

Anaphylaxis: A review of causes and mechanisms

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Anaphylaxis is a life-threatening syndrome resulting from the sudden release of mast cell- and basophil-derived mediators into the circulation. Foods and medications cause most anaphylaxis for which a cause can be identified, but virtually any agent capable of directly or indirectly activating mast cells or basophils can cause this syndrome. This review discusses the pathophysiologic mechanisms of anaphylaxis, its causes, and its treatment. (*J Allergy Clin Immunol* 2002;110:341-8.)

Key words: Anaphylaxis, anaphylactoid reactions, immunopathologic mechanisms, pathophysiology, epinephrine

The Nobel Prize in Medicine or Physiology was awarded to the French physiologist Charles Robert Richet in 1913 for his collaborative research with Paul Portier on anaphylaxis. In 1902, Portier and Richet described the experimental induction of hypersensitivity in dogs immunized with venom from coelenterate invertebrates (sea anemones) while attempting to confer sting prophylaxis. The dogs were sensitized to the venom unexpectedly and had fatal reactions to previously non-lethal doses of venom. To describe this phenomenon, Portier and Richet proposed the term *anaphylaxis*, which was derived from the Greek words a- (*against*) and -phylaxis (*immunity, protection*).^{1,2}

EPIDEMIOLOGY AND DEFINITION

Anaphylaxis is not a reportable disease, and both its morbidity and mortality are probably underestimated (Table 1).³⁻¹² Moreover, there is no universally accepted clinical definition of anaphylaxis.¹³ Some clinicians define it broadly as a syndrome of one or more systemic signs and symptoms but do not specify the precise features alone or in combination or to what degree they are necessary to make the diagnosis.^{5,14-18} Others have clas-

Abbreviations used

LT: Leukotriene

NO: Nitric oxide

sified anaphylaxis on the basis of its severity (eg, grade I-IV),¹⁹⁻²² whereas some require either dyspnea or hypotension to make the diagnosis.²³ Brown et al²⁴ analyzed emergency department data for anaphylaxis, defined as documented inflammatory mediator release associated with additional diagnostic criteria recorded within 30 minutes of arrival to the emergency department (bronchospasm, respiratory rate, systolic blood pressure, and Glasgow Coma Scale score), for stratification into mild-to-moderate or severe anaphylaxis. Severe anaphylaxis by this classification requires a systolic blood pressure of less than 90 mm Hg, a respiratory rate of 25 breaths/min or greater, and/or a Glasgow Coma Scale score of less than 15. (The Glasgow Coma Scale is a quickly performed, highly reproducible prognostic tool to score acute brain insult-injury. Assessment is based on verbal output, best motor response, and eye opening, with aggregate scores ranging from 3 [completely unresponsive, worst prognosis] to 15 [best prognosis].) These definitions underscore the need to define terms operationally in any discussion about anaphylaxis.

In this review anaphylaxis is a syndrome with varied mechanisms, clinical presentations, and severity and is an acute life-threatening reaction, usually mediated by an immunologic mechanism but not always so (anaphylactoid reactions are thought not to involve the immune system), that results from the sudden systemic release of mast cells and basophil mediators. It consists of some or all of the following signs and symptoms: diffuse erythema, pruritus, urticaria, and/or angioedema; bronchospasm; laryngeal edema; hyperperistalsis; hypotension; and/or cardiac arrhythmias. Other symptoms can occur, such as nausea, vomiting, lightheadedness, headache, feeling of impending doom, and unconsciousness.

