

Anaphylaxis and Food Allergy

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KEY POINTS

- Food allergy is the leading single cause of anaphylaxis treated in emergency departments in the United States.
- Any food may cause an anaphylactic reaction, but peanut, tree nuts, fish, and shellfish are most often implicated in severe and fatal reactions.
- A careful clinical history is critical for the accurate diagnosis of food-induced anaphylaxis; an algorithm of clinical symptoms has been proposed, which provides a universal standard for accurately diagnosing anaphylaxis.
- Laboratory studies are not diagnostic of anaphylaxis, simply supportive.
- All patients at risk for a food-induced anaphylactic reaction should be provided with an emergency plan and appropriate medications, for example epinephrine autoinjector, to initiate therapy in case of an accidental allergen ingestion.

Introduction

Although fatal allergic reactions have been recognized for over 4500 years [1], it was not until the 20th century that the syndrome of anaphylaxis was fully characterized. In their classic studies, Portier and Richet described the rapid death of several dogs that they were attempting to immunize against the toxic sting of the sea anemone [2]. Since 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 [3]. The first modern-day series of food anaphylaxis in man was published in 1969 by Golbert and colleagues [4]. They described 10 cases of anaphylaxis following the ingestion of various foods, including different legumes, fish, and milk. The reports by Yunginger [5] and then by Sampson [6] and Bock [7,8] further characterized the natural course of near-fatal and fatal food-induced anaphylactic reactions.

Definitions

The term “food-induced anaphylaxis” refers to a serious allergic reaction following the ingestion of a food, typically IgE

mediated, which is generally rapid in onset and may progress to death [9]. Typically the term *anaphylaxis* connotes an immunologically mediated event that occurs after exposure to certain foreign substances, whereas the term *anaphylactoid* indicates a clinically indistinguishable reaction that is not believed to be IgE mediated but probably involves many of the same mediators, for example, histamine. The syndrome results from the generation and release of a variety of potent biologically active mediators and their concerted effects on various target organs. “Biphasic anaphylaxis” is defined as a recurrence of symptoms that develop following the apparent resolution of the initial anaphylactic event. Biphasic reactions have been reported to develop in 1–20% of anaphylactic reactions and typically occur within 1–4 hours following the resolution of the initial symptoms, although some cases have been reported up to 72 hours later [10]. “Prolonged anaphylaxis” is defined as an anaphylactic reaction that lasts for hours or in extreme cases, days [6]. “Food-associated, exercise-induced anaphylaxis” refers to a food-induced anaphylactic reaction that occurs only when the patient exercises within several hours of ingesting a food; when the food is consumed without subsequent exercise or when exercise occurs without the ingestion of the food allergen, the patient will not experience allergic symptoms [11,12].

Anaphylaxis is recognized by a constellation of cutaneous, respiratory, cardiovascular, and gastrointestinal signs and symptoms occurring singly or in combination. To facilitate and standardize the diagnosis of anaphylaxis, the National Institute of Allergy and Infectious Diseases (NIAID) and Food Allergy & Anaphylaxis Network (FAAN) convened

Table 13.1 Diagnostic criteria for anaphylaxis (Reproduced from Sampson *et al.* [13], with permission from Elsevier.)

Anaphylaxis is highly likely when any <i>one</i> of the following three criteria is fulfilled:	
(1) Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g. generalized hives, pruritus, or flushing, swollen lips–tongue–uvula) <i>And at least one of the following:</i>	
(a) Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia) (b) Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g. hypotonia (collapse), syncope, incontinence)	
(2) Two or more of the following that occur rapidly after exposure to <i>a likely allergen for that patient</i> (minutes to several hours):	
(a) Involvement of the skin-mucosal tissue (e.g. generalized hives, itch-flush, swollen lips–tongue–uvula) (b) Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia) (c) Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g. hypotonia (collapse), syncope, incontinence) (d) Persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)	
(3) Reduced BP after exposure to <i>known allergen for that patient</i> (minutes to several hours):	
(a) Infants and children: low systolic blood pressure (age-specific) or greater than 30% decrease in systolic blood pressure* (b) Adults: systolic blood pressure <90 mmHg or >30% decrease from that patient’s baseline	

BP: blood pressure; PEF: Peak expiratory flow.

*Low systolic BP for children: 1 month–1 year < 70 mmHg; 1–10 years < (70 mmHg + (2 × age)); 11–17 years < 90 mmHg.

an international panel of experts from various medical specialties that deal with anaphylactic cases. An algorithm was proposed, as depicted in Table 13.1 [13]. Since anaphylactic reactions may present with varied degrees of severity, which may influence the form of treatment rendered, Table 13.2 presents a simplified scoring system based on the diagnostic algorithm of anaphylaxis proposed by the NIAID–FAAN working group. This chapter focuses on allergic reactions to foods that manifest as signs and symptoms fulfilling the proposed definition of anaphylaxis.

