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From Urticaria to Anaphylaxis: The Spectrum of Allergic Reactions in Children

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Allergic reactions in children are a common problem. However, determining the cause of the reaction and implementing an effective treatment can be a frustrating task for the clinician. Often, no precipitating factor can be identified in the history or physical examination, and treatments may provide only temporary relief.

The clinical spectrum of allergic reactions in children can range from hives or urticaria to life-threatening anaphylaxis. Complicating medical decision-making is that allergic reactions often are rapidly progressive, and the child who presents to triage with hives may develop acute anaphylaxis in the waiting room. As a result, clinicians may have to make clinical decisions and implement therapy rapidly with only limited information.

This article outlines a systematic approach to the recognition and management of the widely varied clinical spectrum of allergic emergencies, from urticaria to anaphylaxis. Pertinent pathophysiology is discussed, important historical and physical examination findings are stressed, and detailed discussions of clinical syndromes are provided. Special attention is given to management decisions in the child who presents with urticaria and anaphylaxis.

—The Editor

Introduction

Children frequently will present to the emergency department (ED) following an allergic reaction. Two clinical case studies are described here that represent typical presentations of children with allergic reactions.

An 11-year-old, previously healthy young boy presents to the ED with the acute onset of wheezing, respiratory distress, and hives following the administration of an influenza vaccine. He is treated in the ED with subcutaneous epinephrine, diphenhydramine, albuterol, and corticosteroids and is admitted to the hospital for observation. He is discharged home the following morning, but returns to the ED four days later when he develops hives after eating egg pudding.

A 2-year-old, previously healthy girl presents to the ED with hives, facial swelling, and wheezing after eating peanut butter candy. Her parents deny ever giving her any type of peanut prod-

uct prior to the candy and deny any family history of peanut allergy. She is treated with subcutaneous epinephrine, diphenhydramine, albuterol, and corticosteroids and admitted to the hospital for observation.

While most allergic reactions in children are minor, some reactions can be life-threatening. It is common for minor reactions to continue to evolve even after a child has presented to the ED for evaluation. Thus, emergency medicine physicians may be faced with a rapidly evolving clinical situation, often with a paucity of historical information. In addition, the ED physician must maintain a heightened awareness for the potential for deterioration, especially for those children who present with a minor reaction.

Thankfully, most children with an allergic reaction present only with hives, and serious morbidity and mortality rarely occur. However, hives may be characterized by an intense pruritus or burning that can be particularly troublesome to children. While multiple therapies are available for treating both hives and pruritus, some symptoms can be resistant to treatment, and it is not uncommon for children to return to the ED multiple times because of persistent symptoms.

Complicating management decisions is determining the etiology of the reaction. Unfortunately, in many cases the precipitating allergen is difficult or impossible to identify. As a result, parents often become frustrated and fearful that further reactions may occur. Thus, the emergency medicine physician will be asked to provide families with education and reassurance in addition to providing medical treatment.

While most emergency medicine physicians easily recognize hives, physicians also must be able to recognize the dramatic and varied life-threatening presentation of anaphylaxis. Unfortunately, acute anaphylaxis may be subtle in some children presenting with a paucity of skin findings, which may result in costly delays in recognition and treatment. Therefore, a heightened suspicion must be maintained as clinical situations can change rapidly and serious morbidity and mortality may result.

This review of allergic reactions in children will provide the reader with a framework for the evaluation and management of children who present to the ED following an allergic reaction. In addition, some attention will be paid to specific inciting agents, patient disposition, and education.

Common Definitions

Urticaria, by definition, is an intensely itchy rash consisting of a raised, irregularly shaped wheal with a blanched center surrounded by a red flare. Children may present with a single lesion or multiple lesions that vary in size and shape. Urticaria most often results from histamine that is released from mast cells located in the dermis layer of the skin.[1]

Angioedema is an area of well-circumscribed swelling that may involve any part of the body. However, the lips and eyelids most commonly are involved. It may be caused by immune mechanisms similar to those that result in hives. However, in angioedema, mediators are released in the deep dermis or subcutaneous tissues. Because the reaction is deeper in the dermis, more diffuse swelling is observed rather than a sharply demarcated wheal. Angioedema is typically nonpitting and nonpruritic.[2]

Anaphylaxis is an acute immunologic reaction that occurs when an antigen is introduced rapidly and systematically into an individual who has preexisting IgE antibodies to that antigen fixed to mast cells and basophils. Multiple organ systems are involved, including the cutaneous, pulmonary, cardiovascular, gastrointestinal, and neurologic systems. In contrast to urticaria, anaphylaxis, though involving identical immune mechanisms, involves a more substantial exposure to a precipitating antigen and a more massive release of histamine and other inflammatory or immune mediators.

Anaphylactoid reactions clinically are similar to anaphylaxis,

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but are not IgE-mediated and do not require prior exposure to an inciting agent. Type III and nonimmune reactions are examples of anaphylactoid reactions.

Pathophysiology

Immunologic Mechanisms. There are three basic reactions that can lead to mast cell degranulation, and thus, an allergic reaction: 1) Type I hypersensitivity reactions; 2) Type III reactions; and 3) nonimmune reactions. Type I hypersensitivity reactions occur when the antigen and IgE bind to mast cells and basophils, resulting in degranulation and release of inflammatory mediators such as histamine, leukotrienes, prostaglandins, and kallireins. Some mediators are preformed, such as histamine, but for others, like prostaglandins, leukotrienes, thromboxane, platelet activating factor, and kinins, the binding of antigen and IgE results in their synthesis.

Type I hypersensitivity reactions typically occur in four distinct stages. An initial exposure to an allergen, followed by the development of an IgE antibody response, must occur first. On reexposure to the same antigen, antigen cross-bridging to a pair of IgE antibodies occurs. Antigen cross-bridging takes place directly on a mast cell or basophil, resulting in degranulation. If there is systemic absorption of the allergen, urticaria or anaphylaxis will occur.

Type III (immune complex/complement) reactions result when antigen binds to antibody and activates the complement cascade. Activation of the complement system can cause increased vascular permeability, incite mast cell degranulation, contract smooth muscle, and stimulate macrophages.[3] In particular, C3a and C5a are formed; they act as potent anaphylatoxins and trigger the release of mediators from mast cells and basophils.

Nonimmune reactions will occur either from alteration of the arachidonic acid metabolism or from direct degranulation of mast cells.

Common Mediators

Histamine. Released by the mast cell or basophil, histamine is one of the primary mediators of both local and systemic allergic reactions. Histamine receptors are found on many organ systems and their stimulation leads to the clinical signs and symptoms of allergic reactions. There are three types of histamine receptors located throughout the body that account for the typical signs and symptoms of allergic reactions. In general, though, histamine has direct vasoactive and smooth muscle spasmogenic effects.[2]

The H_1 receptor of histamine, when stimulated, results in coronary artery vasoconstriction, bronchoconstriction, cutaneous vascular permeability, and intestinal smooth muscle contraction.[2] The H_2 receptor stimulates ventricular and atrial isotropy, atrial chronotropy, coronary vasodilatation, and gastric acid secretion.[2] Interestingly, the H_3 receptor inhibits central and peripheral nervous system neurotransmitter release and actually may act to inhibit further histamine formation.[2]

Other Mediators. Other important mediators of allergic reactions include leukotrienes, thromboxane, prostaglandins, platelet activating factor, and nitric oxide. Leukotrienes are formed from arachidonic acid via the lipoxygenase pathway and partially are responsible for bronchoconstriction and for edema formation in the lungs during anaphylaxis. Leukotrienes also may be directly cardiotoxic.