Generalized urticaria and angioedema are the most common manifestations of anaphylaxis (772 [92%] of 835 subjects in retrospective series)¹⁴⁻¹⁶ and occur as the initial signs and symptoms or accompany severe anaphylaxis.²⁵ However, cutaneous manifestations might be delayed or absent in rapidly progressive anaphylaxis. The

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TABLE I. Approximate incidence of anaphylaxis: Overall and with selected agents

Overall	Approximately 154 annual fatal episodes per 1,000,000 hospitalized subjects occur internationally. ⁴ The estimated risk of anaphylaxis per person in the United States is 1% to 3%. ^{5,6} US projection on the basis of data from Olmsted County, Minn: For population of 280 million and mortality rate of 1%, there will be an estimated 84,000 anaphylaxis cases and 840 fatalities annually. ^{3,5}
Selected Agents	
Foods	An estimated 150 fatalities from food-induced anaphylaxis occur each year in the United States ⁷ ; peanuts and tree nuts accounted for 30 (94%) of 32 fatal cases voluntarily reported to a national registry for fatal anaphylaxis. ⁸
Antibiotics	β -Lactam antibiotics are alleged to cause 400 to 800 fatal anaphylactic episodes per year. ⁶
Allergen vaccines	Fatalities from allergen immunotherapy occur in approximately 1 per 2,000,000 injections ⁹ ; fatal reactions to skin testing are rare. ¹⁰
Venoms	Insect stings probably cause at least 50 US fatalities annually; the true incidence of sting anaphylaxis and death is unknown. ¹¹
Idiopathic anaphylaxis	Estimated prevalence of 34,000 individuals in the United States. ¹²

next most common manifestations are respiratory symptoms, followed by dizziness, unconsciousness, and gastrointestinal symptoms. The more rapid the onset of the signs and symptoms of anaphylaxis after exposure to an offending stimulus, the more likely the reaction will be severe and life-threatening.^{26,27} Anaphylaxis often produces signs and symptoms within 5 to 30 minutes, but reactions sometimes might not develop for several hours.

PROPOSED IMMUNOPATHOLOGIC MECHANISMS

Some authors reserve the term *anaphylaxis* only for IgE-dependent events and the term *anaphylactoid* to describe IgE-independent reactions that otherwise are clinically indistinguishable. Coombs and Gell²⁸ first classified 4 types of hypersensitivity (immunopathologic) reactions: I, immediate (IgE-dependent); II, cytotoxic (IgG, IgM dependent); III, immune complexes (IgG, IgM complex dependent); and IV, delayed (T-lymphocyte dependent). Not only can IgE-dependent reactions cause anaphylaxis but so too can cytotoxic (eg, blood transfusion reactions) and immune complex (eg, complexes of gammaglobulin administered intramuscularly or intravenously) reactions. Sell²⁹ has proposed an alternate classification system on the basis of 7 immunopathologic mechanisms with both protective and

destructive functions: (1) immune-mediated inactivation-activation reactions of biologically active molecules; (2) antibody-mediated cytotoxic or cytolytic reactions; (3) immune complex reactions; (4) allergic reactions; (5) T lymphocyte-mediated cytotoxicity; (6) delayed hypersensitivity; and (7) granulomatous reactions. Mechanism 4 in this classification encompasses both anaphylactic and anaphylactoid reactions, but several of these immunopathologic mechanisms might be actively causing anaphylaxis in a given individual. For example, aggregate anaphylaxis involves immune complex formation, and transfusion-related anaphylaxis has cytotoxic features, neither of which involve IgE and yet cause anaphylaxis. Table 2^{3,30} classifies representative agents of anaphylaxis by means of pathophysiologic mechanism.

PATHOPHYSIOLOGY AND CHEMICAL MEDIATORS OF ANAPHYLAXIS

Biochemical mediators and chemotactic substances are released systemically during the degranulation of mast cells and basophils. These include preformed granule-associated substances, such as histamine, tryptase, chymase, and heparin; histamine-releasing factor and other cytokines; and newly generated lipid-derived mediators, such as PGD₂, leukotriene (LT) B₄, platelet-activating factor, and the cysteinyl leukotrienes LTC₄, LTD₄, and LTE₄. Eosinophils might play either a proinflammatory role (eg, release of cytotoxic granule-associated proteins) or an anti-inflammatory role (eg, metabolism of vasoactive mediators).³¹

Histamine activates H₁ and H₂ receptors. Pruritus, rhinorrhea, tachycardia, and bronchospasm are caused by activation of the H₁ receptors, whereas both H₁ and H₂ receptors mediate headache, flushing, and hypotension.³² Serum histamine levels correlate with the severity and persistence of cardiopulmonary manifestations but not with the formation of urticaria.^{33,34} Gastrointestinal signs and symptoms are associated with histamine more so than with tryptase levels.³³