Prevalence

The prevalence of anaphylaxis is unknown since unlike many disorders, there is no requirement to report such reactions to a national registry. In addition, it is likely that many cases are misdiagnosed [14,15]. 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, self-medicate, and simply attempt to avoid that food rather than consult a physician.

Table 13.2 Grading severity of anaphylaxis

Grade	Defined by
(1) <i>Mild</i> (skin and subcutaneous tissues, GI, and/or mild respiratory)	Flushing, urticaria, periorbital erythema, or angioedema; mild dyspnea, wheezing, and upper respiratory symptoms; mild abdominal pain and/or emesis
(2) <i>Moderate</i> (mild symptoms + features suggesting moderate respiratory, cardiovascular, or GI symptoms)	Marked dysphagia, hoarseness, and/or stridor; SOB, wheezing, and retractions; crampy abdominal pain, recurrent vomiting, and/or diarrhea; and/or mild dizziness
(3) <i>Severe</i> (hypoxia, hypotension, or neurological compromise)	Cyanosis or SpO ₂ ≤92% at any stage, hypotension, confusion, collapse, loss of consciousness; or incontinence

Only in the past few years has an *International Classification of Diseases (ICD)* code for food-induced anaphylaxis become available, prior to which it has been extremely difficult to obtain any reliable information regarding the prevalence, incidence, or mortality rates for these reactions. In a retrospective survey, Yocum and Khan [16] 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 and/or cardiovascular symptoms plus evidence of allergic mediator release, for example, 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 (Table 13.3). Allergic reactions to food were found to be the most common single cause of anaphylactic reactions outside of the hospital, more frequent than reactions to bee sting and drugs combined. 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 [17]. From this it was concluded that at least 950 cases of severe food-induced anaphylaxis occur in the United States every year. However, Bock cautioned that his survey was an underestimate of the problem since patients had been referred to him who were not included in the survey, and the proportion of reactions was higher in rural emergency departments serving smaller populations than in the busier metropolitan departments. In a more recent US survey, Yocum reported an annual incidence of food-induced anaphylaxis of 7.6 cases per 100,000 person-years and a food-induced anaphylaxis occurrence rate of 10.8 per 100,000 person-years [18]. The figures were based on a review of the medical records of Olmsted County inhabitants followed in the Rochester Epidemiology Study from 1983 to 1987.

Table 13.3 Three-year retrospective survey of anaphylaxis occurring outside of the hospital treated by the Mayo Clinic Emergency Department (From Yocum and Khan [16], with permission from Elsevier.)

Presumed etiology of anaphylaxis	Number	%
Food	59	33
Idiopathic	34	19
Hymenoptera	25	14
Medications	23	13
Exercise	12	7
Other	8	4
False diagnosis	18	10
<i>Foods implicated in 18 patients who were skin tested:</i>		
Peanut	4	
Cereals	6	
Egg	2	
Nuts	9	
Milk	2	

Assuming that the US population is now 280 million and that the prevalence of food allergy did not increase since the late 1980s (although peanut allergy has been shown to have increased [19,20]) one could estimate that about 30,000 food-induced anaphylactic episodes occur in the United States every year resulting in approximately 2000 hospitalizations and 150 deaths [11]. Food-induced anaphylactic reactions account for over one-third of the anaphylactic reactions treated in emergency departments and are most often due to peanut, tree nuts, fish, or shellfish. Pumphrey [21] and Moneret-Vautrin [22] reported similar findings in the United Kingdom and France, respectively. In Italy, Novembre reported that food allergy was responsible for about one-half of severe anaphylactic episodes in children treated in emergency departments [23]. Similarly, a survey of South Australian pre-school and school-age children revealed a parent-reported food-induced anaphylaxis rate of 0.43 per 100 school children, which accounted for over one-half of all cases of anaphylaxis in this age group [24]. Similarly, the Canadian Pediatric Surveillance Program reported that 81% of anaphylaxis cases in children were due to food [25]. 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 [26]. In a more recent survey from Australia, 526 children with generalized allergic reactions were seen in a local emergency department and 57 were diagnosed with anaphylaxis. This represented an incidence of 9.3 in 1000 emergency department visits for generalized allergic reactions and an anaphylaxis incidence of 1 in 1000 [27]. In a similar series of 304 adults attending an emergency department in the same city over a 1-year period, 162 were diagnosed with acute allergic reactions and 142 with anaphylaxis, including 60 whose anaphylaxis

was severe and one of whom died, for an anaphylaxis presentation incidence of 1 in 439 [28].

