A Practical Guide to Anaphylaxis

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Anaphylaxis is a life-threatening reaction with respiratory, cardiovascular, cutaneous, or gastrointestinal manifestations resulting from exposure to an offending agent, usually a food, insect sting, medication, or physical factor. It causes approximately 1,500 deaths in the United States annually. Occasionally, anaphylaxis can be confused with septic or other forms of shock, asthma, airway foreign body, panic attack, or other entities. Urinary and serum histamine levels and plasma tryptase levels drawn after onset of symptoms may assist in diagnosis. Prompt treatment of anaphylaxis is critical, with subcutaneous or intramuscular epinephrine and intravenous fluids remaining the mainstay of management. Adjunctive measures include airway protection, antihistamines, steroids, and beta agonists. Patients taking beta blockers may require additional measures. Patients should be observed for delayed or protracted anaphylaxis and instructed on how to initiate urgent treatment for future episodes. (Am Fam Physician 2003;68:1325-32,1339-40. Copyright© 2003 American Academy of Family Physicians.)

A patient information handout on anaphylaxis, written by the author of this article, is provided on page 1339.

Anaphylaxis and anaphylactoid reactions are life-threatening events. A significant portion of the U.S. population is at risk for these rare but deadly events which cause approximately 1,500 deaths annually.[1] Anaphylaxis is mediated by immunoglobulin E (IgE), while anaphylactoid reactions are not. Both lead to the release of mast cell and basophil immune mediators *(Table 1)*. Because of their clinical similarities, the term anaphylaxis will be used to refer to both conditions.

Clinical Presentation

Anaphylaxis may include any combination of common signs and symptoms *(Table 2)*.[2] Cutaneous manifestations of anaphylaxis, including urticaria and angioedema, are by far the most common.[3,4] The respiratory system is commonly involved, producing symptoms such as dyspnea, wheezing, and upper airway

TABLE 1
Mediators of Inflammation Implicated in Anaphylaxis and Their Effects

Possible mediators	*Physiologic effects*	*Clinical manifestations*
Platelet activating factor	Increased vascular permeability	Angioedema
Prostaglandins	Peripheral vasodilation	Urticaria
Leukotrienes	Coronary vasoconstriction	Laryngeal edema
Tryptase	Smooth muscle contraction	Hypotension
Kinins	Irritation of sensory nerves	Flush
Heparin	Activation of other inflammatory pathways	Myocardial ischemia
Chymase	Recruitment of inflammatory cells	Wheezing
Tumor necrosis factor alpha	Activation of vagal pathways	Nausea, vomiting, diarrhea, abdominal pain
Interleukin-1 (IL-1)		Pruritus
Nitric oxide		
Histamine		

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See page 1241 for definitions of strength-of-evidence levels.

"Aspirin sensitivity" affects about 10 percent of persons with asthma, particularly those who also have nasal polyps.

obstruction from edema. Gastrointestinal manifestations (e.g., nausea, vomiting, diarrhea, abdominal pain) and cardiovascular manifestations (e.g., dizziness, syncope, hypotension) affect about one third of patients. Headache, rhinitis, substernal pain, pruritus, and seizure occur less frequently.

Symptom onset varies widely but generally occurs within seconds or minutes of exposure. Rarely, anaphylaxis may be delayed for several hours. Anaphylaxis can be protracted, lasting for more than 24 hours, or recur after initial resolution.[5,6]

Etiology

The common etiologies of anaphylaxis include drugs, foods, insect stings, and physical factors/exercise *(Table 3)*.[2] Idiopathic anaphylaxis (or reacting where no cause is identified) accounts for up to two thirds of persons who present to an allergist/immunologist.

Approximately one third of anaphylactic episodes are triggered by foods such as shellfish, peanuts, eggs, fish, milk, and tree nuts (e.g., almonds, hazelnuts, walnuts, pecans); however, the true incidence is probably underestimated. A patient may underestimate the importance of a food antigen, or the antigen may be one of many ingredients in a complex product. Some persons may react just by handling the culprit food.

