

PEDIATRIC ANAPHYLAXIS, INSECT STINGS, AND BITES

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Anaphylaxis is a clinical syndrome for which precise definition is difficult largely because the signs and symptoms of anaphylaxis are the same as those found with other less severe allergic reactions. Typical manifestations of anaphylaxis include urticaria; angioedema, especially of the eye lids, lips, and glottis; conjunctivitis and lacrimation; rhinorrhea and sneezing; bronchospasm; abdominal cramping; nausea; vomiting; diarrhea; arrhythmias; and hypotension. Although no specific guidelines have been proposed for precisely defining anaphylaxis, the principal distinguishing features of anaphylaxis are the severity of symptoms and the simultaneous involvement of multiple organ systems.^{6, 8, 60} In two recent studies, researchers have attempted to define anaphylaxis operationally so that appropriate cases could be identified.^{4, 5} In one study, the authors included cases with two or more typical symptoms: hypotension, bronchospasm, and angioedema or urticaria.⁴¹ The other study required either signs of respiratory obstruction (e.g., laryngeal edema or bronchospasm) or cardiovascular symptoms (e.g., documented hypotension, syncope, or orthostatic hypotension) plus signs of general mediator release, such as pruritus, urticaria, angioedema, or flushing.⁶¹

Both animal studies and case reports suggest that airway obstruction is the most frequent cause of death from anaphylaxis, although hypotension can also be prominent.^{8, 39, 53, 54} Airway obstruction can occur either at the level of the glottis or within the lungs. The risk of intrapulmonary airway obstruction from bronchospasm appears to be especially severe in children who have preexisting asthma and food allergies.⁴⁴

Some authorities carefully distinguish anaphylactic from anaphylactoid reactions. Anaphylactic reactions result from the IgE-mediated release of chemical mediators, whereas anaphylactoid reactions result from non-IgE-mediated mediator release. Although the mechanisms of mediator release may differ, anaphy-

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lactic and anaphylactoid reactions are clinically indistinguishable and the acute symptoms are treated identically.⁸ The distinction is most important in establishing the origin of the event.

PATHOPHYSIOLOGY

Although much progress has been made in understanding the initiation and consequences of IgE production, there is still much to be learned. It is clear that allergen-specific IgE antibodies can be produced to a variety of substances. Usually, detectable quantities of IgE antibodies are produced only after repeated exposure to an allergy. After production, IgE antibodies become bound to tissue mast cells and circulating basophils. If sufficient quantities of IgE antibodies, specific for a given allergen, are present on basophils and mast cells, reexposure to the allergen leads to mediator release by degranulation of the cells. Symptoms such as pruritus and edema are the result of the mediators affecting end organs such as blood vessels. The risk of anaphylaxis appears to depend on the quantity of allergens entering the body and also on the rate at which allergens enter the body.

Binding of allergen to cell-bound IgE antibodies leads to activation of a membrane-associated serine protease, an increase of intracellular cyclic adenosine monophosphate and calcium, changes in the cell membrane, and secretion of mediators. Secreted mediators may be from intracellular stores or may be newly synthesized. Histamine is the most commonly recognized preformed mediator, whereas the prostaglandins and leukotrienes are newly synthesized.

The role of mediators in the pathophysiology of anaphylaxis is not completely understood. Early studies of anaphylaxis in a monkey model showed that the primary events of anaphylaxis were systemic vasodilation and an increase in pulmonary vascular resistance.^{7, 39, 53} Cardiac output slightly increased at 1 minute but then fell by 70% to 80%. The fall in cardiac output seemed to be related more to decreased left ventricular filling than to myocardial dysfunction.^{7, 39, 53} In the monkey model, attempts to mimic anaphylaxis by infusions of histamine or prostaglandins were unsuccessful; however, infusion of compound 48/80 produced mild changes similar to anaphylactic shock, and a leukotriene inhibitor prevented shock. These findings suggested that leukotrienes are major mediators of anaphylactic shock in the monkey.³⁹ A case report of human anaphylaxis after an injection of succinylcholine documented vascular changes similar to those found in the monkey models.³² Within 1 minute of researchers infusing succinylcholine, a profound fall in peripheral vascular resistance occurred. The decrease in peripheral vascular resistance was matched by an increase in cardiac output such that blood pressure decreased only slightly.³² Other human case reports have shown major declines in blood pressure within 5 minutes after induced insect stings.⁵⁵ Studies of isolated myocardial tissue have shown that the tissue could release histamine and thromboxane B₂ after passive sensitization and challenge, suggesting that the heart may be a shock organ during anaphylaxis.^{21, 59} Findings suggestive of myocardial ischemia have been reported in adult humans during anaphylaxis.^{2, 29}