The first of several reports on fatal food-induced anaphylaxis was in 1988 by Yunginger and colleagues who reported seven cases of fatal anaphylaxis evaluated during a 16-month period [5]. In all but possibly one case, the victims unknowingly ingested a food which had provoked a previous allergic reaction. Similarly six fatal and seven near-fatal food-induced anaphylactic reactions in children (aged 2–17 years) were accumulated from three metropolitan areas over a 14-month period [6]. 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. In both these early 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. None of these patients investigated had a significant increase in serum tryptase.

In two reports by Bock and co-workers [7,8], 63 cases of fatal food-induced anaphylaxis were evaluated. As in earlier series, peanuts and tree nuts accounted for more than 90% of the fatalities, but in the second report, milk accounted for 4 of 31 deaths. In these series, all but 2 of the patients were known to have asthma and most of the individuals did not have epinephrine available at the time of their fatal reaction. Of the cumulative 63 fatal food anaphylaxis cases reported, however, 6 individuals (~10%) had received epinephrine in a timely manner but failed to respond. In an earlier series of 48 fatal cases reviewed by Pumphrey, 3 patients (~6%) died despite receiving epinephrine from a self-administration kit appropriately at the onset of their reaction [21].

The incidence of food-dependent exercise-induced anaphylaxis appears to be increasing, possibly due to 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. egg, celery, shellfish, wheat) [29–35] and rarely reactions following the ingestion of any food [30]. Anaphylaxis will occur when a patient exercises within 2–4 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 non-specific reactors) has not been ingested within the past several hours. This disorder is twice as common in females and greater than 60% of cases occur in individuals less than 30 years of age.

In a survey of 199 individuals experiencing exercise-induced anaphylaxis, ingestion of food within 2 hours of exercise was felt to be a factor in the development of attacks in 54% of the cases [32]. More recently, several cases of food- and aspirin-dependent exercise-induced anaphylaxis have been reported [36–38]. 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 and occasionally these patients will have a history of “outgrowing” an allergy to the causative food when they were younger. As discussed below, specific management of this disorder involves identifying the food(s) which cause the reaction (i.e. DBPCFC with exercise).

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 are at increased risk of developing more severe food-allergic reactions [6,9,39]. In the reports of Yunginger *et al.* [5], Sampson *et al.* [6], and Bock *et al.* [7,8] 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 [40], it does tend to predispose to more severe reactions. In general, it has been thought that individuals inherit the ability to produce antigen-specific IgE to food proteins and that hypersensitivity to a specific food is not inherited. However, in a report evaluating twins with peanut allergy, there was a significant concordance rate of peanut allergy among monozygotic twins compared to dizygotic twins suggesting strongly that there is a major genetic influence on the inheritance of peanut allergy [41].

Age may play a factor in predisposing an individual to food-induced anaphylaxis. The prevalence of food allergy appears greatest in the first 2 years of life and decreases with age [12]. Consequently foods introduced during the first year (e.g. cow’s milk, egg, soy, wheat, and peanut (as peanut butter in the United States)) are more apt to induce hypersensitization. Allergic reactions to milk, egg, soybean, and wheat are generally “outgrown” with age [12]. The age of onset of milk allergy is usually in the first year of life, with about 85% of infants “outgrowing” their sensitivity by 7–8 years of age [42,43]. While most food hypersensitivities are outgrown during childhood, food sensitivity to peanuts, tree nuts, fish, and shellfish often persist into adulthood [44,45]. It had been thought to be quite rare to find a patient who develops clinical tolerance to peanuts and tree nuts, although studies now suggest that 20% of children diagnosed with peanut allergy early in life do outgrow their peanut allergy [46,47] and about 10% outgrow their tree nut allergy [48].

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 an increased prevalence of that specific food allergy. In the United States peanut is one of the most common food allergies [49], Americans ingest several tons of peanuts daily (FDA, 1986). By contrast, in Scandinavia, where fish consumption is high, the incidence of allergic reactions to codfish is increased (FDA,1986). Rice and buckwheat allergy are quite rare in the United States but not uncommon in Japan where these foods are frequently ingested [50].

