

Pediatric Anaphylaxis

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ABSTRACT

Anaphylaxis is an acute, potentially life-threatening hypersensitivity reaction that causes an uncertain number of deaths in children each year. The reaction usually results from abrupt IgE-mediated release of chemical mediators, such as histamine, from mast cells and basophils. The most commonly involved agents are drugs, stinging insect venoms, and foods. The importance of recognizing risks, planning preventive management, and understanding acute treatment cannot be overemphasized. This report reviews these principles, pathophysiology, and treatment recommendations.

INTRODUCTION

SINCE THE TURN of the century, researchers have studied and characterized anaphylactic reactions, gaining intricate knowledge of the complex cellular and biochemical events involved. However, new discoveries continue to clarify both the varied pathophysiology and the clinical conditions occurring with acute hypersensitivity reactions. At this time, anaphylaxis is best defined as a clinical syndrome with abrupt life-threatening signs and symptoms resulting from the release of preformed and newly formed chemical mediators of inflammation. The concerted effects of these mediators on involved tissues and organ systems determine the nature and severity of the reaction. The condition may terminate abruptly in death or may be drawn out, with late phase or protracted aftereffects.

PATHOPHYSIOLOGY

Classic anaphylaxis is mediated by antigen-specific IgE bound to membrane receptors on mast cells in tissue and basophils in circulation. In a previously sensitized individual, reexposure results in recognition and binding of antigen by multiple specific IgE antibodies at the cell membranes. Energy-dependent degranulation occurs within several minutes, liberating mediators from cell granules, most notably histamine, and newly formed mediators from cell membrane. Chemotactic factors recruit and activate other cells, including neutrophils, eosinophils, and platelets, which may bring further inflammatory and destructive elements to the reaction sites. These participate in extended inflammatory responses termed *late phase reactions*. Anaphy-

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TABLE 1. MAST CELL AND BASOPHIL MEDIATORS OF ANAPHYLAXIS

<i>Site</i>	<i>Effects</i>
Histamine	Increased vascular permeability, vasodilation, smooth muscle spasm
Platelet-activating factor (PAF, alkyl-glyceryletherphosphorylcholine, AGEPC)	Increased vascular permeability, smooth muscle spasm Platelet aggregation with serotonin release, neutrophil and eosinophil chemotaxis
Leukotrienes and prostoglandin D ₂	Increased vascular permeability, smooth muscle spasm Neutrophil chemotaxis
Eosinophil and neutrophil chemotactic factors	Chemotaxis and activation, infiltration and tissue injury

laxis may be further complicated and amplified by activation of other inflammatory pathways, including coagulation and clot lysis, the complement system, and kinin formation.⁽¹⁻³⁾ A partial list of mediators of anaphylaxis and their local effects is shown in Table 1.

Mast cells and basophils may also degranulate without IgE involvement under the influence of drugs, such as opiates, hyperosmolarity, or anaphylatoxins generated during complement activation or through unclear mechanisms, as with hypertonic intravenous radiocontrast material. In some cases, anaphylactic symptoms may occur without primary mast cell or basophil involvement, as seen in hereditary angioedema and aspirin sensitivity. Collectively, reactions that physiologically mimic anaphylaxis but occur through non-IgE-mediated mechanisms are termed *anaphylactoid*. The distinction has limited clinical usefulness, since the symptoms and acute treatment are usually the same.

CLINICAL MANIFESTATIONS

The immediate symptoms and signs of anaphylaxis are determined by the site, rate, and amount of chemical mediator release plus any individual risk factors, such as asthma, cardiac condition, or use of beta-blocking drugs.^(4,5) Tissue sites most commonly affected are those with increased numbers of mast cells, particularly skin and mucous membranes. Mediator release in tissues with smooth muscle causes symptoms from localized spasm. When antigen exposure or mediator release is widespread, multiple organ systems may be affected, including skin, gastrointestinal, respiratory, and cardiovascular. Table 2 lists the potential sites for anaphylactic symptoms and the clinical effects that may be observed. Typically, two or more organ systems are involved in systemic reactions. The majority of episodes in children result from IgE-mediated reactions to stinging insect venoms, drugs and biologicals, or foods.