In a classic study of the pathology of anaphylaxis in humans, Delage and Irely¹⁶ found respiratory distress and circulatory collapse were the most common initial symptoms in 43 fatal cases. The most prominent pathologic findings were pulmonary congestion in 90% and pulmonary edema in 50% of the cases. Laryngeal edema was found in 38% of the cases, but it was considered severe

enough to block the airway in only 10% of the cases. Four of the 43 fatal cases were children less than 18 years of age, with the youngest being only 4 months old.¹⁶

EPIDEMIOLOGY OF ANAPHYLAXIS

Since anaphylaxis is a relatively rare event, it is hard to obtain reliable estimates concerning the prevalence or risk of anaphylaxis in either adult or pediatric populations. Studies from the 1960s and 1970s estimated that penicillin injections induced 100 to 500 anaphylactic deaths annually in the United States, mostly in adults.⁸ In a study of nearly 5000 Boy Scouts, ages 11 to 16 years, a prevalence of systemic reactions to insect stings of approximately 4 per 1000 scouts was found.⁴⁷ A review of anaphylaxis in northwest England during 1993 to 1994 found 700 reactions in 172 patients who ranged in age from 5 months to 69 years.⁴¹ Eighty-six (50%) of the affected persons were less than 18 years of age. Overall, equal numbers of males and females were affected; however, in the youngest quartile (0 to 4 years of age), 75% of those affected were males, whereas in the oldest quartile, 40+ years, 74% were female. Of the 700 reactions, 2 were fatal, 280 were major, and 430 were minor. When a severity index was calculated and patients were ranked by age at worst reaction, the least severe reactions were found in the youngest quartile (0 to 4 years), and the most severe reactions were found in the third quartile (19 to 39 years). Reactions in children were most often related to foods, especially peanuts and tree nuts.⁴¹

In a Mayo Clinic survey of patients evaluated for anaphylaxis, 176 patients were found over 3.5-year interval.⁶¹ The average age was 36 years, and 66% of the patients were women. In the 142 patients in whom a presumptive cause was identified, the most common causes were food (33%); idiopathic (19%); hymenoptera stings (14%); medications (13%); incorrect diagnosis (10%); exercise (7%); immunotherapy (3%); and human plasma, latex, and aeroallergens, each in less than 1%.⁶¹

ORIGIN

The following is a list of some of the more common causes of anaphylaxis in children:

1. Foods: peanuts, tree nuts, eggs, milk, seafoods, fruits, spices
2. Allergen immunotherapy
3. Insect stings (Order Hymenoptera): bees (*Apis* sp), yellow jackets (*Vespula* sp), hornets (*Dolicho-Vespula* sp), wasps (*Polistes* sp), and fire ants (*Solenopsis* sp)
4. Insect bites: kissing bugs, mosquitos, biting flies
5. Pharmaceuticals: penicillin, sulfonamides, nonsteroidal anti-inflammatory drugs (NSAIDs), intravenous immune gammaglobulin (IVIG)
6. Latex (natural rubber latex)
7. Vaccines
8. Exercise induced, with or without prior ingestion of a specific food
9. Idiopathic, recurrent anaphylaxis without apparent external cause

The table is by no means exhaustive. Long lists of substances associated with anaphylaxis have been compiled for adults, and presumably, any substance

capable of causing anaphylaxis in an adult could also cause anaphylaxis in a child.^{8, 62, 63} Indeed, any protein or any other substance capable of inducing an immune response could potentially become an allergen associated with anaphylaxis. The precise characteristics leading to allergenicity have not been well defined. The route of exposure and the frequency of recurrent exposure appear to be important factors as is the ability of a substance to gain entry into the body in an immunogenic form.