Thromboxane and prostaglandin also are created from arachidonic acid, but through the cyclooxygenase pathway. Prostaglandins can cause airway constriction and vasodilatation and may help mediate inflammatory responses. Platelet activating factor stimulates bronchial smooth muscle constriction and increases vascular permeability, airway inflammation, and chemotaxis. Recent investigations have focused on nitric oxide synthesis, which may be induced during anaphylaxis within the vascular endothelium. Nitric oxide synthesis can lead to vascular permeability and worsening hypotension.[4] It also may result in bronchospasm.

Common Clinical Scenarios

Acute Urticaria. Allergic reactions in children are common. However, children can arrive in the ED with widely varied clinical presentations following a reaction. Whether in isolated patches or widely disseminated, urticaria, in the absence of systemic signs and symptoms, is the most common presenting scenario for children and adults. Close to 20% of individuals will present to their primary care physicians with urticaria at some point.[5]

Children with urticaria usually complain of intense pruritus associated with the lesions, though some children will complain of pain and a burning sensation. The majority of children will not present with other systemic complaints unless the reaction is triggered by a viral or bacterial infection. In fact, the most common cause of urticaria in children is a viral infection.[5] In such cases, patients may present with fever, cough, runny nose, sore throat, vomiting, or diarrhea. Other typical causes of allergic reactions in children include foods, medications, and environmental exposures.

Children may present with one of several physical urticarias, triggered by heat, cold, sunlight, pressure, vibration, or exercise. Physical urticarias account for 20% of all urticarias.[5] The distribution of wheals in children with a physical urticaria may provide a clue to their etiology. For example, cold urticaria most often occurs on the hands, ears, nose, and the lateral thighs of women.[6]

With simple urticaria, children and their parents should be interviewed extensively, with particular attention paid to recent changes in the child's diet, changes in activities or potential changes in environmental exposures. All children should receive a thorough physical examination, looking for both signs of the precipitating allergen and for signs of impending anaphylaxis. Laboratory evaluation generally is not helpful in the acute setting.

Antihistamines most often are used in the initial medical treatment of acute urticaria, in particular H_1 antagonists such as diphenhydramine or hydroxyzine. If children do not respond to an H_1 antagonist, an H_2 antagonist, such as ranitidine, should be

added. Some clinicians have reported that skin receptors respond better to a combination of H_1 and H_2 antagonists.[7]

Corticosteroids should be used in severe cases of urticaria or in children with recurrent or chronic urticaria. Table 1 lists the medications commonly used to treat urticaria.

Often in allergic reactions, the precipitating allergen is not identified. Parents should be encouraged to maintain a diary that details the child's activities as well as signs and symptoms of allergies. Children with extensive or recurrent allergic reactions may benefit from formal allergy testing.

Erythema Multiforme. Erythema multiforme is an acute, self-limiting disease of the skin and mucous membranes. Skin lesions that are located symmetrically on the extremities, are characteristic of erythema multiforme. These lesions most often are described as erythematous rings (target lesions). However, while a single type of lesion may predominate during an attack, children may present with a combination of macules, urticaria, and vesiculobullous lesions.

The primary lesion of erythema multiforme is the target lesion, a red to dusky flat macule. The target lesion also may be a sharply demarcated wheal in the center of which a papule or vesicle develops. Typically, lesions begin as areas of circumscribed erythema with clearly defined margins, which then become raised.[8] After a period of 2-3 days, the center either flattens and becomes dusky or a papule or vesicle develops.[9]

Systemic manifestations rarely occur with erythema multiforme. However, children with Stevens-Johnson syndrome, a severe bullous form of erythema multiforme, will present with toxicity, fever, and signs and symptoms of systemic involvement. The primary distinction between erythema multiforme (also termed erythema multiforme minor) and Stevens-Johnson syndrome (alternatively termed erythema multiforme major) is the involvement of the mucous membranes.[9]

While the exact pathogenesis of erythema multiforme is unknown, it is thought to result from a hypersensitivity reaction to any number of etiologies. Typically, drug reactions and malignancies are identified in older children, while infectious diseases are more common in the younger child. Herpes simplex viruses and mycoplasma pneumoniae frequently are implicated as infectious etiologic agents.[9]

The lesions of erythema multiforme typically last for a week, but can recur in crops for as long as 2-3 weeks. Antihistamines, though typically used to treat children with erythema multiforme, often provide little clinical benefit. Some clinicians will treat children with erythema multiforme with a short course (3-5 days) of oral corticosteroids, though it is not clear that corticosteroids will shorten the course of the eruption or alleviate symptoms.[9,10] The decision to use corticosteroids remains controversial.

Angioedema. Children may present to the ED with an allergic reaction that involves not just urticaria, but areas of swelling, or angioedema, as well. Some patients may present with isolated angioedema. Angioedema, in the absence of urticaria, is thought to occur in 10% of patients.[5]

Table 1. Medications Commonly Used in the Treatment of Urticaria

MEDICATION	DOSAGE
First-Line	
Diphenhydramine	1 mg/kg/dose, up to 50 mg, q4-6h
Hydroxyzine	1 mg/kg/dose, up to 50 mg, q4-6h
Cetirizine hydrochloride	> 12 years, 5-10 mg QD
Second-Line	
Ranitidine	5-10 mg/kg/d, up to 300 mg, q12
Prednisone	2 mg/kg/d, up to 60 mg, q12

Angioedema involves swelling of the deeper cutaneous and subcutaneous tissue. Typically, angioedema is not associated with erythema or pruritus. However, children may present with pain or burning at the site of involvement. Angioedema most frequently occurs on the eyelids, tongue, and extremities.[5] Angioedema also tends to last longer than urticaria.[11]

Angioedema typically occurs through the same mediators that result in urticaria. The evaluation and management of the child with angioedema is similar to that of urticaria. However, children with signs and symptoms suggestive of angioedema involving the airway are at risk of acute airway obstruction and, therefore, require more aggressive monitoring management.

Children with a known history of hereditary angioedema are managed differently than children with typical angioedema. A more detailed discussion of children with hereditary angioedema is presented elsewhere in this review. Suspected hereditary or acquired C1 esterase inhibitor deficiency can be screened for by assaying serum C4.[11] If low, C1 esterase inhibitor deficiency can be confirmed by quantitative and functional C1 esterase assays.

Anaphylaxis. Anaphylaxis is defined as a massive systemic reaction, involving multiple organ systems, to a precipitating allergen. Anaphylactic reactions occur quickly and may be life-threatening if not recognized and treated immediately and aggressively. Anaphylaxis is an IgE-mediated event that is clinically indistinguishable from non-IgE mediated anaphylactoid reactions. Degranulation of mast cells and basophils, as a result of IgE cross-linking with antigen, results in the release of active mediators. Anaphylactoid reactions can be caused by direct activation of mast cells, changes in arachidonic acid metabolism, cytotoxic reactions, or by activation of the complement system via immune or protein complexes.

The exact incidence of anaphylaxis is unknown but is thought to occur as frequently as 1 in 3000 people.[12,13] The incidence is known to be higher in adults than in children.[13] Additional risk factors for developing anaphylaxis include gender (males > females), a history of atopy, and the route and constancy of administration of the antigen. Individuals are more likely to have an anaphylactic event if the antigen is given parenterally and less likely if they constantly are exposed to the antigen. However, the longer the time interval between the anaphylactic event and the next exposure to the allergic agent, the less likely the patient is to

have an adverse response. This is thought to occur because of increased catabolism and decreased synthesis of IgE on cessation of exposure to an antigen.[3]

Common inciting agents of anaphylaxis include foods, drugs, and venoms. A recent five-year review of all children seen at an urban children's hospital with signs and symptoms consistent with anaphylaxis found that 27% of cases were caused by latex, 25% by food, 16% by drugs, and 15% by venoms.[14] Most anaphylactic reactions to drugs occurred following intravenous administration of the medication (38%).

