PERSPECTIVE

The human immune system is an assemblage of cellular and humoral components working together in a highly complex, coordinated, and elegant fashion to achieve the primary goal of protecting the human host (self) from harmful offenders (nonself). Exposure to danger signals activates the various immune mechanisms to bring about immune responses aimed at neutralizing the dangerous nonself while preserving self. The immune system can, however, overreact to otherwise harmless nonself agents, producing inappropriate responses that are harmful to the host, thereby giving rise to allergy or allergic diseases. These hypersensitivity reactions are manifested in clinical symptoms ranging from mildly inconvenient to debilitating to fatal. For practical purposes, the term allergy is used in this chapter to refer to mast cell–mediated hypersensitivity reactions. For most allergic diseases to occur, predisposed individuals need to be exposed to allergens through a process called sensitization. Substances that elicit an allergic reaction are referred to as allergens, and those that elicit an antibody response (activated by B- and T-cell receptors) are called antigens.

In this allergic continuum, there are several important allergic syndromes frequently encountered in the emergency department (ED). Urticaria is a common allergic reaction to foods, drugs, or physical stimuli and is clinically characterized by a red itchy rash. Angioedema is the other important allergic syndrome, mediated by either an allergic mechanism in response to exposure to foods, drugs, or physical stimuli or a nonallergic mechanism (e.g., angiotensin-converting enzyme [ACE] inhibitor). Angioedema is characterized by swelling of the subcutaneous tissues, which can cause airway difficulty if the larynx is involved. At the other extreme of this allergic continuum is anaphylaxis, a life-threatening systemic allergic reaction characterized by acute onset and multiorgan involvement. The term anaphylaxis is derived from Greek (ana, against; phylax, guard or protect), meaning “against protection.” Mechanistically, anaphylaxis is a type I hypersensitivity reaction (allergic), mediated by immunoglobulin E (IgE). In its most common form, anaphylaxis is precipitated by exposure to allergens in previously sensitized individuals. Timely recognition of the syndrome and proper care are essential to bring about beneficial outcomes for patients with anaphylaxis.

The term anaphylactoid reaction refers to a syndrome clinically similar to anaphylaxis that is not mediated by IgE. Its clinical presentation and treatment are identical to those of anaphylaxis. Anaphylactoid reactions appear to result from direct degranulation of mast cells (and basophils) and may follow a single, first-time exposure to certain inciting agents. In this chapter, we use the term anaphylaxis to refer to both IgE- and non–IgE-mediated reactions, obviating the need for the term anaphylactoid reaction.

Epidemiology and Risk Factors

The incidence of anaphylaxis has not been determined with certainty, but recent evidence suggests that it is increasing. There are approximately 100,000 attacks of anaphylaxis in the United States per year, of which approximately 60,000 are first-time events and 1000 to 1500 are fatal.

Factors affecting the incidence of anaphylaxis include time of the year, age, female sex (adults), higher socioeconomic status, northern locations, route of allergen exposure, and history of atopy (Box 119-1). Anaphylactic reactions seem to be more common in the summer and early fall, coincident with the outdoor season; in people of higher socioeconomic status; and in people with a history of atopy. In general, anaphylaxis is more common in adults, but in particular, it is more common in women older than 30 years and in boys younger than 16 years. The dose, frequency, duration, and route of administration of a drug also affect the tendency to develop an anaphylactic reaction; the parenteral route is more likely than the oral route to lead to an anaphylactic reaction. One interesting aspect of drug-related anaphylaxis is the constancy of administration. An anaphylactic reaction may not occur in an otherwise susceptible patient as long as a drug is administered at regular intervals. The same patient may, however, experience an anaphylactic reaction if the drug is resumed after an interruption of therapy.

Risk factors for increased severity and mortality of an anaphylactic reaction include having a recent episode of anaphylaxis, extremes of age, presence of atopy or cardiopulmonary conditions, taking medications that may influence timely recognition of the symptoms or impede the treatment of anaphylaxis, and rapid onset of symptoms after exposure (see Box 119-1). The more rapid an anaphylaxis reaction is after an exposure, the more likely it is to be severe and potentially fatal. Whereas anaphylaxis in an infant is a rare event, timely recognition of an anaphylactic reaction in an infant can be difficult because signs of anaphylaxis, such as flushing, vomiting and diarrhea, lethargy, and dystonia after feeding, can be overlooked as minor reactions. Elders, on the other hand, tend to have worse outcomes in anaphylaxis because of their comorbid conditions, notably heart failure, ischemic heart disease, hypertension, and obstructive lung diseases. A history of asthma and atopy is associated with a more severe or fatal anaphylactic reaction. This is particularly true when the allergen is administered by the mucosal route (e.g., food). Atopy does not, however, seem to be a risk factor when the allergen is administered parenterally (e.g., penicillin). Patients with psychiatric disorders and individuals taking medications and drugs that may impede prompt recognition of an anaphylaxis reaction are also at increased risks (e.g., recreational drugs, alcohol, tranquilizers, and hypnotics). In addition, two classes of medications concurrently...
taken by patients may increase their risks of anaphylaxis severity. ACE inhibitors can cause an accumulation of kinins and bradykinin and thus can exacerbate the angioedema in anaphylaxis. Beta-blockers can oppose the actions of adrenergic agents used in anaphylaxis treatment, potentially leading to protracted hypotension.

**Triggers for Anaphylaxis**

Virtually any agent that is capable of activating mast cells (or basophils) can potentially precipitate an anaphylactic reaction. In approximately one third of the cases, however, an inciting agent cannot be identified. When a cause can be determined, foods, medications, and insect stings are the most common causes of anaphylactic reactions. Box 119-2 lists most common agents by their proposed immunologic mechanism. Reactions without identifiable causative agents are classified as physically induced or iatrogenic anaphylaxis.

**Foods**

Foods are the major identifiable causative agents, accounting for approximately one third of the cases of anaphylaxis. A variety of foods have been identified, ranging from the well-known (nuts, shellfish, and eggs) to the obscure (chamomile tea, which may have cross-reactivity with ragweed). Cow’s milk, egg, peanut, soy, wheat, fish, shellfish, and tree nuts are foods that most commonly cause anaphylaxis. Even for a person with a known history of food allergy, it may be difficult to avoid foods that may cause allergic reactions because their identity may be obscured in processing (e.g., consuming wine contaminated with Hymenoptera venom).

Because allergenic foods are first absorbed transmucosally, symptoms of food anaphylaxis may first appear localized to the upper airway of the respiratory tract. When anaphylactic allergens are administered parenterally, symptoms of anaphylaxis tend to be more cardiovascular and systemic. Allergic reactions to foodstuffs are more common in children, with incidence ranging from 0.3 to 7.5%. Therapeutic and prophylactic use of large quantities of antibiotics is common in the production of beef cattle, swine, fish, poultry, and sometimes vegetables and fruits. Along with antibiotics, sodium and potassium bisulfites and metabisulfites are used as preservatives in foods. Sulfites have been used as antioxidants in the food and restaurant industry to prevent discoloration of vegetables (e.g., salad bars and avocado dips), fruits, and potatoes and to preserve fruit and vegetable juices. They are also used to prevent bacterial contamination and oxidation of wines, beers, and distilled beverages. Sensitivity to ingested sulfites has been well documented, especially among asthmatics. Establishment of a particular foodstuff or preservative as the causative agent of anaphylaxis can be difficult.

**Antibiotics**

Allergic reactions to common antibiotics, such as benzylpenicillin, semisynthetic penicillin, and cephalosporins, are well documented; allergy to penicillin is perhaps the most commonly reported medication allergy. Because of their low molecular
weights, these antimicrobials themselves do not possess antigenic properties (they are hapten). They become immunologically active (i.e., elicit an immunologic response) only after they bind to a “carrier” host protein. Although patients often report a history of penicillin allergy, this may not stand up to close scrutiny.13 Studies have shown that up to 90% of individuals with a reported history of penicillin allergy can safely use penicillin; these individuals usually either are mislabeled as penicillin allergic or lose their allergy after years of avoidance.14 Depending on the studies, the frequency of allergic reactions to penicillin varies from 0.01 to 0.05% (1 to 5 reactions per 10,000), with an anaphylactic reaction rate of less than 0.01% and a fatality rate of less than 0.002% (less than 1 fatality per 50,000 penicillin administrations).15 Parenterally administered penicillin is responsible for most of the anaphylactic reactions. The extensive use of this drug in unsuspected sources such as foods, in which it is used as a bacteriostatic agent, may make it difficult to ascertain historically that penicillin is not the causative agent.