A recent case series from Italy has provided some insights into the causes of anaphylaxis in children.³³ Ninety-five episodes of anaphylaxis occurring in 76 children (50 boys and 26 girls) were analyzed. Ages ranged from 1 to 16 years, with an average age of 6.1 years. Sixty-two of the 76 children (82%) had histories suggestive of other allergies. The most probable causes of anaphylaxis in these cases were foods (57%), drugs (11%), hymenoptera venom (12%), exercise (9%), food additives (1%), vaccines (2%), allergen immunotherapy (1%), latex (1%), and idiopathic (6%). Food-related reactions tended to occur in younger children, whereas exercise-related reactions were more frequent in older children. Among the 54 food-related reactions, the most commonly incriminated were seafoods (16 or 30%), milk (12 or 22%), nuts (7 or 13%), eggs (6 or 11%), and fruits (6 or 11%), with cereals, vegetables, and goat milk in less than three cases each. In the ten cases related to drugs, five were related to NSAIDs, and four were related to antibiotics. The two vaccine-related cases involved a 4-year-old boy given measles vaccine prepared from human diploid cells and a 4-year-old girl given measles-mumps-rubella (MMR) vaccine prepared from chick embryo fibroblasts. The authors speculated that the reason they found only one case of peanut-related anaphylaxis, compared with the frequency of peanut allergy in the United States, probably results from the difference in peanut consumption between the two countries. The average consumption of peanuts in Italy is 0.68 kg per person per year in contrast to 3.5 kg per person per year in the United States.³³

Food Allergies

As in the report from Italy, foods also appear to be the most common causes of anaphylaxis among children in the United States. Studies have suggested that milk, egg, and especially peanuts are the foods most commonly associated with anaphylaxis in children.^{10, 12, 44, 64} There is a general perception that allergies to milk and egg are likely to remit as children grow older, whereas allergies to peanuts tend to persist.^{9, 11} It also appears that food allergies acquired in infancy are more likely to remit than those acquired later in childhood.⁹

Several recent studies have helped to define the problem of peanut allergy in children.^{19, 50} Ewan¹⁹ reported 62 consecutive cases of peanut and nut allergy seen at a British hospital. The patients ranged from 11 months to 53 years of age, but 52 (84%) of the 62 were under 18 years of age. Symptoms had appeared by 2 years of age in 33 (53%) and by 7 years of age in 55 (89%). The most common causes of reactions were peanuts (76%), Brazil nuts (29%), almonds (23%), and hazelnuts (21%). Peanuts were the cause of all reactions in children under 1 year of age and for 82% (27/33) of the reactions of children under 3 years of age. The most common symptom was facial edema, whereas laryngeal edema or swelling of the throat was the most common life-threatening symptom. Hypotension was uncommon. Fifty-five patients were tested for other allergies and 53 were sensitive to other allergens with house dust mite being the most common. This study demonstrated that peanut allergy tends to develop at a

young age and that additional allergies to nuts and airborne allergens tend to develop with increasing age in those presenting with food allergies.

Sicherer and colleagues⁵⁰ evaluated 122 children (median age 8 years) with allergic reactions to peanuts or tree nuts. The median age at which reactions were first noted was 24 months for peanuts and 62 months for tree nuts. Reactions most commonly involved the skin with urticaria and angioedema in 89% of cases, compared with 52% with respiratory symptoms and 32% with gastrointestinal symptoms. Fifty-seven percent of the children had reacted only to peanuts, whereas 28% had reacted to both peanuts and tree nuts, and 16% reacted only to tree nuts. High correlations were found between specific IgE levels for peanuts, walnuts, almonds, and pecans; pistachio, pine, hazel and Brazil nuts; and sesame seeds, but the authors could not determine whether these correlations were the result of cross-reactive proteins or concomitant sensitization. Nut-specific IgE antibody concentrations tended to be higher in symptomatic patients, but there were large overlaps between concentrations in symptomatic and asymptomatic children. No apparent correlation was seen between a child's IgE concentration and the severity of the allergic reaction.⁵⁰ No one knows why peanuts appear to be such potent allergens, but one recent report suggested that peanut allergy may be linked to specific HLA markers.²⁴

Allergy Shots

Allergen extracts are commonly administered to allergic adults and children to help control the symptoms of allergic disease. Estimates suggest that 7 to 10 million allergen injections are given each year in the United States with allergen extracts that are complex mixtures of proteins and other materials such as pigments, carbohydrates, and fungal and plant toxins. Since these extracts are being given to allergic individuals by injection, it is not surprising that recipients may have systemic allergic reactions to the injections. One survey by Lockey and associates³⁰ found 30 cases of fatal anaphylaxis related to allergen extracts; 24 cases involved immunotherapy, and six involved skin testing between 1945 and 1984. Five of the cases involved children 12 or younger. It is impossible to tell how completely cases were ascertained. The risks of serious reactions to allergen injections appear to be highest in those with asthma, especially if the asthma is not well controlled.^{30, 42} Many allergists feel that it is prudent to question all individuals who have asthma about recent asthma symptoms before administering allergen injections. In those who have poor perception of their lung function or of asthma symptoms, checking peak expiratory flow readings before injections may also help to reduce the risks of severe reactions.