Another common cause of anaphylaxis is a sting from a fire ant or *Hymenoptera* (bee, wasp, hornet, yellow jacket, and sawfly). Approximately 40 to 100 deaths per year in the United States result from insect stings, and up to 3 percent of the U.S. population may be sensitized.[1,2] A history of systemic reaction to an insect sting and positive venom skin test confers a 50 to 60 percent risk of reaction to future stings.[7]

TABLE 2
Frequency of Signs and Symptoms

Signs and symptoms	*Frequency (%)*
Urticaria, angioedema	88
Dyspnea, wheeze	47
Dizziness, syncope, hypotension	33
Nausea, vomiting, diarrhea, cramping abdominal pain	30
Flush	46
Upper airway edema	56
Headache	15
Rhinitis	16
Substernal pain	6
Pruritus without rash	4.5
Seizure	1.5

Adapted with permission from Lieberman P. Anaphylaxis and anaphylactoid reactions. In: Middleton E, ed. Allergy: principles and practice. 5th ed. St. Louis: Mosby, 1998:1079-89.

Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) may produce a range of reactions, including asthma, urticaria, angioedema, and anaphylactoid reactions. "Aspirin sensitivity" affects about 10 percent of persons with asthma, particularly those who also have nasal polyps. Overall, aspirin accounts for an estimated 3 percent of anaphylactic reactions.[8] Symptoms may start immediately or several hours after ingestion. Sensitive persons may have similar reactions to NSAIDs antigenically unrelated to aspirin and must take only acetaminophen for mild pain or fever.

At one time penicillin was probably the most common cause of anaphylaxis. Between one and five per 10,000 patient courses with penicillin result in allergic reactions, with one in 50,000 to one in 100,000 courses having a fatal outcome, accounting for 75 percent of anaphylactic deaths in the United States.[9-11]

Latex allergy has become a significant problem since the widespread adoption of universal precautions against infection. Eight to 17

TABLE 3
Some Causes of Anaphylaxis and Anaphylactoid Reactions

Foods
Bananas, beets, buckwheat, Chamomile tea, citrus fruits, cow's milk,* egg whites,* fish,* kiwis, mustard, pinto beans, potatoes, rice, seeds and nuts (peanuts, Brazil nuts, almonds, hazelnuts, pistachios, pine nuts, cashews, sesame seeds, cottonseeds, sunflower seeds, millet seeds),* shellfish*
Venoms and saliva
Deer flies, fire ants, *Hymenoptera* (bees, wasps, yellow jackets, sawflies),* jellyfish, kissing bug (Triatoma), rattlesnakes
Antibiotics
Amphotericin B (Fungizone), cephalosporins, chloramphenicol (Chloroptic), ciprofloxacin (Cipro), nitrofurantoin (Furadantin), penicillins,* streptomycin, tetracycline, vancomycin (Vancocin)
Aspirin and nonsteroidal anti-inflammatory drugs*
Miscellaneous other medications
Allergy extracts, antilymphocyte and antithymocyte globulins, antitoxins, carboplatin (Paraplatin), corticotropin (H.P. Acthar), dextran, folic acid, insulin, iron dextran, mannitol (Osmitrol), methotrexate, methylprednisolone (Depo-Medrol), opiates, parathormone, progesterone (Progestasert), protamine sulfate, streptokinase (Streptase), succinylcholine (Anectine), thiopental (Pentothal), trypsin, chymotrypsin, vaccines
Latex rubber*
Radiographic contrast media*
Blood products
Cryoprecipitate, immune globulin, plasma, whole blood
Seminal fluid
Physical factors
Cold temperatures, exercise
Idiopathic*

*—Relatively common causes.

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percent of health care workers experience some form of allergic reaction to latex, although not all of these reactions are anaphylaxis.[12] Recognizing latex allergy is critical because physicians may inadvertently expose the patient to more latex during treatment. Latex is in gloves, catheters, and countless other medical supplies, as well as thousands of consumer products. Persons allergic to latex also may be sensitive to fruits such as bananas, kiwis, pears, pineapples, grapes, and papayas.

Finally, radiographic contrast media can result in severe adverse reactions at a rate of 0.2 percent for ionic agents and 0.04 percent for lower osmolality, nonionic agents.[13] One study found the risk of death to be one in 100,000 with either type of agent.[14]

Differential Diagnosis

When history of exposure to an offending agent is elicited, the diagnosis of anaphylaxis is often obvious. Cutaneous manifestations of urticaria, itching, and angioedema assist in the diagnosis by suggesting an allergic reaction. However, when gastrointestinal symptoms predominate or cardiopulmonary collapse makes obtaining a history impossible, anaphylaxis may be confused with other entities.

