Anaphylaxis has been defined as “a serious life-threatening generalized or systemic hypersensitivity reaction”; it is usually rapid in onset, presenting with a constellation of clinical features, which are potentially fatal (1–5). Activation of mast cell and basophil populations by either IgE-dependent (i.e., anaphylactic reactions) or IgE-independent (i.e., anaphylactoid reactions) mechanisms results in the release of multiple mediators capable of altering vascular permeability and vascular and bronchial smooth muscle tone, as well as recruiting and activating inflammatory cell cascades. Initial sequelae, which typically occur within minutes to an hour after exposure to an inciting stimulus, include generalized hives, tachycardia, flushing, pruritus, faintness, and a sensation of impending doom. Dermatologic (e.g., urticaria and angioedema), respiratory (e.g., dyspnea, wheeze, stridor, bronchospasm, and hypoxemia), and gastrointestinal (e.g., abdominal distension, nausea, emesis, and diarrhea) manifestations are common. Involvement of the cardiovascular and respiratory systems may result in potentially life-threatening manifestations, such as cardiovascular collapse caused by vasodilatation and capillary leak, myocardial depression, myocardial ischemia and infarction, atrial fibrillation, and severe bronchospasm (6). Prompt recognition and effective early intervention are essential to prevent anaphylaxis fatalities. Several terms are sometimes used to describe anaphylaxis, including severe allergic reactions, acute IgE-mediated reactions, acute allergic reactions, systemic allergic reactions, anaphylactic shock, and anaphylactic or anaphylactoid reactions. However, for the purposes of this chapter, anaphylaxis will be used throughout. In writing this chapter, we have drawn primarily on key evidence-based guidelines from the UK Resuscitation Council, World Allergy Organization, European Academy of Allergy and Clinical Immunology, the International Consensus (ICON) on anaphylaxis (1–5), and rigorously conducted systematic reviews of the evidence.

Reliable global estimates of the incidence, prevalence, morbidity, and mortality of anaphylaxis are lacking, this being partly explained by variations in definition, underrecognition, underdiagnosis, and underreporting (2). However, recent estimates of the incidence in the United States stand at 50/100,000 persons resulting in death (21–23). Nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin are the second most common class of drugs implicated in anaphylaxis (24,25).

With widespread adoption of universal precautions against infections, latex allergy became a significant problem. The subsequent development of low-protein, powder-free gloves has been associated with reduction in occupational contact urticaria caused by latex rubber gloves (3,26). Despite this, latex allergy is still a concern since latex is found in some gloves, catheters, and tubing (27–29). Iodinated radiocontrast media can also cause anaphylaxis; however, life-threatening reactions are rare (30). A history of a previous reaction to radiocontrast media, asthma or atopic disease, treatment with β-blockers, and cardiovascular disease are risk factors for developing anaphylaxis to radiocontrast media (31–33).
**Pathophysiology**