Cephalosporins share the β-lactam ring structure and side chains of the penicillins, and allergic cross-sensitivity has been incriminated in 1 to 8% of patients.16 Patients who have urticaria or anaphylactic reactions after taking penicillin are approximately four times more likely to have an adverse reaction to cephalosporins. Even in this setting, the risk of an anaphylactic reaction to cephalosporins is still less than 0.1%, and the first dose of cephalosporin can be administered orally under medical supervision.17

**Insect Stings**

Hymenoptera venoms and fire ant stings are responsible for significant anaphylactic morbidity and mortality.18 The Hymenoptera venoms are complex mixtures of pharmacologically and biochemically active substances. Honeybee venom contains hyaluronidase, phospholipase A, and other peptides. Yellow jacket venom contains not only phospholipases A and B and hyaluronidase but also kinins. Hornet venom contains acetylcholine in addition to those typical peptides. Fire ant venom is mostly a nonproteinaceous alkaloid suspension containing phospholipase A and hyaluronidase.

Stinging Hymenoptera insects affect up to 13.6 million Americans annually (c. 1999), accounting for approximately 50 to 100 deaths annually.19 Allergic sensitization to Hymenoptera has been reported in 0.4 to 4% of the general population. The principal offenders (in decreasing order of frequency) are yellow jackets, honeybees, wasps, and yellow and bald-faced hornets. The imported fire ant has become a significant pest responsible for anaphylaxis, spreading from the Atlantic and Gulf coasts inland.20 The introduction of killer (Africanized) bees in Brazil and their subsequent northern migration make them a significant cause of sting-induced anaphylaxis in areas of Texas, Arizona, and the southwestern United States.21

**Other Agents**

**Latex and Medical Products.** Latex allergy refers to sensitivity to the proteins or chemicals contained in the latex products. The sensitivity reaction can be delayed (type IV) contact dermatitis or an immediate hypersensitivity (type I) reaction (Box 119-3). The most common symptoms of latex allergy include allergic urticaria, rhinitis, conjunctivitis, and occupational asthma. Although latex allergy used to be more common, with the institution of nonpowdered gloves and nonlatex gloves in hospitals, anaphylactic reaction from latex has become an uncommon event.22 Anaphylactic reactions have also occurred against ethylene oxide (ETO), which is used to sterilize hemodialyzers. ETO can bind with human proteins such as human serum albumin (HSA), rendering the ETO-HSA complex allergenic.

### Box 119-3  Gell and Coombs Classification of Immune Reactions

**Type I: Immediate Hypersensitivity**

Binding of multivalent antigens to IgE on the surface of mast cells and basophils leads to degranulation of mediators. In previously sensitized individuals, the reaction develops quickly (minutes). This type of hypersensitivity reaction is seen in allergic diseases (e.g., hay fever, allergic asthma, urticaria, angioedema, and anaphylaxis). Anaphylactoid reaction refers to the direct release of preformed mediators of mast cells independent of IgE.

**Type II: Cytotoxic Antibody Reaction**

Antibody (IgM, IgG) binding of membrane-bound antigens leads to cytotoxicity and cell lysis of cells through the complement or mononuclear cell system (macrophages, neutrophils, and eosinophils). This type of reaction is seen in transfusion reaction and Rh incompatibility.

**Type III: Immune Complex–Mediated Reaction**

Binding of antibody (IgM, IgG) to antigens forms soluble immune complexes, which are deposited on vessel walls, causing a local inflammatory reaction (Arthus reaction) leading to inflammation and tissue injury. This type of reaction is seen in systemic lupus erythematosus and serum sickness (after antithymocyte globulin administration).

**Type IV: Cell-Mediated Delayed Hypersensitivity**

Sensitized lymphocytes (Tc,1 cells) recognize the antigen, recruit additional lymphocytes and mononuclear cells to the site, and start the inflammatory reaction. No antibodies are involved. This type of reaction is seen in contact dermatitis, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

**Anesthetic Drugs.** Local anesthetics produce occasional adverse reactions.23 Most of these reactions are not allergic in nature but are related to a direct effect of the medication. True allergic reactions are uncommon and are most commonly seen with local anesthetics from the ester family (e.g., procaine, tetracaine, and benzocaine). Allergic reactions to local anesthetics belonging to the amide family (e.g., lidocaine, bupivacaine, mepivacaine, and dibucaine) are rare. Multidose vials of lidocaine contain the preservative methylparaben, which belongs structurally to the ester family. This preservative has been implicated in allergic reactions in patients with a history of previous lidocaine hypersensitivity.24 Only pure lidocaine (without the methylparaben preservative) should be used in intravenous applications (as in Bier’s block).

**Vaccines.** Anaphylactic reactions have occurred after the administration of egg embryo–grown vaccines, including the combined measles, mumps, and rubella (MMR), yellow fever, and influenza vaccines. Patients who are able to tolerate eggs orally are likely to tolerate the vaccines.

**Blood Products.** Anaphylactic-type reactions are an uncommon complication of the administration of whole blood and immunoglobulins. The fixation of antibodies to formed elements such as red blood cells, platelets, and leukocytes and soluble components activates the complement system. This is particularly relevant in IgA-deficient patients exposed to multiple transfusions, who may have produced antibodies to IgA in previous transfusions. With subsequent transfusions, an antigen (IgA)–anti-IgA antibody (IgG) immune complex forms, leading to subsequent activation of the complement cascade.

**Opiates.** Many of the opioid analgesics can cause anaphylactic reaction through a direct histamine release mechanism, although some are IgE mediated. It is unclear how much cross-sensitivity is present among these agents.25
Radiographic Contrast Media. Radiographic contrast media (RCM) represent an important class of drugs that can cause an anaphylactic reaction. Approximately 10 million radiologic studies using RCM are performed in the United States annually. Anaphylactic reactions to RCM are largely idiosyncratic, occur within minutes of infusion, and are independent of the dose. The pathophysiologic mechanism of anaphylactic reactions to RCM is unknown, but it is believed to be nonimmunologic. Suggested mechanisms include direct histamine release, alternative complement pathway activation, and activation of the contact system. Risk factors for an anaphylactic reaction include a previous adverse reaction to RCM, a history of atopy or allergic disease, asthma, and certain medications. A history of allergy to fish or shellfish is not a contraindication to the use of RCM, nor does it increase the risk of an adverse reaction to RCM. Clinically, the risk for severe adverse reaction is 0.16% with ionic contrast materials and 0.03% with nonionic contrast materials. The death rate from RCM reactions is estimated at 1 to 3 per 100,000 administrations of contrast material. Protocols have been developed to minimize risks of a serious allergic reaction in patients who have had a previous adverse reaction to RCM but who still require additional radiographic studies with contrast agents (Box 119-4).

Aspirin and NSAIDs. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) are believed to cause anaphylaxis (or anaphylactoid reaction) through interruption of arachidonic acid metabolism. The incidence of anaphylaxis to aspirin and NSAIDs varies widely, depending on the population (healthy, atopic, or those with nasal polyps). One study estimated the incidence as 2.1 anaphylaxis cases per 100,000 exposed patients. Desensitization protocols have been suggested for cardiovascular patients with a history of aspirin allergy. For aspirin-induced cutaneous disease, an aspirin desensitization protocol that can be used for cardiovascular patients in the ED is to administer aspirin every 15 minutes, starting with 0.1 mg, up to 325 mg at 135 (FD&C Yellow No. 5), may also cause anaphylaxis through modulation of arachidonic acid metabolism.

Immunotherapy Drugs. Allergen extracts are commonly used in skin testing and in immunotherapy (also known as hyposensitization or desensitization). Exposure to therapeutic pollens, by injection or inhalation, can result in local allergic or systemic anaphylactic reactions. High-dose therapy, too frequent administration, or inadvertent intravascular injection increases the risk of anaphylaxis with immunotherapy.

Steroids. Although corticosteroids are used in the management of acute allergic syndromes and anaphylaxis, adverse reactions to these medications have been observed after parenteral administration. Skin testing may demonstrate the specific class of steroids responsible for hypersensitivity, and substitution of a different class should be considered.

Exercise (Physical)–Induced Anaphylaxis. Thermomechanical and physical factors (heat and cold), especially exercise, have increasingly been recognized as etiologic agents in certain anaphylactic-like incidents. The mechanism is unclear, but release of mediators from mast cells and basophils has been implicated. Patients with exercise-induced anaphylaxis are generally dedicated athletes who may have a personal or family atopic history. Exercise-induced anaphylaxis has been demonstrated in some cases to depend on previous ingestion of food to which the patient may be subclinically sensitive. Provocative foods, if identified, should be avoided. Patients should discontinue the exercise at the onset of rash or pruritus. When exercise is continued beyond this point, clinical deterioration is likely in susceptible individuals. Prophylactic treatment with an antihistamine as a single agent or in combination with other agents may be helpful. Avoidance of precipitating factors, modification of exercise, and use of a self-injectable epinephrine kit are recommended for patients with exercise-induced anaphylaxis.