Preformed biologically active mediators released from mast cells and basophils are thought to account for the initial symptoms seen in children with anaphylaxis. However, new additional mediators are generated on stimulation, including prostaglandins, leukotrienes, thromboxane, platelet-activating factor, and kinins. These mediators are thought to account for the late phase of reactions seen in a proportion of patients with anaphylaxis.[13]

Symptoms of anaphylaxis often occur within minutes of exposure to an antigen, but may occur hours later. However, the most severe reactions usually begin 5-10 minutes after exposure.[15] A second wave of symptoms may occur in 25-30% of patients several hours after the first wave.[15] Typically, patients appear to be recovering after the first wave of symptoms, and may even become asymptomatic. The severity of symptoms in the second wave directly correlates to the intensity of symptoms in the first event.

A retrospective analysis of all patients admitted to a children's hospital with acute anaphylaxis found the overall incidence of biphasic reactions to be 6%, with an incidence of significant biphasic reactions of 3%.[16] Delayed delivery of subcutaneous epinephrine was associated with a higher incidence. However, other studies have suggested that early treatment does not necessarily affect the prevalence of biphasic symptoms, which can last from one day to weeks.[17]

Skin manifestations are seen in nearly 90% of all anaphylactic reactions.[3] Urticaria, pruritus, flushing, and angioedema commonly occur. However, children already taking an antihistamine inadvertently may mask the initial skin manifestations of anaphylaxis. Patients also may experience shortness of breath, bronchospasm, wheezing, hoarseness, and stridor. The latter two symptoms may predate life-threatening laryngeal edema. In a review of anaphylaxis, 93% of patients had skin involvement, and 93% had involvement of the respiratory system.[14]

Signs and symptoms of involvement of the cardiovascular system are common in anaphylaxis. Twenty-six percent of children in a recent review had cardiovascular involvement.[14] Children often will be tachycardic with associated poor peripheral and central perfusion, and hypotension may indicate vascular permeability and vasodilatation. Children may present in hypovolemic shock. In addition, children in anaphylaxis are at risk for arrhythmias.

Neurologic involvement in children also may occur. Children may experience an aura, irritability, lethargy, disorientation, headache, dizziness, tremor, syncope, or seizure. Quite commonly, some older children will express a feeling of impending doom.

Complaints of abdominal cramps, vomiting, and diarrhea are quite common and signify involvement of the gastrointestinal tract. Children also may present with rhinitis, conjunctival irritation, and excessive tearing.

The morbidity and mortality of anaphylaxis directly is related to the extent of cardiac and pulmonary involvement. A review of a national registry from the United Kingdom found that half of all fatal episodes of anaphylaxis were thought to be iatrogenic in origin, 25% were due to food, and 25% due to insect venom.[18] Most food-related fatalities resulted from respiratory arrest, while shock more commonly occurred in iatrogenic and venom reactions. Interestingly, the median time to respiratory or cardiac arrest was 30 minutes for food-related events, 15 minutes for venom, and 5 minutes for iatrogenic. Epinephrine was used in only 14% of cases prior to arrest. However, epinephrine overdose accounted for three deaths. In a review of nonfatal cases of anaphylaxis seen at an urban children's hospital, patients requiring intensive care were more likely to have latex as an inciting agent, have a nonenteral route of exposure, and have involvement of the cardiovascular system.[14]

Additional predictors of poor outcome following anaphylaxis include delays in recognition of symptoms, delay in administration of epinephrine, a past history of asthma, and a history of a previously life-threatening anaphylactic episode.[17,19,20] The management of anaphylaxis will be discussed in greater detail later in the review.

Common Inciting Agents

Bee Stings. Bee stings commonly occur in the pediatric population. While the most common reaction to a bee sting consists of local pain and swelling, a portion of children will present with a more extensive reaction.

Bee stings result in both local and systemic reactions that are IgE-mediated. The majority of bee stings produce only a local hive and intense pruritus. However, 10% of children will have a massive local reaction, defined as swelling beyond two joints of an extremity, and 1% of these will have a systemic reaction. About 40 deaths occur each year from bee stings.[21]

Interestingly, only 10% of children (vs 50-60% of adults) who are stung on a second occasion will have a more severe reaction than is observed with the first sting.[22,23] As a result, children younger than 16 years of age experiencing cutaneous reactions alone to a bee sting, such as urticaria and angioedema, are not at an increased risk of developing more severe life-threatening reactions in the future. Thus, the clinical manifestations of a child's reaction to a bee sting are useful for predicting the nature of future reactions and for deciding who should receive immunotherapy. In patients with a prior history of a systemic reaction, the risk of a recurrent systemic reaction is 28%.[24]

As is typical of other trauma-related incidents, boys are more likely to be stung by a bee than girls, and are more likely to

develop an anaphylactic reaction to the sting.[15] Children also are more likely to outgrow their sensitivity to bee stings.[25]

Management of local reactions to a bee sting consists of applying ice to induce vasoconstriction and prescribing an oral antihistamine for 24 hours. When a bee stings, spasm of muscles surrounding the venom sac located at the base of the stinger may result in the continued delivery of venom. Stingers, when identified, should be "flicked" off to avoid squeezing the venom sac and injecting more venom into the wound.

Patients with massive local reactions may benefit from a longer course of antihistamines and a five-day course of oral corticosteroid therapy. More severe reactions will be discussed later in this review.

Antibiotics. Antibiotics are another common cause of allergic reactions in children. The types of antibiotics most often implicated in allergic reactions are the penicillins, cephalosporins, and sulfas. Each year, several hundred deaths occur as the result of allergic reactions stemming from the administration of beta-lactam antibiotics. Reportedly, anaphylaxis occurs in 1-5 patients per 10,000 administrations of beta-lactams, of which 10% are life-threatening and 1% are fatal.[26] Most reactions involve intramuscular or intravenous administration of the antibiotic, though deaths have been reported following oral administration. Again, the spectrum of allergic reactions can range from urticaria to full-blown anaphylaxis.

Foods. One of the more common causes of allergic reactions in children is food. The incidence of food allergy in children appears to be greatest during the first two years of life and decreases with age.[15] Food allergy is an immunologic reaction resulting from the ingestion of a food or food additive. Food allergies may occur within seconds of ingestion. However, the majority occur within four hours of ingestion.

Most exposures to food allergens follow an ingestion, with the body often responding by inducing vomiting.[7] However, in extremely sensitive patients, reactions may occur from simply inhaling the aroma of the offending food or by coming into skin contact with it.[7,27] Systemic anaphylaxis has been reported in a milk-sensitive patient after the application of a diaper rash ointment that contained just 5% caseinate.[28]

In addition to specific types of foods, atopic individuals with a history of asthma and prior allergic reactions to the same food are at particularly high risk for potentially severe allergic reactions and even lethal anaphylaxis.[29] In an analysis of 21 fatal anaphylactic reactions to foods, obtained from a national registry, 20 had a prior history of asthma.[30] Peanut and tree nut allergies were responsible for the majority of anaphylactic reactions.