The largest evaluation of symptoms resulting from food allergy reactions in children was reported from the National Jewish Center for Immunology and Respiratory Medicine.⁽⁶⁾ Double-blind placebo-controlled food challenges were administered in graded amounts beginning with approximately half of that reported to produce symptoms; 185 children had 245 reactions. Peanut, milk, and eggs were responsible for 73% of reactions. Cutaneous reactions were the most frequent (62%), followed by gastrointestinal (56%) and

TABLE 2. SYMPTOMS AND SIGNS OF ANAPHYLAXIS

<i>Site</i>	<i>Clinical effect</i>
General	Sense of impending doom
Skin and mucosa	Flushing, urticaria, angioedema, itching, conjunctivitis
Respiratory	Dyspnea, wheezing, stridor, cough, rhinitis
Cardiovascular	Tachycardia, arrhythmias, hypotension, shock
Gastrointestinal	Nausea, vomiting, cramping, diarrhea
Miscellaneous	Uterine contraction, intravascular coagulation and fibrinolysis, complement activation

respiratory symptoms (39%). Two or more organ systems were involved in nearly half of the reactions. Challenge procedures were performed with sufficient care that only 4 children required epinephrine. None developed shock, and late-phase reactions occurred only in the intestinal tract.

Prospective studies of anaphylactic reactions to stinging insect venoms are limited, and none involve provocative challenges of children. In a landmark study of immunotherapy for insect venom hypersensitivity, 60 adult patients with histories of anaphylactic sting reactions and positive skin tests entered a single-blind treatment protocol culminating in provocative insect sting challenges.⁽⁷⁾ All patients desensitized with *Hymenoptera* venom were protected from anaphylaxis. However, among patients receiving placebo or whole body extract, 60% experienced anaphylactic reaction to sting challenge. Further sting challenges in these groups were terminated after 23 patients had been studied. Fourteen experienced significant reactions. Eleven developed systemic urticaria. Three patients had no cutaneous symptoms but developed abrupt severe anaphylaxis with peripheral vascular collapse and extreme hypotension. One reversed with subcutaneous epinephrine. The other two required intravenous volume expansion and intravenous pressor agents for 2–4 hours. Only one had airflow limitation, and this was bronchial. The magnitude of hemodynamic changes correlated with the levels of plasma histamine. However, in the two patients with severe anaphylaxis resistant to treatment, hypoxia and hypotension persisted after plasma histamine returned to normal. Other laboratory findings included depletion of coagulation factors, complement components, and kininogen. The authors concluded that the length of time between therapeutic interventions and significant clinical response suggests that there may be no ideal therapy for severe anaphylaxis.⁽⁸⁾

A more recent study of 39 patients with anaphylactic reaction to insect sting challenge demonstrated median onset of symptoms in 10 minutes (range 1–40 minutes) and no relation between this time interval and the severity of the reaction.⁽⁹⁾ Significant increases in plasma levels of histamine and tryptase correlated with clinical severity and degree of mean arterial pressure reduction and were detected during mild as well as severe reactions. Plasma levels of PGD₂ were not increased. Three of the patients had cardiovascular collapse, and of these, two had persistent symptoms beyond 4 hours.

Biphasic and protracted anaphylactic reactions have been described.^(10–14) In a prospective study of anaphylaxis in 25 consecutive adults, initial life-threatening manifestations of anaphylaxis were hypotension (68%), upper (36%) and lower (52%) airway obstruction, cardiac arrest (12%), and respiratory arrest (12%).⁽¹⁰⁾ Eighty percent of the reactions were induced by diagnostic or therapeutic drugs, with antibiotics causing 48%. Approximately half of the patients had recurrent or refractory symptoms. Three distinct clinical patterns of anaphylaxis were observed: uniphasic (52%), biphasic (20%), and protracted (28%). In biphasic reactions, the second episodes all included the same major signs and symptoms as the first and were separated by asymptomatic intervals of 1–8 hours. Early administration of epinephrine and glucocorticoids did not appear to attenuate the late-phase responses. Anaphylaxis that began more than 30 minutes after exposure or was provoked by an oral agent was significantly more likely to be complicated by recurrent or prolonged reactions.