Idiopathic Anaphylaxis. In the United States, approximately 20,000 to 47,000 patients annually see allergists for signs and symptoms of idiopathic anaphylaxis (IA). The diagnosis of IA is made only after extensive evaluation by the allergist. Although IA may be life-threatening, it is usually responsive to conventional therapies, including antihistamines, sympathomimetics, and especially prednisone. Some cases of IA may appear to be caused by the act of kissing but are in fact caused by food or conversion disorders. The overall prognosis for IA is good, but certain patients may experience recurrent IA despite intensive prophylactic therapy. Sometimes, IA can represent “progestrone” anaphylaxis. Women suffering from this disorder may present with recurrent episodes of anaphylaxis that are temporally related to the menstrual cycle. Other patients may have anaphylactic reactions to injection of medroxyprogesterone or luteinizing hormone–releasing hormone.

PRINCIPLES OF DISEASE

Because allergy is intimately related to immunology, a brief review of immunology is included in this chapter. Immunologic responses to antigens in humans are coordinated by two systems: the ancient innate immune system, which humans inherited from invertebrates; and the recently evolved adaptive immune system, which is present in humans and vertebrates (Fig. 119-1). The innate immune system is considered the first line of defense, characterized by its nonspecific but rapid responses to offending agents or microbes. Its effector components include resident cells (epithelial cells, mast cells, macrophages, dendritic cells, antimicrobial proteins), infiltrative cells (natural killer cells, neutrophils, monocytes, dendritic cells), and various proteins (antimicrobial peptides, complements, cytokines, pathogenic pattern recognition receptor [PRR] system). Encoded in the germline, PRRs can recognize pathogen-associated molecular patterns (PAMPs) extracellularly or intracellularly. PAMPs are evolutionarily conserved molecular patterns that are present in microbes but not in humans (except in mitochondrial DNA). On exposure of the human host to these PAMPs, the PRR and subsequently the innate system and the inflammatory cascade are activated, leading to the clearance of dangerous PAMPs. The innate system responds to the danger signals rapidly and nonspecifically, whereas the adaptive immune system takes time for the antigen–specific cells (B and T cells) to amplify through a process known as clonal expansion to mount a specific immune response. In contrast to the innate system, the adaptive immune system is characterized by the delayed response, immune memory, enormous diversity, and exquisite specificity. The effector components of the adaptive system include B and T lymphocytes and cytokines. B and T cells are capable of recognizing myriad antigens through a vast library of antibodies and receptors (up to 10^15). This diversity is accomplished by somatic rearrangement of fewer than 400 genes.
**Chapter 119 / Allergy, Hypersensitivity, Angioedema, and Anaphylaxis**

Figure 119-1. Developmental pathways of the immune and hematopoietic systems. CFU-GEMM, colony-forming unit for granulocyte, erythroid, myeloid, and megakaryocyte.

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**Development of the Immune System and Mechanism of Immune-Mediated Injury**

The adaptive and innate immune systems originate from the common pluripotential hematopoietic stem cells, which are derived from the yolk sac and later reside in the bone marrow. These stem cells differentiate and develop into the lymphoid precursor cells and the colony-forming unit for granulocyte, erythroid, myeloid, and megakaryocyte (CFU-GEMM) stem cells. The lymphoid precursor cells differentiate into bursa-equivalent lymphocytes (B cells), thymus-derived lymphocytes (T cells), and natural killer cells. The CFU-GEMM cells develop into mast cells, basophils, and others (see Fig. 119-1). When the host encounters a foreign antigen, the cellular components of the adaptive immune system interact with the cellular and protein components of the innate immune system to mount a concerted defense aimed at neutralization of the antigen.

**T-Cell Development**

Lymphoid precursor cells migrate from the bone marrow into the thymus, where they continue their ontogeny. Under regulation by cytokines and cell-cell interaction, these precursors undergo gene rearrangement and positive and negative selection. In the process, T cells acquire the T-cell antigen receptors and various surface markers. Two types of T cells mature and come out of the thymus: CD4⁺, also called helper T cells (60-70%), and CD8⁺, also called suppressor T cells (30-40%). Depending on the type of cytokine produced, T helper cells differentiate into type 1 helper cells (Th1) and type 2 helper cells (Th2), with opposing activities. Whereas Th1 cells inhibit IgE production and IgE isotype switching, Th2 cells stimulate IgE production and IgE isotype switching. The balance of these stimulatory and inhibitory activities of the Th1 and Th2 cells is believed to determine an individual’s propensity to develop allergic disease or atopy and may help explain the increased prevalence of allergy in urbanized and Western societies in the past three decades. Early in utero and soon after birth, naïve T lymphocytes in the infant’s immune system are dominated by the allergy-prone Th2 cells and their associated cytokines (interleukins 4, 5, and 13). These cytokines are important inducers for production of IgE antibodies. Later, during infancy through early childhood and adolescence, the nonatopic infant’s immune system gradually shifts from this allergy-prone Th2 environment to an allergy-protective Th1 environment. The cytokines associated with this Th1 environment include interleukin-2 and interferon-γ. This shift is thought to be caused by the continual exposure of the young individual’s immune system to allergenic stimuli from the surrounding environment, mainly microbes. Features of Western lifestyles, such as changes in infant diets, widespread use of antibiotics, smaller family size, and cleaner childcare, are believed to reduce this stimulatory antigenic exposure in an individual’s early years, leading to an environment in which the immune system is dominated by a persistent allergy-prone Th2 system (the hygiene hypothesis). This imbalance between the two immune systems supposedly ultimately leads to atopy and thus an allergy-prone population.

**B-Cell Development and Immunoglobulins**

B-cell ontogeny is divided into antigen-independent and antigen-dependent stages. During the antigen-independent stage, B cells mature in primary lymphoid organs (bone marrow and fetal liver), where they undergo gene rearrangement in a stochastic
The term allergy is commonly used to describe clinical illnesses produced by excessive immune responses by a normal immune system to otherwise innocuous allergens. In this chapter, we adapt the classic Coombs and Gell classification to categorize these hypersensitivity reactions (Box 119-5).

**Type I reactions** (immediate hypersensitivity) are IgE mediated and account for most allergic and anaphylactic reactions observed in humans. Exposure to sensitizing allergens causes mediators from mast cells and basophils to be released through both IgE-dependent and direct mast cell degranulation (IgE-independent) mechanisms. Rhinitis caused by ragweed pollen and anaphylaxis caused by foods are examples of the IgE-dependent mechanism; anaphylactic reaction to aspirin is an example of the IgE-independent mechanism.

**Type II reactions** (cytotoxic) denote antibody-mediated cytoxic reaction. Complement-fixing IgG (or IgM) engages cell-bound antigen, activating the classic complement pathway and leading to the fixation of membrane attack complexes on the cell surface and subsequent cell lysis. In the process, anaphylatoxins C3a and C5a cause mast cell mediators to be released, producing the same clinical syndrome seen in allergic anaphylaxis.

**Type III reactions** (immune complex) are IgG or IgM complex mediated. Circulating soluble antigen-antibody immune complexes migrate from the circulation to be deposited in the perivascular interstitial space, thereby activating the complement system. Anaphylactic reactions to blood transfusions and blood component therapy, including serotherapy (immunoglobulin administration), are examples of the overlap of type II and type

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**Classification of Reactions**

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Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

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


*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and <90 mm Hg from 11 to 17 years.

BP, blood pressure; PEF, peak expiratory flow.

III reactivity. They have therefore been classified as complement-mediated or immune complex-mediated anaphylaxis.

Type IV reactions (delayed hypersensitivity) are T-cell-mediated and have no documented relationship to the pathogenesis of anaphylaxis.

PATHOPHYSIOLOGY

Mast cells, basophils, and their mediators are the central effectors in allergy and anaphylaxis. Exposure of a genetically predisposed individual to an allergen leads to the synthesis and release of allergen-specific IgE by plasma cells into the circulation. Fixation of this allergen-specific IgE to surface receptors on mast cells (FceRI) completes the process known as sensitization. These IgE-bearing mast cells usually reside in the mucosal surfaces, submucosal tissue (around venules), and cutaneous surfaces, and they are capable of becoming activated on reexposure to a specific allergen. Cross-linking of the FceRI receptors on the mast cells by a specific multivalent allergen sets off a cascade of conformational and biochemical events, causing the degranulation of preformed mediators, subsequent generation and release of arachidonic acid metabolites, elaboration of cytokines and chemokines, and activation of the cellular components by the innate and adaptive systems. These series of events ultimately lead to the clinical syndrome of allergy and anaphylaxis (see Fig 119-2).

