therapeutic modalities are necessary (71).

Intramuscular epinephrine every 5 to 15 minutes, or as often as necessary, should be given to control symptoms and sustain blood pressure (71-73). Comparisons of intramuscular to subcutaneous injections have not been done during anaphylaxis. However, absorption is complete and more rapid and plasma levels higher in asymptomatic adults and children given epinephrine intramuscularly in the anterolateral thigh (88,89). Obesity or other conditions that accentuate the subcutaneous fat pad may prevent or complicate intramuscular access (90).

The pharmacology of epinephrine is reviewed in detail by Westfall and Westfall (91). The α -adrenergic, vasoconstrictive effects at recommended dosages given intramuscularly reverse peripheral vasodilation and alleviate hypotension and reduce generalized cutaneous erythema and urticaria as well as angioedema. Local injection of epinephrine may reduce further absorption of antigen from a sting or injection site, but this has not been studied systematically. The β -adrenergic properties of epinephrine cause bronchodilation, increase myocardial output and contractility, and suppress further mediator release from mast cells and basophils (81,92). Epinephrine, administered in low concentrations (e.g., 0.1 $\mu\text{g}/\text{kg}$), can paradoxically produce vasodilation, hypotension, and increase the release of inflammatory mediators (91,93).

Epinephrine administration enhances coronary blood flow. Two mechanisms are probably responsible: an increased duration of myocardial diastole compared to systole and a vasodilator effect due to increased contractility. These actions usually offset the vasoconstrictor effects of epinephrine on the coronary arteries (91,94).

Common pharmacologic effects of epinephrine that occur at recommended doses via any route of administration include agitation, anxiety, tremulousness, headache, dizziness, pallor, or palpitations (91). Rarely, and usually associated with excessive doses, epinephrine administration might contribute to or cause myocardial ischemia or infarction (95-100), pulmonary edema (101,102), prolonged QTc interval (103), ventricular arrhythmias, accelerated or malignant states of hypertension, and intracranial hemorrhage in adults and children alike (92,104). Nonetheless, some patients have survived massive doses of epinephrine with no evidence of myocardial ischemia or residual complications (105,106).

Intravenous Epinephrine

Because of the risk for potentially lethal arrhythmias, epinephrine 1:10,000 or 1:100,000 vol/vol can be administered intravenously when treatment for anaphylaxis is failing, during cardiac arrest, or to unresponsive or hypotensive patients who fail to respond to intravenous volume replacement and multiple IM doses of epinephrine (71). One group of investigators suggests that the early use of intravenous epinephrine is safe, effective, and well tolerated when the rate of administration is titrated to the clinical response, but this has not been evaluated systematically by a cohort study comparing this modality to epinephrine injections (49). Continuous hemodynamic monitoring is essential.

High-dose intravenous epinephrine, i.e., the rapid progression to a high dose, should be used for subjects in cardiopulmonary arrest. Administer 1 to 3 mg (1:10,000 vol/vol dilution) IV slowly over three minutes, 3 to 5 mg IV over three minutes, and then 4 to 10 $\mu\text{g}/\text{min}$ infusion is recommended (72). The recommended initial resuscitation dosage in children is

0.01 mg/kg (0.1 mL/kg of a 1:10,000 vol/vol solution), repeated every three to five minutes. Higher subsequent dosages (0.1–0.2 mg/kg; 0.1 mL/kg of a 1:1,000 vol/vol solution) may be considered for asystole or PEA. These arrhythmias are often observed during cardiopulmonary arrest that occurs in anaphylaxis. Administration of atropine in accordance with asystole/PEA algorithms may also be appropriate. Additionally, prolonged resuscitation efforts are encouraged, as necessary, since efforts are more likely to be successful in anaphylaxis, where the subject is often young with a healthy cardiovascular system (72).

