

ANAPHYLAXIS AND FOOD HYPERSENSITIVITY

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In their classic studies of anaphylaxis, Portier and Richet described the rapid death of several dogs that they were attempting to immunize against the toxic sting of the sea anemone.^{36, 53} Because this reaction represented the opposite of their intended prophylaxis, they coined the term *anaphylaxis*, or *without or against protection*. From these studies, they concluded that anaphylaxis required a latent period for sensitization and re-exposure to the sensitizing material. Shortly thereafter, Schlossman reported a patient who developed acute shock after the ingestion of cow's milk.² The first series of modern-day descriptions of food anaphylaxis in humans was published in 1969 by Goldbert et al.¹⁸ They described 10 cases of anaphylaxis following the ingestion of various foods, including different legumes, fish, and milk.

DEFINITION

Clinical anaphylaxis is a syndrome of diverse cause and dramatic presentation of symptoms associated with the classic features of Type I, IgE-mediated hypersensitivity.⁵ Typically the term *anaphylaxis* connotes an immunologically mediated event that occurs after exposure to certain foreign substances. The term *anaphylactoid*, however, indicates a clinically indistinguishable reaction that is not believed to be immunologically

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mediated but probably involves many of the same mediators (e.g., histamine). Both of these reactions result from the generation and release of a variety of potent biologically active mediators and their concerted effects on various target organs. Anaphylaxis is recognized by cutaneous, respiratory, cardiovascular, and gastrointestinal signs and symptoms occurring alone or in combination. This article focuses on allergic reactions to foods that manifest as signs and symptoms involving multiple target organs or the cardiovascular system alone.

EPIDEMIOLOGY

Prevalence

The prevalence of anaphylaxis is unknown because unlike many disorders, there is no requirement to report such reactions to a national register. In addition, it is likely that many cases are misdiagnosed. Also contributing to this lack of scientific data is the fact that many patients who experience a mild anaphylactic reaction recognize the causative relationship to a specific food and simply avoid that food rather than consult a physician. Sorensen et al reviewed all cases of anaphylactic shock occurring outside the hospital in the Thisted Hospital catchment area, in Denmark.⁵⁷ Twenty cases of anaphylaxis were identified, or 3.2 cases per 100,000 inhabitants per year, and 5% were fatal. If similar rates occur in the United States, about 8300 cases of anaphylaxis could be anticipated each year, with about 415 deaths. As suggested previously, these investigators found that 8 of the 20 cases (40%) had been given an incorrect *International Classification of Diseases* code at the time of discharge. In this series, drugs, food, and insect stings accounted for virtually all of the anaphylactic reactions.

Unfortunately there is no *International Classification of Diseases* code for food-induced anaphylaxis, so it is extremely difficult to obtain any reliable information regarding the prevalence, incidence, or mortality rates for these reactions. In a retrospective survey, Yocum and Khan⁶⁵ reviewed all cases of anaphylaxis treated in the Mayo Clinic Emergency Department (United States) over a 3.5-year period. Records were reviewed on all patients experiencing respiratory obstructive symptoms or cardiovascular symptoms plus evidence of allergic mediator release (e.g., urticaria). Overall, 179 patients were identified; 66% were female, 49% were atopic, and 37% had experienced an immediate reaction to the responsible allergen in the past. A probable cause was identified in 142 cases: food, 59 cases (33%); bee sting, 25 cases (14%); medications, 23 cases (13%); and exercise, 12 cases (7%). Allergic reactions to food were the most common cause of anaphylactic reactions outside of the hospital, more frequent than reactions to bee stings and drugs combined. Again, extrapolating from the Sorensen data, this finding would suggest that there are about 2500 food-induced anaphylactic reactions in the United States each year, with about 125 deaths. Peanuts and nuts were the most

common foods causing serious anaphylactic reactions. In a separate study, Bock surveyed 73 emergency departments in Colorado over a 2-year period and identified 25 cases of severe anaphylactic reactions to food, with one death.⁶ From this data, it was concluded that at least 950 cases of severe food-induced anaphylaxis occur in the United States each year. The author cautioned, however, that this survey was an underestimate of the problem because patients had been referred to him who were not included in the survey, and the proportion of reactions was higher in the rural emergency departments serving smaller populations than in the busier metropolitan departments. A 5-year survey of anaphylactic reactions treated at the Children's Hospital of Philadelphia also showed that food allergy was the most common cause of anaphylaxis outside of the hospital.¹⁴ A recent survey of over 4000 households with a validated survey instrument indicated that between 1% and 2% of the population had peanut and tree nut allergy.⁵⁵ This data allows another estimate of the prevalence of food-induced anaphylaxis because of the percentage of individuals who experience systemic reactions after the ingestion of peanuts.