Mediators of Anaphylaxis

The numerous mediators released by mast cells and basophils exert overlapping physiologic effects on target organs and tissues, making it difficult to ascribe specific clinical manifestations to any one mediator. Histamine is the most important mediator and responsible for most of the clinical symptoms (Table 119-1). It is an essential mediator in immediate hypersensitivity and inflammation, and its infusion has been shown to produce the majority of the clinical features of anaphylaxis syndrome.45 There are three classes of histamine receptors: H1, H2, and H3. H1 receptor stimulation produces bronchial, intestinal, and uterine smooth muscle contraction; coronary artery spasm; plaque rupture; and acute myocardial infarction (Kounis syndrome).46 H1 receptor stimulation also increases vascular permeability, nasal mucus production, eosinophil and neutrophil chemokinesis, and chemotaxis. H2 receptor stimulation increases the rate and force of ventricular and atrial contraction, gastric acid secretion, airway mucus production, and vascular permeability while also causing bronchodilation and inhibition of basophil histamine release. H3 receptors are found in neurons (in the central nervous system) and peripheral tissues; these receptors control the synthesis and release of histamine.

In addition to histamine, lipid metabolites elaborated through the prostanoiand leukotriene pathways contribute to the adverse physiologic effects induced by histamine. Prostaglandin D3 (PGD3) is the main arachidonic acid metabolite released by activated mast cells (but not by basophils). PGD3 and thromboxanes are synthesized from arachidonic acid by the cyclooxygenase pathway (through both COX-1 and COX-2). PGD3 is responsible for hypotension, inhibition of platelet aggregation, and bronchospasm; PGD3 is approximately 30 times more potent than histamine in causing bronchoconstriction. The cysteinyl leukotrienes LTD4, LTC4, LTE4, and LTE5 are synthesized from arachidonic acid through the lipoxgenase pathway. LTD4 and LTC4 are first synthesized intracellularly in mast cells and basophils and then secreted; LTC4 is subsequently converted to LTD4 and LTE4 in the extracellular space (by γ-glutamyl transpeptidase and dipeptidase). They are involved in cholinergic-independent bronchospasm, increased vascular permeability, and increased mucous gland production. These three leukotrienes have slow onset but potently add to the bronchoconstriction already induced by histamine (LTC4 and LTD4 are 1000 times more potent than histamine).

Platelet-activating factor (PAF) is a phospholipid and the most potent compound known to cause aggregation of human platelets. Its other actions include neutrophil activation and chemotaxis and ileal and parenchymal lung strip smooth muscle contraction. PAF produces many of the important clinical manifestations of anaphylaxis, including decreased myocardial contractile force, coronary vasoconstriction, pulmonary edema, and prolonged increase in total pulmonary resistance with a decrease in dynamic compliance.47,48 Indeed, blockage of PAF with experimental antagonists leads to improved cardiac function, suggesting that PAF may be involved in the late cardiac dysfunction and lethality associated with anaphylaxis.49

Recent data have highlighted the important roles that nitric oxide and sphingosine 1-phosphate play in anaphylaxis. Sphingosine 1-phosphate can trigger calcium influx, stimulating synthesis of cytokines and mast cell degranulation. Nitric oxide is synthesized in vascular endothelium and is a sufficiently potent vasodilator to cause hypotension in anaphylaxis. Its action can be increased by histamine, leukotriene, tumor necrosis factor alpha, and PAF.50,51

**Physiologic Effects**

At the organ and tissue level, mediators released from mast cells and basophils account for the overall pathophysiologic effects of anaphylaxis, which variably are manifested clinically as urticaria and angioedema, rhinorrhea, conjunctivitis, chest pain, breathing difficulty, respiratory insufficiency, headache, syncope,
hypotension and hemodynamic instability, nausea, vomiting, diarrhea, and other gastrointestinal symptoms (see Table 119-1). Increased vascular permeability caused by histamine leads to urticaria, angioedema, laryngeal edema, nasal congestion, or gastrointestinal swelling with abdominal cramping and vomiting. Vasodilation can lead to flushing, headaches, reduced peripheral vascular resistance, hypotension, and syncope. Contraction of smooth muscle can lead to bronchospasm, abdominal cramping, or diarrhea. Pulmonary vessel vasconstriction can lead to pulmonary hypertension, pulmonary edema, and decreased cardiac filling pressures. Coronary vasoconstriction can lead to myocardial ischemia and decreased myocardial contractile force. Changes in atrial chronotropy and ventricular and atrial isoproterenol can lead to cardiac dysrhythmias. In addition to the direct actions on the target tissues, these preformed mediators, lipid-derived mediators, and cytokines activate a number of inflammatory pathways, including the complement system, the clotting and clot lysis systems, and the kallikrein-kinin (contact) system, to add to the clinical manifestations of allergy and anaphylaxis. Deaths in anaphylaxis are caused most commonly by acute respiratory failure due to laryngeal angioedema and less commonly by cardiovascular collapse.

Hemodynamic instability in anaphylaxis is typically the result of peripheral vasodilation, enhanced vascular permeability, leakage of plasma, and intravascular volume depletion (the “empty ventricle” syndrome). Up to 50% of intravascular volume can shift to the extravascular space within 10 minutes of exposure. In a number of clinical settings, the hypotension in anaphylaxis is also associated with depressed cardiac index and increased pulmonary vascular resistance. The use of pressors alone in anaphylaxis may not improve hemodynamics. Aggressive volume expansion with crystalloid (2-7 L of normal saline) is needed for hypotension in anaphylaxis.

**CLINICAL FEATURES**

Anaphylactic reactions vary in duration and severity, affecting organs that are rich in mast cells—the cutaneous, upper and lower respiratory, cardiovascular, neurologic, and gastrointestinal systems. Clinical presentations of anaphylaxis depend on the degree of hypersensitivity; the quantity, route, and rate of antigen exposure; the pattern of mediator release; and the target organ sensitivity and responsiveness. Symptoms of anaphylaxis usually occur minutes after an exposure, although some reactions take longer (>30 minutes). Protracted anaphylaxis may last up to 32 hours. Up to 20% of patients may present with biphasic anaphylaxis, in which clinical symptoms recur 8 to 24 hours after resolution of symptoms from the index event. There are no firmly established factors that can be used to predict which group of patients is at risk for this biphasic attack, although delayed and inadequate administration of epinephrine after the index event and the lack of steroid use have been cited in some studies. Fatal cases of anaphylaxis are usually caused by acute respiratory failure due to laryngeal edema and less commonly by cardiovascular collapse.

The first clinical manifestation of anaphylaxis usually involves the skin (88%), described as generalized warmth and tingling of the face, mouth, upper chest, palms, soles, or the site of antigenic exposure. Pruritus is a nearly universal feature and may be accompanied by generalized flushing and urticaria. Patients presenting with angioedema may complain of swelling and a sensation of burning under the skin but no itchy rash. This may be followed by mild to severe respiratory distress. The patient may describe a cough; a sense of chest tightness, dyspnea, and wheeze from bronchospasm; or throat tightness, dyspnea, odynophagia, or hoarseness associated with laryngeal edema or oropharyngeal angioedema. Hypotension or dysrhythmias may be manifested as lightheadedness or syncope. Seizure activity caused by decreased cerebral perfusion may rarely be observed. Any of these clinical patterns may occur independently or in association with nasal congestion and sneezing; ocular itching and tearing; cramping abdominal pain with nausea, vomiting, diarrhea, and tenesmus; incontinence; pelvic pain and uterine cramping; headache; or a sense of impending doom. Although urticaria and angioedema are the most common presenting symptoms in anaphylaxis (88%), fatal anaphylaxis syndromes with laryngeal edema and circulatory collapse may occur even in the absence of any premonitory warning symptoms or signs or cutaneous manifestations.

The physical examination may reveal tachypnea, tachycardia, and hypotension. Laryngeal stridor, hypersalivation, hoarseness, and angioedema indicate upper airway obstruction, whereas coughing, wheezing, rhonchi, and diminished air flow suggest lower respiratory tract bronchoconstriction. Tachycardia and hypotension suggest cardiac insufficiency. Commonly observed dysrhythmias include sinus tachycardia, premature atrial and ventricular contractions, nodal rhythm, and atrial fibrillation. Other electrocardiographic changes include nonspecific and ischemic ST-T wave changes, right ventricular strain, and intraventricular conduction defects. The patient may have a depressed level of consciousness because of hypotension; rarely, this may be caused
by a postictal state due to seizure activity. Urticaria, angioedema, rhinitis, and conjunctivitis may be evident. A summary of the observed clinical manifestations of anaphylaxis along with their related pathophysiologic changes is presented in Table 119-2.