The foods that commonly cause anaphylaxis are listed in Table 2. Allergy to egg white is the most common cause of allergic reactions in infants, followed by cow's milk. The egg yolk is considered less allergenic than the egg white.[31]

Peanut allergy is the most worrisome food allergy. The use of peanuts and peanut oil is very common in everyday life, and as a result, children may come in contact with peanuts without realizing it. Many restaurants use peanut oil for cooking, which would not necessarily be evident on a menu. Reactions to peanuts frequently are severe and occasionally are fatal. Atopic children seem to be at particularly high risk.[32] What makes peanut allergies particularly troublesome is that there have been reports of children reacting to peanuts even with the very first exposure.[32,33] Sensitization also may occur because of cross-sensitization to a similar antigen and may even occur in utero.[34]

Because of this, peanut-allergic children and their parents, relatives, teachers, and friends require extensive education about avoiding peanut exposures and in emergency treatment measures. It is not uncommon for parents who wish to have one of their children attend a daycare, preschool, or school, to be asked to ensure that their child does not bring peanuts or a peanut-containing snack to class when there is a peanut-sensitive child who attends.

Other significant foods that can cause allergies include sesame oil, shellfish, and fish. In addition, soybeans, a member of the legume family (like peanuts) can cause extreme food allergies in children. Soybeans commonly are used as food extenders in many commercial food products to which children are likely to be exposed.[35] Cross-reactivity can occur among members of the legume family so that children who are allergic to soybeans also may be allergic to peanuts, and vice versa. Other members of the legume family to consider include green beans, kidney beans, navy beans, black-eyed peas, green peas, and string beans. However, data suggest that the strength of cross-reactivity among members of the legume family is not as strong as once believed.[32] Some clinicians do not routinely advise patients to avoid eating soybeans, string beans, etc., if they are known to be allergic to peanuts. Interestingly, cross-reactivity among members of the legume family also may occur with licorice.[32]

Similarly, cross-reactivity commonly occurs among tree nuts, though tree nut allergies are more common in adults than in children. Tree nuts include almonds, cashews, pecans, pistachios, and walnuts.

It is important to note that children typically will outgrow sensitivity to dairy products and eggs by 3-4 years of age. However, nut and fish allergies often last throughout the child's lifetime.[7,35]

Cross-reactivity among similar antigens may occur between foods and environmental allergens. Patients with ragweed hay fever may experience symptoms when eating bananas and foods

Table 2. Foods that Commonly Cause Anaphylaxis

- Peanuts
- Milk: Cow's, goat's
- Fruit: Kiwi, banana
- Tree nuts: Hazelnuts, walnuts, pistachios, Brazil nuts
- Cereal: Wheat, barley, oat
- Seeds: Cotton, sesame, sunflower
- Potato
- Shellfish: Shrimp, crab, oyster, scallop
- Fish
- Beans: Soybeans, green peas, pinto, green, kidney

that are members of the gourd family.[32] Those with birch pollenosis may react to apples, carrots, or potatoes.

Not all reactions to foods are considered hypersensitivity or IgE-mediated. However, it may be difficult to differentiate between allergy and food intolerance, as signs and symptoms may be similar. No matter the mechanism, in a reaction to a food, symptoms involving the gastrointestinal system will predominate, including nausea, vomiting, and diarrhea. The signs and symptoms of acute allergy or anaphylaxis to a food can occur within minutes or hours of ingestion. Some patients with a food allergy may complain of almost immediate lip, tongue, and throat tingling; itching; swelling; and throat burning or tightness after ingesting a food to which they are allergic. Others may develop hives hours later. Patients with extreme food allergy typically will develop symptoms within minutes of exposure.

Aspirin and Nonsteroidal Anti-inflammatory Drugs (NSAIDs). Aspirin and NSAID allergic reactions rarely occur, but are important to recognize. The incidence of allergic reactions to aspirin is estimated to be 1%.[2] In patients with a history of chronic urticaria, the incidence rises to 20-50%. However, true IgE-mediated hypersensitivity is rare. It is believed that aspirin-induced inhibition of cyclooxygenase enhances the lipoxygenase products of arachidonic acid metabolism, leading to vasodilation and edema.[36] It is important to note that children who are allergic to aspirin also will be allergic to NSAIDs. However, patients will tolerate acetaminophen.

Hereditary Angioedema (HAE) (Deficiency of C1 Inhibitor). Hereditary angioedema (HAE) is a rare cause of allergic reactions in children. Characterized by a deficiency of C1 esterase inhibitor, HAE results in skin lesions that have a tawny, brown appearance. Typically, skin lesions are not pruritic. In addition, children may experience acute attacks of severe abdominal pain related to edema occurring within the abdominal wall.[7] The disorder is autosomal dominant in inheritance and is diagnosed by measuring decreased levels of C1 esterase inhibitor and C4. Children can be treated with danazol, a synthetic androgen. Current investigations have focused on treating children with actual C1 esterase inhibitor. Traditional therapy for urticaria and anaphylaxis (H_1 antagonists and corticosteroids) are not thought to be effective in the treatment of HAE.

Latex Allergy. Allergic reactions to latex and rubber products have become a major public health concern during the past 10 years. Though IgE-mediated, the exact antigen that incites a reaction has not yet been identified. In fact, IgE antibodies from latex-sensitive individuals are known to react with a variety of different protein components, supporting the idea that there may be more than one clinically important latex antigen.[37]

Patients who are allergic to latex often will present with localized pruritus and urticaria following skin contact. Conjunctivitis, sneezing, and rhinitis may occur following aerosol exposure or direct facial contact. Systemic reactions, including signs and symptoms consistent with anaphylaxis, occur with more substantial exposure. Intraoperative anaphylaxis is a common and serious consequence of latex allergy.

There are a number of high-risk groups of patients that have been identified as more susceptible to developing latex hypersensitivity. These include patients with spina bifida, medical workers, and atopic persons.[38] Interestingly, cross-reactivity between latex and other antigens, including foods, has been described. Banana, avocado, and chestnut are known to be antigenically similar to latex, and patients with a latex allergy may develop an allergic reaction when exposed to these substances.[39,40]

As with other allergens, the cornerstone of treatment of latex allergy is avoidance. Measures should be taken by health care providers to provide safe care for latex-sensitive patients. In EDs, this may involve designating and preparing a treatment room as "latex free." Charts of patients should be identified as "latex sensitive." In all other aspects, treatment of symptomatic patients with latex allergy remains the same.

Idiopathic. Idiopathic allergic reactions are defined as a reaction in which there is no identifiable antigen. Allergic reactions in children often are thought to be idiopathic because an inciting agent is not identified. However, this may be because common viral triggers often are neither looked for nor discovered in children presenting with urticaria. Other antigens simply may be unrecognized by a child or his or her parents. However, true idiopathic allergic reactions and anaphylaxis are known to occur.[41] It has been hypothesized that the disease results from either an inability to appropriately control histamine release at a cellular level or secondary to T lymphocyte activation.[42,43] Pediatric idiopathic anaphylaxis can present at any age. Symptoms usually will respond to a tapering course of oral glucocorticosteroids.[44]

Patient Assessment

Allergic reactions can progress rapidly. A patient who presents with hives in triage may progress to anaphylaxis. Therefore, patients who present with allergic reactions should be assessed rapidly and frequently. Often, decisions regarding optimal therapy will need to be made before a complete patient database has been obtained.

Critical to achieving a good outcome is an early suspicion of the diagnosis. Medical therapy may need to be instituted prior to any history being obtained and after only a limited physical examination. Initial historical questions should be focused on determining the most likely precipitating agent while simultaneously paying attention to the ABCs (airway, breathing, and circulation). Children and parents should be asked about recent medication use, new foods in the diet, new soaps and detergents, and any recent illnesses. A prior history of allergic reactions for the child or a family history of allergic reactions should be obtained as well. When time permits, clinicians should obtain precise details about the child's actions during the hours leading up to the reaction.

Physical examination of the child who presents with an allergic reaction should begin with the ABCs. In particular, the clinician should evaluate for signs of stridor, wheezing, decreased tissue

perfusion, prolonged capillary refill, and altered mental status.