Etiology

Foods

A large variety of foods have been reported to have precipitated an anaphylactic reaction. The list of foods that may induce an anaphylactic reaction is unlimited, and in theory, any food protein is capable of causing an anaphylactic reaction. As indicated in Table 13.4, 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 much lesser extent other legumes: soybeans, lupine, lentils, peas, garbanzo beans), fish (e.g. cod, whitefish, salmon), shellfish (shrimp, lobster, crab, scallops, oyster), tree nuts (hazelnuts, cashews, pistachio, walnuts, pecans, Brazil nuts, almonds), cow’s milk, egg, fruits (banana, kiwi), seeds (sesame seed, mustard), and cereals or grains (wheat, rice, rye, millet, buckwheat) [12]. The potency of particular foods to induce an anaphylactic reaction appears to vary and is also dependent on 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 where 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

Table 13.4 Foods most frequently implicated in food-induced anaphylaxis

Peanut	
Tree nuts	(hazel nuts (filberts), walnuts, cashews, pistachios, Brazil nuts)
Fish	(less often tuna)
Shellfish	(shrimp, crab, lobster, oyster, scallop)
Cow’s milk	(goat’s milk)
Hen’s egg	
Seeds	(cotton seed, sesame seed, pine nuts, sunflower seed)
Beans	(soybeans, green peas, pinto beans, garbanzo beans, green beans)
Fruit	(banana, kiwi)
Cereal grains	(wheat, barley, oat, buckwheat)
Potato	

be positive after 500mg of the food and then in the subsequent challenge 1 year later the patient may tolerate 5g 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 have been numerous reports of an anaphylactic reaction occurring after the first known exposure to a food substance. In one series of children allergic to peanuts and tree nuts, a significant number of these patients reacted on their first known exposure to the food [51,52]. Several possibilities may account for this apparent paradox: most often infants are sensitized to foods passed in maternal breast milk during lactation; sensitization following allergen contact on the skin in infants with atopic dermatitis [53], 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 (e.g. babysitter or grandparent), or food contained in another product which was not suspected of containing the antigen in question); and sensitization may occur because of cross-sensitization to a similar allergen (e.g. kiwi or banana allergy in a latex-sensitive individual) [54]. Some data suggest that sensitization may occur *in utero* [55].

Food additives

Although food additives are often suspected of provoking anaphylactic reactions, the only food additives for which there is significant evidence of precipitating an anaphylactic reaction are sulfites and papain, both of which are quite rare. One of the initial reports detailed an atopic, non-asthmatic patient who experienced an anaphylactic reaction after consuming a restaurant meal which contained significant sodium bisulfite [56]. 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 [57,58].

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 [59]. 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 MSG could provoke asthma and anaphylaxis in some patients, but this remains controversial [60].

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. 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 25–30% of patients will experience a biphasic reaction [6,61,62], where patients typically develop classical symptoms initially, appear to be recovering (and may become asymptomatic), and then experience the recurrence of significant, often catastrophic symptoms, which may be more refractory to standard therapy. The intervening quiescent period may last up to 1–3 hours. In the report by Sampson and colleagues, three of seven patients with near-fatal anaphylaxis experienced protracted anaphylaxis, with symptoms lasting from 1 day to 21 days [6]. Most reports suggest that the earlier epinephrine is administered in the course of anaphylaxis the better the chance of a favorable prognosis, but there is no data to indicate that the timing of epinephrine affects the prevalence of biphasic or protracted symptoms [61]. In addition, it should be noted that in about 5–10% of cases in which patients have received an initial injection of epinephrine in a timely manner, they still progressed to fatal anaphylaxis [7,8]. Even with appropriate treatment in a medical facility, it rarely may be impossible to reverse an anaphylactic reaction once it has begun.

The symptoms of anaphylaxis are generally related to the gastrointestinal, respiratory, cutaneous, and cardiovascular systems [9]. Other organ systems may be affected but much less commonly. The sequence of symptom presentation and severity will vary from one individual to the other. Additionally, one patient who experiences anaphylaxis to more than one type of food may experience a different sequence of symptoms with each food. While many patients will develop similar allergic symptoms on subsequent occasions following the ingestion of a food allergen, patients with asthma and peanut and/or 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 who later developed asthma and then experienced a catastrophic anaphylactic event after ingesting peanut in their teenage years.

The first symptoms experienced often involve the oropharynx. Symptoms may include edema and pruritus of the lips, oral mucosa, palate, and pharynx [9,63]. 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” or croupy cough and/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, and/or wheezing. Cutaneous symptoms of anaphylaxis may include flushing, urticaria, angioedema, and/or an

erythematous macular rash. The development of cardiovascular symptoms, along with airway obstruction, is of greatest concern in anaphylactic reactions. Although cardiovascular symptoms occur less frequently in food-induced anaphylactic reactions compared to insect-sting or medication-induced anaphylaxis, it is important to recognize the symptoms early and the potential complications. Symptoms associated with hypotension can include nausea, vomiting, diaphoresis, dyspnea, hypoxia, dizziness, seizures and collapse [64]. Extravasation of fluid and vasodilation can lead to a decrease in circulating blood volume of up to 35% within 10 minutes [65]. In addition, cardiac dysfunction associated with non-specific electrocardiographic changes and normal coronary arteries has been reported [66]. Therefore, aggressive fluid resuscitation, as well as placing the patient in a supine position and elevating the legs to prevent pooling of blood in the lower extremities, is recommended. In fact, upright posture has been found to lead to fatalities in cases of food-induced anaphylactic shock [67].