H₃ receptors have been implicated in the canine model of anaphylaxis.³⁵ These inhibitory presynaptic receptors modulate release of endogenous norepinephrine from sympathetic fibers that innervate the cardiovascular system. Pretreatment of study animals with the H₃ receptor antagonist thioperamide maleate is associated with a higher heart rate and greater left ventricular systolic function compared with that of the nontreatment group or the other treatment arms involving receptor blockade for H₁, H₂, cyclooxygenase, and LT pathways.³⁵ Potential implications for human subjects and anaphylaxis have not been studied.

Tryptase is the only protein that is concentrated selectively in the secretory granules of human mast cells. Tryptase plasma levels correlate with the clinical severity of anaphylaxis.³⁶ Because β -tryptase is stored in mast cell secretory granules, its release might be more specific for activation than that of α -protryptase, which appears to be secreted constitutively.³⁷

TABLE II. Representative agents that cause anaphylaxis

Anaphylactic (IgE dependent)
Foods (peanut, tree nuts, and crustaceans)
Medications (eg, antibiotics)
Venoms
Latex
Allergen vaccines
Hormones
Animal or human proteins
Colorants (insect derived, such as carmine)
Enzymes
Polysaccharides
Aspirin and other nonsteroidal anti-inflammatory drugs (probably)*
Exercise (possibly, in food- and medication-dependent events)
Anaphylactoid (IgE independent)
Multimediation complement activation-activation of contact system
Radiocontrast media
Angiotensin-converting enzyme inhibitor administered during renal dialysis with sulfonated polyacrylonitrile, cuprophane, or polymethylmethacrylate dialysis membranes
Ethylene oxide gas on dialysis tubing
Protamine (possibly)
Nonspecific degranulation of mast cells and basophils
Opioids
Muscle relaxants
Idiopathic
Physical factors
Exercise
Temperature (cold, heat)
Immune aggregates
Intravenous immunoglobulin
Dextran (possibly)
Possibly antihaptoglobin in anaphthoglobinemia (in Asian subjects)
Cytotoxic
Transfusion reactions to cellular elements (IgG, IgM)
Psychogenic
Factitious
Undifferentiated somatoform idiopathic anaphylaxis

*Many authors place nonsteroidal anti-inflammatory drugs in the anaphylactoid category because there is no consistent or reliable detection of drug-specific IgE. However, reactions almost always are agent specific (unlike the cross-reactivity observed in aspirin-sensitive respiratory disease [commonly called aspirin triad or Samter syndrome]), they require 2 or more previous specific drug exposures, and the subject group characteristically has no underlying nasal polyps or asthma.³⁰ Modified with permission from *Immunol Allergy Clin North Am*. 2001;21:611-34.

Postmortem measurements of serum tryptase might be useful in establishing anaphylaxis as the cause of death in subjects experiencing sudden death of uncertain cause.³⁸⁻⁴¹ Increased postmortem tryptase levels have been reported in 12% of otherwise healthy adults who died suddenly and in at least 40% of victims of sudden infant death syndrome.^{40,42,43} Causation, however, is challenged by one report that found 40% of infants with sudden infant death syndrome had increased tryptase levels but only those in the prone position at death.⁴⁴ Buckley et al⁴⁵ observed that 5 (16%) of 32 patients had abnormally high tryptase levels, reflecting increased β -tryptase (anaphylaxis-specific) levels but no increased α -tryptase levels.⁴⁵ Serum for postmortem tryptase levels should be obtained within 15 hours of death to exclude nonspecific increases not due to anaphylaxis.³⁹

Histamine binding to H₁ receptors during anaphylaxis also stimulates endothelial cells to convert the amino acid