In the child who presents with simple urticaria and has no signs or symptoms of systemic involvement, a more thorough history and physical examination can be obtained prior to instituting therapy. Again, a detailed history of the child's most recent actions should be sought, focusing on changes in the child's diet and environment. In anaphylaxis, management decisions must be made promptly, and a thorough, detailed history should be obtained only after the patient has been stabilized.

Management

ABCs. The initial management of the child who presents with a clinical picture consistent with an allergic reaction should begin with the ABCs. Determining or securing a stable airway is important because respiratory symptoms can develop or progress rapidly. Patients who present with stridor and hoarseness may have laryngeal edema that can progress rapidly to complete airway obstruction.

Children in anaphylaxis should be provided with supplemental oxygen, an intravenous line should be placed, and intravenous fluids should be started. In addition, patients should be placed on a cardiac-respiratory monitor, and vital signs should be checked frequently. Children with more minor reactions will not require intravenous access or supplemental oxygen, but should be placed in a monitored environment for a period of time to ensure that the reaction is not progressing.

One consideration frequently neglected in the management of children with an allergic reaction is that the offending allergen may still be present on the patient's skin or clothing. Patients should be disrobed when possible and placed in hospital gowns. If skin contact is assumed, the patient's skin should be cleansed to remove any remaining allergen.

A complete history is essential in a child presenting with a minor allergic reaction. However, in the early evaluation of a child in anaphylaxis, a focused history is more pragmatic. Questions should focus on possible exposures, past and family history of allergic reactions, allergies to medicines, and current medications.

Many medications are used in the treatment of anaphylaxis. Table 3 lists the medications most commonly used.

Epinephrine. Epinephrine is considered first-line treatment for anaphylaxis and should be given immediately following recognition of the signs and symptoms of anaphylaxis. Epinephrine generally is not required for minor allergic reactions. Epinephrine, via its combined alpha- and beta-adrenergic effects, antagonizes the effect of the mediators of anaphylaxis and impairs their further release.[19] Epinephrine's alpha-agonist effects result in increased peripheral resistance and decreased urticaria and angioedema.[13] Its beta-agonist effects include increasing inotropic effects on the heart, bronchodilation, and an increase in cyclic adenosine monophosphate, which inhibits further mediator release.[13]

Epinephrine usually will acutely reverse the features of anaphylactic reactions if administered immediately. A delay in the recognition of symptoms of anaphylaxis, resulting in a delay in epinephrine administration, has been reported as the principal reason for poor outcome and mortality following anaphylactic reactions.[17,19]

The initial dose of epinephrine can be administered either intramuscularly or subcutaneously, though intramuscularly is preferred. In general, epinephrine is not given intravenously for anaphylaxis because intravenous administration has been associated with an increased risk of myocardial ischemia and arrhythmias.[13] Additional doses of epinephrine can be given at five- to 10-minute intervals and are recommended if a clinical effect is not achieved with the initial dose. A retrospective study of epinephrine administration in 105 cases of anaphylaxis following a bee sting found that 38 (35.5%) required more than one injection.[19] Children with more severe episodes of anaphylaxis were more likely to receive more than one injection. Some investigators recommend that a second injection of epinephrine be delivered into the site of an insect sting, drug injection, or allergen injection to retard systemic absorption of the antigen.[45] In addition, a lightly placed tourniquet, proximal to the site of the offending sting or injection site, also may slow absorption of the antigen.

Table 3. Treatment of Anaphylaxis

First-Line Treatment

- Remove inciting agent if applicable
- ABCs
- ECG monitoring

MEDICATION	DOSE
Oxygen	100% FiO_2
Crystalloids	20 cc/kg, IV bolus
Epinephrine	SQ: (1:1000) 0.01 cc/kg
	IM: (1:1000) 0.01 cc/kg

Second-Line Treatment

MEDICATION	DOSE
Diphenhydramine	IM 1 mg/kg
	IV 0.5 – 1.0 mg/kg
Cimetidine	IV 5 – 10 mg/kg
Ranitidine	IV 0.5 mg/kg
Methylprednisolone	IV: 1 - 2 mg/kg

Special Circumstances

SIGNS OF UPPER AIRWAY OBSTRUCTION	
Racemic epinephrine	Nebulized: 0.5 cc
BRONCHOSPASM	
Albuterol	Nebulized: 15 mg/hr
PERSISTENT HYPOTENSION	
Dopamine IV	5-10 mcg/kg/min

Aerosolized epinephrine can be given for signs and symptoms of upper airway edema.

Volume Repletion. Poor perfusion and hypotension often occur during anaphylaxis and may be resistant to treatment. Multiple fluid boluses may be required to improve perfusion and reverse hypotension. If tissue perfusion and hypotension do not improve following the administration of multiple fluid boluses and epinephrine, vasopressor agents such as dopamine may be required. In general, all children who present with signs and symptoms of anaphylaxis should have an intravenous line placed. Intravenous fluids should be instituted, even if the patient has a normal blood pressure and perfusion. Children with minor allergic reactions do not routinely require intravenous fluid replacement.

Antihistamines. Skin manifestations of anaphylaxis, in particular urticaria, usually are the first and most recognized sign of allergic reactions. As such, antihistamines often are given immediately to temper the extent of the urticaria and decrease pruritus. However, it is important to recognize that many of the signs and symptoms of anaphylaxis are mediated by histamine, and antihistamines will help to alleviate some of them. Antihistamines, such as diphenhydramine, improve urticaria and decrease laryngeal edema and bronchospasm. However, antihistamines should not be used as the primary therapeutic agent.

Most antihistamines act at the H_1 receptor. H_1 blockers can be given at six- to eight-hour intervals as needed. H_2 blockers also may provide some clinical benefit. The combination of both an H_1 and an H_2 blocker, given intramuscularly or intravenously, may be even more effective than either antihistamine given alone.

Antihistamines should be administered either intramuscularly or intravenously for all children who present with anaphylaxis. Intravenous administration is preferred, but intramuscular injections can be used if IV access is delayed. Children who present with minor allergic reactions should be treated with oral antihistamines.

Glucocorticosteroids. In general, corticoteroids should be given to every child who presents with anaphylaxis but not necessarily every child who presents with an allergic reaction. For minor allergic reactions, corticosteroids offer little additional clinical benefit in comparison to the risks of their use. With more extensive allergic reactions (e.g., with extensive urticaria, severe pruritus, facial swelling), but not anaphylaxis, a three- to five-day oral course of corticosteroids may help alleviate symptoms.

Every child who presents with anaphylaxis should be given corticosteroids intravenously. While steroids are of little clinical benefit in the acute management of anaphylaxis, they may help prevent the onset of late-phase reactions.

Albuterol. Involvement of the respiratory system is common during anaphylaxis, and children often will present with tachypnea, increased work of breathing, and wheezing. Nebulized beta-agonists should be used to treat continued bronchospasm. Children with minor allergic reactions do not routinely require nebulized beta-agonist medications.

Glucagon. Children who are receiving beta-adrenergic blockade medications may require special care and consideration when they develop anaphylaxis. Beta-blockers can minimize the beta-adrenergic effects of epinephrine and leave the alpha-adrenergic stimulation unopposed, resulting in bradycardia, refractory hypotension, and relapsing symptoms.[46,47] Glucagon has positive inotropic and chronotropic effects on the heart and is probably the drug of choice in the therapy of patients receiving beta-adrenergic blockade medications.[48] Intravenous and aerosolized atropine also can be used to treat bradycardia in such patients.