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 (manifested as lower back pain similar to “labor” pains). Patients often report an impending “sense of 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 [7,8,21], with late deaths generally resulting from organ damage experienced early in the course of anaphylaxis.

Several factors appear to increase the risk of more severe anaphylactic reactions. Patients taking β -adrenergic antagonists or calcium channel blockers may be resistant to standard therapeutic regimens and therefore at increased risk for severe anaphylaxis [9]. Patients with asthma appear to be at increased risk for severe symptoms as noted in a number of recent reports concerning fatal and near-fatal food anaphylactic reactions [7]. Similar findings have been reported in patients with insect-sting allergy [68] and from patients experiencing anaphylaxis as a result of immunotherapy [69,70]. In these patients significant, acute bronchospasm developed along with other symptoms of anaphylaxis.

The skin is the most commonly affected organ in anaphylaxis, appearing in more than 80% of cases [9,62]. However, up to 20% of cases do not present with skin findings, particularly in children reacting to foods [6,27]. In these cases, a history of allergy and possible exposure, along with symptoms consistent with criteria no. 2 listed in Table 13.1 would establish the diagnosis. In rare cases, hypotension has been reported to be the primary symptom of anaphylaxis. These situations would satisfy the third criteria if the patient had exposure to a known allergen. The annual incidence of anaphylaxis with cardiovascular compromise is 8–10 per 100,000 inhabitants [18,71]. In six cases of fatal food-induced

anaphylaxis [6], initial symptoms developed within 3–30 minutes and severe respiratory symptoms within 20–150 minutes. Symptoms involved the lower respiratory tract in 6 of 6 children, the gastrointestinal tract in 5 of 6 patients, and the skin in only 1 of 6 children. *Anaphylaxis should never be considered ruled-out on the basis of absent skin symptoms.*

Diagnosis

Using the algorithm presented in Table 13.1, the diagnosis of anaphylaxis should be readily apparent [13]. Young children presenting with anaphylaxis most often present with cutaneous and gastrointestinal symptoms [27], whereas adults will often have respiratory and cardiovascular symptoms [66]. In many cases where 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 an episode of anaphylaxis is a very careful history, especially when the cause of the episode is not straightforward [39]. 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, for example, exercise, alcohol, NSAIDs.

Basically, any food may precipitate an anaphylactic reaction, but there are a few specific foods which appear to be most often implicated in the etiology of food-induced anaphylactic reactions: peanuts, tree nuts, fish, and shellfish. In cases where the etiology of the anaphylactic 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 “glue” 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 carry-over. Another infrequent (but not rare) cause of food contamination occurs during the manufacturing process. This contamination may happen with scraps of candy or dough that are “reworked” into the next batch of candy or cookies, or in processing plants where 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 which determined that 10% of the almond butter produced in that plant was contaminated with peanut butter (FDA, 1986). This occurred after a production change in the manufacturing process from peanut butter to almond butter. Other examples include

popsicles run on the same line as creamsicles (milk), fruit juices packaged in individual cartons where milk products have been packaged, milk-free desserts packaged in dairy plants [72], etc. Food items with “natural flavoring” designated on the label may contain an unsuspected allergen, for example casein in canned tuna fish, hot-dogs, or bologna, soy in a variety of baked goods, etc. However, the *Food Allergen Labeling and Consumer Protection Act (FALCPA)* became law on January 1, 2006 in the United States and mandated that foods containing any amount of milk, egg, peanut, tree nuts, fish, shellfish, soy, or wheat must declare the food in plain language on the ingredient label, that is “milk” and not “sodium caseinate.” FALCPA has made label reading to ascertain ingredients much easier for millions of Americans. In the European Common Market countries, similar legislation has been enacted.

Food allergy can develop at any age, although it appears more commonly in the first 3 years of life. Not uncommonly a patient will present who has tolerated a food (i.e. shrimp) for his/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.

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. Following the algorithm in Table 13.1 should enable physicians to accurately identify individuals with anaphylaxis.

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 [73,74]. Systemic mastocytosis results in flushing, tachycardia, pruritus, headache, abdominal pain, diarrhea, and syncope. A factitious allergic emergency may occur when patients knowingly and secretively ingest a food substance to which they are known to be allergic.

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 syncope 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 [75], but asystole

and bradycardia have been reported to be associated with blood drawing [76]. Hyperventilation may cause breathlessness and collapse. It is usually not associated with other signs and symptoms of anaphylaxis, except peripheral and perioral tingling sensations.