The systemic manifestations of anaphylaxis represent sequelae that result from the release of inflammatory mediators by mast cells and basophils, leading to a cascade of mediators, including tryptase, histamine, and platelet-activating factor (34–36). While the classic anaphylactic-type response occurs through allergen-induced cross-linking of IgE tightly bound to the high-affinity FcεRI receptor constitutively expressed by mast cells (37), other non–IgE-mediated immunologic mechanisms and direct mast cell activation have also been found to be important (3,4,19,36). Release of histamine from preformed mast cell granules seems to be the primary pathophysiologic mediator, resulting in systemic vasodilation, increased vascular permeability, bronchoconstriction, pruritus, and increased mucus production. However, a number of other preformed mediators are released, including heparin, serotonin, and mast cell proteases such as chymase and tryptase (36,38). In addition, other important mediators of anaphylaxis are generated by the metabolism of membrane phospholipids. Activation of the 5-lipoxygenase pathway results in the synthesis of leukotrienes, including leukotrienes C4, D4, E4 (termed the slow-reacting substance of anaphylaxis, SRSA), and B4. Leukotrienes C4, D4, and E4, along with the intermediary products 5-hydroxyeicosatetraenoic acid and 5-hydroperoxyeicosatetraenoic acid, elicit increases in vascular permeability and bronchoconstriction, whereas leukotriene B4 possesses eosinophil and neutrophil chemotactic properties. Activation of the cyclooxygenase pathway leads to the production of prostaglandin D2, which produces bronchoconstriction. Platelet-activating factor is also newly synthesized by activated mast cells and can result in bronchoconstriction, increased vascular permeability, platelet aggregation, and neutrophil chemotaxis. It also leads to further production of platelet-activating factor through stimulation of nuclear factor (NF)-κB, a positive feedback mechanism involving the cytokines interleukin-1 (IL-1) and tumor necrosis factor (TNF)-α, and contributes to a biphasic pattern seen in some patients (39). Combined, these primary mediators then facilitate the production of a diverse number of secondary mediators by platelets, neutrophils, eosinophils, and other cells, resulting in activation of the complement, coagulation, and fibrinolytic pathways (40).

**Table 49.1** Etiologic Agents for Anaphylaxis (IgE-Mediated)

<table>
<thead>
<tr>
<th>Haptens</th>
<th>β-Lactam Antibiotics</th>
<th>Sulfonamides</th>
<th>Nitrofurantoin</th>
<th>Demethylchlortetracycline</th>
<th>Streptomycin</th>
<th>Vancomycin</th>
<th>Local anesthetics</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Products</td>
<td>γ-Globulin</td>
<td>Immunotherapy for allergic diseases</td>
<td>Heterologous serum</td>
<td>Foods</td>
<td>Nuts (peanuts, brazil nuts, hazelnuts, cashews, pistachios, almonds, soy nuts)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Foods</td>
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<td></td>
</tr>
<tr>
<td>Venom</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hormones</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Enzymes</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
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<td></td>
</tr>
</tbody>
</table>

**Table 49.2** Etiologic Agents for Anaphylactoid Reactions

<table>
<thead>
<tr>
<th>Complement-Mediated Reactions</th>
<th>Blood</th>
<th>Serum</th>
<th>Plasma</th>
<th>Plasmate (but not albumin)</th>
<th>Immunoglobulins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonimmunologic Mast Cell Activators</td>
<td>Opiates and narcotics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiocontrast Media</td>
<td>Dexters</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Neuromuscular blocking agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arachidonic Acid Modulators</td>
<td>Nonsteroidal anti-inflammatory drugs</td>
<td></td>
<td></td>
<td>Tartrazine (possible)</td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>Mast common conclusion after thorough evaluation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>Sulfites</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>Others</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Thermoregulatory Mechanism**

Cold temperature, exercise

**Boldface:** Relatively common causes.


**PATHOPHYSIOLOGY**
Many of these mediators have complicated effects, and their relative roles in mediating anaphylaxis in vivo have been difficult to evaluate. Mouse models of anaphylaxis using strains with targeted deletions of specific mediators have been useful in elucidating the importance of different effector molecules, such as the leukotrienes (41-43), and in identifying regulatory pathways, such as IL-10 (44), but have also provided some surprises that may lead to clinically useful information. For example, mice with targeted deletions of either the high-affinity FcεRI receptor or IgE, not surprisingly, had a markedly decreased susceptibility to IgE-mediated anaphylaxis (38,45). This pathway can also be blocked with targeted deletion of histamine receptor 1 and, to a lesser extent, platelet-activating factor (37,38). However, such mice also revealed the presence of an alternate IgE-independent pathway of anaphylaxis (46). This pathway was mediated largely through platelet-activating factor, which was triggered by the binding of IgG to FcyRIII receptors present on macrophages (37,47). Like the classic IgE-mediated pathway, this alternative pathway required prior exposure to antigen, but differed in that much higher concentrations of antigen were required. The importance of this pathway in humans is as yet unclear (37). However, the administration of biologic agents, such as the anti-TNF antibody infliximab, has been reported to cause an IgE-independent anaphylactic response (48), and may be an example of this alternative pathway (49,50). The use of these biologic agents is expected to continue to increase and they are currently being used for other conditions, such as rheumatoid arthritis, Crohn disease, and inflammatory bowel disease.