Insect Stings

Stinging insects are all members of the order Hymenoptera, including bees, wasps, yellow jackets, hornets, and imported fire ants. A history of the circumstances surrounding the sting can suggest the most likely insect. Domestic honey bees or European bees (*Apis mellifera*) rarely sting without provocation. Their barbed stinger with the attached venom sac usually remains in the skin at the site of the sting. Since honey bees are the only stinging insect with such a barbed stinger, finding the stinger provides presumptive identification. A more recent arrival in the United States is the African honeybee. These bees are becoming established in the Southwest and along the Gulf Coast as they migrate north-

ward from South America where they were originally imported. Although their venom is quite similar to that of the European honeybees, the African bees have been called "killer bees" in the press. This designation comes from the aggressive behavior of hives. When the hive perceives a threat, large numbers of workers attack and sting. This can lead to large numbers of stings and acute toxicity from the venom.³

The term *vespids* can collectively be applied to yellow jackets (*Vespula* species), hornets (*Dolicho-Vespula* species), and wasps (*Polistes* species). Yellow jackets chiefly nest in the ground or at low levels, such as in rotting logs. They are scavengers, often appearing as uninvited guests at picnics, especially in late summer. They are also frequently found around garbage cans and rotting fruit on the ground in orchards. Wasps typically have very narrow waists and build mud or paper nests in protected areas such as the eaves of houses. Their color varies widely from black to gray to red brown to yellow. Hornets are usually encountered around their large paper nests built in trees or bushes. Wasps and hornets both sting principally in defense of their nests.³⁸

The imported fire ants continue to spread across the southeastern United States. Their size and color varies widely. They build large earth mounds that sometimes reach two feet in height. When disturbed they bite with their mandibles to attach themselves to the invader and sting repeatedly. The pain from the sting is variable, in part depending on the size of the ant; however, usually a slight distinct stinging sensation is felt immediately. A characteristic 2- to 6-mm pustule appears within a few minutes after the sting. The pustules are often in clusters because they result from multiple stings from a single ant. A recent study of medical students moving to an endemic fire ant area found that the risk of allergic sensitization was approximately 13%.⁵⁷ Multiple stings can produce severe reactions.²²

Insect Bites

Insect bites cause systemic allergic reactions in children much less commonly than do insect stings. Considering the frequency of insect bites in children, the risk of systemic allergic reactions is very low. Systemic allergic reactions and anaphylaxis have, however, been reported from tick, kissing bug, and mosquito bites.^{13, 43, 58} Apparently all of these blood-sucking insects inject saliva into the host as they begin to feed. Given sufficient exposure, IgE antibodies can be produced to proteins in the saliva. Since most of these insects feed during the night when children are often asleep, they should be considered in the differential diagnosis of anaphylaxis occurring during the night.

Pharmaceuticals

A wide variety of medications, vaccines, and diagnostic agents have been associated with anaphylaxis. Antibiotics appear to be the most common type of pharmaceutical associated with allergic reactions in children, probably because of the frequent exposure of children to these drugs. Penicillins are well known as causes of anaphylaxis, but the majority of reactions in children associated with penicillins are probably not allergic.³¹ Morbilliform rashes have been reported in approximately 2% of persons receiving penicillin and in nearly 10% of those receiving amoxicillin.⁶³ When amoxicillin is given to persons who have Epstein-Barr virus or cytomegalovirus infections, reactions occur in the majority of

individuals.¹⁷ Unfortunately, it is very hard to diagnose the few individuals with true IgE-mediated reactions from the vast majority with non-IgE-mediated reactions based on history.