No Evidence Supports Epinephrine Administration by Other Routes

No data support the use of epinephrine in anaphylaxis by a nonparenteral route. However, alternative routes of administration have been anecdotally successful. These include, for example, inhaled epinephrine in the presence of laryngeal edema or sublingual injection if an intravenous route cannot be obtained. Intraosseous (IO) administration at doses equivalent to intravenous dosing have been recommended when intravenous access is not available and in instances where the clinician has received training and has maintained proficiency in the technique. IO cannulation provides access to a noncollapsible venous plexus, which is attainable in all age groups and several studies have documented its safety and efficacy (107). Access often can be obtained in 30 to 60 seconds. Any drug or fluid that is administered IV can be given IO. The technique requires a rigid needle, preferably a specially designed IO or bone marrow needle from an IO access kit (108). Endotracheally administered dosages of epinephrine previously proposed for use when intravenous access is not available in intubated patients experiencing cardiac arrest are no longer recommended. Furthermore, recent animal studies suggest that the lower drug concentrations achieved when epinephrine is administered endotracheally may produce transient, detrimental β -adrenergic effects, such as hypotension and impaired coronary artery perfusion (107).

How to Use Ancillary Medications

H₁ and H₂ Antihistamines

The standard treatment of anaphylaxis should usually include H₁ antihistamines and corticosteroids. However, antihistamines have a much slower onset of action than epinephrine, they exert minimal effect on blood pressure, and they should not be administered as treatment alone (71). Even at maximum dosages, the antihistamines cannot abort anaphylaxis if histamine already occupies its receptor. They do, however, attenuate cutaneous symptoms, such as urticaria or generalized pruritus, and they may prevent recurrence. Diphenhydramine, 25 to 50 mg for adults and 12.5 to 25 mg for children, may be administered intravenously once the cardiovascular and respiratory conditions are stabilized by epinephrine and/or fluids. Intravenous administration ensures effective dosing will not be impaired by hemodynamic compromise, which adversely affects gastrointestinal or intramuscular absorption, but maximal effect may not be observed for one hour (109). However, oral or intramuscular administration of antihistamines may suffice for milder anaphylaxis.

The role for H₂ antihistamines, such as cimetidine and ranitidine, is more controversial (22). H₂ receptors mediate coronary vasodilation and some case reports suggest that intravenously administered H₂ antagonists may help to relieve persistent hypotension during anaphylaxis. Because cimetidine may inhibit the metabolism of β -adrenergic antagonists in vitro and theophylline metabolism in vivo, ranitidine 50 mg (1 mg/kg) in adults and 12.5 to 50 mg in children, infused over 10 to 15 minutes, is recommended (71). When bolus intravenous administration is desired, ranitidine may be diluted in 5% dextrose to a total volume of 20 mL and injected over five minutes. Cimetidine, 4 mg/kg in adults, should be administered slowly since rapid intravenous administration may produce hypotension (71). There are no established dosages for cimetidine in children with anaphylaxis. Since H₂ blockade without concomitant H₁ blockade could increase available histamine and H₁ receptor stimulation, H₂ antagonists should not be administered prior to H₁ antagonists. As above, oral administration of H₂ antihistamines may suffice for milder anaphylaxis.

Corticosteroids

Systemic corticosteroids may not produce appreciable effects for several hours, but they may prevent persistent or biphasic reactions. Subjects with asthma or other conditions recently

treated with a corticosteroid may be at increased risk for severe or fatal anaphylaxis and may receive additional benefit if corticosteroids are administered to them during anaphylaxis. We recommend corticosteroid treatment for all subjects with anaphylaxis. Corticosteroids should be given intravenously early in the treatment of anaphylaxis at a dosage equivalent to 1.0 mg/kg of methylprednisolone every six hours. Oral administration of prednisone, 0.5 mg/kg, may suffice for milder attacks.