DIAGNOSIS

Anaphylaxis is a medical emergency as it is associated with a rapid, critical destabilization of vital organ systems. Signs of anaphylaxis may be clinically indistinguishable and may become rapidly fatal if appropriate therapy is not instituted immediately. Initial symptoms can appear within seconds to minutes, but may on rare occasions be delayed by as much as 1—rarely more—hour after exposure to an inciting agent (51), and are often nonspecific (52). Cutaneous manifestations occur in 80% to 90% of patients; absence of skin signs can make it difficult to recognize and diagnose anaphylaxis (3). The clinical features vary from person to person and these reactions can also vary within the same person (3). Common symptoms and signs of anaphylaxis include tachycardia, faintness, cutaneous flushing, urticaria, diffuse or palmar pruritus, and a sensation of impending doom (53). Of these, generalized urticaria is the most common, occurring in approximately 90% of patients (Table 49.3) (54,55). Target organ in anaphylaxis is variable, but common involvement includes the cutaneous system, gastrointestinal tract, respiratory tract, cardiovascular system, and central nervous system (3). Involvement of the cardiovascular and/or respiratory systems is responsible for the fatal complications of anaphylaxis and it is for this reason that these features are particularly emphasized in some definitions (56). An unsettling sensation—including hoarseness, dysphonia, or dyspnea—may precede acute upper airway obstruction secondary to laryngeal edema. Other pulmonary manifestations include acute bronchospasm, intra-alveolar pulmonary hemorrhage, bronchorrhea, and a noncardiogenic, high permeability–type pulmonary edema (21,57). Tachycardia and syncope may precede the development of hypotension and frank cardiovascular collapse (38,59). Anaphylactic shock occurs as a consequence of diminished venous return secondary to systemic vasodilation and intravascular volume contraction caused by capillary leak. Although transient increases in cardiac output may occur at the onset of anaphylaxis, hemodynamic parameters later reveal decreases in cardiac output, systemic vascular resistance, stroke volume, pulmonary artery occlusion, and central venous pressures (60–66). In addition, the acute onset of a lactic acidosis and diminished oxygen consumption has been noticed after anaphylaxis (67). Other potentially serious cardiovascular manifestations are myocardial ischemia and acute myocardial infarction, atrioventricular and intraventricular conduction abnormalities such as prolonged PR interval, transient left bundle branch block, and supraventricular arrhythmias such as atrial fibrillation. Severe, but reversible, myocardial depression also has been reported (59). Hematologic manifestations, such as disseminated intravascular coagulation (DIC) and thrombocytopenia secondary to volume contraction, also may complicate anaphylactic and anaphylactoid reactions (53). Gastrointestinal manifestations include nausea, bloating, abdominal cramps, and diarrhea. In 1% to 20% of patients,

<table>
<thead>
<tr>
<th>TABLE 49.3 Clinical Manifestations of Anaphylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>System</td>
</tr>
<tr>
<td>Respiratory</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
</tr>
<tr>
<td>Cutaneous</td>
</tr>
<tr>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Neurologic</td>
</tr>
<tr>
<td>Nasal</td>
</tr>
<tr>
<td>Ocular</td>
</tr>
<tr>
<td>Hematologic</td>
</tr>
</tbody>
</table>

DIC, disseminated intravascular coagulation.
there is a recurrence of symptoms after a period of recovery, termed biphasic anaphylaxis (68) and reactions can be prolonged. In most such cases, the clinical features occurred 1 to 8 hours after the initial presentation, although there have been reports of recurrence up to 72 hours later. There are no features of the primary response that reliably predict the occurrence of a secondary response (69).