Fatal-Food Anaphylaxis

The first of several reports on fatal food-induced anaphylaxis was in 1988 by Yunginger et al who reported seven cases of fatal anaphylaxis evaluated during a 16-month period.⁶⁶ In all but possibly one case, the victims unknowingly ingested a food that had provoked a previous allergic reaction. Similarly, six fatal and seven near-fatal food-induced anaphylactic reactions in children (ages 2 to 17 years) were accumulated from three metropolitan areas over a 14-month period.⁴⁴ Common risk factors were noted in these cases: all patients had asthma (although generally well controlled); all patients were unaware that they were ingesting the food allergen; all patients had experienced previous allergic reactions to the incriminated food, although in most cases symptoms had been much milder; and all patients had immediate symptoms with about half experiencing a quiescent period prior to a major respiratory collapse. Factors that suggest increased risk for severe anaphylaxis are as follows:

- History of a previous severe anaphylactic reaction
- Patient with asthma, especially if poorly controlled
- Allergy to peanuts, tree nuts, fish, or shellfish
- Patients on beta blockers or acetylcholinesterase (ACE)-inhibitors
- Females ?

In both series, no patient who died received adrenaline immediately; however, three patients with near-fatal reactions did receive adrenaline within 15 minutes of developing symptoms but still went on to develop respiratory collapse and hypotension requiring mechanical ventilation and vasopressor support for 12 hours to 3 weeks. Interest-

ingly, patients investigated with life-threatening food-induced anaphylaxis had no significant increase in serum tryptase, raising some question about the exact mechanism of food-induced anaphylaxis.⁴⁴

Food-Dependent Exercise-Induced Anaphylaxis

The incidence of food-dependent exercise-induced anaphylaxis appears to be increasing, possibly because of the increased popularity of exercising over the past decade. Two forms of food-dependent, exercise-induced anaphylaxis have been described: reactions following the ingestion of specific foods (e.g., celery, shellfish, and wheat),^{15, 26, 28, 31, 38} and, rarely, reactions following the ingestion of any food.³⁴ Anaphylaxis occurs when a patient exercises within 2 to 4 hours of ingesting a food, but otherwise the patient can ingest the food without any apparent reaction and can exercise without any apparent reaction as long as the specific food (or any food in the case of nonspecific reactors) has not been ingested within the past several hours. This disorder is twice as common in women, and more than 60% of cases occur in individuals less than 30 years of age. In a recent survey of 199 individuals experiencing exercise-induced anaphylaxis, ingestion of food within 2 hours of exercise was believed to be a factor in the development of attacks in 54% of the cases.²¹ Symptoms generally start with a sensation of generalized pruritus that progresses to urticaria and erythema, respiratory obstruction, and cardiovascular collapse. Patients with specific food-dependent exercise-induced anaphylaxis generally have positive prick skin tests to the food that provokes symptoms and occasionally have a history of reacting to the food when they were younger. Specific management of this disorder involves identifying the food(s) that cause the reaction (i.e., open challenge or possibly double-blind placebo-controlled food challenge with exercise).

Predisposing Factors

Several factors appear to predispose an individual to food-induced anaphylaxis, including a personal history of atopy, family history of atopy, age, and dietary exposure. Atopic patients with asthma have an apparent increased risk of developing more severe food-allergic reactions.^{3, 13, 44} In the reports of Yunginger et al⁶⁶ and Sampson et al,⁴⁴ the majority of individuals were highly atopic, and all had histories of asthma. Although atopy reportedly does not predispose individuals to an increased risk of anaphylaxis,⁵² it does tend to predispose to more severe reactions. Individuals inherit the ability to produce antigen-specific IgE to food proteins, although there is no conclusive information that hypersensitivity to a specific food is inherited.

Age

Age may play a factor in predisposing an individual to food-induced anaphylaxis. The incidence of food allergy appears greatest in the first 2 years of life and decreases with age. Consequently, foods introduced during the first year (e.g., cow's milk, egg, soy, wheat, and peanut) are more apt to induce hypersensitization. Allergic reactions to milk, egg, soybean, and wheat are generally "outgrown" with age.^{7, 45} The age of onset of milk allergy is usually in the first year of life, with about 85% of infants "outgrowing" their sensitivity by the third year of life.^{19, 22} Although most food hypersensitivities are outgrown during childhood, food sensitivity to peanuts, tree nuts, fish, and shellfish often persist into adulthood.^{3, 8} It is quite uncommon to find a patient that develops clinical tolerance to peanuts or tree nuts.²³

Dietary Factors

Dietary exposure can influence the occurrence of food-induced anaphylaxis in several ways. Different populations and nationalities may consume more of certain foods, and the increased exposure may result in increased prevalence of that specific food allergy. In the United States peanut is one of the most common food allergies.^{41, 49} Americans ingest several tons of peanuts daily.⁸ By contrast, in Scandinavia, where fish consumption is high, the incidence of allergic reactions to codfish is increased. Rice and buckwheat allergy are quite rare in the United States but are not uncommon in Japan where these foods are eaten in large quantities.

ETIOLOGY

Foods

A large variety of foods have been reported to precipitate an anaphylactic reaction. The list of foods that potentially may induce an anaphylactic reaction is unlimited, and in theory, any food protein is capable of causing an anaphylactic reaction. Certain foods tend to be cited most frequently as the cause of anaphylaxis, although any food may be the cause. Foods most often responsible for anaphylactic reactions include peanuts (and to a lesser extent other legumes, such as soybeans, pinto beans, peas, green beans, and garbanzo beans), fish (e.g., cod or whitefish), shellfish (shrimp, lobster, crab, scallops, or oysters), tree nuts (hazelnuts, walnuts, cashews, almonds, or pistachios), cow's milk, egg, fruits (banana or kiwi), seeds (cotton seed or sunflower seed), and cereals or grains (wheat, rice, rye, millet, or buckwheat).