Oxygen and β_2 Agonists

Oxygen should be administered and pulse oximetry monitored during anaphylaxis for those who require multiple doses of epinephrine, have protracted anaphylaxis, or have preexisting hypoxemia or myocardial dysfunction. Inhaled β_2 agonists, e.g., albuterol 0.5 mL or 2.5 mg of a 5% solution, may be administered for bronchospasm refractory to epinephrine.

Persistent Hypotension—Appropriate Roles of Volume Replacement and Glucagon

Usual doses of epinephrine administered during anaphylaxis to subjects taking β -adrenergic antagonists may not produce the desired clinical response and may instead cause predominantly α -adrenergic effects. In such situations, isotonic volume expansion, in some circumstances, up to 7 L of crystalloid, is necessary and glucagon administration is recommended (22,110). Glucagon directly activates adenylyl cyclase and completely bypasses the β -adrenergic receptor and therefore may reverse refractory hypotension and bronchospasm associated with anaphylaxis (110). The recommended dosage for glucagon is 1 to 5 mg [20–30 μ g/kg (maximum 1 mg) in children] administered intravenously over five minutes and followed by an infusion, 5 to 15 μ g/min, titrated to clinical response. Protection of the airway is particularly important in severely drowsy or obtunded subjects since glucagon can cause emesis with the attendant risk for aspiration.

Some investigators report elevated endogenous levels of norepinephrine, epinephrine, and angiotensin II in individuals who experience hypotension during insect sting-induced anaphylaxis (48). This may explain why more epinephrine fails to help some subjects with anaphylaxis. The subject whose hypotension persists despite epinephrine should receive intravenous crystalloid solutions and volume expanders, such as hydroxyethyl starch (Hespan[®]). Large volumes are often required. A volume of 1 to 2 L of normal saline is administered to adults at a rate of 5 to 10 mL/kg in the first five minutes. Children should receive up to 30 mL/kg in the first hour. Adults receiving colloid solution should receive 500 mL rapidly followed by slow infusion (22).

Clinicians who are adequately trained and proficient at obtaining IO access for either adults or children may consider it if attempts at IV access are unsuccessful. IO cannulation provides access to a noncollapsible venous plexus, which is attainable in all age groups, and several studies have documented its safety and efficacy. Fluids administered IO for volume replacement should be infused under pressure using an infusion pump, pressure bag, or manual pressure to overcome venous resistance (107). Less than 1% of patients have complications after an IO infusion (111).

Many sites may be used for IO infusions. For young children, the proximal tibia just distal to the growth plate is most commonly used. For older children and adults, appropriate IO insertion sites include the medial or lateral malleolus, the distal tibia just proximal to the medial malleolus, the distal femur, the anterior-superior iliac spine, the distal radius or ulna, and the sternum (111).

Vasopressors, such as dopamine, should be given if epinephrine $\pm$ antihistamines and volume expansion fail to alleviate hypotension. Dopamine, 400 mg in 500 mL of 5% dextrose, should be administered at 2 to 20 μ g/kg/min and titrated to maintain systolic blood pressure. Central venous access is helpful to facilitate administration of fluids and to continue to assess intravascular volume status. As mentioned above, oxygen should be administered to subjects with protracted anaphylaxis since subjects with prolonged hypoxemia and/or hypotension may experience myocardial dysfunction, possibly resulting in refractory hypotension and/or end-organ damage. A critical care specialist may need to be consulted for a subject with intractable hypotension.