In its native form, the penicillin molecule is too small to initiate an immune response.¹⁷ However, under physiologic conditions, the β -lactam ring of penicillin spontaneously opens and forms amide linkages to proteins, producing penicilloyl groups. Since more than 90% of administered penicillin molecules irreversibly combine with proteins to form penicilloyl groups, the penicilloyl group is designated the major determinant. Minor determinants of penicillin are formed via other metabolic pathways as a small percentage of penicillin is degraded to penicilloate and penilloate. These minor determinants are important because most allergic reactions appear to result from the minor determinants and 5% to 10% of penicillin allergic individuals are skin-test positive only to these determinants. A commercial skin-test reagent is available for the major but not for the minor penicillin determinants.¹⁷ Some reports have suggested that persons can be uniquely sensitized to amoxicillin or ampicillin, but these findings have not been widely confirmed by others.⁴⁰

Cephalosporins also possess a β -lactam ring, but the cephalosporins differ from penicillins in having a six-member dihydrothiazine ring in place of the five-member thiazolidine ring. There is considerable controversy about the risk of cross sensitization to cephalosporins in persons who are allergic to penicillin. Rates of cross reactivity between 2% and 25% have been published. The true risk of cross reactivity probably varies because of the criteria used to diagnose penicillin allergy, the criteria used to establish cross reactivity, and the generation of the specific cephalosporin studied.^{17, 40}

Iodinated Contrast Media

Severe reactions to iodinated contrast media appear to be more common in adults than in children. These reactions do not appear to be caused by IgE antibodies specific for any portion of the contrast media, but there is no uniformly accepted theory of pathogenesis. Currently, the most widely accepted theory is that reactions are related to the hypertonic nature of the contrast media, probably leading to mediator release from osmolar shock. The risk of reaction appears to be much lower when the newer lower osmolar contrast media are used.

Intravenous Gamma Globulin

As the use of IVIG has increased for the treatment of conditions such as Kawasaki's disease and idiopathic thrombocytopenia, the number of reported adverse reactions has increased. Children seem to tolerate IVIG better than adults do. Most reactions during IVIG administration are not IgE mediated and can be controlled by reducing the rate of infusion. IgE anti-IgA antibodies have been reported in children who are IgA deficient and may be associated with anaphylactic reactions.¹⁴

Vaccines

Severe allergic reactions in children have rarely been associated with vaccines. A report from Norway found six instances of allergic type reactions after

measles vaccination during an 18-month period when approximately 60,000 doses of vaccine (1:10,000) were given to children 1 to 3 years old. The authors could not identify sensitivity to egg, cow's milk, or calf serum proteins in the children who had the reactions.⁴ A report from Chicago suggested that allergic reactions to measles (rubeola) vaccine were related to sensitization to ovalbumin,²³ but subsequent studies have shown that MMR vaccine is well tolerated by egg-allergic children.^{20, 25} One case report identified gelatin as a cause of anaphylaxis after MMR vaccination.²⁷ Now it appears that MMR can be given to egg-allergic children without undue risk, but the rare child who has a gelatin allergy may need to be evaluated before vaccination. Reactions to other vaccines have been extremely rare in the United States.

Exercise

Anaphylaxis induced by exercise is relatively rare in children, but it must be considered in any child who suddenly develops urticaria, wheezing, or signs of hypotension during physical activity.^{5, 49} The onset of this syndrome can be abrupt. Boys appear to be at higher risk than girls, and there is some suggestion that the problem is more common in those who are very active physically.³³ For some individuals, exercise-induced anaphylaxis occurs within only a few hours of food ingestion. For some, ingestion of a specific food is required, whereas in others, any food ingestion leads to a reaction. In those cases associated with specific foods, the patient usually has a positive skin test to the associated food.^{15, 18}

Idiopathic Anaphylaxis

Idiopathic anaphylaxis has been reported in adults and children.³⁴ The age of onset, in a series of 12 pediatric cases, ranged from 3 to 15 years.³⁷ Idiopathic anaphylaxis can be defined as recurrent episodes of anaphylaxis for which the cause remains unknown after appropriate evaluation, observation, and challenge testing.³⁴ Fatal episodes of idiopathic anaphylaxis have been reported.³⁶ The nagging question in idiopathic anaphylaxis is always whether a cause could be found if the right testing was applied. In one study of 102 adults who had diagnoses of idiopathic anaphylaxis, it was found that 31% of the individuals were skin-test positive to one or more antigens in a series of 79 food antigens. Avoidance of the food, in two patients, and positive challenges, in five patients, suggested that at least 7% of these idiopathic cases were food related.⁵⁶ In some active children it can be difficult to distinguish idiopathic anaphylaxis from exercise-induced anaphylaxis or vocal cord dysfunction.²⁸