**DIAGNOSTIC STRATEGIES**

The diagnosis of anaphylaxis remains clinical. A good history and physical examination offer emergency physicians the best tools in diagnosis of anaphylaxis. The diagnosis of anaphylaxis is “highly likely” in a patient presenting with skin symptoms (itchy urticaria, flushing, and swollen lips, tongue, or throat) and either respiratory difficulty (dyspnea, wheezing, and stridor) or reduced blood pressure, after an acute exposure (see Box 119-5). Diagnostic laboratory testing is limited and seldom used in the ED. Anaphylaxis can be confirmed by testing for allergen-specific IgE and serum tryptase, serum histamine, or 24-hour urine histamine in select cases. Screening studies are aimed at ruling out of other emergencies (Box 119-6). The initial screening studies can include a complete blood count, complete metabolic panel (hypoglycemia), coagulation panel (prothrombin time, partial thromboplastin time, and international normalized ratio), cardiac enzymes, electrocardiogram, urine analysis, erythrocyte sedimentation rate, and portable chest radiograph. Serum levels of serotonin and urinary 5-hydroxyindole acetic acid, catecholamines, and vanillylmandelic acid are useful to rule out carcinoid syndrome. Serial arterial blood gas analysis may help monitor clinical response. Blood acid are useful to rule out carcinoid syndrome. Serial arterial blood gas analysis may help monitor clinical response.

**DIFFERENTIAL DIAGNOSIS**

The diagnosis of anaphylaxis is readily apparent in a patient presenting with acute rash, respiratory difficulty, or cardiac insufficiency after an allergenic exposure. Considerations for confounders and other diseases with overlapping presentations are shown in Box 119-6.

**Urticaria and Angioedema**

Generalized urticaria is usually allergic in nature (i.e., mast cell mediated). In half of the cases, it is accompanied by angioedema and may meet the definition for anaphylaxis. Similarly, most cases of angioedema are allergic and usually associated with urticaria. Angioedema caused by bradykinin excess (e.g., hereditary angioedema or ACE inhibitor) usually is manifested without urticaria. The treatment of this “nallergic” angioedema is rapidly evolving with ongoing clinical trials and new medications approved by the Food and Drug Administration (FDA). Adverse cutaneous drug reactions (ACDR) comprise a spectrum of skin manifestations due to complications from drug therapy. The majority of these ACDRs are minor allergic reactions (e.g., IgE-mediated urticarial rash to penicillin). Severe, life-threatening ACDRs (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis, fixed drug eruption, drug hypersensitivity syndrome) may mimic drug-induced anaphylaxis.

**Flush Syndrome**

Flush syndrome refers to a group of diverse clinical entities that are characterized by the onset of redness and a feeling of warmth of the face, neck, trunk, and abdomen. Flushing of the face induced by alcohol is common in Asian patients. Monosodium glutamate (MSG) and its cyclization product pyroglutamate are common seasonings in Chinese foods and can provoke flushing. Scombroidosis, a type of histamine poisoning, is caused by the ingestion of spoiled fish that have a high histidine content (generally dark meat fish such as tuna); histamine and cis-urocanic acid are produced by histidine-decarboxylating bacteria that cleave histamine from histidine when the fish are not properly stored.

Patients usually present with a frightening flush (sunburn like) but no urticaria, palpitations, syncope, nausea, vomiting, or diarrhea. A number of neoplastic disorders (mastocytosis, carcinoid syndrome, VIPoma, medullary carcinoma of the thyroid) secrete vasoactive substances that are present in anaphylaxis. Harlequin syndrome refers to the hemifacial flushing and sweating induced by exercise.

**Respiratory Insufficiency**

Epiglottitis, supraglottitis, retropharyngeal and peritonsillar abscess, laryngeal spasm, foreign body aspiration, tumor, obstructive lung diseases such as acute asthma, and status asthmaticus can be manifested with acute respiratory difficulty but are usually not associated with other symptoms and signs of anaphylaxis. Exercise-induced anaphylaxis can be differentiated from exercise-induced asthma as the former is usually accompanied by pruritus and other systemic manifestations of anaphylaxis. Patients with acute pulmonary embolism may present with respiratory difficulty and shock but without the cutaneous stigmata of anaphylaxis.

**Shock and Cardiovascular System**

Patients with anaphylactic shock may present with urticarial rash, angioedema, respiratory insufficiency, hypotension, vasodilation, and signs and symptoms of end-organ hypoperfusion. This form of shock must be differentiated from early presentations of septic shock (end-organ hypoperfusion, rash, vasodilation, hypotension). A history of recent allergenic exposure is helpful in making the diagnosis of anaphylaxis. Spinal shock also presents with hypotension and vasodilation but usually without the urticarial rash and in the setting of significant spinal injury. In all these forms of shock, the skin is usually moist and warm, suggesting a state of decreased peripheral vascular resistance. Cardiogenic, restrictive, hypovolemic, or hemorrhagic shock, on the other hand, would more likely be seen with signs and symptoms of end-organ hypoperfusion and cold, clammy skin, suggesting a state of heightened peripheral vascular resistance. In addition to history, measurement of central venous pressures may add useful data in teasing out the different forms of shock.

**Syncope**

Vasovagal syncope is the most common differential diagnosis in the patient arriving with collapse as a result of parenteral administration of an antigen. Classically, the patient has bradycardia, hypotension, and pallor as opposed to the tachycardia, hypotension, and flush skin usually associated with anaphylaxis. The absence of any other clinical manifestations of anaphylaxis, along with history of stress, pain, and previous episodes of simple fainting, helps point toward the diagnosis of vasovagal syncope. Other causes of syncope, such as seizure, stroke, hypoglycemia, acute coronary syndrome, and cardiac dysrhythmia, also need to be considered. Ordinary allergic reactions and especially anaphylaxis can precipitate an acute coronary syndrome.

**MANAGEMENT**

**Out-of-Hospital Care**

When a susceptible patient is reexposed to an antigen to which there has been a previous reaction, self-administered epinephrine is recommended at the first onset of clinical manifestations of...
Table 119-2 Clinical Manifestations of Anaphylaxis and Related Pathophysiologic Changes

<table>
<thead>
<tr>
<th>ORGAN SYSTEM</th>
<th>REACTION</th>
<th>SYMPTOMS</th>
<th>SIGNS</th>
<th>PATHOPHYSIOLOGIC CHANGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory tract</td>
<td>Rhinitis</td>
<td>Nasal congestion, nasal itching, sneezing</td>
<td>Nasal mucosal edema, rhinorrhea</td>
<td>Increased vascular permeability</td>
</tr>
<tr>
<td>Upper</td>
<td>Laryngeal edema</td>
<td>Hoarseness, throat tightness, hoarseness</td>
<td>Laryngeal stridor, supraglottic and glottic edema</td>
<td>Stimulation of nerve endings, As above, plus increased exocrine gland secretions</td>
</tr>
<tr>
<td>Lower</td>
<td>Bronchospasm</td>
<td>Cough, wheeze, rhonchi, tachypnea</td>
<td>Cough, wheeze, rhonchi, tachypnea</td>
<td>As above, plus bronchiole smooth muscle contraction</td>
</tr>
<tr>
<td>Cardiovascular system</td>
<td>Circulatory collapse</td>
<td>Lightheadedness, generalized weakness, syncope, ischemic chest pain</td>
<td>Tachycardia, hypotension, shock</td>
<td>Increased vascular permeability</td>
</tr>
<tr>
<td></td>
<td>Dysrhythmias</td>
<td>As above, plus palpitations</td>
<td>ECG changes: tachycardia, nonspecific and ischemic ST-T wave changes, right ventricular strain, premature atrial and ventricular contractions, nodal rhythm, atrial fibrillation</td>
<td>Decreased cardiac output, decreased mediator-induced myocardial suppression, decreased effective plasma volume, decreased preload, hypoxia and ischemia, dysrhythmias, iatrogenic effects of drugs used in treatment, preexisting heart disease</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td></td>
<td></td>
<td>Pulseless</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>Urticaria</td>
<td>Pruritus, tingling and warmth, flushing, hives</td>
<td>Urticaria, diffuse erythema</td>
<td>Increased vascular permeability</td>
</tr>
<tr>
<td></td>
<td>Angioedema</td>
<td>Nonpruritic extremity, periorbital and perioral swelling</td>
<td>Nonpitting edema, frequently asymmetrical</td>
<td>Vasodilation</td>
</tr>
<tr>
<td>Eye</td>
<td>Conjunctivitis</td>
<td>Ocular itching, increased lacrimation, red eye</td>
<td>Conjunctival inflammation</td>
<td>Stimulation of nerve endings</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>Dysphagia</td>
<td>Dysphagia, cramping, abdominal pain, nausea and vomiting, diarrhea (rarely bloody), tenesmus</td>
<td>Nonspecific</td>
<td>Increased secretion of mucus, gastrointestinal smooth muscle contraction</td>
</tr>
<tr>
<td>Miscellaneous central nervous system</td>
<td>Anxiety</td>
<td>Apprehension, sense of impending doom, headache, confusion</td>
<td>Anxiety, seizures (rarely), coma (late)</td>
<td>Secondary to cerebral hypoxia and hypoperfusion, vasodilation</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Fibrinolysis and disseminated intravascular coagulation</td>
<td>Abnormal bleeding and bruising</td>
<td>Mucous membrane bleeding, disseminated intravascular coagulation, increased uterine tone, vaginal bleeding</td>
<td>Mediator recruitment and activation, uterine smooth muscle contraction, bladder smooth muscle contraction</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Pelvic pain, vaginal bleeding, urinary incontinence</td>
<td>Urinary incontinence</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ECG, electrocardiographic.