SPECIAL MANAGEMENT PROBLEMS

Management of Persistent Airway Obstruction

Persistent Upper Airway Obstruction

Severe laryngeal edema may occur so quickly during anaphylaxis that endotracheal intubation becomes impossible. Therefore, an endotracheal tube should be quickly inserted if laryngeal edema is not reversed promptly with epinephrine. An endotracheal tube measuring at least 7.5 mm in diameter is preferred in adults since larger sizes reduce resistance to air flow. Aerosolized epinephrine, along with supplemental oxygen and extension of the neck, may be helpful for difficult endotracheal intubation. If intubation fails, a cricothyrotomy is next since it is more easily accomplished than is an emergency tracheostomy. To do so, the subject's neck is hyperextended, and the area of the cricothyroid membrane is palpated below the thyroid cartilage and above the cricoid cartilage. A small incision is made, the membrane is punctured, and the opening is enlarged with a blunt instrument such as a scalpel handle. Finally, a small-diameter (4-5 mm) endotracheal tube is inserted. Alternatively, high-flow oxygen delivery through an 11-gauge needle or polyethylene catheter may suffice for the short term if an endotracheal tube is not available. Potential complications of cricothyrotomy include vocal cord injury, bleeding, and subcutaneous emphysema (72).

Persistent Lower Airway Obstruction

Epinephrine reduces bronchospasm associated with anaphylaxis, but ventilation and oxygenation may remain a problem despite an adequate airway. This persistent airway obstruction should be treated as is status asthmaticus. Arterial blood gas determinations and continuous pulse oximetry help guide therapy. Subjects usually respond to inhaled β agonists, such as albuterol (0.5 mL or 2.5 mg of a 5% solution) delivered with oxygen nebulization.

Since adequate oxygenation also depends on ventilation, it may be necessary to establish and maintain an airway and/or provide ventilatory assistance. Again, one of the quickest, easiest, and most effective ways to support ventilation involves a one-way valve face mask with oxygen inlet port (e.g., Pocket-Mask or similar device). Oxygen saturations comparable to endotracheal intubation have been demonstrated in patients who require artificial ventilation via the mouth-to-mask technique with oxygen attached to the inlet port. Subjects with adequate, spontaneous respirations may breathe through the mask.

Ambubags of less than 700 mL are not recommended in adults unless an endotracheal tube is in place since ventilated volume will not overcome the 150 to 200 mL of anatomic dead space and thus provide effective tidal volumes. Recommended tidal volume during artificial ventilation is 6 to 7 mL/kg over 1.5 to 2 seconds. Ambubags may be used in children if the reservoir volume of the device is sufficient. Avoid overinflation. Endotracheal intubation or cricothyroidotomy may be considered where appropriate, depending on the skills of the physician and other health care professionals.

The rate of administered oxygen depends on the clinical response and the device used. A nasal cannula delivers 25% to 40% oxygen with a 4- to 6-L/min flow. A simple plastic face mask delivers 50% to 60% oxygen with an 8- to 12-L/min flow. By comparison, the one-way valve face mask with oxygen inlet valve permits ventilation with up to 50% oxygen at a flow rate of 10 L/min and approaches 90% to 100% if the rescuer periodically occludes the opening of the mask with his/her tongue during mouth-to-mask ventilation.

Mechanical ventilation itself may present a danger for subjects requiring ventilator support during anaphylaxis. Frequent complications of mechanical ventilation include pulmonary barotrauma and hemodynamic compromise, which may result if extremely high inspiratory pressures are necessary to overcome airway obstruction. Mechanical ventilation may have serious consequences for subjects with persistent hypotension despite adequate ventilation. High inspiratory pressure and an inadequate internal diameter of the endotracheal tube also may decrease venous return and increase right ventricular afterload, which leads to inadequate oxygen delivery, arrhythmias, and possible cardiac arrest.

Problems Posed by β -Adrenergic Antagonists During Anaphylaxis

β -Adrenergic antagonists (β -blockers) are used to treat cardiovascular disease, arrhythmias, hypertension, migraine headaches, anxiety, glaucoma, and thyrotoxicosis. Numerous cases of

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unusually severe or refractory anaphylaxis are reported in patients taking topical or oral β -adrenergic blockers (71). Subjects taking β -adrenergic antagonists may be more likely to experience severe anaphylaxis characterized by paradoxical bradycardia, severe hypotension, and bronchospasm. These agents may also impede epinephrine treatment. Use of selective β_1 -antagonists does not reduce the risk for anaphylaxis since both β_1 and β_2 antagonists may inhibit the β -adrenergic receptor (71).