Recent reports appear to indicate that certain foods are more likely to induce an anaphylactic reaction. These foods include peanuts and tree

nuts,^{44, 65, 66} fish,⁴⁹ and shellfish.⁴⁹ These food sensitivities are the ones that individuals typically do not "outgrow," in contrast to other foods like milk, eggs, and soybeans. The potency of particular foods to induce an anaphylactic reaction appears to vary and is also dependent upon the sensitivity of the individual. In general, it appears that for some foods, such as peanuts, microgram quantities may be sufficient to induce a reaction. In oral food challenge studies in which food-allergic patients are challenged on a regular basis (e.g., annually) over a period of years, patients who eventually become tolerant to a food often appear to tolerate more of the antigen in successive years. For example, the initial challenge may be positive after 500 mg of the food and then in the subsequent challenge 1 year later the patient may tolerate 5 g of the food. The next challenge the following year may reveal that the patient is no longer sensitive to that food.

Prior exposure and sensitization to food allergens theoretically must precede the initial anaphylactic reaction; however, there are patients who have had an anaphylactic reaction after the first known exposure to a food substance. In a recent study of patients with either peanut or tree nut allergy, almost 75% of the patients who were allergic to peanuts had a clinical reaction on their first known exposure.⁵⁴ Several possibilities may account for this apparent paradox: (1) most often, infants are sensitized to foods passed in maternal breast milk during lactation; (2) sensitization may occur following an unknown exposure to a food antigen (e.g., milk formula given during the night in the newborn nursery, food given by another caregiver, or food contained in another product that was not suspected of containing the antigen in question); and (3) sensitization may occur because of cross-sensitization to a similar allergen (e.g., kiwi or banana allergy in a latex-sensitive individual³²). Recent data has also suggested that sensitization may occur in utero.⁶¹

Food Additives

Although food additives are often suspected of provoking anaphylactic reactions, the primary food additives for which there is significant evidence of precipitating an anaphylactic reaction include sulfites, papain, and some spices.^{9, 64} One of the initial reports detailed an atopic, nonasthmatic patient who experienced an anaphylactic reaction after consuming a restaurant meal that contained significant sodium bisulfite.³⁷ Specific IgE to sodium bisulfite was demonstrated by skin testing and transfer of passive cutaneous anaphylaxis, and an oral food challenge produced itching of the ears and eyes, nausea, warmth, cough, tightness in the throat, and erythema of the shoulders. These symptoms resolved following treatment with epinephrine. There have been other scattered case reports in the literature confirming sulfite-induced anaphylaxis.^{11, 59, 60}

One patient has been reported with papain-induced anaphylaxis following the ingestion of a beefsteak that had been treated with papain

as a meat tenderizer.³⁰ The patient was found to have specific IgE to papain by prick skin testing and experienced a positive oral challenge to papain with palatal itching and throat tightness. One study suggested that monosodium glutamate could provoke asthma and anaphylaxis in some patients, but this finding remains somewhat controversial.¹

CLINICAL FEATURES

The hallmark of a food-induced anaphylactic reaction is the onset of symptoms within seconds to minutes following the ingestion of the food allergen.²⁴ The time course of the appearance and perception of symptoms and signs will differ among individuals. Almost invariably, at least some symptoms will begin within the first hour after the exposure. Generally, the later the onset of anaphylactic signs and symptoms, the less severe the reaction. About 25% to 30% of patients will experience a biphasic reaction,⁴⁴ whereas patients typically develop classical symptoms initially, appear to be recovering (and may become asymptomatic), and then they experience the recurrence of significant, often catastrophic symptoms. The intervening quiescent period may last up to 1 to 3 hours. In the report by Sampson et al, three of seven patients with near-fatal anaphylaxis experienced protracted anaphylaxis, with symptoms lasting from 1 day to 3 weeks.⁴⁴ Most would suggest that the earlier epinephrine is administered in the course of anaphylaxis, the better the chance of a favorable prognosis, but this does not necessarily affect the prevalence of biphasic or protracted symptoms.⁴⁴ In addition, there are very rare cases in which patients have received a single injection of epinephrine almost immediately but still progressed to fatal anaphylaxis. Even with appropriate treatment in a medical facility, in some cases it may be impossible to reverse an anaphylactic reaction once it has begun.

The symptoms of anaphylaxis are generally related to the cutaneous, gastrointestinal, respiratory, and cardiovascular systems. Other organ systems may be affected but much less commonly. The sequence of symptom presentation and severity varies from one individual to the next. Additionally, one patient who experiences anaphylaxis to more than one type of food may experience a different sequence of symptoms with each food. Although many patients develop similar allergic symptoms on subsequent occasions following the ingestion of a food allergen, patients with asthma and peanut or tree nut allergy seem to be less predictable. There are many cases of peanut-allergic children who reacted with minimal cutaneous and gastrointestinal symptoms as a young child but who later developed asthma and then experienced a catastrophic anaphylactic event after ingesting peanut in their teenage years.⁴¹