Latex

It has been recognized that latex is an allergen capable of producing anaphylaxis in both adults and children. Children who have spina bifida and those who have urogenital anomalies appear to be at an especially high risk for latex allergy.^{26, 48} Surveys have shown that from 14% to 70% of children who have spina bifida are at risk for latex allergy.^{26, 48, 52} This high risk appears to be related to the fact that these children usually undergo surgery in the first days of life

and that they usually require multiple surgeries. The risk may also be related to their need for indwelling urinary tract catheters and for bowel disimpactions, all of which may be associated with latex exposure. Latex allergy has also been recognized in children who lack histories of multiple surgeries. The cause of latex sensitization in these children is unknown but may be from everyday exposure to common latex items such as toy balloons, baby bottle nipples, and rubber bands.

The treatment of latex allergy is strict avoidance of contact with latex after a diagnosis has been made. Latex allergy should be suspected in children in high-risk groups (e.g., spina bifida), those who have unexplained reactions during surgery or medical examinations involving latex exposure, and any child having a history of itching, swelling, or skin rash after contact with items made from natural rubber (e.g., swollen lips after blowing up balloons). For children in high-risk groups, latex exposure should be eliminated whenever possible to reduce the risk that the child will become allergic. Thus, a child born with spina bifida should be cared for in a latex-reduced setting and the parents should be educated about the risks of latex allergy so that they understand the reasons for these precautions.

DIAGNOSIS OF ANAPHYLAXIS

An accurate diagnosis is essential for all children who have had anaphylactic reactions. Given the multitude of possible causes and the potential for serious outcomes, evaluation by an allergist is usually indicated. In many cases the diagnosis is relatively clear from the history and can be confirmed with an appropriate test for specific IgE. Some cases may require other diagnostic tests or specific challenges to confirm a diagnosis. The first step is to establish whether an episode resulted from anaphylaxis or from some other cause. Other diagnostic considerations include vasovagal syncope, seizures, foreign body aspiration, cardiac arrhythmias, and acute poisoning. In some situations it may be necessary to distinguish anaphylaxis from symptoms associated with cold urticaria, C1 esterase deficiency, or systemic mastocytosis.

Syncope is the most common problem confused with anaphylaxis, especially in the context of medical care. Vasovagal episodes are commonly preceded by nausea and occur in frightening situations. Typical manifestations include hypotension, bradycardia, pallor, profuse sweating, weakness, and, occasionally, syncope. Recovery from syncope is usually rapid without specific therapy beyond placing the child in a recumbent position. Although some have suggested using bradycardia as a useful criteria for distinguishing syncope from anaphylaxis, this is unreliable. Bradycardia can be an early manifestation of hypovolemic shock, and the heart rate has been reported to be increased, decreased, or normal during anaphylaxis.⁶² Other signs of anaphylaxis, such as urticaria, are not part of syncope episodes.

A careful history is the most important tool for establishing a correct diagnosis.^{60, 63} The setting in which the episode began must be examined in detail. Where had the child been and what had he or she been doing before the onset of symptoms? Had he or she be playing outside or sitting indoors eating? In addition to establishing what had happened, it is essential to establish the sequence of events and the time between the events and the onset of symptoms. Severe cases of anaphylaxis usually begin during or a few minutes after exposure. A common history with food allergy is that the child bit into a food and then suddenly spit it out complaining that something was wrong. Minutes later

the child has swelling of the lips along with a facial flush and hives. Although symptoms typically occur within minutes after exposure, there are occasional cases in which symptoms are delayed for as long as a few hours.^{33, 44} It is therefore essential to determine all exposures for several hours preceding the onset of the reaction. For example, a child was given a dose of an oral antibiotic, quickly ate supper, and then went outside to play in a neighbor's swimming pool. Within 30 minutes of going outside, he was stung by an insect and began to develop generalized urticaria. In a case like this the parent may only report the insect sting, but the antibiotic, the foods eaten, the exercise, and perhaps the cold exposure from the water in the pool must all be considered as potential causes of the reaction. It is also important to learn if there were any previous events that could have been milder reactions after similar exposures. Although reactions may occur without prior warning, milder reactions may have been overlooked and may help establish a probable cause.

It is also important to establish the extent of the physical reaction. What was the extent of angioedema, did blood pressure fall, was there obstruction to airflow, did vomiting or diarrhea occur? After the acute reaction has subsided, there are usually no physical findings of diagnostic significance.