Management of Anaphylaxis in Pregnancy

Anaphylaxis rarely occurs during pregnancy and, therefore, data are insufficient to make recommendations for treatment. With a few modifications, however, consensus treatment modalities used are identical to those used for anaphylaxis occurring in nonpregnant subjects (112). The uteroplacental arteries are very responsive to α -adrenergic stimulation, and great care is necessary when epinephrine or other agents with α -adrenergic effects are utilized. Epinephrine and diphenhydramine both increase the risk of fetal malformations. However, at least in the case of epinephrine, the lack of an equally effective substitute combined with the tentative nature of the data concerning epinephrine teratogenic risk strongly suggest epinephrine must be used during pregnancy for this potentially life-threatening emergency. Ensuring adequate oxygenation and intravascular volume are especially important during pregnancy (112).

Management of Idiopathic Anaphylaxis

Treatment for subjects with idiopathic anaphylaxis depends on its frequency. The treatment of the acute episode is the same as for any other form of anaphylaxis. Various protocols are published for use to prevent recurrent episodes. They recommend the administration of H_1 and H_2 antagonists, β agonists, leukotriene modifiers, and corticosteroids. All are successful in individual cases. The decision to begin preventive therapy should be individualized (71).

Self-Treatment by Subject

All subjects at risk for anaphylaxis should carry and know how to self-administer epinephrine (Figs. 3 and 4). Data from Vander Leek et al. suggest that epinephrine should be prescribed for any child or adult with confirmed peanut allergy, regardless of the severity of the initial reaction (56). In one report, more than 80% of subjects who died from food anaphylaxis were not given appropriate information to avoid inadvertent food-induced reactions or self-administer epinephrine to treat such reactions (7). Pumphrey determined that epinephrine was administered in 62% of fatal anaphylactic reactions in the United Kingdom, only 14% prior to cardiac arrest (113). In a follow-up analysis of 48 cases of fatal food anaphylaxis from 1999 to 2006, Pumphrey and Gowland (86) reported 19 (40%) received epinephrine autoinjectors, but over half of the fatalities occurred in patients whose previous clinical reactions were so mild that, in the opinion of the investigators, it was unlikely that a physician would have prescribed an epinephrine syringe for self-administration.

Demonstration of proper self-administration technique using a placebo trainer is recommended since two studies report that many subjects receive improper or no instructions

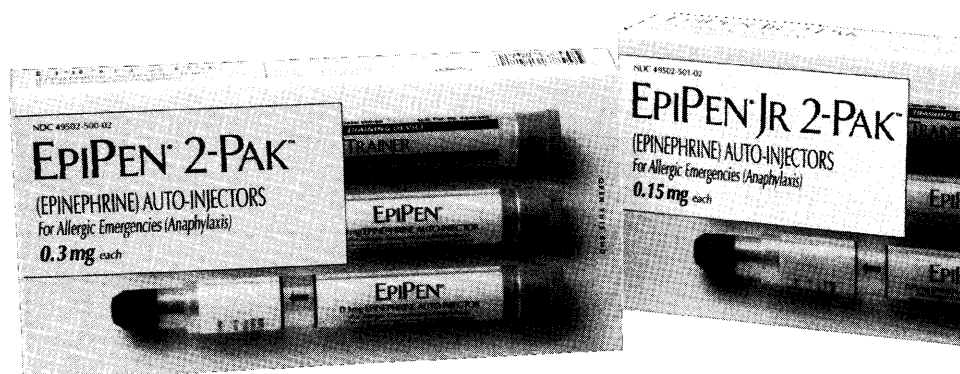


Figure 3 EpiPen[®] epinephrine autoinjector. Single devices are also available. *Source:* Photo courtesy of Dey Laboratories, Napa, California, U.S. www.anaphylaxis.com