Anaphylaxis (adult dose, 0.2-0.5 mL of 1:1000 [1 mg/mL] intramuscularly; pediatric dose, 0.01 mg/kg of 1:1000 intramuscularly). Delayed administration of epinephrine is associated with increased risks of adverse outcomes. Susceptible patients can use aerosolized epinephrine from a metered-dose inhaler to counteract the effects of laryngeal edema, bronchoconstriction, and other manifestations of anaphylaxis. Multiple inhalations (e.g., 10-20 doses, resulting in the inhalation of 1.5-3 mg of epinephrine) produce therapeutic plasma levels, with the advantages of ease of administration, rapid absorption, and locally high
epinephrine levels in the upper and lower airways. Epinephrine should be used with caution in elders and those with a history of cardiovascular disease or hypertension, but it must be stated that there are no absolute contraindications to the use of epinephrine in anaphylaxis. Oral (and parenteral) diphenhydramine (50 mg) can also be administered, but this is only an adjunct therapy.

Out-of-hospital personnel may be required to resuscitate a moribund patient with basic life support. Their first priority is to establish and to maintain ventilation, intravenous access, cardiac monitoring, and administration of supplemental oxygen.

Local measures to decrease antigen absorption from an extremity include dependent positioning of the extremity, ice to vasoconstrict locally, and application of a loose tourniquet to obstruct the venous and lymphatic circulation. The tourniquet should be released for 1 minute of every 10 minutes and should never be applied continuously for more than 2 hours. If an insect stinger remains in the wound, the wound should not be squeezed because the stinger may inject more venom into the patient; the stinger should be removed gently with instruments, avoiding disturbance of the venom apparatus.

### Emergency Department

Because most of the morbidity and mortality associated with anaphylaxis are caused by acute respiratory failure or cardiovascular collapse, the treatment of anaphylaxis focuses on the triad of providing a patent airway, expanding intravascular volume with crystalloid (or colloid), and early administration of epinephrine. Antihistamines (H1 and H2) and steroids are commonly given in cases of anaphylaxis, although there is no objective evidence that they will improve the outcome. Box 119-7 summarizes the treatment algorithm in anaphylaxis.

### Airway

Patients at risk of losing their airway are preoxygenated while the airway is assessed. Because upper airway obstruction from laryngeal angioedema can progress rapidly, preparations for a difficult airway, including a surgical airway, must be made early. Premedication with nebulized epinephrine may help maximize visualization. The success rate of intubation is improved when it is performed early, before significant soft tissue swelling from orolaryngeal angioedema occurs.

### Volume Expansion

Along with airway preparation, start aggressive fluid resuscitation, which may include 1 to 2 L of normal saline (NS) infused rapidly through large-bore (e.g., 16-gauge) intravenous lines (5 to 10 mL/kg in first 5 minutes). NS is preferred to lactated Ringer’s solution, which has the potential to exacerbate metabolic acidosis. The use of a colloid solution (e.g., 5% albumin) in addition to NS may be helpful because of the increased vascular permeability in anaphylaxis. Large volumes of NS (2–7 L) may be required to reverse the fluid lost to extravascular space in anaphylaxis. Patients with heart failure or renal failure should be monitored closely for signs of volume overload.

### Epinephrine

Epinephrine is the drug of choice and the first drug to be given at the first suspicion of an anaphylactic reaction. Oral (and parenteral) diphenhydramine (50 mg) can also be administered, but this is only an adjunct therapy.

Epinephrine derives its therapeutic value from its combined alpha-adrenergic and beta-adrenergic actions. Its alpha1-adrenergic stimulation increases vasoconstriction, increases peripheral vascular resistance, and decreases mucosal edema. Its beta2-adrenergic stimulation brings about positive inotropic and chronotropic cardiac activity, and its beta2-adrenergic stimulation results in stabilization of mast cells and basophils and bronchodilation. As a result, epinephrine decreases mediator release from mast cells (and basophils), improves hives and bronchospasm, decreases mucosa edema and swelling, and reverses systemic hypotension. Epinephrine therefore works directly to improve the clinical features most commonly observed in a fatal anaphylactic reaction.

Epinephrine can, however, produce untoward side effects, such as palpitations, anxiety, and headache. Excessive alpha-agonist activity (as in overdose) can result in a hypertensive crisis and
Emergency Measures (taken simultaneously)

Remove any triggering agent. If the patient had a sting or immunization injection, place a loose tourniquet proximal to the site; if the reaction site is on an extremity, place the extremity in dependent position.

Place patient in the Trendelenburg position if hypotensive. Begin cardiac monitoring, pulse oximetry, and blood pressure autonomic monitoring; apply oxygen non-rebreather mask, establish large-bore intravenous lines, draw blood, obtain stat electrocardiogram and portable chest radiograph. Establish a patent airway.

Open the airway by head tilt/chin lift or jaw thrust as clinically appropriate.

Be prepared for endotracheal intubation with or without rapid sequence intubation.

Be prepared to use adjunct airway technique (laryngeal mask airway, fiberoptic, jet ventilation, surgical airway) as per local custom.

Administer racemic epinephrine (L-epinephrine acceptable) 0.5 mL of 2.25% solution in 2.5 mL of NS by nebulizer while awaiting definitive airway management.

Start rapid infusion of isotonic crystalloid (NS): 500 mL in the first 5 minutes in the adult; several liters of NS may be required.

Antianaphylactic Drugs

Epinephrine is the first-choice drug, to be given simultaneously with the above general emergency measures, at the first suspicion of an anaphylactic reaction.

Intramuscular (1:1000 concentration)
- Adult: 0.3-0.5 mL every 5 minutes, more often as clinically indicated, titrated to effects
- Pediatric: 0.01 mL/kg, every 5 minutes as necessary, titrated to effects
- Alternatively, epinephrine (EpiPen, 0.3 mL; or EpiPen Jr, 0.15 mL) can be administered into anterolateral thigh.

Removal of clothing is unnecessary.

Intravenous (1:100,000 concentration; 0.1 mL of 1:1000 epinephrine in 10 mL of NS)
- Continuous hemodynamic monitoring required
- 10 mL of 1:100,000 during 10 minutes, titrated to effects; repeat as necessary

Antihistamines

Diphenhydramine: intravenous (intramuscular acceptable)
- Adult: 50 mg, up to 400 mg/24 hr, titrated to effects
- Pediatric: 1 mg/kg, up to 300 mg/24 hr, titrated to effects

Ranitidine: intravenous
- Adult: 50 mg IV (150 mg oral)
- Pediatric: 1 mg/kg IV or oral

Aerosolized beta-agonists

Adult
- Albuterol: 2.5 mg, diluted to 3 mL of NS; may be given continuously
- Levalbuterol: 0.625-1.25 mg, diluted to 3 mL of NS; may be given continuously
- Ipratropium: 0.5 mg in 3 mL of NS; repeat as necessary

Pediatric
- Albuterol: 2.5 mg, diluted to 3 mL of NS; may be given continuously
- Levalbuterol: 0.31-0.625 mg, diluted to 3 mL of NS; may be given continuously
- Ipratropium: 0.25 mg in 3 mL of NS; repeat as necessary

Methylprednisolone
- Adult: 125-250 mg IV
- Pediatric: 1-2 mg/kg IV

Special Situations

Refractory Hypotension

Consider continuous epinephrine drips
- Dilute 1 mg (1 mL 1:1000) in 250 mL D/W to yield a concentration of 4 µg/mL
- Infuse this diluted solution at 1 to 4 µg/min, up to 10 µg/min, titrated to effects

Glucagon: 1-5 mg IV during 5 minutes, followed by 5-15 µg/min continuous infusion

Consider vasopressors:
- Dopamine, 5-20 µg/kg/min continuous infusion and/or dobutamine 5-20 µg/kg/min continuous infusion, titrated to effects
- Norepinephrine: 8-12 µg/min (2-3 mL/min; 4 mg added to 1000 mL of D/W provides a concentration of 4 µg/mL), titrated to effects
- Phenylephrine, 40-180 µg/min, titrated to effects
- Vasopressin, 2-4 IU/hr, titrated to effects

Patients Receiving Beta-Blockade

Glucagon: 1-5 mg IV during 5 minutes, followed by 5-15 µg/min continuous infusion

Transcutaneous pacing for bradycardia

Atropine for bradycardia
- Adult: 0.3-0.5 mg IV or subcutaneous, to a maximum of 3 mg
- Pediatric: 0.02 mg/kg IV or subcutaneous, to a maximum of 2 mg

D/W, 5% dextrose in water; NS, normal saline.