Experimental studies of IgE-mediated allergic reactions in skin and respiratory tissues have characterized the occurrence of biphasic and delayed reactions. In these models, the late-phase reaction occurs 4–8 hours after antigen exposure, involves a second wave of mediator release, and can be suppressed with glucocorticoids.⁽¹⁵⁾ It is unclear whether similar immunologic mechanisms are involved in late-phase and protracted systemic anaphylactic reactions. It is generally accepted that histamine plays a major role in the immediate symptoms of anaphylaxis. There is no current evidence indicating that biphasic and protracted reactions involve continued mast cell or basophil mediator release. This and the apparent resistance to glucocorticoid intervention suggest that different mechanisms predominate in these most serious cases. Whether corticosteroids provide a modulating action remains speculative. There is evidence that primary cardiac involvement may occur during some anaphylactic reactions, as the human heart has plentiful functionally intact mast cells.⁽¹⁶⁾

There is no specific pattern of findings during postmortem investigation after anaphylactic death.⁽¹⁷⁾ Serum tryptase levels are significantly elevated in nearly all fatal cases of IgE-mediated insect venom and drug reactions but inconsistently for food reactions.^(12,18) Delage and Irey have characterized the clinical and postmortem pathologic findings in 43 patients with fatal anaphylactic drug reactions.⁽¹⁷⁾ Four were children. Parenteral penicillin reactions caused 75%. Ninety percent of reactions were clinically evident within 20

minutes. Table 3 summarizes their clinical and pathologic findings. It is noteworthy that less than 10% had cutaneous symptoms as the initial sign of anaphylaxis. Acute pulmonary emphysema was observed in only 11 of 40 cases.

Most fatal cases of anaphylaxis appear to result from abrupt arteriolar contraction with venule and capillary dilation leading to cardiopulmonary shock and loss of intravascular volume. Some patients succumb to airway edema and obstruction. In those who survive the immediate attack, there is significant risk for late-phase and protracted reactions. This is particularly true after oral exposure or when the initial symptoms do not appear until more than 30 minutes after antigen encounter.

ACUTE MANAGEMENT

The acute management of anaphylaxis is shown in Table 4. Epinephrine is essential and should be administered immediately because it restores vasomotor tone, relaxes respiratory smooth muscle, and may inhibit further mediator release.⁽²⁰⁾ Reports of fatal and near fatal anaphylactic reactions to foods suggest increased survival if epinephrine is administered when anaphylactic symptoms first emerge, even if these symptoms are not obviously life threatening.^(12,21) Similarly, when insect stings provoke systemic reaction, epinephrine is the first drug of choice for anything but minor reactions.⁽²²⁾ The initial route of choice for epinephrine is subcutaneous. Vital signs and airway patency must be assessed immediately and the patient must be placed in Trendelenburg position and given oxygen at a high flow rate. If the reaction has resulted from injection or sting in an extremity, proximal tourniquet and local epinephrine injection help retard systemic antigen exposure. If there is an insect stinger with attached venom sac, correct removal is important, since venom may be further injected by spasm of the sac or pressure from squeezing and other removal efforts. The proper technique is flicking with a sharp edge, such as with a credit card.

After such procedures have been performed, further treatment is determined by evaluation of patient status, etiology, and any risk factors. Antihistamine and corticosteroid should be administered to all patients with anaphylaxis to reduce the risk of relapsing symptoms and possibly late-phase sequelae. Persistent hypotension after subcutaneous epinephrine frequently results from increased capillary permeability as well as vasodilation. The net effect is loss of intravascular volume and reduced central venous pressure. After epinephrine, the most important immediate treatment for hypotension is restoration of intravascular volume with isotonic solution.

The chemical mediators of anaphylaxis may cause arrhythmia and impaired cardiac output. These effects plus the stress of intravascular hypovolemia, hypoxia, and acidosis can lead to cardiogenic shock, particularly in the patient with an underlying cardiac condition. Correction of acidosis and treatment of the arrhythmia should not be overlooked. Patients taking beta-blocking drugs are at increased risk for cardiovascular anaphylaxis resistant to epinephrine.^(4,5) This resistance may be partially overcome with glucagon infusion.⁽¹⁹⁾ The effects of histamine on the cardiovascular system can be reduced further by giving an H₂