The diagnosis of anaphylaxis is established primarily on the basis of a detailed clinical history of the specific episode, taking into account the exposures and events preceding onset of symptoms (foods eaten, medications taken, exercise, etc.) and characteristic findings on examination (3,4,19). Expert consensus is that laboratory tests are most often not helpful in diagnosing anaphylaxis upon patient presentation, although serial mast cell tryptase measurements may be helpful in subsequently confirming the diagnosis (3,4,19,56). The mainstay of diagnosis involves careful pattern recognition of the characteristic symptoms and signs, usually rapid in onset and occurring within minutes to a few hours of exposure to potential trigger (3,4). Fatality can occur within minutes of onset of anaphylaxis (3,4,19). Better symptom recognition requires improved training of health care professionals and standardized application of clinical criteria across settings (19). Sometimes anaphylaxis may be difficult to diagnose, particularly due to the presence of concomitant medical conditions—asthma, chronic obstructive pulmonary disease, or congestive heart failure—use of CNS-active medications such as sedatives, hypnotics, and antidepressants, and concomitant impaired vision, neurologic disease, and psychiatric illnesses (3). Diagnostic difficulty may also occur in the very young and pregnant patients (70,71). For improved diagnosis, the National Institute of Allergy and Infectious Diseases (NIAID), the Food Allergy and Anaphylaxis Network (FAAN), the World Allergy Organization (WAO), and the European Academy of Allergy and Clinical Immunology (EAACI) have provided evidence-based guidelines (1,3,4,19). The NIAID and FAAN clinical criteria are shown in Figure 49.1 (1). Because of the multisystem nature of anaphylactic reactions, the list of differential diagnoses that must be considered is extensive. Diagnostic possibilities include cardiac dysrhythmias, myocardial infarction, distributive or hypovolemic shock, vasovagal syncope, asthma, pulmonary embolism, upper airway obstruction secondary to ingestion of a foreign body, hypoglycemia, and the carcinoid syndrome (Table 49.4).

Demonstration of acute elevations of markers specific to mast cell activation such as histamine and tryptase have been

### TABLE 49.4 Differential Diagnosis of Anaphylaxis

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flush Syndrome</td>
<td>Carcinoid, Pheochromocytoma, Peri-postmenopausal hot flushes, Medullary carcinoma of thyroid, Red man syndrome (vancomycin)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Septic shock, Hemorrhagic shock, Cardiogenic shock, Hypovolemic shock, Vasovagal reaction</td>
</tr>
<tr>
<td>Respiratory Distress</td>
<td>Status asthmaticus, Airway foreign body, Epiglottitis, Pulmonary embolism, Asthma and COPD exacerbation, Vocal cord dysfunction</td>
</tr>
<tr>
<td>Postprandial Collapse</td>
<td>Airway foreign body, Monosodium glutamate ingestion, Sulfit, Scombroid fish poisoning</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Panic attacks, Systemic mastocytosis, Basophilic leukemia, Hereditary angioedema, Hyper-IgE syndrome</td>
</tr>
</tbody>
</table>

IgE: Immunoglobulin E; COPD: Chronic obstructive pulmonary disorder.

**FIGURE 49.1** Clinical criteria for diagnosing anaphylaxis. Fewer signs are required for diagnosis as the history of allergen exposure becomes more certain. Signs or symptoms of skin involvement: generalized hives, pruritus, or flushing. Signs of mucosal involvement: swollen lips, tongue, and/or uvula. Signs of respiratory compromise: dyspnea, wheeze, bronchospasm, stridor, reduced peak expiratory flow, and/or hypoxemia. Definition of reduced blood pressure (BP): adults—systolic BP less than 90 mmHg or greater than 30% decrease from that person’s baseline; children—systolic BP less than 70 mmHg from 1 month to 1 year, less than (70 mmHg + (2 × age)) from 1 to 10 years, and less than 90 mmHg from 11 to 17 years or associated signs: hypotension, syncope, incontinence. Persistent gastrointestinal symptoms: crampy abdominal pain and vomiting.
proposed to help confirm the diagnosis of anaphylaxis (72,73). However, in a series of 97 patients presenting to an emergency department and given the diagnosis of anaphylaxis, only 42% were found to have elevated plasma histamine levels, and 24% had increased plasma tryptase levels (74). However, serial tryptase levels have been shown to be much more useful, particularly in nonfood-triggered anaphylactic reactions. Skin testing or serum antibody tests can help demonstrate the presence of IgE against a specific allergen. Skin testing should be repeated after 4 weeks if unexpectedly negative to allow the dermal mast cells to replenish intracellular mediators (75).