Intracranial bleeding; worsen myocardial oxygen consumption through increased wall tension, contractility, and chronotropism; and cause myocardial ischemia, myocardial infarction, and pulmonary edema. Increased automaticity and chronotropism can produce hemodynamically significant supraventricular and ventricular tachydysrhythmia. Despite these concerns, the benefits of early administration of epinephrine in anaphylaxis far outweigh any of the stated risks. Serious adverse effects of epinephrine administration, such as myocardial ischemia and pulmonary edema, are usually attributable to an overdose or inappropriately rapid intravenous infusion.22 There are no absolute contraindications to the use of epinephrine, and it is the drug of first choice in anaphylaxis and anaphylactic shock.23

If the patient remains hypotensive after multiple doses of intramuscular epinephrine and aggressive volume expansion, intravenous epinephrine should be considered.24 Intravenous epinephrine infusion increases the risks of cardiac dysrhythmias, thus requiring continuous cardiac and hemodynamic monitoring. Dilution and slow administration are recommended to reduce untoward effects by epinephrine. The initial intravenous dose is 10 mL of a 1:100,000 dilution of aqueous epinephrine during 10 minutes. This is done by dilution of 0.1 mL of 1:1000 epinephrine in 10 mL of NS and infusion during 10 minutes (i.e., 100 µg epinephrine infusion given intravenously during 10 minutes at 10 µg/min). If no improvement is observed, a continuous infusion can be set up by mixing 1 mg of epinephrine (i.e., 1 mL of 1:1000 epinephrine) in 250 mL of 5% dextrose in water, giving a concentration 4 µg/mL. This solution can be started at 1 µg/min and titrated to effects or 10 µg/min.25 In children and infants, an infusion rate of 0.1 µg/kg/min is advised, increasing in increments of 0.1 µg/kg/min to a maximum of 1.5 µg/kg/min. A convenient dosing method for pediatric patients is the “rule of 6”: 0.6 x body weight (in kilograms) = milligrams of epinephrine to be diluted to 100 mL NS; then 1 mL/hr of this solution delivers 0.1 µg/kg/ min.26 Central line access is usually recommended for intravenous administration of epinephrine because of the risk of tissue necrosis from possible extravasation. Extravasation of epinephrine from peripheral access is treated with phenolamine. In addition to
the intramuscular route of administration for epinephrine, successful administration of epinephrine through the intravenous, sublingual, intraglottal, and endotracheal routes has been reported anecdotally, although only the parenteral route is recommended in the 2010 anaphylaxis treatment guidelines. The dosage and concentration guidelines for these routes of administration of epinephrine are the same as those for intravenous administration.

**Antihistamines**

In addition to epinephrine, antihistamines are routinely used in the treatment of anaphylaxis. Through competitive blockade of circulating histamines at target tissue cell receptors, they theoretically decrease symptoms of histaminemia such as itching, flush and rhinorrhea, and myocardial contractility, although they have no role in decreasing mediator release and have no effect on the leukotrienes. Diphenhydramine hydrochloride is the most commonly used H1 antihistamine (50 mg intravenously or orally every 4 to 6 hours in adults or 1 to 2 mg/kg in children). Ranitidine (50 mg intravenously in adults, 1 mg/kg in children) and cimetidine (300 mg intravenously every 6 hours) are commonly used H2 blockers. Antihistamines should be not given as lone agents in the treatment of true anaphylaxis.

**Corticosteroids**

Along with epinephrine and antihistamines, systemic corticosteroids are commonly administered in the treatment of anaphylaxis. A typical regimen involves an initial intravenous loading dose of methylprednisolone (Solu-Medrol, 125 to 250 mg) or oral prednisone (0.5-1 mg/kg). Steroids have an onset of action of approximately 4 to 6 hours after administration and therefore are of limited benefit in the acute treatment. They are most useful for protracted symptoms and may confer theoretic benefits in preventing the biphasic reaction. Rare cases of deterioration after corticosteroid administration may be the result of the patient’s hypersensitivity reaction to steroid.

**Aerosolized Beta-Agonists**

Bronchospasm in anaphylaxis refractory to epinephrine may respond to a nebulized beta-agonist. Continuous nebulization of the beta-agonists (albuterol sulfate, levalbuterol) may be helpful for persistent bronchospasm. The use of anticholinergic therapy with ipratropium bromide (Atrovent, 0.5 mg [2.5 mL of a 0.02% solution]) is an additional option in the management of acute bronchospasm. Anticholinergic medications decrease cyclic guanosine monophosphate levels, thereby decreasing mediator release and reversing the action of mediators on target tissue cells.

**Vaspressors**

Patients with persistent hypotension despite adequate epinephrine injections require aggressive volume expansion with crystalloid fluids. Large volumes of NS (>2 L) are often infused quickly, at a rate of 5 to 10 mL/kg for the first 5 minutes. Watch for signs of volume overload in patients with a history of reduced cardiac function, renal insufficiency, or congestive heart failure. As a last resort, dopamine, vasopressors (e.g., norepinephrine, phenylephrine), or vasopressin infusion (2-4 IU/hr) should be considered for refractory hypotension.

**Patients Receiving Beta-Blockade**

Glucagon, with positive inotropic and chronotropic cardiac effects mediated independently of alpha and beta receptors, may be helpful in patients who are receiving beta-blockers and who do not respond to epinephrine and other standard treatment modalities. Glucagon is thought to effect positive inotropism by augmenting cyclic adenosine monophosphate synthesis through a nonadrenergic pathway. The initial dose is 1 to 5 mg for adults and 20 to 30 µg/kg (maximum dose 1 mg) for children intravenously, followed by an infusion of 1 to 5 mg/hr. Side effects include nausea, vomiting, hypokalemia, and hyperglycemia. Atropine can be tried as second-line therapy for symptomatic bradycardia.

**DISPOSITION**

Most patients with anaphylaxis respond to aggressive management and can be safely discharged to home. Patients with mild to moderate anaphylaxis who completely respond to treatment are appropriate for discharge after an observation period (2-6 hours) in the ED. Advise these patients about symptoms of biphasic anaphylaxis and to return to the ED at the earliest onset of symptoms in the next 72 hours. There are established clinical predictors for biphasic response; severity of the initial presentation, hypotension, laryngeal edema, delayed or inadequate dosage of epinephrine, and chronic beta-blocker medication use have been advanced as risk factors for a biphasic attack. Patients with these clinical features may thus be candidates for hospital observation. Those going home are commonly prescribed a 7-day course of an oral H1 antihistamine (either first or second generation, e.g., diphenhydramine hydrochloride 50 mg every 6 hours) and H2 antihistamine (e.g., ranitidine 150 mg every day). The select patients who present with moderate anaphylaxis symptoms may benefit from outpatient steroid therapy (prednisone 1 mg/kg/day for 7 to 10 days). Consider hospital admission for patients who present with protracted anaphylaxis, hypotension, airway involvement, prolonged bronchospasm, and poor social support and for those who may be at risk for biphasic anaphylaxis.