TABLE 3. ANAPHYLACTIC DEATHS^a

<i>Initial symptoms</i>	<i>%</i>	<i>Pathologic findings</i>	<i>%</i>
Respiratory distress	40	Pulmonary vasodilation	90
Circulatory collapse	30	Pulmonary edema	50
Seizures	25	Alveolar hemorrhage	45
Cyanosis	25	Bronchial secretions	45
Vomiting	20	Laryngeal edema	40
Syncope	15	Air trapping	30
Urticaria	7	Splenic eosinophils	25
Numbness or tingling	7		
Facial angioedema	2		
Sudden death	10		

^a From Delage C, Irely NS.¹⁷

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TABLE 4. ACUTE MANAGEMENT OF ANAPHYLAXIS

Immediate

1. *Epinephrine* 1:1000, 0.01 ml/kg up to 0.3 ml sc, repeat every 15 min as needed
2. Establish airway, administer oxygen
3. Recumbent position, legs and feet elevated
4. Tourniquet above injection or sting site, remove briefly every 10 min, infiltrate site with additional epinephrine 1:1000 up to 0.2 ml, remove stinger and venom sac by flicking (not squeezing)
5. Monitor vital signs
6. Give *antihistamine*, e.g., diphenhydramine 1 mg/kg up to 50 mg every 4–6 hours IV or IM
7. Give *corticosteroid* to modulate late-phase sequelae, e.g., hydrocortisone 5–10 mg/kg up to 500 mg every 4–6 hours IV, methylprednisolone 1–2 mg/kg up to 125 mg every 4–6 hours, or prednisone 1–2 mg/kg per day as single oral dose or divided schedule

Dependent on evaluation

1. For bronchospasm, give aerosolized beta-agonist and consider aminophylline 6 mg/kg IV over 20 min
2. If hypotension persists after initial epinephrine, begin isotonic crystalloid or colloid to replace intravascular volume deficit and restore central venous pressure
3. If hypotension persists, correct metabolic acidosis when present, begin IV epinephrine 1:1000 1 ml in 250 ml D₅W (concentration 4 µg/ml) or 0.5 ml in 100 ml (concentration 5 µg/ml). Begin the infusion at 0.1 µg/kg/min and titrate upward in 0.1 µg/kg/min increments up to 1 µg/kg/min to achieve adequate systolic blood pressure
4. Give IV H₂ antihistamine, e.g., cimetidine 5–10 mg/kg up to 300 mg or ranitidine 1–2 mg/kg up to 50 mg
5. For refractory hypotension caused by beta blockade, give glucagon 1 mg IV over 1 min and begin continuous infusion 1–5 mg/hour^a

^a From Zuloga GP, DeLaney W, Holmboe E, et al.¹⁹

antihistamine in addition to an H₁ antihistamine.⁽²³⁾ When hypotension is persistent or relapsing, continuous intravenous epinephrine infusion, establishment of central venous access, and determination of cardiac filling pressures are essential.⁽²⁰⁾ Patients with bronchial hyperreactivity are at increased risk for bronchospasm during anaphylaxis. After epinephrine, further treatment may be necessary, including beta-agonist inhalation and aminophylline.

DIFFERENTIAL DIAGNOSIS

In most cases, the diagnosis of anaphylaxis is easily made. However, several entities (Table 5) may mimic anaphylaxis.⁽²⁴⁾ Vasovagal syncope can be distinguished by the presence of bradycardia as opposed to tachycardia. An anxiety reaction with hyperventilation is usually apparent with observation. Globus hystericus lacks physical findings and stridor. Acute vocal cord dysfunction may be difficult to differentiate from laryngospasm or bronchospasm. This condition results from a psychologic conversion reaction producing

TABLE 5. DIFFERENTIAL DIAGNOSIS OF ANAPHYLAXIS

Vasovagal episode
Anxiety attack with hyperventilation
Globus hystericus
Vocal cord dysfunction
Primary cardiac event
Pseudoanaphylaxis
Factitious anaphylaxis
Hereditary angioedema
Systemic mastocytosis

involuntary adduction of the false vocal cords, often with hyperventilation. The diagnosis is made most readily by flexible rhinolaryngoscopy, and the treatment includes psychotherapy and speech therapy.