TABLE 4
Differential Diagnosis for Anaphylaxis

Presentation	*Differential diagnosis*
Hypotension	Septic shock
	Vasovagal reaction
	Cardiogenic shock
	Hypovolemic shock
Respiratory distress with wheezing or stridor	Airway foreign body
	Asthma and chronic obstructive pulmonary disease exacerbation
	Vocal chord dysfunction syndrome
Postprandial collapse	Airway foreign body
	Monosodium glutamate ingestion
	Sulfite ingestion
	Scombroid fish poisoning
Flush syndrome	Carcinoid
	Postmenopausal hot flushes
	Red man syndrome (vancomycin [Vancocin])
Miscellaneous	Panic attacks
	Systemic mastocytosis
	Hereditary angioedema
	Leukemia with excess histamine production

Some of these differential diagnoses are listed in *Table 4*.

If the diagnosis of anaphylaxis is not clear, laboratory evaluation can include plasma histamine levels, which rise as soon as five to 10 minutes after onset but remain elevated for only 30 to 60 minutes. Urinary histamine levels remain elevated somewhat longer. Alternatively, serum tryptase levels peak 60 to 90 minutes after onset of anaphylaxis and remain elevated for up to five hours. Some patients have isolated abnormal tryptase or histamine levels without the other.

Emergency Management

The initial management of anaphylaxis includes a focused examination, procurement of a stable airway and intravenous access, and administration of epinephrine.[2,10] [Evidence level C, consensus and expert opinion] Vital signs and level of consciousness should be documented. Examination may reveal urticaria, angioedema, wheezing, or laryngeal edema. If the antigen was injected (e.g., insect sting), the portal of entry may be noted.

Epinephrine 1:1,000 dilution, 0.2 to 0.5 mL (0.2 to 0.5 mg) in adults, or 0.01 mg per kg in children, should be injected subcutaneously or intramuscularly, usually into the upper arm. The site may be gently massaged to facilitate absorption. The dose may be repeated two or three times at 10 to 15 minutes intervals. If severe hypotension is present, epinephrine may be given as a continuous intravenous infusion. The following regimen is reasonable: 1:10,000 (100 mcg per mL) epinephrine at 1 mcg per minute, increased to 10 mcg per minute as needed. Patients receiving intravenous epinephrine require cardiac monitoring because of potential arrhythmias and ischemia. If an intravenous line cannot be established, the intramuscular dose can be injected into the posterior one third of the sublingual area, or the intravenous dose may be injected into an endotracheal tube.

The patient should be placed supine or in Trendelenburg's position. Supplemental oxygen may be administered. Intravenous access should be obtained for fluid resuscitation, because large volumes of fluids may be required to treat hypotension caused by increased vascular permeability and vasodilation. While volume replacement is central to management of hypotension in anaphylaxis, other pressors such as dopamine (Intropin), 2 to 20 mcg per kg per minute, may be required.

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At this point, the patient should be assessed for response to treatment. Additional measures then may be individualized.[2,10] [Evidence level C, consensus and expert opinion] To slow absorption of injected antigens (e.g., insect stings), a tourniquet may be placed proximal to the injection site. It should be released every five minutes for at least three minutes, and the total duration of tourniquet application should not exceed 30 minutes. The tourniquet pressure should ideally occlude venous return without compromising arterial flow. Alternatively, 0.15 to 0.3 mL of 1:1,000 aqueous epinephrine (0.1 to 0.2 mL in children) may be injected into the site.

Persistent respiratory distress or wheezing requires additional measures. Nebulized beta-adrenergic agents such as albuterol (Proventil) may be administered, and intravenous aminophylline may be considered. Endotracheal intubation may be needed to secure the airway. Rarely, airway edema prevents endotracheal intubation and a surgical airway (e.g., emergency tracheostomy) is needed.

Antihistamines sometimes provide dramatic relief of symptoms. Simultaneous H_1 and H_2 blockade may be superior to H_1 blockade alone, so diphenhydramine (Benadryl), 1 to 2 mg per kg (maximum 50 mg) intravenously or intramuscularly, may be used in conjunction with ranitidine (Zantac), 1 mg per kg intravenously, or cimetidine (Tagamet), 4 mg per kg intravenously.

Although the exact benefit of corticosteroids has not been established, most experts advocate their administration. Their benefit is not realized for six to 12 hours after administration, so their primary role may be in prevention of recurrent or protracted anaphylaxis. There is no established drug or dosage of choice; *Table 5*[10] lists several possible regimens.