L-arginine into nitric oxide (NO), a potent autacoid vasodilator.^{46,47} NO activates guanylate cyclase, leading to vasodilation and the production of cyclic guanosine monophosphate. Physiologically, NO helps modulate vascular tone and regional blood pressure. Enhanced NO production decreases venous return, thus contributing to the vasodilation that occurs during anaphylaxis. However, in vivo animal studies demonstrate that NO inhibitors cause myocardial depression by facilitating histamine release, LT production, and coronary vasoconstriction. NO inhibitors during anaphylaxis also promote bronchospasm, suggesting that NO might decrease the signs and symptoms of anaphylaxis but exacerbate associated vasodilation.⁴⁶

Metabolites of arachidonic acid include products of the lipoxygenase and cyclooxygenase pathways. Of note, LTB₄ is a chemotactic agent and thus theoretically might contribute to the late phase of anaphylaxis and to protracted reactions. There are other inflammatory pathways that

are probably important in the prolongation and amplification of anaphylaxis. During severe episodes of anaphylaxis, there is concomitant activation of complement, coagulation pathways, and the kallikrein-kinin contact system. Decreases in C4 and C3 and generation of C3a have been observed in anaphylaxis. Demonstrable evidence for coagulation pathway activation includes decreases in factor V, factor VIII, and fibrinogen. Decreased high-molecular-weight kininogen and the formation of kallikrein-C1 and factor XIIa-C1 inhibitor complexes indicate contact system activation. The activation of kallikrein not only results in the formation of bradykinin but also activation of factor XII. Factor XII itself can cause clotting and clot lysis through plasmin formation. Plasmin itself can also activate complement. In contrast, some mediators might have salutary effects that limit anaphylaxis. For example, chymase might activate angiotensin II, which can modulate hypotension. Heparin inhibits clotting, kallikrein, and plasmin. It also opposes complement formation and modulates trypsin activity.⁴⁸

SHOCK ORGANS IN ANAPHYLAXIS

Organ system involvement, which varies from species to species, determines the clinical course of anaphylaxis of whatever cause. Factors that determine a specific shock organ include variations in the immune response, the location of smooth muscle, and the distribution and rate of degradation and responsiveness to chemical mediators.²⁶ In the guinea pig there is bronchial smooth muscle constriction, which leads to bronchospasm, hypoxemia, and death.^{49,50} Anaphylaxis in rabbits produces fatal pulmonary artery vasoconstriction with right ventricular failure.^{50,51} The primary shock organ in the dog is the venous system of the liver, which contracts and produces severe hepatic congestion.⁵⁰ In the human subject the predominant shock organs are the lung and the heart, with common clinical manifestations of laryngeal edema, respiratory failure, and circulatory collapse.⁵⁰

THE HEART AS SHOCK ORGAN IN ANAPHYLAXIS

Chemical mediators of anaphylaxis appear to affect the myocardium directly.^{34,52} H₁ receptors mediate coronary artery vasoconstriction and increase vascular permeability, whereas H₂ receptors increase atrial and ventricular contractile forces, atrial rate, and coronary artery vasodilation. The interaction of H₁ and H₂ receptor stimulation appears to mediate decreased diastolic pressure and increased pulse pressure.⁵³ Animal studies suggest a possible modulatory role for H₃ receptors.³⁵ Platelet-activating factor also decreases coronary blood flow, delays atrioventricular conduction, and has depressor effects on the heart.⁵⁴

Anaphylaxis has been associated clinically with myocardial ischemia and with conduction defects, atrial and ventricular arrhythmias, and T-wave abnormalities.⁵⁴ Whether such changes are related to direct mediator

effects on the myocardium or to exacerbation of preexisting myocardial insufficiency by the hemodynamic stress of anaphylaxis is unclear. Raper and Fisher⁵² describe 2 previously healthy subjects who had profound myocardial depression during anaphylaxis. Echocardiography, nuclear imaging, and hemodynamic measurements confirmed the presence of myocardial dysfunction. The anaphylaxis treatment was supplemented with intra-aortic balloon counterpulsation 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 resolved. Both subjects recovered, with no subsequent evidence of myocardial dysfunction.