TREATMENT

The management of anaphylaxis can usefully be considered under two headings: (a) acute or emergency treatment and (b) longer-term management (2–5,19,76,77). Acute treatment centers on stopping anaphylactic reactions and administering necessary measures to prevent fatality (2–5,19,76,77). Longer-term management, on the other hand, aims to prevent possible recurrence of anaphylaxis episodes and minimizing risks if subsequent reactions occur (2–5,19,76,77).

For acute management, prompt injection of epinephrine (adrenaline) is the mainstay of initial treatment, and should preferably be injected through the intramuscular route into the mid-anterolateral thigh (2–5,19,76,77). However, in cases of severe laryngospasm or frank cardiovascular collapse, or when there is an inadequate response to intramuscular epinephrine administration and fluid resuscitation, intravenous epinephrine is an option (1); this carries risks of inducing fatal dysrhythmias and should therefore only be performed by those with relevant training while undertaking cardiac monitoring. When epinephrine is administered i.v., the clinician should be aware of the potential adverse consequences of severe tachycardia, myocardial ischemia, hypertension, severe vasospasm, and gangrene—the latter when infused by peripheral venous access (3,4,19,46). Epinephrine decreases mediator synthesis and release by increasing intracellular concentrations of cyclic adenosine monophosphate (cAMP) and antagonizes many of the adverse actions of the mediators of anaphylaxis (63).

Aqueous epinephrine, 0.01 mg/kg (maximum dose 0.5 mg in adults; 0.3 mg in children) administered intramuscularly every 5 to 15 minutes as necessary to control symptoms and maintain blood pressure, is recommended (2–5,19,63,78). There is no established dosage regimen for intravenous epinephrine in anaphylaxis, but suggested dosages are 5 to 10 μg bolus (0.2 μg/kg) for hypertension and 100 to 500 μg in the setting of cardiovascular collapse (1,78). To be effective, administration of epinephrine should be done in a timely manner, in appropriate doses, and through the recommended route; delayed administration increases the risk of death (2–5,19,76,77).

An emergent evaluation for the inciting etiologic agent must accompany initial therapeutic interventions. After the etiologic agent is identified, the clinician should attempt to prevent further access to the circulation or limit further absorption. Infusions of possible etiologic agents should be stopped and the contents saved for analysis. If a Hymenoptera sting is responsible, the stinger should be removed. A tourniquet may be placed proximal to the injection site and pressure applied to occlude venous return. After successful pharmacologic therapy, the tourniquet may be cautiously removed and the patient carefully observed for recurrent adverse sequelae. In cases where the offending agent was ingested, consideration may be given to insertion of a nasogastric tube to perform gastric lavage and gastric instillation of activated charcoal.