Diagnostic tests are of limited value in establishing a diagnosis of anaphylaxis. Plasma histamine levels are usually elevated during the first 30 minutes of acute anaphylaxis, but obtaining accurate measurements is difficult unless venous access was established prior to the onset of the reaction. Inserting a needle into a vein may liberate enough histamine to produce a falsely positive concentration of histamine in a blood sample. The most promising mediator for confirming the anaphylactic origin of a reaction is mast-cell tryptase.^{45, 46} Serum levels of mast-cell-derived tryptase typically peak approximately 45 minutes after onset of symptoms, and accurate levels can be obtained from serum samples obtained with normal techniques. Tryptase levels can remain elevated for hours.⁴⁶ The concern about tryptase is that tryptase levels may not be elevated in children who have food-related anaphylaxis. One study of fatal and near fatal, food-related, anaphylactic reactions in children failed to find elevated tryptase levels.⁴⁴

After a probable cause has been determined from the history, tests for allergen-specific IgE may be useful to help confirm the diagnosis. When considering tests for specific IgE antibodies a physician should remember that, when properly done, tests are rarely falsely negative but falsely positive tests are relatively common. In the face of multiple positive tests, challenges with specific foods or other agents may be necessary to establish a diagnosis. The relative merits of skin versus in vitro tests are beyond the scope of this article.³⁵

IMMEDIATE THERAPY

Many different health care providers may be called on to treat a child who has anaphylaxis. Paramedic ambulance attendants are frequently the first to see a child, but parents may rush a child directly to their pediatrician's office, to the local hospital, or to a clinic for treatment. As outlined in the following list, treatment should begin with a rapid assessment of the child's status, paying special attention to the level of consciousness, adequacy of the airway, and evidence of adequate perfusion:

1. Rapidly assess patient, paying special attention to respiratory status and level of consciousness

2. Measure and record vital signs, especially blood pressure
3. Query about onset of reaction to establish probable diagnosis and recent medications
4. Administer aqueous epinephrine (1:1,000), 0.01 mL/kg (maximum 0.3 mL), intramuscularly or subcutaneously.
5. If work of breathing is increased, administer oxygen and consider inhalation treatment with beta-agonist.
6. If there are indications of reduced cardiac output, start peripheral IV and be prepared to use epinephrine, 0.1–0.5 $\mu\text{g/kg/min}$, iso-oncotic colloid solution, and/or dopamine.
7. Consider use of additional agents as indicated: H_1 and H_2 antihistamines, glucocorticoids, glucagon 20–30 $\mu\text{g/kg}$, maximum 1 mg

Maintenance of respiration and cardiac output are the first concern. Vital signs and body weight should be measured or estimated for drug dosing. The initial drug of choice for treating anaphylaxis is epinephrine 1:1000 (1 mg/mL), administered in a dose of 0.01 mg/kg of body weight, up to a maximum of 0.3 mL.¹ Epinephrine can be administered either subcutaneously or intramuscularly. A recent study has shown that absorption is more rapid and complete after intramuscular injection in children, suggesting that this should be the preferred route.⁵¹ This dose of epinephrine can be repeated every 10 to 15 minutes if needed. If there is any doubt about the child's status, epinephrine should be given. The risk of epinephrine in an otherwise healthy child or adolescent is minimal compared with the risk of delaying treatment.^{44, 51} One study found a strong association between delayed administration of epinephrine and fatal outcomes from anaphylaxis in children.⁴⁴

If the child appears to be having respiratory difficulty, oxygen should be given while the effect of the initial dose of epinephrine is being evaluated. If the child is hypotensive, the best position is recumbent with the legs elevated; however, if the predominant symptom is respiratory difficulty, the child may be more comfortable with their head elevated or in a seated position. If respiratory symptoms are present a beta-agonist may be given by nebulization in addition to the oxygen. If signs suggestive of hypotension are present, such as a light headedness, dizziness, or decreased level of consciousness, blood pressure should be monitored frequently and IV access should be secured. If hypotension is present and fails to respond to the injection of epinephrine, epinephrine diluted to 1:10,000 can be cautiously given intravenously in a dose of 1 to 5 $\mu\text{g/kg}$. If hypotension persists, volume expansion with an iso-oncotic fluid and a dopamine drip should be considered.