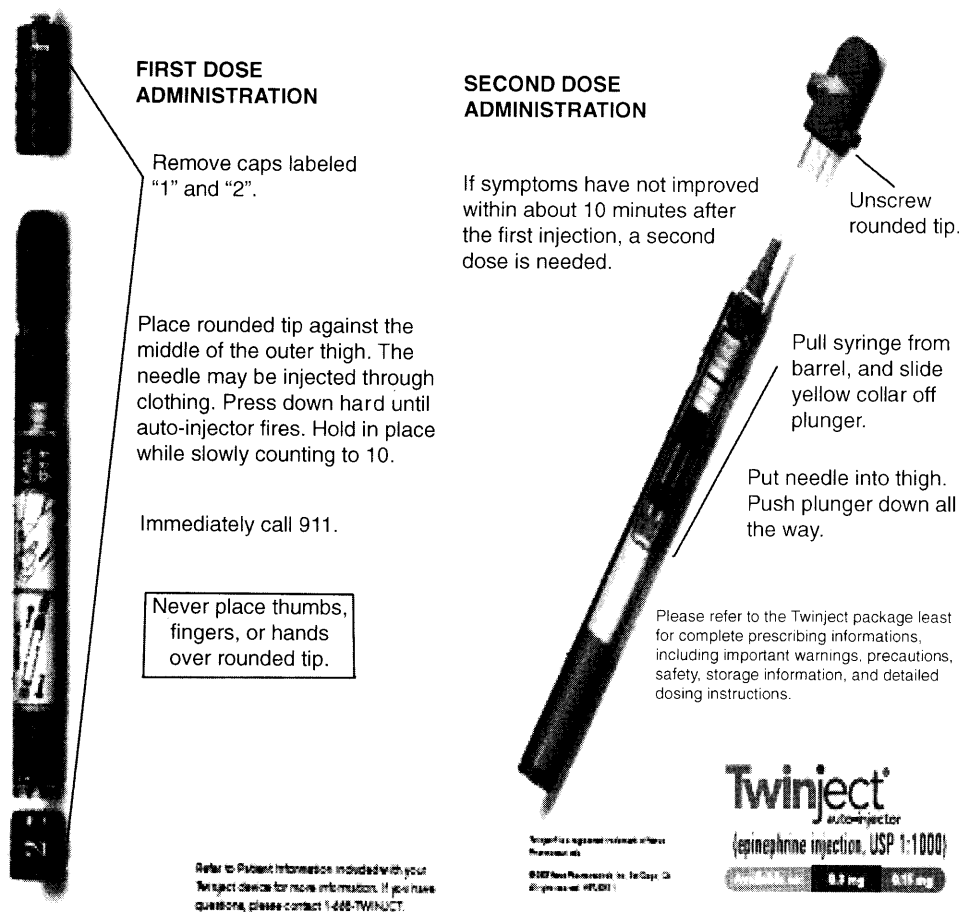


Figure 4 Twinject® epinephrine device. *Source:* Photo courtesy of Verus Pharmaceuticals, San Diego, California, U.S.

as to how to self-administer epinephrine (114,115). An EpiPen[®] (Dey Laboratories, Napa, California, U.S.) autoinjector for adults is available with a single 0.3 mg (1:1000 vol/vol) dose. Similarly, an EpiPen Jr.[®], with a 0.15 mg (1:2000 vol/vol) dose, is available for children weighing less than 30 kg. The Twinject[®] (Verus Pharmaceuticals, San Diego, California, U.S.) is a pen-sized device containing two doses of epinephrine available either as a 0.15- or a 0.3-mg formulation. The first of the two doses in both cases is delivered by autoinjector while the second is injected manually.

