Food anaphylaxis

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Food anaphylaxis is now the leading single cause of anaphylactic reactions treated in emergency departments in Westernized countries. In the US, it is estimated that there are 29,000 anaphylactic reactions to foods treated in emergency departments and 125–150 deaths each year. Peanuts, tree nuts, fish and shellfish account for the vast majority of severe food anaphylactic reactions. Immunopathogenic mechanisms responsible for food anaphylaxis may differ somewhat from other forms of anaphylaxis, since elevation of serum tryptase is rarely seen following food anaphylactic reactions. Education regarding the strict avoidance of food allergens, the early recognition of anaphylactic symptoms, and the early use of self-injectable epinephrine remain the mainstays of therapy. However, clinical trials are now underway for the treatment of patients with peanut anaphylaxis utilizing anti-IgE antibody therapy and novel immunomodulatory therapies utilizing 'engineered' recombinant proteins, overlapping peptides, and immunostimulatory deoxyoligonucleotide sequences are being tested in animal models of anaphylaxis.

Three years after Portier and Richet first described anaphylaxis[1], Schlossman reported the first case of food anaphylaxis in the US[2], but it was not until 1969 that the first series of food anaphylaxis in man was published[3]. Now food anaphylaxis is the leading single cause of anaphylaxis treated in American emergency departments[4,5], a change some feel has come about in the last 10–20 years. Food anaphylaxis is an allergic syndrome manifested by an abrupt onset of symptoms within minutes to hours of ingesting a food and is associated with the classic features of IgE-mediated hypersensitivity. The syndrome results from the generation and release of a variety of potent biologically active mediators and their combined effects on various target organs. Anaphylaxis is recognized by cutaneous, respiratory, cardiovascular, and gastrointestinal signs and symptoms occurring singly or in combination. The majority of food anaphylactic reactions in the US and Europe are the result of allergic reactions to peanuts, tree nuts, fish and shellfish.

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Prevalence

The prevalence of food anaphylactic reactions appears to vary somewhat with the dietary habits of a region. In Denmark, Sorensen

found a prevalence of 3.2 cases per 100,000 inhabitants per year with ~5% fatality rate[6]. In a more recent US survey, Yocum reported an annual incidence of food anaphylaxis of 7.6 cases per 100,000 person-years and a food anaphylaxis occurrence rate of 10.8 per 100,000 person-years[5]. 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. Based on this survey, one would predict about 29,000 food anaphylactic episodes in the US each year resulting in approximately 2000 hospitalizations and 150 deaths. Food anaphylactic reactions accounted for over one-third of anaphylactic reactions treated in emergency departments and were most often due to peanut, tree nuts, fish or shellfish. Pumphrey[7] in the UK and Moneret-Vautrin[8] in France reported similar findings. A survey of South Australian preschool and school-age children revealed a parent-reported food anaphylaxis rate of 0.43 per 100 school children, which accounted for over one-half of all cases of anaphylaxis in this age group[9]. Similarly, Novembre reported that food allergy was responsible for about one-half of severe anaphylactic episodes in Italian children treated in emergency departments[10]. While food anaphylaxis accounts for one-third to one-half of anaphylaxis cases treated in emergency departments in North America, Europe and Australia[5,7,9–13], it seems to be uncommon in non-Westernized countries.

In 1988, Yunginger reported 7 cases of fatal food anaphylaxis evaluated during a 16 month period[14], and, in 1992, we reported 6 fatal and 7 near-fatal food anaphylactic reactions in children (ages 2–17 years) that occurred in 3 metropolitan areas over a 14 month period[15]. Common risk factors for these severe reactions included the following: asthma (even if well controlled); inability to identify the responsible food allergen in the meal, 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 series, no patient who died received adrenaline immediately; however, in more recent reports, 7–10% of patients receiving injected epinephrine failed to reverse anaphylactic symptoms.[7,14] In a series of 48 fatal cases of food anaphylaxis reviewed by Pumphrey[7], 3 patients received epinephrine from a self-administration kit appropriately at the onset of their reaction, which failed to prevent a fatal outcome. Of 32 fatal food anaphylaxis cases reported by Bock and co-workers[14], 2 of 32 individuals experiencing fatal outcomes had received intramuscular epinephrine immediately but failed to respond. Interestingly, in most cases of fatal food anaphylaxis in which serum tryptase was measured, a significant increase in tryptase was not found, raising some question about the exact mechanism involved in food anaphylaxis[15].