The first symptoms the patient often notices involves the oropharynx. Symptoms may include edema and pruritus of the lips, oral mucosa, palate, and pharynx. Young children may be seen scratching at their tongue, palate, anterior neck, or external auditory canals (presumably

from referred pruritus of the posterior pharynx). Evidence of laryngeal edema includes a "dry staccato" cough or dysphonia and dysphagia. Gastrointestinal symptoms include nausea, vomiting, crampy abdominal pain, and diarrhea. Emesis generally contains large amounts of "stringy" mucus. Respiratory symptoms may consist of a deep repetitive cough, stridor, dyspnea, or wheezing. Cutaneous symptoms of anaphylaxis may include flushing, urticaria, angioedema, or an erythematous macular rash. The development of cardiovascular symptoms, along with airway obstruction, are of greatest concern in anaphylactic reactions. Cardiovascular symptoms include syncope, a feeling of faintness, or chest pain. Hypotension or shock may be the result of vascular collapse, cardiac arrhythmia, or asphyxia. Anaphylaxis may be complicated by myocardial ischemia.

Other signs and symptoms reported frequently in anaphylaxis include periocular and nasal pruritus, sneezing, diaphoresis, disorientation, fecal or urinary urgency or incontinence, and uterine cramping. Patients often report a "sense of impending doom." In some instances the initial manifestation of anaphylaxis may be the loss of consciousness. Death may ensue in minutes but has been reported to occur days to weeks after anaphylaxis.⁶⁰ Late deaths are generally manifestations of organ damage experienced early in the course of anaphylaxis.

Several factors, as listed previously, appear to increase the risk of more severe anaphylactic reactions. Patients taking beta-adrenergic antagonists or calcium channel blockers may be resistant to standard therapeutic regimens and are at increased risk for severe anaphylaxis.²⁷ Patients with asthma appear to be at increased risk for severe symptoms as noted in two of the reports concerning fatal and near-fatal food anaphylactic reactions.^{44, 66} Similar findings have been reported in patients with insect sting allergy⁵¹ and from patients experiencing anaphylaxis as a result of immunotherapy.²⁹ In these patients, significant, acute bronchospasm developed along with other symptoms of anaphylaxis.

In a review of 43 fatal cases of anaphylaxis, approximately 80% of which were caused by injections of medications, Delage and Ireys¹² noted that symptoms developed within 20 minutes in 86% of cases, and death ensued within 30 minutes in 33% of individuals, within 1 hour in 51%, and within 5 hours in 19% of cases. Respiratory distress and circulatory collapse were the presenting symptoms in 37% and 33% of patients, respectively, and skin symptoms were the presenting symptom in only 7% of cases. Pathologic findings consisted of pulmonary congestion in 90% of patients, pulmonary edema in 50%, intra-alveolar hemorrhage in 45%, tracheobronchial secretions in 45%, and laryngeal edema in 38% of cases (marked laryngeal edema in only 10%). In six cases of fatal food-induced anaphylaxis,⁴⁴ initial symptoms developed within 3 to 30 minutes and severe respiratory symptoms within 20 to 150 minutes. Symptoms involved the lower respiratory tract in six of six children, the gastrointestinal tract in five of six patients, and the skin in only one of six children. *Anaphylaxis should never be considered ruled-out on the basis of absent skin symptoms.* In evaluation of Hymenoptera-allergic patients

undergoing venom immunotherapy, intentional bee stings resulted in 14 systemic reactions.⁴ Three patients experienced severe bronchospasm and hypotension, which was initially refractory to epinephrine, and large volumes of fluid; none developed any skin symptoms.

DIAGNOSIS

Because of its abrupt and dramatic nature, the diagnosis of systemic anaphylaxis is generally readily apparent (Table 1). In many cases in which a food is implicated, the inciting food is obvious from the temporal relationship between the ingestion and the onset of symptoms. The initial step in determining the cause of the episode of anaphylaxis is to take a very careful history, especially when the cause of the episode is not straightforward. Specific questions to address include the type and quantity of food eaten, the last time the food was ingested, the time frame between ingestion and the development of symptoms, the nature of the food (cooked or uncooked), other times when similar symptoms occurred (and if the food in question was eaten on those occasions), and whether any other precipitating factors appear to be involved, such as exercise.

Basically, any food may precipitate an anaphylactic reaction, but there are a few specific foods that appear to be most often implicated in the cause of food-induced anaphylactic reactions: peanuts, tree nuts, fish, and shellfish. In cases in which the cause of the anaphylactic

Table 1. CLINICAL SIGNS AND SYMPTOMS OF ANAPHYLAXIS

Respiratory [major shock organ]

Laryngeal—pruritus and sensation of tightness in the throat, dysphagia, dysphonia and hoarseness; dry “staccato” cough; and sensation of itching in the external auditory canals

Lung—shortness of breath, dyspnea, chest tightness, “deep” cough, and wheezing

Nose—pruritus, congestion, rhinorrhea, and sneezing

Cardiovascular

Feeling of faintness, syncope, chest pain, arrhythmia, hypotension

Skin

Flushing, pruritus, urticaria, angioedema, morbilliform rash, and pilor erecti

Gastrointestinal

Nausea, abdominal pain (colic), vomiting (large amounts of “stringy” mucus), and diarrhea