Laboratory and Radiographic Studies. There is little role for routine laboratory or radiographic tests in children presenting with typical signs and symptoms of an allergic reaction. Tryptase and histamine levels may help in the diagnosis of anaphylaxis but are not routinely run in most laboratories and will not be of timely help. Instead, these tests should be reserved when patients present with atypical signs and symptoms of anaphylaxis and there remains doubt as to whether the patient has experienced an allergic reaction.

Disposition

Deciding on the disposition of children following an allergic reaction will depend on the severity of the reaction. Children who have experienced a mild allergic reaction probably should be monitored for a period of several hours following the onset of symptoms to ensure that the child does not develop late signs and symptoms of anaphylaxis. If a child presents to the ED several hours after the onset of a reaction, and the child does not have signs and symptoms of a more serious reaction, he or she can be discharged immediately home after therapy has been instituted.

Children who experience mild anaphylactic reactions should be observed for a period of 4-8 hours in a monitored environment in the ED. If no further symptoms occur, patients can be discharged home. Patients should continue to be treated with an oral antihistamine and an oral glucocorticosteroid for at least 2-3 days and should be instructed to follow up with their primary care provider at that time. Children and their parents also should receive careful instructions as to the signs and symptoms of anaphylaxis and be given a prescription for an EpiPen. The clinician should review with the child, if old enough, and parents, the use of the EpiPen and when to use it. In addition, patients also should be given a prescription for an antihistamine medication and instructed to fill the prescription and keep the medication readily accessible and be instructed on when to use it.

Patients who have had more severe symptoms, in particular symptoms involving the respiratory and cardiovascular system, or who received multiple doses of epinephrine should be observed for 24 hours in a monitored environment. Patients with the most severe reactions probably should be monitored in an intensive care setting because the likelihood of a late-phase reaction increases in proportion to the severity of symptoms during the acute phase. Again, when children are discharged home, they should be treated with oral antihistamines and glucocorticosteroids for at least 2-3 days and be given prescriptions for an EpiPen and antihistamine medications.

Often, the inciting allergen is not identified in children who present with allergic reactions. Children who have experienced anaphylaxis should be referred for formal allergy testing. A diary kept by the parents detailing the occurrence of urticaria or other allergic symptoms, as well as the child's eating habits and possible environmental triggers, may be helpful. Once an inciting agent is identified, parents and children should be educated on avoidance of exposure to the allergen.

Finally, children and parents should be encouraged to purchase a Medic Alert bracelet that identifies a patient's allergies. Children should be encouraged to wear their Medic Alert bracelets at all times.

EpiPens. The EpiPen is a spring-loaded, auto-injector device capable of delivering a known quantity of epinephrine. EpiPens should be used in children weighing at least 25 kg and will deliver 0.3 mg of epinephrine. EpiPen Jr. delivers 0.15 mg of epinephrine and is used in children who weigh 15-25 kg. EpiPen prescriptions should be provided to children who have a history of severe allergic or anaphylactic reactions. Parents should be instructed as to their use and to ensure that they are always readily available. Clinicians should be aware that reliable self-injection by a child generally is not possible until the child reaches 8 years of age.

Parents should be aware that EpiPens have a one-year shelf-life and should be replaced every year. However, a recent prospective, randomized, crossover study measured epinephrine bioavailability in rabbits after injection from outdated autoinjectors.[49] Interestingly, more than 50% of the original amount of epinephrine could still be delivered by autoinjectors up to 90 months beyond their expiration date.

A recent survey of EpiPen use in children with a history of anaphylaxis found that large numbers of children or their parents did not know how to use an EpiPen and that, often, the physician who prescribed it did not explain its use.[50] A survey of children with a history of anaphylaxis who had a recent anaphylactic reaction found that a prescribed EpiPen was used in only 29% of recurrent anaphylactic reactions.[51] In addition, the majority of parents and children were unfamiliar with its use. A study of health care professionals reported that 81% did not have an epinephrine auto-trainer to help educate parents, and 75% of these professionals were not able to correctly describe the steps in using the auto-injector.[52] More recently, a use assessment of self-administered epinephrine among food allergic children found that a substantial portion of parents were unable to demonstrate correctly the use of their self-injectable epinephrine and a large number did not have the medication readily available at the time of need.[53] A sampling of pediatricians also demonstrated that many were not familiar with the devices and failed to review their use with their patients.

A recent investigation looked at the use of epinephrine metered dose inhalers (MDI) as a substitute for EpiPens.[54] The study, in a randomized, blinded, placebo-controlled fashion, measured mean peak plasma epinephrine concentration following inhalation of either a placebo or epinephrine from an MDI in asymptomatic children with a history of anaphylaxis. The mean age of children using the epinephrine MDI was 9 years. The investigators reported that mean plasma concentrations of epinephrine were no different between groups and concluded that epinephrine MDIs should not be used as a prophylactic medication for children with a history of anaphylaxis or severe allergic reactions.

An EpiPen or EpiPen Jr. should be prescribed for all children who have experienced an anaphylactic reaction. In general, such devices are not required for children who have experienced a minor reaction. Emergency medicine physicians who prescribe their use should be familiar with the devices and should instruct families on their proper use.

Summary

Allergic reactions are common in children. Unfortunately, they can be particularly frustrating to parents, children, and treating physicians. At times, medical treatments may be ineffective in relieving symptoms and inciting agents are not always identified. Parents and children are often fearful that a similar or worse reaction will recur, especially when they don't know what caused the initial reaction.

When faced with a potential allergic reaction, emergency medicine physicians must work quickly, often with little historical information, to manage patients. Significant morbidity and mortality can occur with delays in treatment, and simple urticaria can turn into life-threatening anaphylaxis. Initial management should focus on identifying precipitating agents, managing the ABCs, and reversing the actions of inflammatory mediators. Epinephrine remains the mainstay of treatment and should be given first for all severe allergic reactions and anaphylaxis. Additional pharmacologic therapies are available and can be used to complement the actions of epinephrine. Finally, children with a history of severe allergy should be provided with a prescription for an EpiPen, an antihistamine, and a Medic Alert bracelet.

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Physician CME Questions

51. The most dangerous food allergy for children is thought to be:
    A. bananas
    B. peanuts.
    C. strawberries.
    D. milk.

52. What other foods might a child who is allergic to peanuts have an allergic reaction to?
    A. Soybeans
    B. Walnuts
    C. Chestnuts
    D. Bananas

53. Which drug is considered first-line treatment in children who present in anaphylaxis?
    A. Diphenhydramine
    B. Methylprednisolone
    C. Epinephrine
    D. Glucagon

54. Bee sting reactions are mediated by what mechanism?
    A. Type 1 hypersensitivity
    B. Type 3 immune/complement activation
    C. Direct toxic effect on mast cells
    D. Alteration of the arachidonic acid metabolism

55. Patients who are taking beta-blockers may not respond well to traditional medical therapy for anaphylaxis. Which drug may aid in blunting the effects of the beta-blockers?
    A. Diphenhydramine
    B. Glucagon
    C. Epinephrine
    D. Albuterol

56. One of the primary mediator of allergic reactions is:
    A. neuron specific enolase.
    B. histamine.
    C. norepinephrine.
    D. dopamine.