Table 1 Foods most frequently implicated in food anaphylaxis

Peanuts	
Tree nuts	Walnuts, hazel nuts (filberts), cashews, pistachios, Brazil nuts, pine nuts, almonds
Fish	Less often tuna
Shellfish	Shrimp, crab, lobster, oyster, scallop]
Milk	Cow, goat
Chicken eggs	
Seeds	Cotton seed, sesame seed, mustard seed, psyllium
Fruit	Kiwi

Reports of food anaphylaxis associated with exercise (food-associated exercise-induced anaphylaxis) have been reported with increasing frequency, possibly due to the increased popularity of aerobic exercising over the past decade. Two forms of food anaphylaxis associated with exercise have been described: reactions following the ingestion of specific foods (e.g. celery, shellfish, wheat)[16–18], and, rarely, reactions following the ingestion of any food[19]. In most cases, anaphylaxis occurs when an afflicted individual exercises within 2–4 h of ingesting a specific food. Otherwise, the patient can ingest the food without any apparent reaction and can exercise without any apparent reaction as long as the specific food has not been ingested within the past several hours. This disorder appears to be twice as common in females and > 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 h of exercise was felt to be a factor in the development of attacks in about one-half of the cases[19]. Symptoms often start with pruritus about the scalp that becomes more generalized. Urticaria and flushing are common followed by respiratory obstruction, and sometimes cardiovascular collapse. Patients with specific food anaphylaxis associated with exercise usually have positive skin tests to the food that provokes symptoms and occasionally have a history of reacting to the food when they were younger.

Foods implicated in anaphylaxis

The list of foods implicated in anaphylactic reactions is unlimited and, in theory, any food protein is capable of causing an anaphylactic reaction. As indicated in Table 1, certain foods appear more likely to provoke severe or fatal anaphylaxis, although any food may be the cause. In Westernized countries, peanuts and tree nuts[4,7,14,15] fish (*e.g.* cod, whitefish), and shellfish (shrimp, lobster, crab, scallops, oyster)[11] are most often implicated. Unfortunately, these foods tend to induce

'life-long sensitivities' in contrast to other foods frequently associated with allergy, such as milk, eggs, and soybeans.

Signs and symptoms of food anaphylaxis

Symptoms of food anaphylaxis may appear within seconds to a few hours after the food allergen is ingested, with the vast majority developing within the first hour. In general, the more prolonged the onset of anaphylactic symptoms, the less severe the overall reaction. About one-third of patients will experience a biphasic reaction[15]. In such cases, patients develop classical symptoms of anaphylaxis, appear to recover (and may become asymptomatic) and then experience a recurrence of symptoms. Bronchospasm often is severe and largely refractory to β-agonists leading to severe hypoxia. While severe initial symptoms more often precede the biphasic response, this is not always the case and premature discharges from emergency departments have resulted in fatal outcomes due to the second phase response. The intervening 'quiescent' period typically lasts for up to 1–3 h, so patients should be observed for about 4 h after initial symptoms abate. In a report of 7 cases of near-fatal food anaphylaxis, three experienced protracted anaphylaxis, with symptoms lasting from 1 day to 3 weeks[15]. Most reports suggest that the earlier epinephrine is administered in the course of anaphylaxis the better the chance of a favourable outcome. However, this does not necessarily prevent biphasic or protracted symptoms, and as noted above, does not always prevent fatal anaphylaxis.

Table 2 Clinical signs and symptoms of anaphylaxis

Oral	Pruritus of lips, tongue and palate, and oedema of lips and tongue	
Gastrointestinal	Nausea, abdominal pain (colic), vomiting (large amounts of 'stringy' mucus), and diarrhoea	
Skin	Flushing, pruritus, urticaria, angio-oedema, morbilliform rash, and pilor erecti	
Respiratory (major shock organ		
	Laryngeal	Pruritus and 'tightness' in the throat, dysphagia, dysphonia and hoarseness, dry 'staccato' cough, and sensation of itching in the external auditory canals
	Lung	Shortness of breath, dyspnoea, chest tightness, 'deep' cough, and wheezing
	Nose	Pruritus, congestion, rhinorrhoea, and sneezing
Cardiovascular	Feeling of faintness, syncope, chest pain, arrhythmia, hypotension	
Other	Peri-orbital pruritus, erythema and oedema, conjunctival erythema, and tearing; uterine contractions in women, and aura of 'doom'	