Increased vascular permeability during anaphylaxis can result in a transfer of 50% of the intravascular fluid into the extravascular space within 10 minutes.^{55,56} This shift in effective blood volume activates the renin-angiotensin-aldosterone system and causes compensatory catecholamine release,⁵⁷⁻⁵⁹ both of which have variable clinical effects. Some subjects experience abnormal elevations of peripheral vascular resistance (maximal vasoconstriction),⁶⁰ whereas others have decreased systemic vascular resistance, despite increased levels of catecholamines.⁶¹ Mast cells accumulate at sites of coronary plaques and might contribute to coronary artery thrombosis.⁶² Because antibodies attached to mast cell receptors can trigger degranulation, some investigators suggest that any allergic reaction might potentially facilitate plaque disruption.⁶³ Histamine released from mast cells might also promote plaque disruption by increasing the arterial hemodynamic stress on the plaque, inducing vasospasm, or both.⁶⁴

AGENTS THAT CAUSE ANAPHYLAXIS

Virtually any agent capable of activating mast cells or basophils might potentially cause anaphylaxis. Table 2 classifies common causes by their proposed pathophysiologic mechanism. However, as previously stated, more than one mechanism might be active in some cases of anaphylaxis. The most common identifiable causes of anaphylaxis are foods, medications, insect stings, and allergen immunotherapy injections.^{5,24,48,65} Anaphylaxis to peanuts or tree nuts is of special concern because of its life-threatening potential, especially in subjects with asthma, and the propensity for life-long sensitivity to these foods. Investigators have reported that the majority (52%) of children with peanut allergy experience life-threatening symptoms with subsequent reactions, even when atopic dermatitis previously has been the only adverse clinical manifestation.⁶⁶

Idiopathic anaphylaxis is one of the most common causes, accounting for approximately one third of cases in retrospective studies.^{5,15,24,67} However, it remains a diagnosis of exclusion. Detailed serial histories and diagnostic tests for foods, spices, and vegetable gums have occasionally identified the culprit in subjects previously presumed to have idiopathic anaphylaxis.⁴⁸

TABLE III. Physician-supervised management of anaphylaxis^{3,74-76}

I. Immediate intervention

- a. Assessment of airway, breathing, circulation, and adequacy of mentation
- b. Administer aqueous epinephrine 1:1000 dilution, 0.3-0.5 mL (0.01 mg/kg in children; maximum dose, 0.3 mg), intramuscularly into the arm (deltoid) every 5 minutes, as necessary, to control symptoms and blood pressure. The arm permits easy access for the earliest administration of epinephrine. However, intramuscular injection into the anterolateral thigh (vastus medialis) produces higher and more rapid peak plasma levels compared with those of injections administered intramuscularly into the arm (see text). Therefore subjects with moderate, severe, or progressive anaphylaxis should receive epinephrine injections in the anterolateral thigh. Alternatively, an epinephrine autoinjector (eg, EpiPen [0.3 mg] or EpiPen Jr [0.15 mg]) may be administered through clothing into the anterolateral thigh. Repeat every 5 minutes as necessary (avoid toxicity).
- c. Aqueous epinephrine 1:1000, 0.1-0.3 mL in 10 mL of normal saline (1:100,000 to 1:33,000 dilution), administered intravenously over several minutes may be used and repeated as necessary in anaphylaxis not responding to epinephrine injections and volume resuscitation. Continuous hemodynamic monitoring is essential.*
- d. For potentially moribund subjects, a still more aggressive option follows: Draw up, in a tubercular syringe, aqueous epinephrine 1:1000, 0.1 mL, and insert into a vein or intravenous tubing to aspirate 0.9 mL of blood or intravenous fluid (producing a 1:10,000 dilution). This epinephrine dilution may be administered intravenously over several minutes, as needed, to restore blood pressure. Continuous hemodynamic monitoring is essential.* (See also V below.)

II. General measures

- a. Place subject in recumbent position and elevate lower extremities.
- b. Establish and maintain airway (endotracheal tube or cricothyrotomy might be required).
- c. Administer oxygen at 6-8 L/min.
- d. Administer normal saline intravenously for fluid replacement and venous access. If severe hypotension exists, rapid infusion of volume expanders (colloid-containing solutions) is necessary.
- e. A venous tourniquet above the reaction site might decrease absorption of an injected allergen or venom.