57. Histamine is released from what cells during an allergic reaction?
    A. Neutrophils
    B. Lymphocytes
    C. Mast cells
    D. Platelets

58 . Patients who are allergic to aspirin often are allergic to:
    A. Peanuts
    B. Shellfish
    C. NSAIDs
    D. Acetaminophen

59. A 5-year-old child presents with stridor, respiratory distress, hives, and facial swelling following ingestion of a product containing peanuts. Which of the following therapies is indicated?
    A. 100% oxygen
    B. Epinephrine administration
    C. IV access
    D. All of the above

60. Which of the following is *not* associated with a poor outcome in a patient with anaphylaxis?
    A. Past history of asthma
    B. Early administration of epinephrine
    C. Previous history of life-threatening anaphylaxis
    D. Delays in recognition of symptoms

In Future Issues: **Congenital Heart Defects**

PEDIATRIC Emergency Medicine Reports

The Practical Journal of Pediatric Emergency Medicine

Allergic Reactions

Medications Commonly Used in the Treatment of Urticaria

MEDICATION	DOSAGE
First-Line	
Diphenhydramine	1 mg/kg/dose, up to 50 mg, q4-6h
Hydroxyzine	1 mg/kg/dose, up to 50 mg, q4-6h
Cetirizine hydrochloride	> 12 years, 5-10 mg QD
Second-Line	
Ranitidine	5-10 mg/kg/d, up to 300 mg, q12
Prednisone	2 mg/kg/d, up to 60 mg, q12

Foods that Commonly Cause Anaphylaxis

- Peanuts
- Milk: Cow's, goat's
- Fruit: Kiwi, banana
- Tree nuts: Hazelnuts, walnuts, pistachios, Brazil nuts
- Cereal: Wheat, barley, oat
- Seeds: Cotton, sesame, sunflower
- Potato
- Shellfish: Shrimp, crab, oyster, scallop
- Fish
- Beans: Soybeans, green peas, pinto, green, kidney

Treatment of Anaphylaxis

First-Line Treatment

- Remove inciting agent if applicable
- ABCs
- ECG monitoring

MEDICATION	DOSE
Oxygen	100% FiO_2
Crystalloids	20 cc/kg, IV bolus
Epinephrine	SQ: (1:1000) 0.01 cc/kg
	IM: (1:1000) 0.01 cc/kg

Second-Line Treatment

MEDICATION	DOSE
Diphenhydramine	IM 1 mg/kg
	IV 0.5 – 1.0 mg/kg
Cimetidine	IV 5 – 10 mg/kg
Ranitidine	IV 0.5 mg/kg
Methylprednisolone	IV: 1 - 2 mg/kg

Special Circumstances

SIGNS OF UPPER AIRWAY OBSTRUCTION	
Racemic epinephrine	Nebulized: 0.5 cc
BRONCHOSPASM	
Albuterol	Nebulized: 15 mg/hr
PERSISTENT HYPOTENSION	
Dopamine IV	5-10 mcg/kg/min

Supplement to *Pediatric Emergency Medicine Reports*, June 2002: "From Urticaria to Anaphylaxis: The Spectrum of Allergic Reactions in Children." *Author*: **Raymond D. Pitetti, MD, MPH, FAAP**, Assistant Professor of Pediatrics, Division of Pediatric Emergency Medicine, Department of Pediatrics, University of Pittsburgh School of Medicine/Children's Hospital of Pittsburgh.

BIOTERRORISM WATCH
Preparing for and responding to biological, chemical and nuclear disasters

They don't call it bio*terror* for nothing: Fear is the foe when anthrax spores are found within hospital walls

'We feel we were able to ward off a panic . . .'

Clinicians nationwide were beset with hoax powder scares last year at the height of the anthrax attacks, but at one hospital, the threat turned out to be real. Positive cultures for *Bacillus anthracis* were found within hospital walls, setting off a wave of anxiety that threatened to descend into panic.

"There was a mounting level of anxiety among our health care workers," said **Maureen Schultz**, RN, infection control coordinator at Veterans Affairs (VA) Medical Center in Washington, DC. "It had to be dealt with before we could work out any other aspect of the situation."

The events began to unfold last October, when it was discovered that the anthrax letter sent to Sen. Tom Daschle (D-SD) might have contaminated other federal buildings through cross-contamination of mail processed at the Brentwood postal building in Washington, DC.

"It was several days before the contamination was discovered, and by that time, several downstream facilities, including our VA hospital, were contaminated," she said recently in Salt Lake City at the annual meeting of the Society for Healthcare Epidemiology of America (SHEA).[1] In light of the situation, it was recommended that mailrooms in federal buildings be cultured for anthrax.

"One of the things we found frustrating was that we were not given any guidance as to how we should screen the mail," Schultz said. "So we [took] cotton swabs and ran each swab over an approximately 10 to 50 square inch area."

Four of 34 environmental swabs taken in the hospital mailroom grew *B. anthracis*, with colony counts varying from one to 11. The anthrax was found on a canvas mail tote, a cardboard box that had been mailed, on the top of a mailroom speaker, and on a canvas mail cart.

The fear factor

"Even before the contamination was discovered, [we] decided to take some action because of the growing concern among our employees," she said. "So [we] convened a group from the emergency response team, infection control, safety, and public affairs."

The focus of the response was to determine risk level, provide prophylaxis as needed, decontaminate the environment, and get accurate information to all 1,700 health care workers, patients, and visitors, Schultz said. In order to reduce the high level of anxiety, a series of educational sessions were held, information was posted on the hospital web page, press releases were distributed, and printed materials were given to staff, patients, and families. In addition, a series of "town-hall" meetings was held to fully air the concerns of employees.

"These were informal sessions that we had in our auditorium where many health care workers could come and interact on an informal basis," Schultz said.

The risk to hospital workers was determined to

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be low, and only eight staff members were started on prophylactic antibiotics. Those included five mailroom employees who were encouraged to take full 60-day regimens. Another three workers, considered at lower risk, were given 10-day regimens due to possible contact with contaminated mail. The mailroom and surrounding area were decontaminated by an outside contractor.

Overall, some 500 health care workers attended the education sessions, and each town-hall meeting drew more than 200 staff members. With the colony counts low and the contamination limited, the decision was made to limit prophylaxis to only the eight aforementioned employees. That approach was not well received by other health care workers who feared they could have been unknowingly exposed.

"We refused treatment to all other employees, and initially, this created a lot of anxiety among the health care workers, particularly in these large town-hall meetings," Schultz said. "They were demanding ciprofloxacin or doxycycline in case they had come in contact with something contaminated. But we did hold firm on this, and we did not provide prophylaxis to any other employees."

Still, at the SHEA meeting, the Centers for Disease Control and Prevention (CDC) conceded that many of its initial assumptions about anthrax turned out to be false, including the perception that mail handlers were not at risk for inhalational anthrax. Given that acknowledgment, *Bioterrorism Watch* asked Schultz if she would now reconsider the decision to limit antibiotic prophylaxis to a few workers. "Based on the information we have now, no. I don't think we would change that decision." There really was no evidence that any widespread contamination had occurred, she added.

A total of 34 workers reported to the occupational health service for clinical evaluation, but there were no reports of staff refusing to work, and patient care was not interrupted. The initial level of fear and anxiety among many of the workers eased off under the continuous education and communication effort.

"We feel we were able to ward off a panic situation by the actions that we took," she said.

NYC hospital faces similar situation

A similar contamination incident was feared at Memorial Sloan Kettering Institute, a 431-bed cancer center in New York City. Some 1,200 health care workers at Sloan Kettering work in the same building as Gov. George Pataki's Manhattan office, which was reported to be the target of anthrax mailing. On Oct. 17, possible anthrax (positive by polymerase chain reaction test) was discovered in the governor's office. Pataki and staff vacated their part of the building, and infection control staff and hospital administration at Sloan Kettering developed a response plan to protect their workers.

The hospital employees worked on 10 floors of the 40-story building, including three floors that shared an air-ventilation system with the governor's offices. The response was honed to focus on mailroom staff and some 250 employees who worked on the three floors with shared air. With incomplete information on the scope of potential contamination of Pataki's offices, hospital clinicians decided to perform nasal cultures on the employees on the three floors, **Janet Eagan**, RN, an infection control professional at Sloan Kettering reported at the SHEA conference.[2] All of the 245 cultures taken were negative.