The symptoms of anaphylaxis are generally related to the skin, gastrointestinal tract, respiratory tract, and cardiovascular systems (Table 2). The sequence, timing and severity of symptoms are highly variable among individuals, and may even vary in the same individual in response to different foods. Subsequent anaphylactic reactions to a food often provokes similar allergic symptoms, but reactions in patients with asthma and peanut, nut and/or seafood allergy appear to be somewhat less predictable. Peanut allergic toddlers, who reacted with minimal cutaneous and gastrointestinal symptoms before developing asthma, frequently experience severe anaphylactic reactions after ingesting peanut in later years.

The first symptoms experienced in food anaphylaxis often involve the oral cavity and throat. Symptoms may include tingling, pruritus and oedema of the lips, oral mucosa, palate, and pharynx. Young children may be seen scratching at their tongue, palate, anterior neck, or external auditory canals. These symptoms should not be confused with a similar symptom complex in patients with oral allergy syndrome due to cross-reactivity with birch, ragweed, grass or mugwort pollens. Evidence of laryngeal oedema includes a 'dry staccato' cough and/or dysphonia and dysphagia. In Pumphrey's series, severe upper airway oedema was considered the cause of death in ~10% of cases[20], but this has not been reported in other series. Gastrointestinal symptoms frequently follow including nausea, colicky abdominal pain, vomiting and diarrhoea. Emesis may contain large amounts of 'stringy' mucus. Skin symptoms during anaphylaxis may include flushing, urticaria, angio-oedema, and/or an erythematous macular rash, but may be absent in severe reactions[15]. Respiratory symptoms often consist of a deep repetitive cough, stridor, dyspnoea, and/or wheezing. The development of cardiovascular symptoms along with airway obstruction is of greatest concern in anaphylactic reactions. In the second phase of the biphasic response, it is often extremely difficult to ventilate patients due to extreme bronchospasm, and tension pneumothoraces are a frequent complication of high ventilatory pressure. Cardiovascular symptoms may include syncope, a feeling of faintness, palpitations and/or chest pain. Hypotension or shock may be the result of vascular collapse, cardiac arrhythmia, or asphyxia. Anaphylaxis may be complicated by myocardial ischaemia.

Other signs and symptoms reported frequently in food-induced anaphylaxis include peri-ocular and nasal pruritus, sneezing, diaphoresis, disorientation, faecal or urinary urgency or incontinence, and uterine cramping in women (lower back pain). Patients often report a '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[21]. In 6 cases of fatal food-induced anaphylaxis[15], initial symptoms developed within 3–30 min

and severe respiratory symptoms within 20–150 min. Symptoms involved the lower respiratory tract in all children, the gastrointestinal tract in 5 of 6, and the skin in only 1 of 6 children. The clinician must be aware that skin symptoms may be absent in food anaphylaxis.

Several factors appear to predispose individuals to more severe food anaphylaxis including a personal history of atopy, older age, the presence of asthma, and the particular food to which they are allergic[15,22,23]. In the reports of Yunginger[14] and Sampson[15], individuals were highly atopic and all had histories of asthma. Although atopy reportedly does not predispose individuals to an increased risk of anaphylaxis[24], it does tend to predispose to more severe reactions.

Diagnostic features

In light of its abrupt and dramatic nature, the diagnosis of food anaphylaxis is generally readily apparent (Table 2). Occasionally disorders such as scombroid poisoning, aspiration with upper airway obstruction, myocardial infarction, or a hysterical reaction may be mistaken for food anaphylaxis. In the majority of cases where a food is implicated, the responsible food is apparent from the temporal relationship between the ingestion and the onset of symptoms. When evaluating the cause of anaphylaxis, a very careful history is critical, especially when the cause of the episode is not straightforward. Specific questions should include whether any other precipitating factors appear to be involved, such as exercise. In cases where the aetiology 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 often be a minor ingredient in the meal or a contaminant[25].