Adherence with an action plan to keep epinephrine available at all times and to inject it during anaphylaxis is another concern. Kemp et al. (116) determined in a follow-up survey of patients that 32 (47%) of 68 did not have their epinephrine syringe with them when they again experienced anaphylaxis from a previously identified allergen. In contrast, 31 (91%) of 34 patients with idiopathic anaphylaxis had epinephrine available at a subsequent episode. Implementation of an educational protocol with emphasis on carrying epinephrine increased the frequency of adherence from 53% to 92% over the ensuing 10 years (55). Other studies indicate that 50% to 75% of patients prescribed epinephrine will carry it with them; 30% to 40% of them demonstrate proper administration technique (80). Some carry the epinephrine kit but choose not to use it (83,117) or prefer to seek emergency medical assistance with anaphylaxis (113).

Observation After Anaphylaxis

A reasonable evidence-based recommendation appears to be that observation periods after complete resolution of uniphasic anaphylaxis should be individualized, particularly since

Table 4 Preventive Measures for Subjects with Anaphylaxis

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|-----|---|
| I. | General measures |
| • | Obtain thorough history to diagnose life-threatening food or drug allergy |
| • | Identify cause of anaphylaxis and those individuals at risk for future attacks |
| • | Provide instruction on proper reading of food and medication labels, where appropriate |
| • | Avoidance of exposure to antigens and cross-reactive substances |
| • | Optimal management of asthma and coronary artery disease |
| • | Implement a waiting period of 20–30 min after injections of drugs or other biologic agents |
| • | Consider a waiting period of 2 hr if a patient receives an oral medication in the office he/she has never previously taken |
| II. | Specific measures for high-risk patients |
| • | Individuals at high risk for anaphylaxis should carry self-injectable syringes of epinephrine at all times and receive instruction in proper use with placebo trainer |
| • | MedicAlert® (MedicAlert Foundation, Turlock, California, U.S.) or similar warning bracelets or chains |
| • | Substitute other agents for β -adrenergic antagonists, tricyclic antidepressants, monoamine oxidase inhibitors, and certain tricyclic antidepressants whenever possible. Angiotensin-converting enzyme inhibitors may also be a potential problem |
| • | Slow, supervised administration of agents suspected of causing anaphylaxis, orally, when possible |
| • | Where appropriate, utilize specific preventative strategies, including pharmacologic prophylaxis, short-term challenge and desensitization, and long-term desensitization |
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Source: Modified from Ref. 120.

there are no reliable predictors of biphasic anaphylaxis. An observation period, based on the severity and response to treatment, is appropriate. Initial phases of anaphylaxis characterized by hypotension, respiratory failure or hypoxemia, repeated doses of epinephrine, poorly controlled asthma, or prior history of biphasic anaphylaxis are reasonable indications for a prolonged observation period of 24 hours or even longer. At discharge, all patients should be provided an epinephrine autoinjector and receive proper instruction on how to self-administer it in case of a subsequent episode. Patients should also have ready and prompt access to emergency medical services for transportation to the closest emergency department for treatment. Further prospective studies on biphasic anaphylaxis are needed (67,68,71,73).

PREVENTION OF ANAPHYLAXIS

Certain Anaphylactic Reactions Are Preventable

Some anaphylactic reactions are so severe that treatment is unsuccessful and death occurs. This underscores the critical importance of education, avoidance, and prevention. Table 4 outlines basic principles for the prevention of future anaphylaxis. An allergist-immunologist can provide comprehensive professional advice on these matters.

Agents that cause anaphylaxis must be identified, whenever possible, and subjects should be instructed how to minimize future exposure. β -Adrenergic antagonists should be discontinued where feasible. There is some preliminary evidence that angiotensin-converting enzyme (ACE) inhibitors may also potentiate anaphylaxis by preventing compensatory angiotensin II mobilization during anaphylaxis (22). More clinical data are necessary to recommend that they not be used when a patient is susceptible to anaphylaxis. Monoamine oxidase inhibitors and some tricyclic antidepressants render epinephrine usage more hazardous by interfering with its degradation.