Primary cardiac events with abrupt hypotension may mimic anaphylaxis, particularly when they occur after an injection, insect sting, or suspicious food ingestion. Cardiac evaluation and specific tests for hypersensitivity usually establish the etiology. Pseudoanaphylaxis has been described when the idiosyncratic or pharmacologic effects of a drug produce anaphylactoid symptoms. Procaine injections have been associated with seizures, hallucinations, and combativeness. Factitious anaphylaxis is defined as repeated self-induced anaphylactic episodes. Patients with hereditary angioedema have episodes of recurrent laryngeal edema resistant to epinephrine, nonpruritic angioedema, and abdominal pain, all of which occur with increased frequency after trauma. The serum C4 level usually is reduced, and C1 esterase inhibitor activity is deficient. Systemic mastocytosis produces recurrent flushing, tachycardia, abdominal pain, and diarrhea. Patients may have urticaria and dermographism. Occasionally, anaphylactic episodes with hypotension occur. A definitive diagnosis is made by biopsy. Symptoms due to excessive histamine may occur after scrombroid poisoning from eating fish.

When the diagnosis of anaphylaxis is unclear, measurement of serum tryptase may be helpful. Elevated levels occur with high specificity for mast cell degranulation in most cases of IgE-mediated drug and insect sting anaphylactic reactions.^(9,18) However, elevated tryptase levels are inconsistent after food-induced anaphylaxis and may have no significant value when evaluating suspected food reactions.⁽¹²⁾ When anaphylaxis is suspected but the diagnosis is uncertain or the etiology is unclear, a specialist in allergy and immunology should be consulted. In some patients with recurrent episodes, extensive efforts fail to reveal the etiology. This syndrome has been named idiopathic anaphylaxis.⁽²⁵⁾

CAUSATIVE AGENTS

Hundreds of agents are known to cause anaphylaxis, and additional etiologies are continually described. Some of the most frequently responsible agents are shown in Table 6. Parenteral penicillin has been the most common drug provoking anaphylaxis in children. The penicillin molecule is metabolized via breakdown of the two-ring structures into major (95%) and minor (5%) metabolites. These act as haptens and bind to protein in the patient. Skin tests with penicilloyl polylysine and a minor determinant mixture or aqueous penicillin provide high sensitivity for determining penicillin allergy and should be used to evaluate uncertain reactions or before administration of penicillin to patients with possible hypersensitivity.⁽²⁶⁾ Tests for sensitivity to aspirin, radiocontrast material, and other antibiotics are either not available or lack significant negative predictive value.

When an IgE-mediated hypersensitivity reaction is suspected, immunologic evidence should be sought. Standardized skin testing with pure *Hymenoptera* venoms is appropriate for any patient with insect sting anaphylaxis. Skin tests and, occasionally, radioallergosorbent assays are valuable tools for evaluating suspected food reactions. In many instances, the most accurate diagnostic tool is provocative challenge. This

TABLE 6. AGENTS CAUSING ANAPHYLAXIS

Category	Agents
Drugs and biologics	Penicillins, cephalosporins, other antibiotics, hyperosmolar radiocontrast material, plasma expanders, dextran, aspirin and other prostaglandin synthetase inhibitors, hormones, antisera, vaccines, allergy extracts, opiates, muscle relaxants, protamine, intravenous anesthetics, enzymes, seminal fluid, inhalants (pollens, epidermals)
Foods	Milk, eggs, peanut, fish, shellfish, nuts, others
Insects	<i>Hymenoptera</i> (bees, yellow jackets, others), fire ants, <i>Triatoma</i>
Physical factors	Exercise, cold, heat, sunlight
Miscellaneous	Idiopathic, ethylene oxide gas, latex rubber

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should be pursued only by those with expertise and facilities for the evaluation and management of allergic emergencies after careful consideration of risks and benefits.⁽²⁷⁾

The wide variety of substances provoking anaphylaxis has been reviewed in detail elsewhere.^(1,24,28) Of recent interest is the recognition of IgE-mediated allergy to latex (rubber) as a significant medical problem.⁽²⁹⁾ Children with spina bifida who have had multiple surgical procedures are at high risk. Life-threatening reactions have been reported during surgery. Prick skin testing before surgery is a useful screening procedure in all patients with a history of local reaction to rubber products.⁽³⁰⁾