Patients taking beta-adrenergic blockers present a special challenge because beta blockade may limit the effectiveness of epinephrine. These patients may have resistant severe hypotension, bradycardia, and a prolonged course. Atropine may be given for bradycardia (0.3 to 0.5 mg intramuscularly or subcutaneously every 10 minutes to a maximum of 2 mg). Glucagon exerts positive inotropic and chronotropic effects on the heart, independent of catecholamines. Therefore, glucagon, 1 mg intravenous bolus, followed by an infusion of 1 to 5 mg per hour, may improve hypotension in one to five minutes, with a maximal benefit at five to 15 minutes. (The U.S. Food and Drug Administration has not approved glucagon for this use.) Nausea and vomiting may limit therapy with glucagon.

All patients with anaphylaxis should be monitored for the possibility of recurrent symptoms after initial resolution.[5,6] An observation period of two to six hours after mild episodes, and 24 hours after more severe episodes, seems prudent. Laboratory testing may help if the diagnosis of anaphylaxis is uncertain.

At discharge, the patient should be told to return for any recurrent symptoms. Some experts advocate a short course of antihistamines with oral corticosteroids (e.g., 30 to 60 mg of prednisone).[2,15]

Management of the Patient with a History of Anaphylaxis

A patient with a history of anaphylaxis should be instructed on how to initiate treatment for future episodes using pre-loaded epinephrine syringes. Two strengths are available: 0.3 mL of 1:1,000 epinephrine for adults, and 0.3 mL of 1:2,000 for children. Training kits containing empty syringes are available for patient education. Family members and caregivers of young children should be trained to inject epinephrine. Written instructions should be given. The patient also may take an antihistamine at the onset of symptoms. The patient must be told to seek immediate professional help regardless of initial response to self-treatment. If possible, the patient should avoid taking beta blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II receptor blockers, and monoamine oxidase inhibitors, because these drugs may interfere

TABLE 5
Protocol for Treatment of Anaphylaxis

Diagnose the presence or likely presence of anaphylaxis.
Place patient in recumbent position and elevate lower extremities.
Monitor vital signs frequently (every two to five minutes) and stay with the patient.
Administer epinephrine 1:1,000 (weight-based) (adults: 0.01 mL per kg, up to a maximum of 0.2 to 0.5 mL every 10 to 15 minutes as needed; children: 0.01 mL per kg, up to a maximum dose of 0.2 to 0.5 mL) by SC or IM route and, if necessary, repeat every 15 minutes, up to two doses).
Administer oxygen, usually 8 to 10 L per minute; lower concentrations may be appropriate for patients with chronic obstructive pulmonary disease.
Maintain airway with an oropharyngeal airway device.
Administer the antihistamine diphenhydramine (Benadryl, adults: 25 to 50 mg; children: 1 to 2 mg per kg), usually given parenterally.
If anaphylaxis is caused by an injection, administer aqueous epinephrine, 0.15 to 0.3 mL, into injection site to inhibit further absorption of the injected substance.
If hypotension is present, or bronchospasm persists in an ambulatory setting, transfer to hospital emergency department in an ambulance is appropriate.
Treat hypotension with IV fluids or colloid replacement, and consider use of a vasopressor such as dopamine (Intropin).
Treat bronchospasm, preferably with a beta II agonist given intermittently or continuously; consider the use of aminophylline, 5.6 mg per kg, as an IV loading dose, given over 20 minutes, or to maintain a blood level of 8 to 15 mcg per mL.
Give hydrocortisone, 5 mg per kg, or approximately 250 mg intravenously (prednisone, 20 mg orally, can be given in mild cases). The rationale is to reduce the risk of recurring or protracted anaphylaxis. These doses can be repeated every six hours, as required.
In refractory cases not responding to epinephrine because a beta-adrenergic blocker is complicating management, glucagon, 1 mg intravenously as a bolus, may be useful. A continuous infusion of glucagon, 1 to 5 mg per hour, may be given if required.
In patients receiving a beta-adrenergic blocker who do not respond to epinephrine, glucagon, IV fluids, and other therapy, a risk/benefit assessment rarely may include the use of isoproterenol (Isuprel, a beta agonist with no alpha-agonist properties). Although isoproterenol may be able to overcome depression of myocardial contractility caused by beta blockers, it also may aggravate hypotension by inducing peripheral vasodilation and may induce cardiac arrhythmias and myocardial necrosis. If a decision is made to administer isoproterenol intravenously, the proper dose is 1 mg in 500 mL D5W titrated at 0.1 mg per kg per minute; this can be doubled every 15 minutes. Adults should be given approximately 50 percent of this dose initially. Cardiac monitoring is necessary and isoproterenol should be given cautiously when the heart rate exceeds 150 to 189 beats per minute.
Medical offices in which the occurrence of anaphylaxis is likely should consider periodic anaphylaxis drills.
Protocols for use in schools to manage children at risk of anaphylaxis are available through the Food Allergy Network. These protocols include materials for educating teachers, office workers, and kitchen staff in the prevention and treatment of anaphylaxis. Furthermore, patients should be given written information with suggested strategies for their own care.