When only hives and angioedema are present, epinephrine is still the drug of choice. Epinephrine rapidly controls these symptoms as well as the intense itching that is frequently present. Other symptoms such as nasal congestion, sneezing, and tearing also respond well to epinephrine.⁶³ The prompt use of epinephrine may also reduce the risk of the child developing more severe symptoms.

Drugs other than epinephrine have limited roles in the treatment of acute anaphylaxis. H_1 antihistamines, whether given orally or by injection, are much less effective than epinephrine for itching and swelling, and they take longer to act. Both H_1 and H_2 antihistamines may help reduce itching and vasodilation not responding to epinephrine. Glucocorticoids may be helpful in the resolution of symptoms and in the prevention of refractory or biphasic anaphylaxis. Glucocorticoids are also indicated if the child has been on systemic glucocorticoids in

the preceding 6 months because of the possibility of adrenal insufficiency during the stress of a generalized reaction.^{8, 63}

LONG-TERM MANAGEMENT

The management of a child who has had an anaphylactic reaction must be based on an accurate diagnosis. This is usually best accomplished by referring the child to an experienced allergist. After an accurate diagnosis has been made, the child and parents must be instructed in prevention strategies. Although prevention is simple in principle, it can be difficult in practice. Patients and parents need specific, detailed instructions about how to avoid allergen exposure. Parents and children may also need support when dealing with others such as schools or other family members. Unfortunately, a poorly informed family member may try to show the parents and child that the problem is all psychological by deliberately giving the child the food disguised in another food.

Although avoidance is the goal, the parent and child must be prepared for the occasional unintended exposure. The child should be encouraged to always wear a Medic-Alert tag (Medic Alert Foundation, Turlock, CA). The parent and child (if old enough) should be given a prescription for and instruction in the use of epinephrine for self-administration (Epi-Pen or AnaKit). Specific instructions are also needed concerning how to recognize the onset of a reaction, when to self-administer epinephrine, whether other medications should be taken, and when and how to seek emergency care. Because of the importance of all of these instructions, the family should be seen again for review of these a few weeks or months later to assist them with adherence and to answer any questions that may have arisen. Precautions for the child at the baby sitter, daycare, school, or grandparent's house should also be reviewed as appropriate.

Avoiding specific foods can be challenging. Parents and children need to know how to read food labels to ensure that the food does not contain an allergen. This often requires learning multiple terms that can indicate a specific food, such as milk solids, whey, casein, and caseinates, as terms for milk. Up-to-date information on these terms is available from several lay organizations and from the public information sections of professional organizations. Much of this information can now be quickly found on the worldwide web. When a common food item such as milk or eggs must be avoided, a registered dietitian or nutritionist can be very helpful to the parents to assure that the food is avoided while proper nutrition is maintained. Because peanuts are used in so many ways in so many foods, avoidance requires special diligence. The family must understand the hazards of restaurants and the necessity of making sure that the waiter and chef appreciate the importance of specific food avoidance.

Schools are a special challenge for allergen avoidance.⁴⁴ Food avoidance may be difficult because the persons serving food in school cafeterias may not know the precise ingredients in the foods. Left to themselves, children often decide to trade foods that they have either bought or brought from home. School outings must be communicated well ahead of time with the parents of at-risk children both because of the potential for exposure to foods but also to other environments. Physicians must assist families and schools to make sure that teachers have been educated about the recognition and the potential risks of systemic allergic reactions. Schools should have guidelines about how to handle apparent reactions and when to summon emergency help. A number of lay allergy organizations have drafted model plans for schools to assist with the process if a school does not have an appropriate plan in place.

Children who have systemic reactions from insect bites or stings should be evaluated by an allergist. Specific immunotherapy has been shown to be safe and effective with all of the stinging insects, but the potential risks and benefits of immunotherapy need to be considered in light of the severity of the child's reaction. Specific immunotherapy has also been effective for reactions after the bites of some insects. Allergy evaluation is also indicated to confirm the cause of a reaction.

SUMMARY

Anaphylaxis is a frightening and potentially life-threatening reaction that can be produced by many different allergens. After management of the acute episode, an accurate diagnosis is necessary to assist with preventing additional episodes. Education and assistance of the family is necessary for adequate prevention. Families must also be given education concerning recognition and emergency management of episodes if prevention fails. Although anaphylaxis is rare, the potentially devastating consequences of anaphylaxis require all physicians to be familiar with this problem.

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