PREVENTION OF ANAPHYLAXIS

The best treatment of anaphylaxis is prevention. The most important measure to prevent anaphylaxis is a thorough drug allergy history and use of unrelated substitutes. It is recommended that patients with life-threatening penicillin anaphylaxis avoid parenteral cephalosporins unless penicillin skin tests are negative.⁽³¹⁾ Aspirin-sensitive individuals are at risk for reactions to related drugs but can be desensitized orally.⁽³²⁾ Protection persists as long as drug use continues. Desensitization therapy with pure *Hymenoptera* venom is highly effective for preventing anaphylaxis. This treatment is recommended for all patients with insect sting anaphylaxis except children with only cutaneous reactions.^(33,34)

Patients at risk for a recurrent episode should carry a Medic Alert identification, be taught the self-injection of epinephrine, and keep a loaded syringe of epinephrine with them at all times. Life-threatening anaphylactic reactions to foods may occur at any age, including infancy. Parents must be counseled in a constructive sympathetic fashion. The Food Allergy Network (FAN) is a nonprofit organization devoted to distributing information about food allergies, particularly anaphylaxis (FAN, 4744 Holly Avenue, Fairfax, VA 22030). They provide personalized emergency care cards, "How to Read a Label" cards, and practical information. In children with known food allergy, most serious reactions occur when the antigen is hidden in other foods, such as pastry or candy.⁽¹²⁾ Serious reactions to milk protein have occurred after ingesting foods that are labeled "nondairy."⁽³⁵⁾

When anaphylaxis occurs away from immediate medical attention, patients must be advised that seemingly mild initial symptoms may lead ultimately to death. Epinephrine should be administered at the time that symptoms are recognized, and the patient should be evaluated promptly in an emergency medical facility. An observation period of 3–4 hours is recommended for mild reactions and longer for those with more serious reactions. Discharged patients should leave with an epinephrine kit and be advised that late-phase reactions may occur up to 8 hours after the initial event.

Prevention of anaphylaxis requires first and foremost an appreciation of the risk for fatality. Parents/patients and their physicians must be aware of this fact. Accurate identification of the etiologic agent is essential and may require expert review of the history and, in many cases, specific allergy testing. A well-defined and communicated management plan emphasizing avoidance and prompt intervention is fundamental.

REFERENCES

1. Wasserman SI, Marquardt DL. Anaphylaxis. In: E Middleton, Jr, CE Reed, EF Ellis, NF Adkinson, Jr, JW Yunginger, eds. *Allergy: principles and practice*. St. Louis: CV Mosby, 1988;2:1365–1376.
2. Lieberman PL. Anaphylaxis and anaphylactoid reactions. In: PL Lieberman, LV Crawford, eds. *Management of the allergic patient*. New York: Appleton-Century-Crofts, 1982;121–141.
3. Bochner BS, Lichtenstein LM. Anaphylaxis. *N Engl J Med* 1991;324:1785–1790.
4. Jacobs RL, Rake GW, Fournier DC, et al. Potentiated anaphylaxis in patients with drug induced beta-adrenergic blockade. *J Allergy Clin Immunol* 1981;68:125–127.
5. Toogood JH. Risk of anaphylaxis in patients receiving beta-blocker drugs. *J Allergy Clin Immunol* 1988;81:1–5.