Oral

Pruritus of lips, tongue, and palate, and edema of lips and tongue

Other

Periorbital pruritus, erythema and edema, conjunctival erythema, and tearing; uterine contractions in women; and aura of “impending doom”

reaction is not apparent, a dietary history should review all ingredients of the suspected meal, including any possible concealed ingredients or food additives. The food provoking the reaction may be merely a contaminant (knowingly or unknowingly) in the meal. For example, peanuts or peanut butter are frequently added to cookies, candies, pastries, or sauces such as chili, spaghetti, and barbecue sauces. Chinese restaurants frequently use peanut butter to hold together the overlapping ends of an egg roll, pressed or "extruded" peanut oil in their cooking, and the same wok to cook a variety of different meals resulting in residual contaminant carryover. Another infrequent, but not rare, cause of food contamination occurs during the manufacturing process. This contamination may happen with scraps of candy that are "re-worked" into the next batch of candy or in processing plants in which there is a production change from one product to the next. As an example, a reaction to almond butter by a peanut-allergic patient started an investigation that determined that 10% of the almond butter produced in that plant was contaminated with peanut butter. This discovery was made after a production change in the manufacturing process from peanut butter to almond butter. Other examples include popcicles that are run on the same line as creamsicles, fruit juices packaged in individual cartons in which milk products have been packaged, milk-free desserts packaged in dairy plants,¹⁷ and so forth. Food items with "natural flavoring" designated on the label may contain an unsuspected allergen (e.g., casein in canned tuna fish, hot dogs, or bologna, or soy in a variety of baked goods). In addition, some foods do not indicate the presence of certain proteins when they represent less than 2% of total protein (e.g., Ritz crackers contain milk protein; Fig Newtons contain egg).

Age of Diagnosis

Food allergy can develop at any age, although it appears more commonly in the first 3 years of life. Not uncommonly, a patient presents who has tolerated a food for his or her entire life and then at some point in mid-adulthood experiences a major allergic reaction after ingestion of the food. These patients may experience no forewarning of their impending episode, but on detailed questioning will not infrequently describe some minor symptoms previously, such as oral pruritus or nausea and cramping. It is also possible that cooking or processing of some foods may remove, diminish, or even enhance their allergenicity.

Differential Diagnosis

Some conditions may be confused with food anaphylaxis. Among these clinical problems are scromboid poisoning, factitious allergic emergency, and vasovagal collapse. In the absence of urticaria and angioedema, one must consider arrhythmia, myocardial infarction, hereditary

angioedema, aspiration of a bolus of food, pulmonary embolism, and seizure disorders.

With the presence of laryngeal edema, especially when accompanied by abdominal pain, the diagnosis of hereditary angioedema must be considered. In general, this disorder is slower in onset, does not include urticaria, and often there is a family history of similar reactions. Systemic mastocytosis results in flushing, tachycardia, pruritus, headache, abdominal pain, diarrhea, and syncope. A factitious allergic emergency may occur when patients knowingly and secretly ingest a food substance to which they are known to be allergic.⁶³

In vasovagal syncope, the patient may collapse after an injection or a painful or disturbing situation. The patient typically looks pale and complains of nausea prior to the syncopal episode but does not complain of pruritus or become cyanotic. Respiratory difficulty does not occur, and symptoms are almost immediately relieved by recumbency. Profuse diaphoresis, slow pulse, and maintenance of blood pressure generally complete the syndrome. Hyperventilation may cause breathlessness and collapse. It is usually not associated with other signs and symptoms of anaphylaxis, except peripheral and perioral tingling sensations. Blood pressure and pulse are generally normal.

LABORATORY EVALUATION

The laboratory evaluation of patients with an anaphylactic reaction should be directed at identifying specific IgE antibodies to the food in question. IgE antibody can be recognized *in vivo* by prick or puncture skin testing. Although not absolutely proven in patients with anaphylaxis, a negative prick or puncture skin test is an excellent predictor for a negative IgE-mediated food reaction to the suspected food. In contrast, a positive prick skin test does not necessarily mean that the food is the inciting agent, but in patients with classic histories of anaphylaxis to ingestion of an isolated food and a positive prick or puncture skin test to that food, this laboratory test appears to be a good positive predictor of allergic reactivity.

There may be some limitations to skin testing that need to be recognized. There is speculation that skin testing shortly after the occurrence of anaphylaxis may fail to yield a positive response owing to temporary anergy. Although not demonstrated in food allergy, this phenomenon has been demonstrated in Hymenoptera sensitivity following an insect sting.⁵⁰ Possible causes of false-negative prick skin tests include: (1) improper skin test technique, (2) concomitant use of antihistamines, or (3) the use of food extracts with reduced or inadequate allergenic potential. With some foods, the processing of the food for commercial extracts may diminish antigenicity,³⁵ which is especially true for some fruits and vegetables. If there is a high index of suspicion that a food may have precipitated an anaphylactic reaction even though the prick skin test is negative, however, the patient should be tested with the

natural food utilizing the "prick-plus-prick" method to ensure an absence of detectable specific IgE antibody.³⁵ Some caution should be exercised in doing this procedure because the amount of antigen on the prick device will not be controlled, and appropriate negative controls also should be performed.