III. Specific measures that depend on the clinical scenario

- a. Aqueous epinephrine 1:1,000, one half dose (0.1-0.2 mg), at the reaction site after sting or injection might delay allergen absorption.
- b. Diphenhydramine, 50 mg or more in divided doses orally or intravenously, with maximum daily dose of 300 mg (5 mg/kg) for children and 400 mg for adults.
- c. Ranitidine, 50 mg in adults and 12.5-50 mg (1 mg/kg) in children, may be diluted in 5% dextrose to a total volume of 20 mL and injected intravenously over 5 minutes. Cimetidine (4 mg/kg) alternatively may be administered to adults, but no pediatric dosage in anaphylaxis has been established.
- d. For bronchospasm resistant to epinephrine, administer nebulized albuterol, 2.5-5 mg in 3 mL of saline, or levalbuterol (Xopenex), 0.63-1.25 mg unit dose, and repeat as necessary. Levalbuterol is a consideration for albuterol-intolerant subjects.
- e. Aminophylline, 5 mg/kg over 30 minutes intravenously, might be useful if no response to inhaled β -agonist. Note: adjust dosage on the basis of age, concurrent medications, disease states, or current use of theophylline.
- f. For hypotension refractory to volume replacement and epinephrine injections, dopamine, 400 mg in 500 mL of 5% dextrose in water, may be administered intravenously at 2-20 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, with the rate titrated to maintain adequate blood pressure. Continuous hemodynamic monitoring is essential.
- g. Glucagon, 1-5 mg (20-30 $\mu\text{g}/\text{kg}$ [maximum, 1 mg] in children), administered intravenously over 5 minutes, followed by an infusion of 5-15 $\mu\text{g}/\text{min}$, may be used when β -blocker therapy complicates treatment. Aspiration precautions should be observed because glucagon may cause nausea and emesis.
- h. Systemic glucocorticosteroids, such as methylprednisolone 1-2 mg/kg per 24 hours, are usually not helpful acutely but might prevent prolonged reactions or relapses.

IV. Vasodepressor (Vaso-vagal) reaction only

Definition: Nonallergic reaction characterized by slow pulse, nausea, pallor, sweating, clammy skin, and hypotension.

- a. Place patient in supine position with elevation of the lower extremities and monitor vital signs.
- b. For vasodepressor reaction only (ie, bradycardia, nausea, pallor, sweating, cool clammy skin, and hypotension), administer atropine, 0.3-0.5 mg (0.02 mg/kg), subcutaneously every 10 minutes (maximum, 2 mg for adults and 1 mg for children).
- c. If hypotension persists, establish intravenous access and administer normal saline rapidly until blood pressure stabilizes.

V. Key additional interventions for cardiopulmonary arrest occurring during anaphylaxis

- a. High-dose epinephrine administered intravenously (ie, rapid progression to high dose). A commonly used sequence is 1-3 mg (1:10,000 dilution) slowly administered intravenously over 3 minutes, 3-5 mg administered intravenously over 3 minutes, and 4-10 $\mu\text{g}/\text{min}$ infusion. The recommended initial resuscitation dosage in children is 0.01 mg/kg (0.1 mL/kg of a 1:10,000 solution) repeated every 3-5 minutes for ongoing arrest. Higher subsequent dosages (0.1-0.2 mg/kg, 0.1 mL/kg of a 1:1,000 solution) may be considered for unresponsive asystole or pulseless electrical activity. These arrhythmias are often observed during cardiopulmonary arrest that occurs in anaphylaxis.
- b. Rapid volume expansion is mandatory.
- c. Use atropine and transcutaneous pacing if asystole or pulseless electrical activity are present.
- d. Prolonged resuscitation efforts are encouraged, if necessary, because efforts are more likely to be successful in anaphylaxis, in which the subject is often a young individual with a healthy cardiovascular system.