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 absolute, a negative prick/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 a patient with a classic history of anaphylaxis to ingestion of an isolated food and a positive prick/puncture skin test to that food, this laboratory test appears to be a good positive predictor of allergic reactivity. In cases of food-associated or aspirin-associated exercise-induced anaphylaxis, prick skin tests performed following exercise/ingestion of aspirin are enhanced compared to tests done prior to exercise/aspirin ingestion in many patients [37].

There are some limitations to skin testing which need to be recognized. There is speculation that skin testing shortly following the anaphylactic event 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 [77]. Possible causes of false-negative prick skin tests include improper skin test technique, concomitant use of antihistamines, or 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 [78]. This is especially true for some fruits and vegetables, and occasionally shellfish. However, 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, the patient should be tested with the natural food utilizing the “prick-plus-prick” method to ensure an absence of detectable IgE antibody [79]. Some caution should be exercised in doing this procedure since the amount of antigen on the prick device will not be controlled, and appropriate negative controls should also 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 etiology of the anaphylactic reaction. In cases of idiopathic anaphylaxis, more extensive prick testing may occasionally prove helpful in making the diagnosis [80]. 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 an etiology in this serious disorder.

Intradermal skin tests are sometimes performed following negative prick/puncture skin tests in other allergic diseases, but the diagnostic significance of a positive intradermal test to food following a negative prick/puncture test is dubious and of no clinical benefit [81]. Fatal anaphylactic reactions have been documented following intradermal skin tests to foods [69,82], so extra caution should be exercised if intradermal tests are performed (if done at all). *Under no circumstances should an intradermal skin test be performed prior to performing a prick/puncture test.* In cases where 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 IgE *in vitro* tests, for example, UniCAP®; Phadia, Uppsala, Sweden. The UniCAP System appears to be slightly more sensitive than the older standard RAST. In a number of studies, predictive curves and diagnostic decision points have been established using the UniCAP System for predicting a positive food challenge for at least milk, egg, and peanuts [83,84]. At the present time there is no laboratory test that will predict the potential severity of an allergic reaction. A study investigating peanut-allergic patients' IgE binding to allergenic peanut epitopes demonstrated that individuals with binding to large numbers of epitopes (epitope diversity) tended to have more severe reactions than those binding fewer epitopes [85].

Massive activation of mast cells during anaphylaxis results in a dramatic rise in plasma histamine and somewhat later a rise in plasma serum tryptase [86,87]. Plasma histamine rises over the first several minutes of a reaction, generally remains elevated for only several minutes, requires special collection techniques, and will breakdown unless the plasma sample is frozen immediately. Consequently, measurement of plasma histamine to document anaphylaxis is often 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 post-mortem specimens [87]. Total tryptase has been shown to be markedly elevated in some cases of bee-sting or drug-induced anaphylaxis [87], but several recent studies have found it less often elevated than plasma histamine [39,88,89]. Unfortunately, total tryptase is rarely elevated in food-induced anaphylaxis [6]. Mature β -tryptase is a better indicator of mast cell activation, and if the assay for β -tryptase becomes more available, it may prove to be a better indicator of anaphylaxis than total tryptase [39]. Other mediators being evaluated for potential use as a laboratory marker of anaphylaxis include carboxypeptidase and platelet-activating factor [39].

Double-blind placebo-controlled food challenges are the "gold standard" for diagnosing food allergy, but 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. However, if several foods were ingested and the patient has positive skin tests to several foods, it is essential that the responsible food be identified. Patients have been reported who experienced repeated anaphylactic reactions because physicians incorrectly assumed that they had identified the responsible food [6]. 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 food 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. While 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 (Table 13.5)

Fatalities may occur if treatment of a food-induced anaphylactic reaction is not immediate [5–8]. 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 [90]. Although epinephrine is clearly the medicine of first choice for the treatment of anaphylaxis, a multi-center study of US emergency room visits for food allergies revealed that only 16% of 678 patients presenting to the emergency room with acute allergic reactions to foods received epinephrine. Even in the group determined to have anaphylaxis (51%), only 22% received epinephrine [91]. 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. β -blockers), and the suspected cause of the reaction [9]. The patient should be placed in the supine position with the legs elevated, if tolerated, to help maintain adequate perfusion and blood pressure [67]. Initial therapy should be directed at the maintenance of an effective airway and circulatory system. The first step in the acute management of anaphylaxis is the intramuscular injection of 0.01 ml/kg of aqueous epinephrine 1:1000 (maximal dose 0.3–0.5 ml, or 0.3–0.5 mg). Intravenous administration of epinephrine may cause fatal arrhythmias or myocardial infarction, particularly in adults, and should be reserved for refractory hypotension requiring cardiopulmonary resuscitation [92]. In patients with pulmonary symptoms, supplemental oxygen should be administered.