Blood pressure measurements should be taken frequently, and an indwelling arterial catheter for beat-to-beat measurement of blood pressure should be inserted in cases of moderate to severe anaphylaxis. High-flow oxygen given via endotracheal tube or a nonrebreather mask should be administered to patients experiencing hypoxemia, respiratory distress, or hemodynamic instability (1). Orotracheal intubation may be attempted if airway obstruction compromises effective ventilation despite pharmacologic intervention; however, attempts may be unsuccessful if laryngeal edema is severe. If endotracheal intubation is unsuccessful, then either needle–catheter cricothyroid ventilation, cricothyrotomy, or surgical tracheostomy is required to maintain an adequate airway. Clinicians need to be familiar with at least one of these techniques in the event that endotracheal intubation cannot be accomplished. It has been suggested that inhaled β₂-agonists such as albuterol may be useful for bronchospasm refractory to epinephrine (1,79). Patients should be placed in the recumbent position, with lower extremities elevated to increase fluid return centrally, thereby increasing cardiac output (80). Airway protection should be ensured in the event of vomiting. Cardiopulmonary resuscitation should be initiated as indicated.

Second-line agents include H₁- and H₂-histamine receptor blockers and corticosteroids (1–5). H₁- and H₂-histamine receptor blockers are particularly useful in the treatment of symptomatic urticaria–angioedema and pruritus. Studies suggest that treatment with a combination of H₁- and H₂-histamine receptor blockers may be more effective in attenuating the cutaneous manifestations of anaphylaxis than H₁-blockers alone (74,81). Diphenhydramine hydrochloride (25 to 50 mg i.v. or i.m. for adults and 1 mg/kg, up to 50 mg, for children) and ranitidine (50 mg i.v. over 5 minutes) are sometimes used (82–84). It may, however, be safer to administer these agents via the oral route. However, if hypotension persists despite administration of epinephrine, aggressive volume resuscitation should be instituted and this should precede administration of H₁- and H₂-blockers. Up to 35% of the blood volume may extravasated in the first 10 minutes of a severe reaction, with subsequent reduction in blood volume due to vasodilatation, causing distributive shock (85). Persistent hypotension may require multiple fluid boluses (10 to 20 mL/kg under pressure) as well as colloid and crystalloid infusions (1). Vaspressors such as norepinephrine, vasopressin, Neo-Synephrine, or even metaraminol may be useful in persistent hypotension (52).

There have been no placebo-controlled trials evaluating the efficacy of corticosteroids in anaphylaxis, but their contribution in other allergic diseases has led to their inclusion in anaphylaxis guidelines. Due to their slow onset of action, they are not useful in acute management. However, it has been suggested that they may prevent protracted or biphasic reactions (79,86). The usual dose is 100 mg (maximum for the child) to 200 mg (maximum for the adult) of hydrocortisone orally or i.v. every 6 hours (3,4,19,43).

The management of anaphylaxis in patients receiving β-antagonist medications, such as β-blockers, represents a special circumstance in which the manifestations of anaphylaxis may be exceptionally severe (87). β-blockade increases mediator synthesis and release, as well as end-organ sensitivity.
addition, β-blockade antagonizes the beneficial β-mediated effects of epinephrine therapy, thereby resulting in unopposed α-adrenergic and reflex vagotonic effects: vasoconstriction, bronchoconstriction, and bradycardia. Therapy of anaphylaxis occurring in patients receiving β-antagonist drugs, however, is similar to that of other patients. In addition, atropine may be useful for heart block and refractory bronchospasm, whereas glucagon—which increases cAMP levels through a β-receptor-independent mechanism—have been reported to reverse the cardiovascular manifestations of anaphylaxis in patients receiving β-antagonists (87). Glucagon can be administered as a 1- to 5-mg (20 to 30 μg/kg with maximum dose of 1 mg in children) intravenous infusion over 5 minutes, followed by an infusion of 5 to 15 μg/min titrated to clinical response (1). Furthermore, these patients may require extended periods of observation because of the long duration of action of many β-antagonist medications.