IM = intramuscular; IV = intravenous; SC = subcutaneous.

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with successful treatment of future anaphylactic episodes or with the endogenous compensatory responses to hypotension. Finally, the patient should be advised to wear or carry a medical alert bracelet, necklace, or keychain to inform emergency personnel of the possibility of anaphylaxis.

Prevention of future episodes is vital *(Table 6)*. This requires identification of the anaphylactic trigger, which is often difficult. The physician's primary tool is a detailed history of recent exposures to foods, medications, latex, and insects known to cause anaphylaxis. Previous tolerance of a substance does not rule it out as the trigger. Despite a detailed history, a cause remains elusive in many patients. Direct skin testing and radioallergosorbent testing (RAST) are available for some antigens, including heterologous sera, *Hymenoptera* venom, some foods, hormones, and penicillin. Skin testing itself carries a risk of fatal anaphylaxis and should be performed by experienced persons only. Scratch and prick tests should precede intradermal testing to decrease the risk of an unexpected severe reaction. Penicillin skin testing includes major and minor determinants; the minor determinants are more predictive of future anaphylactic events. RAST checks in vitro for the presence of IgE to antigen and carries no risk of anaphylaxis. However, it is limited to the same antigens that are available for skin testing. Both skin testing and RAST have imperfect sensitivity and specificity.

When there is no choice but to re-expose the patient to the anaphylactic trigger, desensitization or pretreatment may be attempted. Desensitization carries a risk of anaphylaxis and should be performed by experienced persons in a well-equipped location. In this procedure, the patient is exposed to gradually increasing amounts of antigen, usually via intradermal, then subcutaneous, then intravenous routes. Immunotherapy is recommended for insect sting anaphylaxis, because it is 97 percent effective at preventing recurrent severe reactions.[16] Protocols are available for oral and parenteral desensitization to penicillin, as well as a number of other antibiotics and medications.[17,18] Desensitization must be repeated if treatment with the agent is interrupted.

Desensitization carries a risk of anaphylaxis.

In situations where desensitization is not possible, pretreatment with steroids and antihistamines is an option. For a sensitive patient urgently requiring radiocontrast, 50 mg of oral prednisone 13 hours, seven hours, and one hour before contrast plus 50 mg of diphenhydramine one hour before the procedure dramatically reduce the rate of recurrent reaction.[19] Some experts advocate the addition of 25 mg of ephedrine, and 300 mg of cimetidine orally one hour before the procedure.[20] If the patient cannot take oral medications, 200 mg of hydrocortisone intravenously may replace prednisone in these regimens. The use of nonionic contrast media provides additional protection.[13]

TABLE 6
Prevention and Early Treatment of Future Episodes of Anaphylaxis

Advise patient to wear or carry a medical alert bracelet, necklace, or keychain to warn emergency personnel of anaphylaxis risk.
Advise patient to keep epinephrine self-injection kit and oral diphenhydramine (Benadryl) for future exposures.
Avoid prescribing beta blockers, angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, monoamine oxidase inhibitors, and some tricyclic antidepressants.
Avoid administering cross-reactive agents.
Refer to allergist if causative agent or diagnosis is unclear, if in-depth patient education is needed, or if reactions are recurrent.
If re-exposure to an offending medicine is necessary, administer the questionable medicine orally and observe the patient for the following 20 to 30 minutes; consider pretreatment with steroids and antihistamines. Consider desensitization if available.

Consultation with an allergist can help (1) confirm the diagnosis of anaphylaxis; (2) identify the anaphylactic trigger through history, skin testing, and RAST; (3) educate the patient in the prevention and initial treatment of future episodes; and (4) aid in desensitization and pretreatment when indicated.

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