In order to ensure that patients receive epinephrine as early as possible, it is important that they, their family members,

Table 13.5 Acute management of anaphylaxis

<i>Rapid assessment of</i>	Extent and severity of symptoms Adequacy of oxygenation, cardiac output, and tissue perfusion potential confounding medications Suspected cause of the reaction
<i>Initial therapy</i>	Epinephrine – 0.01 mg/kg/dose up to 0.3–0.5 mg i.m. up to 3 times every 15–20 minutes (EpiPen®, Twinject®, epinephrine ampule – 1:1000) Oxygen – 40–100% by mask Lie patient in supine position with legs elevated, if tolerated Intravenous fluids – 30 ml/kg of crystalloid up to 2 l (or more depending on blood pressure and response to medications)
<i>Secondary medications</i>	Nebulized albuterol – may be continuous Antihistamines: H ₁ antagonist (diphenhydramine – 1 mg/kg up to 75 mg; cetirizine – 0.25 mg/kg up to 10 mg) H ₂ antagonist (cimetidine – 4 mg/kg up to 300 mg; ranitidine – 1–2 mg/kg up to 150 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 – (5–15 µg/min) for hypotension refractory to epinephrine and Norepinephrine; especially patients on β-blockers
<i>Discharge</i>	Emergency plan and medications Appointment for evaluation of cause if not known

and other care providers are instructed in the self-administration of epinephrine. Preloaded syringes with epinephrine are available and should be given to any patient at risk for food-induced anaphylaxis, that is patients with a history of a previous anaphylactic reaction and patients with asthma and food allergy, especially if they are allergic to peanuts, nuts, fish, or shellfish. In the United States, premeasured doses of epinephrine can be obtained from two sources in two doses: Epi-Pen® (0.3 mg) and Epi-Pen, Jr® (0.15 mg) distributed by Dey Laboratories (Napa, CA) and Twinject® (0.3 mg) and Twinject Jr® (0.15 mg) distributed by Verus Pharmaceuticals (San Diego, CA). Both devices are a disposable drug delivery system with a spring-activated concealed needle. The Epi-Pen is intended for a single intramuscular injection while the Twinject disassembles to provide a second dose administered with a small syringe. Both are obtained in two doses: 0.3 mg for those weighing over 28 kg and 0.15 mg for those weighing less than 28 kg. Children are generally advanced to the 0.3-mg dose when they reach 23–28 kg [93], depending on the severity of previous reactions. Since parent or caregivers attempting to measure and administer epinephrine from a vial is so inaccurate [94], the 0.15-mg epinephrine dose is often used in small children weighing 8 kg or more. Those individuals who experienced previous severe symptoms should be advanced to the 0.3-mg dose earlier than those with a history of milder reactions. Since 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. It is imperative that the patient and/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 therefore should be renewed every year.

Sustained-release preparations of epinephrine are not appropriate treatment for acute anaphylaxis. While inhaled epinephrine (either nebulized or via metered-dose inhaler; Primatine Mist® in the United States) has been recommended in the past [95], a minimum of 20 puffs inhaled correctly by adults or 10–15 puffs by children are necessary to produce blood levels similar to an injection of 0.3 mg or 0.15 mg, respectively [96]. However, a study by Simon and co-workers demonstrated that most children are unable to inhale sufficient epinephrine to produce adequate systemic levels [97]. 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 antihistamines (i.e. diphenhydramine – 1 mg/kg up to 75 mg) either intramuscularly or intravenously and an H₂ antihistamine (i.e. 4 mg/kg up to 300 mg of cimetidine) administered intravenously may be more effective than either administered alone [98]. Both histamine antagonists should be infused slowly if given intravenously since rapid infusion of diphenhydramine is associated with arrhythmias and cimetidine with fall 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 [9]. Patients who have been receiving glucocorticosteroid therapy for other reasons should be assumed to have hypothalamic–pituitary–adrenal axis suppression and should be administered stress doses of hydrocortisone intravenously

during resuscitation. If wheezing is prominent, an aerosolized β -adrenergic agent (e.g. albuterol) is recommended intermittently or continuously depending on 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%, a tracheotomy may be required to prevent fatal laryngeal obstruction [99]. Hypotension, due to a shift in fluid from the intravascular to extravascular space, may be severe and refractory to epinephrine and antihistamines. Depending on 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 [100]. An alternative to crystalloid solution is the colloid, hydroxyethyl starch. Children may need up to 30ml/kg of crystalloid over the first hour [101] and adults up to 2l [66] over the first hour to control hypotension. Patients taking β -blockers may require much larger volumes (e.g. 5–7l) of fluid before pressure is stabilized [102].