6. Bock SA, Atkins FM. Patterns of food hypersensitivity during sixteen years of double-blind, placebo-controlled food challenges. *J Pediatr* 1990;117:561–567.
7. Hunt KJ, Valentine MF, Sobotak AK, et al. A controlled trial of immunotherapy in insect hypersensitivity. *N Engl J Med* 1978;299:157–161.
8. Smith PL, Sobotka AK, Bleecker ER, et al. Physiologic manifestations of human anaphylaxis. *J Clin Invest* 1980;66:1072–1080.
9. Van der Linden PWG, Hack CE, Poortman J, et al. Insect sting challenge in 138 patients: Relation between clinical severity of anaphylaxis and mast cell activation. *J Allergy Clin Immunol* 1992;90:110–118.
10. Stark BJ, Sullivan TJ. Biphasic and protracted anaphylaxis. *J Allergy Clin Immunol* 1986;78:76–82.
11. Bernard JH. Studies of 400 *Hymenoptera* sting deaths in the United States. *J Allergy Clin Immunol* 1973;52:259–264.
12. Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 1992;327:380–384.
13. Popa VT, Lerner SA. Biphasic systemic anaphylactic reaction: Three illustrative cases. *Ann Allergy* 1984;53:151–155.
14. Batson JM. Anaphylactoid reactions to oral administration of penicillin. *N Engl J Med* 1960;262:590–595.
15. Lemanske RF, Kaliner MA. Late phase allergic reactions. In: E Middleton, Jr, CE Reed, EF Ellis, NF Adkinson, Jr, JW Yunginger, eds. *Allergy: principles and practice*. St Louis: CV Mosby, 1988;2:224–246.
16. Wasserman SI. The heart in anaphylaxis. *J Allergy Clin Immunol*. 1986;77:663–666.
17. Delage C, Irely NS. Anaphylactic deaths: A clinical pathologic study of 43 cases. *J Forensic Sci* 1972;17:525–540.
18. Yunginger JW, Nelson DR, Squillace DL, et al. Laboratory investigation of deaths due to anaphylaxis. *J Forensic Sci* 1991;36:857–865.
19. Zuloga GP, DeLaney W, Holmboe E, et al. Glucagon reversal of hypotension in a case of anaphylactic shock. *Ann Intern Med* 1986;105:65–66.
20. Barach EM, Nowak RM, Lee TG, et al. Epinephrine for treatment of anaphylactic shock. *JAMA* 1984;251:2118–2122.
21. Yunginger JW, Sweeney KG, Sturmer WQ, et al. Fatal food-induced anaphylaxis. *JAMA* 1988;260:1450–1452.
22. Valentine MD. Insect venom allergy: Diagnosis and treatment. *J Allergy Clin Immunol* 1984;73:299–304.
23. Kaliner M, Sigler R, Summers R, et al. Effects of infused histamine: Analysis of the effects of H-1 and H-2 histamine receptor antagonists on cardiovascular and pulmonary responses. *J Allergy Clin Immunol* 1981;68:365–371.
24. Yunginger JW. Anaphylaxis. *Ann Allergy* 1992;69:87–96.
25. Dykewicz MS, Blaser M, Evans R, et al. Pediatric idiopathic anaphylaxis: A report of three cases with recommendations for evaluation and management. *Pediatr Asthma Immunol* 1990;4:217–223.
26. Green GR, Rosenblum AL, Sweet LC. Evaluation of penicillin hypersensitivity: Value of clinical history and skin testing with penicilloyl-polylysine and penicillin G. *J Allergy Clin Immunol* 1977;60:339–345.
27. Bock SA, Sampson HA, Atkins FM, et al. Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: A manual. *J Allergy Clin Immunol* 1988;82:986–997.
28. Saryan JA, O'Loughlin JM. Anaphylaxis in children. *Am J Asthma Allergy Pediatr* 1992;5:89–95.
29. Blaiss MS. Latex allergy in children: A review. *Pediatr Asthma Allergy Immunol* 1992;6:71–75.
30. Sussman GL, Tarlo S, Dolovich J. The spectrum of IgE-mediated responses to latex. *JAMA* 1991;265:2844–2877.
31. Anderson JA. Penicillin allergy. In: LM Lichtenstein, AS Fauci, eds. *Current therapy in allergy, immunology and rheumatology*, 3rd ed. Philadelphia: BC Decker, 1988;68–76.
32. Settipane GA. Aspirin sensitivity in rhinosinusitis and asthma. In: LM Lichtenstein, AS Fauci, eds. *Current Therapy in Allergy, Immunology and Rheumatology*, 3rd ed. Philadelphia: BC Decker, 1988, pp 36–39.
33. Schubert KC, Lichtenstein LM, Sobotka KA, et al. Epidemiologic study of insect allergy in children. II. effect of accidental stings in allergic children. *J Pediatr* 1983;102:361–365.

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34. Valentine MD. Insect venom allergy: Diagnosis and treatment. *J Allergy Clin Immunol* 1984;73:299–304.
35. Gern JE, Yang E, Evrard HM, et al. Allergic reactions to milk-contaminated “nondairy” products. *N Engl J Med* 1991;324:976–979.

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