"I think the nasal swabs were more to allay fear," she said. "We wanted to do something that was proactive."

Public health investigators first used the nasal swab approach after the first anthrax case in Florida, but the CDC would later advise against routine use of the practice. The reliability of the swabs came into question, in part, because even those exposed may test negative as the nose clears of spores. At a Nov. 1, 2002, press briefing, the CDC advised against using nasal swabs "as a nonspecific probe to determine whether anthrax has ever been present in an environment."

Of course, clinicians at Sloan Kettering were dealing with a situation before that clarification was issued, but even then there were doubts about the wisdom of swabbing the workers.

"By the time we agreed to do the nasal swabs, I was kicking myself, thinking what on earth are we going to do with this information," **Ken Sepkowitz**, MD, epidemiologist at the hospital told SHEA attendees. "The nasal swabs was a screw-up, but with the information we had . . ."

With all the swabs negative, no antibiotics were administered. Additional efforts were needed to reassure the "worried well" that they were not at risk. Personnel from infection control, safety, security, and social work all met with the staff. Building management conducted an independent environmental survey of the building.

"E-mails went to all staff that all 245 employees tested had negative results," Eagan said.

"Communication is key. We believe that by having a hands-on approach — actually being there meeting with staff — prevented panic in employees that were very vulnerable."

Then word came that the original specimen from the governor's office had been found culture negative on retesting. The hospital had been through an intense false alarm drill, but overall had met the challenge, Eagan said.

"Decisions were made using incomplete information at a time-sensitive pace," she said. "Staff responded in a positive manner to the high visibility of administrative leadership, infectious disease, and infection control in numerous educational sessions and e-mail alerts."

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APIC: Smallpox plan uses outdated infection control

Designating patient facilities a mistake

The Centers for Disease Control and Prevention (CDC) has based its smallpox bioterrorism response plan on "outdated concepts," and entire sections need to be revised to reflect current epidemiologic strategies, the nation's leading group of infection control experts warned.

The Association for Professionals in Infection Control and Epidemiology (APIC) commented on the *CDC Interim Smallpox Response Plan and Guidelines*, which has been released as something of a work in progress.

"In general, we are concerned that the draft guidelines appear to be based on outdated strategies used to control this disease decades ago and do not appropriately integrate those infection control strategies and environmental controls utilized in our hospitals today," the APIC letter stated.

The CDC response plan calls for investigators to rapidly immunize a "ring" around the first cases. The ring concept uses isolation of confirmed and suspected smallpox cases followed by contact tracing, vaccination, and close surveillance of contacts. The ring approach was used to successfully eradicate smallpox from the world in 1980. But the ring concept was effective when the demographics of smallpox were very different, when few were infected, and the vast majority of people already were immune.

As part of the ring response, vaccine would be administered to people involved in the direct medical care, public health evaluation, or transportation of confirmed or suspected smallpox patients.

"Vaccination, like any preventive strategy, is more effective if given prior to exposure," APIC argued. "If health care workers are not immunized prior to case identification, these individuals [especially emergency department staff, direct caregivers, and laundry personnel] should be vaccinated immediately upon documentation of a case in their community. It is crucial that we not wait for a case to present in the facility before taking preventative action."

In addition, it may not be possible to distinguish between febrile response to vaccine or actual exposure in health care workers, APIC warned.

"Approximately 20% of vaccinated employees will develop fever and not be able to work if vaccine is given in response to a suspect or confirmed case," the association stated. "We need to develop strategies for dealing with staffing shortages whether they are due to febrile reaction to vaccination, true infection / disease, or refusal to care for patients in a smallpox emergency."

'Misuse of resources'

APIC also questioned the CDC concept of a "Type C isolation facility" for smallpox patients. As proposed, the sites would be facilities that are at least 100 yards from any other occupied building, or those that have nonshared air-ventilation systems with filtered exhaust.

"We believe it would be a misuse of resources to design, build / retrofit, and maintain a designated facility that is not integrated with the existing health care system," APIC stated. "Using alternative structures rather than enhancing the current infrastructure is not a wise use of our limited resources."

Instead, existing facilities could substantially

benefit from dedicating resources to ensuring appropriate air handling and ventilation systems for existing clinics, emergency departments, and isolation rooms. "This would provide the added benefit of controlling more likely exposures to infectious droplet nuclei [tuberculosis, disseminated zoster, chicken pox, measles, etc.] in addition to minimizing or eliminating the likelihood of intrafacility transmission of smallpox," APIC stated.

The association expressed concern that health care delivery might be compromised in separate Type C facilities, particularly if they are not designed to provide services such as intensive care, ventilator support, dialysis, and laboratory resources. Rather then designate facilities for smallpox patients, each hospital should be prepared in advance to activate its program when the first case is identified, APIC argued.

"There needs to be a predetermined area [building or wing, etc.] that meets the 'Type C' facility requirements for isolation," APIC noted. "Part of a facility's planning would include a determination regarding the number of patients that could be housed in the designated area."

Some of the cleaning and disinfection recommendations in the document are out of date with current sterilization principles and practices. That includes "fogging" rooms to disinfect environmental surfaces, the association charged.

"CDC has not recommended the fogging of rooms for many years," APIC stated. "We strongly suggest the deletion of any archaic references to fogging." ■

Stanford sets the standard for bioterrorism planning

A separate piece: Stand-alone plan advised

It's not enough merely to update the bioterrorism component of your current disaster preparedness plan, experts say; you must create a detailed bioterrorism response plan that stands on its own.

That's precisely the philosophy behind the Stanford (CA) Hospital and Clinics (SHC) & Lucile Packard Children's Hospital (LPCH) Bioterrorism Response Preparedness Plan, which is gaining widespread recognition as a model for such plans. In fact, several Kaiser Permanente facilities in California already have adopted the plan.

"You need a separate [bioterrorism] plan," asserts **Eric A. Weiss**, MD, assistant professor of emergency medicine at Stanford, associate director of trauma at Stanford Hospital, and chairman of the disaster committee and bioterrorism task force. "During most disasters, for instance, you don't rely on the microbiology lab to identify pathogens. Also, infectious disease and infection control staff take on a major, heightened role."

In disasters such as an earthquake, Weiss notes, you generally don't have to worry about the quarantine of patients or the spread of infectious agents. Similarly, you may not have to put on protective clothing or worry about cross-contamination of existing patients who may be immunosuppressed.

A bioterrorism plan had been in place prior to 2001, Weiss says, "but it was really just a skeleton plan — not very comprehensive. It was part of a larger disaster preparedness plan, but a plan to deal with mass casualties from bioterrorism is very different."

When you have a major disaster such as the collapse of the World Trade Center, Weiss notes, local health care providers are likely to come to the hospital and offer to chip in and help wherever they can.

"But what happens when the word goes out that patients are walking around with smallpox?" he asks. "Are providers going to want to stream down to the hospital and potentially infect themselves and their families? You need a response plan to address the safety of health care providers, so they will feel comfortable and want to show up for work."

To create such a plan, the Bioterrorism Planning Task Force was formed, incorporating personnel from 30 or more different departments at both facilities. Those departments include infectious diseases, infection control, emergency medicine, pediatrics, critical care, intensive care units, nursing and hospital administration, dermatology, psychology, social services, and environmental health and safety.

"We began putting the plan together when we identified the fact that the current plan was not adequate," notes Weiss. "We accelerated our activities after Sept. 11. After Sept. 11, *everybody* wanted to be part of it."

[Editor's note: The bioterrorism plan is available on the Stanford web site at www.stanfordhospital.com.] ■