**Prevention**

Emergency physicians can take an active role in educating patients under their care about allergy and anaphylaxis, arranging for specialty care follow-up, and prescribing epinephrine for self-administration in case of allergic emergency. The SAFE acronym (Seek support, Allergen identification and avoidance, Follow-up for specialty care, and Epinephrine for emergencies) is a useful reminder tool to use in providing care for patients with anaphylaxis in the ED. Physicians should spend a few minutes to advise patients of risks for future anaphylactic attacks and the need to seek emergency care as quickly as possible at the first signs of another anaphylactic reaction. Discharge planning includes referral to a primary care physician or allergist for further diagnostic workups and allergy management, a prescription for self-injectable epinephrine kits including education on how and when to self-administer, and a recommendation to carry a warning identification stating the hypersensitivity (MedicAlert bracelet or wallet card).

**URTICARIA AND ANGIOEDEMA**

**Clinical Features**

Urticaria and angioedema are common allergic presentations encountered in the ED. Urticaria (hives) is the clinical manifestation of a wheal and flare (allergic) reaction, appearing as papules or wheals that are nonpitting, edematous, pruritic, slightly erythematous, and raised circular or annular; they range in size from millimeters to several centimeters (Fig. 119-3). The centers of the wheals are usually clear while the borders are erythematous,
Angioedema refers to abrupt vasodilation and edema and resultant swelling of the deeper dermal and subcutaneous layers of the skin. Because the swelling is located in the deeper layers of the skin, the skin may appear normal color (or pink) and pruritus is variable. Instead of itch, patients may complain of pain associated with angioedema. Angioedema commonly involves the face, mouth, lips, tongue, extremities, and genitalia. Angioedema of the larynx can cause an acute upper airway obstruction and is a medical emergency. Recurrent episodes of angioedema and urticaria that last less than 6 weeks are considered acute (90%), and those that persist longer than 6 weeks are classified as chronic (10%).

Urticaria and angioedema represent clinical symptoms and signs of potentially distinct underlying disease entities. Similar to anaphylaxis, the majority of cases of acute urticaria and angioedema are hypersensitivity reactions, commonly triggered by allergens (e.g., foods, drugs, RCM, Hymenoptera venom) and, rarely, by physical stimuli (e.g., heat, wet, cold, vibratory, exercise). Angioedema caused by an allergic mechanism is called allergic angioedema. Nonallergic angioedema is caused by bradykinin excess, either by reduced degradation of bradykinin by ACE inhibitors or by excessive bradykinin production by a genetic defect as in hereditary angioedema (HAE). Differentiation of the two forms of angioedema is crucial to successful therapy.

Nonallergic angioedema (angioedema without urticaria and pruritus) is usually kinin related; its causes include HAE, acquired C1 inhibitor deficiency (ACID), and ACE inhibitors. All three result in elevated bradykinin levels. In the case of HAE and ACID, the deficiency of C1 inhibitor causes activation of the kallikrein-kinin system, with consumption of kininogen, and results in increased production of bradykinin. In the case of ACE inhibitor drugs, the inhibition of ACE, one of the main inactivators of bradykinin, results in increased bradykinin levels. Substance P is also thought to play a role in ACE inhibitor–associated angioedema.

HAE affects fewer than 200,000 people in the United States and may account for 15,000 to 30,000 ED visits annually. It is an autosomal dominant condition caused by C1 esterase inhibitor deficiency or functional deficiency, which is biochemically confirmed by low levels of C4 and C1 esterase inhibitor activity. This ultimately results in intermittent elevated bradykinin levels and other mediators, resulting in angioedema. The cardinal symptoms and signs of HAE include edema of the airway, face, genitalia, or extremities and abdominal pain associated with nausea, vomiting, and diarrhea. These clinical manifestations may occur singly or in combination. Trauma and stress are common precipitating factors. There is usually a family history.

ACID is clinically indistinguishable from HAE attacks and is often associated with underlying lymphoproliferative diseases. The underlying disease results in consumption of C1 inhibitor or the development of anti–C1 inhibitor autoantibodies. It is less common than HAE, it typically involves older patients, and a family history is usually absent.

ACE inhibitor–induced angioedema has an incidence of 0.1 to 0.7% and has a predilection for the tongue, lips, and laryngeal soft tissue. The highest incidence occurs in the first month of therapy, but it can occur as many as 10 years after therapy is started. Increased risk factors include African American race, smoking, older age, and female gender. Diabetes decreases the risk. The pathophysiologic mechanism is thought to be related to decreased metabolism of bradykinin and substance P, both of which are potent mediators of tissue inflammation. Most patients who have angioedema while receiving ACE inhibitors should be able to tolerate angiotensin receptor blocker drugs.

The clinical evaluation of angioedema starts with a focused search for emergency conditions, followed by a detailed history aimed at identification of the underlying cause. Life-threatening airway compromise can occur if the angioedema involves the upper airway. HAE, ACID, ACE inhibitors, thermal burn, and local allergic reaction to inhaled drugs (e.g., Quincke’s disease) tend to cause glossopharyngeal angioedema, resulting in upper airway obstruction, dysphagia, or both. The detailed history is aimed at eliciting exposures to foods, drugs, physical stimuli, infection (especially viral hepatitis), occupational elements, and insect stings.

Diagnostic Strategies

Diagnostic considerations are vast and include evolving anaphylaxis syndrome, erythema multiforme minor, bullous pemphigoid and dermatitis herpetiformis, urticarial vasculitis, mastocytosis, HAE (C1 esterase deficiency), ACID, ACE inhibitor–associated angioedema, and serum sickness, among others. The constellation of pruritus, urticarial rash or angioedema, hypotension, and wheezing after exercise should raise the possibility of exercise-induced anaphylaxis. Angioedema of the upper extremity raises the possibility of superior vena cava syndrome. Brawny edema and shock raise the possibility of capillary leak syndrome.

Management

Angioedema with Urticaria

Management of allergic angioedema that occurs in conjunction with urticaria (mast cell related) is first focused on stabilization of respiratory insufficiency and hemodynamic instability. Antihistamines (both H1 and H2) are the first-line therapeutic drugs. Epinephrine can be considered for moderate to severe cases but should be used with caution in patients older than 35 years to minimize the risk of precipitating an acute coronary syndrome. Steroids may be helpful in preventing recurrence. In the longer term, the most effective treatment of urticaria and angioedema involves removal of the etiologic factors. Second-generation H1...
Antihistamines such as cetirizine, loratadine, and fexofenadine, at increased doses (up to fourfold the conventional doses for allergic rhinitis), are the first-line drugs. The older antihistamines (hydroxyzine and diphenhydramine) can be tried when the newer H1 antihistamines are ineffective. Because 85% of histamine receptors in the skin are H2 and 15% are H3, the addition of an H2 antihistamine (e.g., ranitidine or cimetidine) benefits a histamine-induced urticarial reaction. Besides those common antihistamines, low-dose tricyclics (e.g., doxepin 25-100 mg/day) have both H1 and H2 activity and are used as second-line drugs, especially in cases of chronic urticaria. Heavy sedating effects limit the usefulness of doxepin, however. The addition of a short course of corticosteroids (0.5 mg/kg daily, up to 1 week) may shorten the duration of acute urticaria.

Angioedema without Urticaria

Management of angioedema that occurs without urticaria (kinin-related) is somewhat more of a problem with fewer therapeutic options. Life-threatening acute attacks of kinin-related angioedema do not usually respond satisfactorily to treatment with epinephrine, antihistamines, or steroids. Active airway management is the mainstay of treatment. Aerosolized racemic epinephrine (1-epinephrine is acceptable) may help stabilize the airway edema. Several new agents have recently been approved by the FDA for use in the United States; several others either are being used in other countries or are under clinical trial for the treatment of HAE.

For HAE, fresh frozen plasma (FFP), which contains C1 inhibitor, has been reported to be effective in abolishing acute attacks; however, there are rare reports of exacerbation of the angioedema by FFP. Steroids have not been shown to be helpful during acute attacks of HAE. Both types of products have been shown to shorten time to relief of symptoms, but the recombinant product has a shorter half-life.

Ecallantide (Kalbitor, 30 mg subcutaneously) is a small peptide kallikrein inhibitor and prevents the generation of bradykinin. It has been approved for use in the United States since 2009. It may be used intravenously because of a reported 3.9% risk of anaphylaxis. A bradykinin receptor-2 antagonist (Icatibant) has been approved by the European Medicines Agency for use in the European Union but has not been approved for use in North America. For ACE inhibitor–induced angioedema, the treatment is mainly supportive. There is a report of FFP being used with success in severe cases of ACE inhibitor–induced angioedema. It is thought that the benefits conferred by FFP are due to the effect of kininase II in breaking down the accumulated bradykinin. Because elevation in bradykinin is observed in both ACE inhibitor–induced angioedema and HAE (among others), perhaps the bradykinin receptor blocker class of drug that is being evaluated for HAE may also be found to be effective in the treatment of ACE inhibitor–induced angioedema.
References