Appropriate skin testing is indicated in each patient, although in vitro measurement of food-specific IgE may be evaluated initially. In many patients with anaphylaxis, limited prick skin testing is necessary to confirm the cause of the anaphylactic reaction. In cases of idiopathic anaphylaxis, more extensive prick testing may be helpful for diagnosis.⁵⁹ The clinician must decide how many skin tests are practical and justified, taking into account the anticipated low yield of positive results in idiopathic anaphylaxis and the value of discovering a cause of this serious disorder.

Intradermal skin tests are sometimes performed following negative prick or puncture skin tests, but the diagnostic significance of a positive intradermal test following a negative prick or puncture test is dubious and probably of no clinical benefit.⁴ Anaphylactic reactions have been documented following intradermal skin tests to foods,¹ so extra caution should be exercised if intradermal tests are performed. *Under no circumstances should an intradermal skin test be performed prior to performing a prick or puncture test.*

In cases in which extreme hypersensitivity is suspected, alternative approaches may be warranted including the further dilution of the food extract prior to prick skin testing or the use of a food-specific in vitro test (e.g., radioallergosorbent test [RAST]). Overall, the RAST is considered less sensitive and specific than the prick skin test. In high-quality laboratories a 3+ to 4+ RAST [on a 1+ to 4+ Phadebas RAST scale] probably has a similar positive predictive accuracy as prick skin test 3 mm greater than the negative control.⁴⁰ The new CAP-RAST appears to be slightly more sensitive than the standard RAST and has improved predictive values.⁴²

Massive activation of mast cells during anaphylaxis results in a dramatic rise in plasma histamine and somewhat later a rise in plasma or serum tryptase.^{35, 39, 50} Plasma histamine rises over the first several minutes of a reaction, generally remains elevated for a brief period of time, requires special collection techniques, and breaks down unless the plasma sample is frozen immediately. Consequently, measurement of plasma histamine to document anaphylaxis is impractical except in research situations. Whether measurement of urinary methyl-histamine will be useful in the documentation of anaphylaxis remains to be demonstrated. Serum tryptase rises over the first hour and may remain elevated for many hours. It is fairly stable at room temperature and can be obtained from postmortem specimens. Tryptase has been shown to be markedly elevated in most cases of bee sting or drug-induced anaphylaxis.^{39, 50} Unfortunately, tryptase is frequently not elevated in food-induced anaphylaxis⁴⁴; the reason for this is not clear but suggests

that other cells, such as basophils or monocytes or macrophages, may be more important in food-induced anaphylaxis.

Double-blind placebo-controlled food challenges are contraindicated in patients with an unequivocal history of anaphylaxis following the isolated ingestion of a food to which they have evidence of significant IgE antibodies. If several foods were ingested and the patient has positive skin tests to several foods, however, it is essential that the responsible food be identified. It has been reported that patients have experienced repeated anaphylactic reactions because physicians incorrectly assumed that they had identified the responsible food.⁴⁴ Young children who experience anaphylactic reactions to foods other than peanuts, tree nuts, fish and shellfish may eventually outgrow their clinical reactivity, so an oral challenge may be warranted following an extended period of food elimination with no history of reactions to accidental ingestions.

TREATMENT

Treatment of food-induced anaphylaxis may be subdivided into acute and long-term management. Although management of an acute attack is something physicians spend hours preparing for, it is the long-term measures that provide the best quality of life for the food allergic patient.

Acute Management

Fatalities may occur if treatment of a food-induced anaphylactic reaction is not immediate.^{44, 66} Data from the review of fatal bee sting-induced anaphylactic reactions indicate that the longer the initial therapy is delayed, the greater the incidence of complications and fatalities.²⁴ Initial treatment must be preceded by a rapid assessment to determine the extent and severity of the reaction, the adequacy of oxygenation, cardiac output, and tissue perfusion, any potential confounding medications [e.g., beta blockers], and the suspected cause of the reaction (Table 2).⁵ Initial therapy should be directed at the maintenance of an effective airway and circulatory system. Epinephrine (adrenaline) is the drug of choice in the treatment of anaphylaxis. The first step in the management of anaphylaxis is the subcutaneous or intramuscular injection of 0.01 mL/kg of aqueous epinephrine 1:1000 (maximal dose 0.3 to 0.5 mL or 0.3–0.5 mg). Recent reports indicate that in fact intramuscular administration may achieve a faster and higher rate of absorption.⁵⁶ Intravenous administration of epinephrine may cause fatal arrhythmias or myocardial infarction, particularly in adults, and should be reserved for refractory hypotension requiring cardiopulmonary resuscitation. In patients with pulmonary symptoms, supplemental oxygen should be administered.

The importance of epinephrine in the treatment of anaphylaxis is

Table 2. ACUTE MANAGEMENT OF ANAPHYLAXIS

Rapid assessment of	Extent and severity of symptoms Adequacy of oxygenation, cardiac output, and tissue perfusion Potential confounding medications Suspected cause of the reaction
Initial therapy	Epinephrine—0.01 mg/kg dose up to 0.3–0.5 mg SC or IM up to 3 times every 20 min Oxygen—40% to 100% by mask Intravenous fluids—30 mL/kg of crystalloid up to 2 L (or more depending upon blood pressure & response to medications)
Secondary medications	Nebulized albuterol, may be continuous antihistamines: H ₁ antagonist (diphenhydramine—1 mg/kg up to 75 mg) H ₂ antagonist (cimetidine—4 mg/kg up to 300 mg) Corticosteroids: Solumedrol, 1–2 mg/kg dose Dopamine, for hypotension refractory to epinephrine (2–20 µg/kg/min) Norepinephrine, for hypotension refractory to epinephrine Glucagon, for hypotension refractory to epinephrine and norepinephrine, especially patients on beta blockers

SC = subcutaneous; IM = intramuscular.

best seen in the cases of fatal and near-fatal food-induced anaphylaxis. In general, patients who die from anaphylactic reaction have received no epinephrine or an inadequate dose during their acute reaction.^{4, 44, 66} In contrast, patients who have survived a near-fatal anaphylactic reaction generally receive epinephrine early in the course of their reaction and many have received repeated doses of epinephrine.