A period of observation should be considered for all patients following treatment of anaphylaxis. On the basis of extant clinical data, the NIAID/FAAN symposium recommends that observation periods be individualized on the basis of severity of initial reaction, reliability of the patient, and access to care. A reasonable time would be 4 to 6 hours for most patients, with prolonged observation or hospital admission for severe or refractory symptoms and patients with reactive airway disease (1). The steps listed below are the therapeutic pearls that are recommended for the emergency management of anaphylaxis:

1. Rapidly assess and maintain the airway, breathing, and circulation. Initiate CPR, if indicated. If airway obstruction is imminent, perform endotracheal intubation; if unsuccessful, consider needle–catheter cricothyroid ventilation, cricothyrotomy, or tracheostomy. Patients should be placed in a recumbent position with the lower extremities elevated, unless precluded by shortness of breath or vomiting.

2. Remove the inciting agent (e.g., remove Hymenoptera stinger, stop the infusion, etc.) and follow with an intramuscular epinephrine injection in the anterior lateral thigh. Consider gastric lavage and administration of activated charcoal if the inciting agent was ingested.

3. Administer aqueous epinephrine, 0.01 mg/kg (maximum dose, 0.5 mg) intramuscularly every 5 to 15 minutes as necessary for controlling symptoms and maintaining blood pressure.

4. Establish intravenous access for hydration and provide high-flow supplemental oxygen.

5. Consider aggressive fluid resuscitation with multiple fluid boluses (10 to 20 mL/kg under pressure), including colloid as well as crystalloid, in patients who remain hypotensive despite epinephrine.

6. Administer histamine antagonists to block vasodilation, capillary leak, and shock (H₁ blockade, 25 to 50 mg of diphenhydramine for adults, and 1 mg/kg—up to 50 mg—for children; H₂ blockade, 50 mg of ranitidine; preferably oral administration) (4).

7. Administer vasopressors for persistent hypotension and titrate to a mean arterial pressure of 60 mmHg.

8. Administer inhaled β₂-agonists such as albuterol or salbutamol for bronchospasm refractory to epinephrine (88).

9. Consider corticosteroid therapy for protracted anaphylaxis or to prevent biphasic anaphylaxis (e.g., 1.0 to 2.0 mg/kg methylprednisolone i.v. every 6 hours). Oral prednisone at 1.0 mg/kg, up to 50 mg, may be used for milder attacks. Corticosteroids are not effective therapy for the acute manifestations of anaphylaxis.

10. Consider glucagon administration (1 to 5 mg i.v. over 1 minute, then 1 to 5 mg/hr by continuous infusion) in the setting of prior β-blockade because of its positive inotropic and chronotropic effects mediated by a β-receptor-independent mechanism.

11. Admission to the intensive care unit is warranted for invasive monitoring with arterial and pulmonary artery catheters, electrocardiography, pulse oximetry, and frequent arterial blood gas measurements.

The aims of longer-term management of patients with anaphylaxis are to minimize the risk of recurrence and to reduce the risk of fatality if a further reaction ensues. This, therefore, entails development of self-management plans for at-risk individuals, including development of guidance on identifying and then avoiding triggers of anaphylactic reactions, preparing for reactions, recognizing reactions when they occur, and initiating appropriate self-management if and when reactions occur (2–5,19,76,77). Along these lines, expert recommendation is that at-risk individuals should, together with the health care practitioners, develop action plans that include regular carriage of epinephrine, required skills to use epinephrine, managing concomitant disease conditions, and regular follow-up assessments (1–5,19,76,77). Consideration should be given to encourage wearing patient identification jewelry (e.g., MedicAlert bracelets/pendants) to help during emergencies, the electronic flagging of records of patients who may be at risk, avoidance of treatments with potential of increasing risk of reactions or reduce the impact of epinephrine (e.g., ACE inhibitors), and establishing contacts with family physicians for regular review and training of patients (89–91). These action plans can reduce the risk of further reactions (1,4). Desensitization (also sometimes known as immunotherapy or allergen immunotherapy) can prove effective in the long-term management of anaphylaxis triggered by venom and drugs, and although trials show it is effective in those with certain food allergies, further work is needed to establish its safety profile (92–94).