*There are no absolute contraindications to epinephrine administration in anaphylaxis.⁷⁷ However, several anaphylaxis fatalities have been attributed to injudicious use of intravenous epinephrine.⁷⁸

β -ADRENERGIC BLOCKADE

Subjects taking any β -adrenergic antagonists, orally or topically, might be more likely to experience severe anaphylactic reactions characterized by paradoxical bradycardia, profound hypotension, and severe bronchospasm. These agents might impede treatment effectiveness with epinephrine. Dosage increases of isoproterenol (a nonselective β -adrenergic agonist) up to 80-fold are necessary experimentally to overcome β -receptor blockade.⁶⁸ Both β_1 and β_2 antagonists might inhibit the β -adrenergic receptor.⁶⁹

RECURRENT AND PERSISTENT ANAPHYLAXIS

Recurrent or biphasic anaphylaxis occurs 8 to 12 hours after the initial attack in up to 20% of subjects who experience anaphylaxis.^{15,70-73} Stark and Sullivan⁷³ reported biphasic anaphylaxis in 5 (20%) of 25 subjects. Douglas et al,⁷¹ however, observed incidences of 5% and 7% in 44 outpatients and 59 inpatients, respectively, over a 4-year period. Brazil and MacNamara⁷⁰ retrospectively reviewed 34 subjects admitted for observation after anaphylaxis. Six (18%) had biphasic episodes. The investigators observed that subjects with biphasic episodes did not differ clinically at initial presentation but required significantly more epinephrine to ameliorate their initial symptoms ($P = .03$) when compared with those with uniphasic reactions (mean epinephrine dose of 1.2 mg vs 0.6 mg, respectively).

Persistent anaphylaxis, anaphylaxis that might last from 5 to 32 hours, occurred in 7 (28%) of 25 subjects in the Stark and Sullivan⁷³ report. Of 13 subjects analyzed in a report on fatal or near-fatal anaphylaxis to foods, 3 (23%) experienced persistent anaphylaxis.⁷² Data from other investigators, however, suggest that persistent anaphylaxis is uncommon. Kemp et al¹⁵ retrospectively analyzed 266 consecutive subjects with nonfatal anaphylaxis, none of whom had biphasic or persistent anaphylaxis.

Neither biphasic nor persistent anaphylaxis can be predicted from the severity of the initial phase of an anaphylactic reaction. Because life-threatening manifestations of anaphylaxis might recur, it is necessary to communicate with subjects for up to 24 hours after their initial phase.

INTRAMUSCULAR INJECTIONS OF EPINEPHRINE IN ANAPHYLAXIS

Absorption is complete and more rapid (mean maximum plasma epinephrine concentration of 2136 ± 351 pg/mL at a mean time of 8 ± 2 minutes) in children who receive epinephrine intramuscularly in the thigh with an autoinjector.⁷⁴ Intramuscular injection into the thigh (vastus lateralis) in adults is also superior to intramuscular or subcutaneous injection into the arm (deltoid), neither of which achieves elevated plasma epinephrine levels compared with endogenous epinephrine levels associated with saline.⁷⁵ Spring-loaded, automatic epinephrine syringes administered intramuscularly and intramuscular epinephrine

injections into the thigh in adults provide dose-equivalent plasma levels.^{74,75} Simons et al⁷⁴ do not specify the injection site for comparative subcutaneous administration in children. Intramuscular thigh injections are implied by use of an autoinjector.

The UK consensus panel on emergency guidelines states that the subcutaneous route of administration for epinephrine has "no role" in anaphylaxis,¹³ and the new international consensus guidelines for emergency cardiovascular care appear to concur.⁷⁶ Both publications also propose that epinephrine may judiciously be repeated every 5 minutes, as clinically needed, in both adults and children.^{13,76}

A sequential approach to the treatment of anaphylaxis is proposed (Table 3).^{3,74-78} A more detailed discussion of anaphylaxis management is beyond the scope of this review. Reviews, practice parameters, and consensus emergency management guidelines concerning anaphylaxis and its management have been published elsewhere.^{3,13,76,77}

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