Although epinephrine and fluids are the mainstay of treatment for hypotension, the use of other vasopressor drugs may be necessary [11,103]. Dopamine administered at a rate of 2–20 μ g/kg/minute while carefully monitoring the blood pressure may be lifesaving. In addition, 1–5 mg of glucagon given as a bolus followed by an infusion of 5–15 μ g/minute titrated against clinical response may be helpful in refractory cases or in patients taking β -blockers. The best approach to treating patients experiencing anaphylaxis while taking β -adrenergic blocking drugs remains uncertain. If combined β_1 and β_2 receptor blockers (e.g. propranolol) are used, it may be possible to administer epinephrine for its α -adrenergic activity and isoproterenol to attempt to overcome the β -blockade. Since patients may experience a biphasic response, all patients should be monitored for a minimum of 4 hours, longer in cases of more severe anaphylaxis [9].

Although controversial, some authorities have suggested the use of activated charcoal in an attempt to prevent further absorption of food allergens from the gut [104]. However, the volume required and the disagreeable taste often precludes patients from taking adequate quantities and the consequences of aspiration are grave. Others have suggested that some attempt should be made to evacuate the stomach, if vomiting has not already occurred, such as 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 to them at all times, for example, Medic Alert™ bracelet or necklace. This information may be lifesaving since it will expedite the diagnosis and appropriate treatment for a patient experiencing an anaphylactic reaction.

Long-term management (Table 13.6)

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 etiology should be promptly initiated so that a lethal reoccurrence can be prevented, as discussed above. The central focus of prevention of food-induced anaphylaxis requires the appropriate identification and complete dietary avoidance of the specific food allergen [9], especially those at higher risk for anaphylaxis, as discussed previously. An educational process is imperative to ensure the patient and family understands 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 and Anaphylaxis Network* is a non-profit organization in Fairfax, Virginia, USA (Phone: 703-691-3179 or 800-929-4040; Fax: 703-691-2713; <http://www.foodallergy.org>) which can assist in providing patients information about food allergen avoidance and which has several programs for schools and parents of children with food allergies and anaphylaxis. Self-injectable epinephrine should be prescribed and patients/parents should be thoroughly educated in the use of the device.

It is not uncommon for patients experiencing a previous food-allergic reaction to subsequently demonstrate some instinctive avoidance measure. This 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/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, they must always be very cautious and not hesitate to ask very specific and detailed questions concerning ingredients of foods they are planning 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.

Table 13.6 Long-term management of food-induced anaphylaxis

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| <ul style="list-style-type: none"> • Identify positive food which provoked anaphylactic reaction • Educate patient, family, and/or care providers how to avoid all exposure to food allergen • Provide patient at risk with self-injectable epinephrine and thoroughly teach them when and how to use this medication (i.e. practice with Epi-Pen[®] trainer) • Provide patient with liquid antihistamine (diphenhydramine or hydroxyzine) and teach them when and how to use this medication • Establish a formal <i>Emergency Plan</i> in case of a reaction: proper use of "emergency medications" transportation to nearest emergency facility (capable of resuscitation and endotracheal tube placement) |
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Although changes in food labeling laws in the United States have simplified somewhat the reading of labels for food-allergic individuals, several problems still remain. These problems fall into one of the four categories: (1) misleading labels, for example “non-dairy” creamers usually contain some milk proteins; (2) ingredient switches, for example 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, for example casein in canned tuna fish; and (4) inadvertent contamination which may occur when more than one product is run on a line and residual protein from the previous run adulterates the subsequent run, for example non-dairy ice cream desserts. It is still imperative that patients and their families scrupulously read all labels of products because certain food allergens 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. Children who develop their food sensitivity after 3 years of age are less likely to lose their food reactions over a several year period. Approximately 20% of children who develop peanut allergy early in life [46,47] will outgrow this sensitivity. There are rare reports of children who appear to outgrow their peanut allergy only to have allergic reactivity recur at a later date [105,106]. Allergies to foods such as tree nuts, fish, and seafood are generally not outgrown and these individuals appear likely to retain their allergic sensitivity for a lifetime. With better characterization of allergens and understanding of the immunological mechanism involved in this reaction, investigators have developed several therapeutic modalities potentially applicable to the treatment and eventual prevention of food allergy. Among the therapeutic options currently under investigation, there is peptide immunotherapy, mutated allergen protein immunotherapy, DNA immunization, immunization with immunostimulatory sequences, a Chinese herbal formulation, and anti-IgE therapy [107–109]. These novel forms of treatment for allergic disease hold promise for the safe and effective treatment of food-allergic individuals and the prevention of food allergy in the future.

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