Compared to other age groups, the disproportionately greater morbidity and fatality from anaphylaxis among adolescents means that long-term management among this age group requires particular attention (95–101). Transition into adolescence carries with it notable changes in the psychosocial environments of young people, which may increase their risk-taking decisions and can eventually lead to poor adherence to recommended anaphylaxis management approaches (95–101). Current management strategies among adolescents are still those tailored for parents of young children and those directed at adults, and the success rates of these among adolescents has been poor (101). There is, therefore, the need for further work in developing management approaches that are more closely tailored toward adolescents, which take into account the challenges of the developmental transitions they face and the priorities they grapple on a day-to-day basis (101). Recently, a tripartite framework for the management of anaphylaxis has been proposed, which highlights that a more integrated approach is required among adolescents that takes into account three things: the challenges of adolescents’ developmental transition, the shortcomings of current clinical...
management strategies among adolescents, and adolescents’ social network (101). Although the effectiveness of the proposed framework has not been evaluated in real life, it provides a new perspective that warrants further exploration (101).

CONTROVERSIES

The key controversies around anaphylaxis center on how to rigorously study and establish the effectiveness of established interventions that are seen by the clinical community as potentially lifesaving. Epinephrine is a particular case in point as it is universally seen as the first-line agent, but its effectiveness has not been established through rigorous randomized controlled trials (84,102,103). There is, more generally, a paucity of high-quality evidence on other supportive and second-line treatment approaches commonly used in the management of anaphylaxis reactions. Well-designed trials of these supportive and second-line treatment approaches should be considered.

Although the effectiveness of immunotherapy has been shown for venom- and drug-triggered anaphylaxis, its safety for food-triggered anaphylaxis remains a source of concern and debate; more work is needed on investigating alternative up-dosing and maintenance schedules, the role of adjuvant therapy in improving safety, and alternative routes (e.g., epicutaneous) and preparations (e.g., peptide immunotherapy).

For long-term management of adolescents with anaphylaxis, there is a need to evaluate the effectiveness of holistic strategies which are both cognizant of the barriers and facilitators to effective self-management.

Key Points

- Anaphylaxis most commonly results through a type I immune responses mediated by IgE bound to mast cells or basophils, but other mechanisms are now also recognized. Common triggers include a variety of foods (particularly in children and young people), venom of stinging insects, a range of drugs, latex, radiocontrast media, and exercise. A proportion of reactions are idiopathic, i.e., no clear trigger can be identified.
- Anaphylaxis can become rapidly fatal if appropriate therapy is not instituted immediately. Symptoms appear on the skin in 80% to 90% of patients and can vary from person to person, and within each person unique episodes can differ. Common clinical features include tachycardia, faintness, cutaneous flushing, urticaria, diffuse or palmar pruritus, and a sensation of impending doom. Target organs most commonly affected include the cutaneous system, gastrointestinal tract, respiratory tract, cardiovascular system, and central nervous system. Of these, cardiovascular and respiratory features are the most important as these are often implicated in fatal reactions.
- Diagnosis of anaphylaxis is established primarily on the basis of a detailed clinical history of the specific episode, which takes into account the exposures and events preceding onset of symptoms, e.g., foods eaten, medications taken, and exercise, and the findings on examination. Laboratory tests are not helpful in diagnosing the acute reaction, but may prove helpful in subsequently confirming a reaction. The mainstay of diagnosis involves careful pattern recognition of the characteristic symptoms and signs. Better symptom recognition requires improved training of health care professionals and standardized application of clinical criteria.
- Epinephrine is the initial drug of choice for the management of the acute reaction, supported by a fluid bolus, high-flow oxygen, and inhaled β2-agonists, as necessary. H1- and H2-blocking agents and corticosteroids (104) should be considered as second-line treatments. Long-term management involves the development of tailored self-management plans aimed at preventing future recurrences of reactions, including guidance on avoiding triggers, recognizing reactions, preparing for reactions, and appropriate self-management of reactions if they occur. For adolescents, greater attention is required and management approaches should be tailored to their needs by integrating existing management strategies and their transitional developmental challenges.

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