Meals may potentially have unsavory surprises for highly allergic individuals. A case report illustrates that anaphylaxis may occur in latex-allergic subjects whose food handlers wear latex gloves. Baked goods commonly contain peanuts and nuts, and accidental ingestion of these foods is common. Approximately 35% to 50% of subjects allergic to peanuts will have an inadvertent peanut ingestion within three to four years (118). Pumphrey (113) observed that commercial catering causes 76% of food-related anaphylactic reactions in the United Kingdom. Education is of paramount importance, and the Food Allergy and Anaphylaxis Network (telephone, 800-929-4040; www.foodallergy.org) is a helpful nonprofit resource for many food-allergic individuals.

The potential for anaphylaxis may be determined by skin tests in some circumstances (e.g., allergy to β -lactam antibiotics). However, the immunochemistry of most drugs and biologic agents is not well defined, and reliable *in vivo* or *in vitro* testing for most agents is unavailable (119).

Situations may arise for which it is medically necessary to administer an agent to an individual in whom it has previously caused an anaphylactic episode. Numerous protocols enable prevention or reduction of the severity of anaphylaxis. All protocols should only be conducted in clinical settings where anaphylaxis, if it occurs, can be properly managed. Examples of these protocols are antihistamine and corticosteroid prophylaxis to prevent or reduce the severity of IgE-independent reactions (e.g., radiocontrast media); administration of gradual incremental doses of medication over several hours (e.g., short-term penicillin desensitization); or the highly effective, long-term desensitization with venom immunotherapy for stinging insect anaphylaxis (see chap. 24).

Potential Future Options to Reduce Risk of Anaphylaxis

Potential future therapeutic options may feature modified allergens for SCIT to reduce allergenicity. Options being explored include novel vaccine delivery systems, DNA-based vaccination, conjugation of immunostimulatory DNA motifs to specific allergens, plasmid vectors containing DNA, vaccines with highly purified and defined allergens, and "non-anaphylactic" allergens/allergen fragments/peptides for active immunotherapy. Others include IgE-binding haptens of major allergens for passive saturation of effector cells and induction of blocking antibodies, allergen-specific antibodies and antibody fragments for passive immunotherapy in the allergic effector organs, and immunotherapy with humanized anti-IgE monoclonal antibodies or IgE mimotopes. Clinical trials are evaluating optimal dosing of oral peanut desensitization to reduce the risk of peanut anaphylaxis.

SALIENT POINTS

- Fatal anaphylaxis from SCIT occurs at a rate of approximately 1/2,500,000 injections.
- Anaphylaxis associated with SCIT occurs more frequently with accelerated dosage schedules than with traditional, more leisurely schedules.
- β -Adrenergic antagonists may increase the risk for refractory anaphylaxis.
- Mast cell tryptase levels correlate with the severity of anaphylaxis in many instances. However, a normal tryptase level does not necessarily exclude anaphylaxis.
- Some subjects with anaphylaxis have atypical findings such as bradycardia, vasomotor collapse without urticaria, or isolated gastrointestinal symptoms.
- Myocardial dysfunction and arrhythmias may be prominent features of anaphylaxis.
- Peanuts cause the greatest concern in food-associated anaphylaxis because of (i) the life-threatening severity of anaphylaxis to the peanut, especially in subjects with concomitant asthma, and (ii) the propensity for subjects to remain allergic to peanuts for life.
- Exercise avoidance remains the best treatment for EIA since medical prophylaxis is not very effective.
- Epinephrine is the most important therapeutic agent used to treat anaphylaxis. Epinephrine must be used in appropriate doses.
- Glucagon is indicated for subjects on β -blockers not responding to epinephrine given for anaphylaxis.
- Intravenous epinephrine is indicated when severe and life-threatening anaphylaxis is not responding with optimal therapy.

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