To ensure that patients receive epinephrine as early as possible, it is important that they, their family members, and other care providers are instructed in the self-administration of epinephrine. Preloaded syringes with epinephrine are available and should be given to any patients at risk for food-induced anaphylaxis (i.e., patients with a history of a previous anaphylactic reaction and patients with asthma and food allergy, especially if they are allergic to peanuts, tree nuts, fish, or shellfish). In the United States, premeasured doses of epinephrine can be obtained in two forms: Epi-Pen (Center Laboratories, Port Washington, NY) and Ana-Kit or Ana-Guard (Miles Inc., Allergy Products, West Haven, CT). The Epi-Pen is a disposable drug delivery system and can be obtained in two sizes: the Epi-Pen—0.3 mg for adults and the Epi-Pen Jr.—0.15 mg for children less than 22 to 25 kg. The device is pressed firmly into the thigh muscle (or is trigger-activated with the newer version of the Epi-Pen) and held in place for several seconds to allow the medication to be injected. Because the Epi-Pen can deliver only a single dose, two Epi-Pens may be prescribed for patients who have

experienced a previous anaphylactic reaction or who are at high risk and do not have ready access to a medical center. The Ana-Guard and Ana-Kit each contain a special calibrated syringe that allows separate delivery of two doses. Prior to injecting the medication, the plunger needs to be turned clockwise 90°. Pushing the plunger to the first stop will deliver 0.3 mg of epinephrine either subcutaneously (SC) or intramuscularly (IM). Lesser amounts of adrenaline can be injected by discarding a specified portion of the medication because the syringes have 0.1 mL calibration marks. Whichever device is prescribed, it is imperative that the patient or family members practice with appropriate training devices to ensure their ability to use the device proficiently in case of an emergency. Also, it should be made clear to the patients that these preloaded devices carry a 1-year shelf life and should be renewed each year.

Sustained-release preparations of epinephrine are not appropriate treatment for acute anaphylaxis. Inhaled epinephrine (either nebulized or via metered-dose inhaler) has been recommended by the European Academy of Allergy and Clinical Immunology.³³ A minimum of 20 puffs inhaled correctly can produce blood levels similar to an injection of 0.3 to 0.5 mg of epinephrine in adults and 10 to 15 puffs in a child can deliver the equivalent of 0.15 mg injected subcutaneously.^{20, 62} Lesser doses may be beneficial to reverse laryngeal edema or persistent bronchospasm.

Once epinephrine has been administered, other therapeutic modalities may be of benefit. Studies have suggested that the combination of an H₁ antihistamine (i.e., diphenhydramine, 1 mg/kg up to 75 mg) either intramuscularly or intravenously and an H₂ antihistamine (i.e., cimetidine, 4 mg/kg up to 300 mg) administered intravenously may be more effective than either administered alone.²⁰ Both histamine antagonists should be infused slowly if given intravenously because rapid infusion of diphenhydramine is associated with arrhythmias, and cimetidine is associated with falls in blood pressure. The role of corticosteroids in the treatment of anaphylaxis remains unclear; however, most authorities recommend giving prednisone (1 mg/kg orally) for mild-to-moderate episodes of anaphylaxis and solumedrol (1–2 mg/kg intravenously) for severe anaphylaxis in an attempt to modulate the late-phase response. If wheezing is prominent, an aerosolized beta-adrenergic agent (i.e., albuterol) is recommended intermittently or continuously, depending upon the patient's symptoms and the availability of cardiac monitoring. Intravenous aminopylline may also be useful for recalcitrant respiratory symptoms. Aerosolized epinephrine may be useful for preventing life-threatening upper airway edema; however, in about 10% of patients a tracheotomy may be required to prevent fatal laryngeal obstruction.¹² Hypotension caused by a shift in fluid from the intravascular to extravascular space may be severe and refractory to epinephrine and antihistamines. Depending upon the blood pressure, large volumes of crystalloid (e.g., lactated Ringer's solution or normal saline) infused rapidly are frequently required to reverse the hypotensive state. An

alternative to crystalloid solution is the colloid, hydroxyethyl starch. Children may need up to 30 mL/kg of crystalloid over the first hour,⁴⁶ and adults may need up to 2 liters¹⁶ over the first hour to control hypotension. Patients taking beta blockers may require much larger volumes (e.g., 5–7 L) of fluid before pressure is stabilized.¹⁶ Although epinephrine and fluids are the mainstay of treatment for hypotension, the use of other vasopressor drugs may be necessary. Dopamine administered at a rate of 2 to 20 $\mu\text{g/kg}$ per minute, while carefully monitoring the blood pressure, may be lifesaving. In addition, 1 to 5 mg of glucagon given as a bolus followed by an infusion of 5 to 15 μg per minute titrated against clinical response may be helpful in refractory cases or in patients taking beta blockers. The best treatment for patients experiencing anaphylaxis while taking beta-adrenergic blocking drugs remains a matter of some concern. If combined β_1 and β_2 receptor blockers (e.g., propranolol) are used, it may be possible to administer epinephrine for its alpha-adrenergic activity and isoproterenol to attempt to overcome the beta blockade. Because patients may experience a biphasic response, all patients should be monitored for a minimum of 4 hours, longer in cases of more severe anaphylaxis.

Although still controversial, some authorities have suggested the use of activated charcoal in an attempt to prevent further absorption of food allergens from the gut. Others have suggested that some attempt should be made to evacuate the stomach, if vomiting has not already occurred. Some have advocated the use of gastric lavage when large amounts of the allergen have been ingested. Whether or not these measures are beneficial in ameliorating food-induced anaphylaxis remains to be demonstrated.

Patients who are at risk for food-induced anaphylaxis should have medical information concerning their condition available on them at all times (e.g., Medic Alert bracelet). This information may be lifesaving; it will expedite the diagnosis and appropriate treatment of a patient experiencing an anaphylactic reaction.

Long-Term Management

The life-threatening nature of anaphylaxis makes prevention the cornerstone of therapy. If the causative food allergen is not clearly delineated, an evaluation to determine the cause should be promptly initiated so that a lethal reoccurrence can be prevented; steps for long-term management of food-induced anaphylaxis are as follows:

- Identify positively food that provoked anaphylactic reaction
- Educate patient, family, or care providers how to avoid all exposure to food allergen
- Provide patient at risk with self-injectable epinephrine and thoroughly teach him or her when and how to use this medication (i.e., practice with Epi-Pen trainer)
- Provide patient with liquid antihistamine (diphenhydramine or

hydroxyzine) and teach him or her when and how to use this medication

- Establish a formal emergency plan in case of a reaction (proper use of "emergency medications" and transportation to nearest emergency facility that is capable of resuscitation and endotracheal tube placement)

The central focus of prevention of food-induced anaphylaxis requires the appropriate identification and complete dietary avoidance of the specific food allergen. Certain factors listed previously place some individuals at increased risk for more severe anaphylactic reactions: (1) history of a previous anaphylactic reaction, (2) history of asthma, especially if poorly controlled, (3) allergy to peanuts, tree nuts, fish, and shellfish, (4) patients on beta blockers or ACE-inhibitors, and (5) possibly being female. An educational process is imperative to ensure that the patient and family understand how to avoid all forms of the food allergen and the potential severity of a reaction if the food is inadvertently ingested. The Food Allergy Network is a nonprofit organization in Fairfax, Virginia (1-800-929-4040) that can assist in providing patients information about food allergen avoidance and that has several programs for schools and parents of children with food allergies and anaphylaxis.

It is not uncommon for patients experiencing a previous food-allergic reaction to subsequently demonstrate some instinctive avoidance measure. This reaction may be typified by extreme dislike for the taste or even smell of the offending food. A very proactive role is required for the sensitized person to completely avoid a food that has caused a previous anaphylactic reaction. For many, this may even require total removal of the food from the household. Educational measures must be directed at the patient, his or her family, and school personnel and other caretakers or fellow workers so that they understand the potential severity and scope of the problem. If a patient ingests a food prepared outside the home, he or she must always be very cautious and not hesitate to ask very specific and detailed questions concerning ingredients of foods he or she plans to eat. Unfortunately, it is not uncommon for patients dining in restaurants to ingest a food that they were assured did not exist in the meal they were eating.

Although changes in food labeling laws in the United States have simplified somewhat, several problems still remain. These problems fall into one of five categories: (1) misleading labels (e.g., "non-dairy" creamers usually contain some milk proteins; (2) ingredient switches (e.g., a name brand food may alter the ingredients with no significant change on the label); (3) "natural flavoring" designation often allows a product to contain a small amount of other food proteins for purposes of flavoring without having to identify that protein (e.g., casein in canned tuna fish); (4) legal labeling loopholes that allow proteins at less than 2% of total protein to be included in a product without designating its presence; and (5) inadvertent contamination that may occur when more than one product is run on a line and residual protein from the previous run

adulterates the subsequent run (e.g., nondairy ice cream desserts). It is still imperative that patients and their families be taught the many "words" that indicate a particular food protein is one of the ingredients of a food product and try to be aware of products where certain food proteins may unexpectedly occur.

PROGNOSIS

For many young children diagnosed with anaphylaxis to foods such as milk, egg, wheat, and soybeans, there is a good possibility that the clinical sensitivity may be outgrown after several years.^{7, 45} Children who develop their food sensitivity after 3 years of age are less likely to lose their food reactions over a several year period. Allergies to foods such as peanuts, tree nuts, fish, and seafood are generally not outgrown no matter at what age they develop. These individuals appear likely to retain their allergic sensitivity for a lifetime. Consequently, several groups are evaluating new strategies to "desensitize" patients to these foods.^{10, 58}

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