The laboratory evaluation of a food anaphylaxis is generally directed at testing a patient for specific IgE antibodies to the food in question. Limited prick skin testing or RAST determinations are necessary to demonstrate whether the patient possesses IgE antibodies to the suspected aetiological agent. In individuals with negative prick skin test to a suspected food, intradermal skin tests are sometimes performed. However, a positive intradermal test following a negative prick test is of questionable significance, unlikely to reflect clinical sensitivity[26], and probably should not be performed. In addition, anaphylactic reactions (including fatal reactions) following intradermal skin tests to foods have been documented[27]. In typical anaphylactic reactions, 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[28–30]. Following the onset of symptoms in a food anaphylactic reaction,

plasma histamine rises over the first several minutes of a reaction and generally remains elevated for only a few minutes[28]. Quantitation of plasma histamine requires special collection techniques not generally available in emergency departments and consequently is impractical except in research situations. Whether measurement of urinary methylhistamine is useful for confirming anaphylaxis remains to be demonstrated. In bee sting and drug-induced anaphylaxis, serum tryptase has been shown to rise over the first hour and may remain elevated for up to 12 h.[29,30] It is stable at room temperature and can be obtained from post-mortem specimens. Strangely, serum tryptase is rarely elevated in food anaphylaxis[15]. The reason for this is not clear, but suggests that other cells, such as basophils or monocytes/macrophages may be more important in the pathogenesis of food anaphylaxis.

Food challenges are usually contra-indicated in patients with an clear-cut history of anaphylaxis following the isolated ingestion of a food to which they have IgE antibodies. However, in many cases patients have ingested several foods prior to their anaphylactic reaction and have positive skin tests to several foods. In such cases it is essential that the responsible food be identified and physician-supervised food challenges are warranted. Many young children who experience food anaphylaxis eventually outgrow their clinical reactivity (except to peanuts, tree nuts, fish and shellfish), so an oral challenge is appropriate following an extended period of food elimination with no history of adverse reactions. In these patients, quantitating their level of food-specific IgE antibodies may be useful in determining when they have 'outgrown' their sensitivity and it is safe to challenge them[31].

Treatment

Acute management of food anaphylaxis

Treatment of food anaphylaxis is similar to treatment of anaphylaxis of other causes. A review of fatal anaphylactic reactions due to bee stings indicated that the longer the initial therapy is delayed, the greater the incidence of complications and fatalities[21]. Reports of fatal food anaphylaxis have suggested similar findings[7,14,15]. 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, and the suspected cause of the reaction[32]. Initial therapy should be directed at the maintenance of an effective airway and circulatory system. Intramuscular epinephrine (adrenaline) is the drug of choice in the treatment of anaphylaxis (0.01 ml/kg of aqueous epinephrine 1:1000; maximal

dose 0.3–0.5 ml, or 0.3–0.5 mg)[33,34]. Although there are reports suggesting that inhalation of racemic epinephrine may be used as an alternative form of therapy for anaphylaxis[35,36], a recent controlled trial failed to confirm the efficacy of this therapeutic approach in children[20]. In patients with pulmonary symptoms, supplemental oxygen should be administered.

Epinephrine for self-administration should be prescribed to individuals at high risk for food anaphylaxis, *i.e.* food allergic patients who have asthma (regardless of the severity) or who have experienced a previous reaction involving the airway or cardiovascular systems. In addition, their family members and other care-providers should be instructed in the administration of epinephrine. Preloaded syringes with epinephrine generally are recommended for use in emergency situations, since both the patient and care-givers are typically very distraught and the scene often chaotic. In the US, there are two forms of premeasured epinephrine: Epi-Pen® and Ana-Kit®. The Epi-Pen® is a disposable drug delivery system with a spring-activated, concealed needle used for a single intramuscular injection. It comes in two forms: the Epi-Pen® – 0.3 mg for adults and the Epi-Pen Jr® – 0.15 mg for children less than 22–5 kg. The Ana-Kit® contains a syringe with two doses of 0.3 mg of epinephrine. Sustained-release preparations of epinephrine are not appropriate treatment for acute anaphylaxis. Inhaled epinephrine may be beneficial to reverse laryngeal oedema or persistent bronchospasm, but should not be considered first-line therapy.

Studies suggest that the combination of H_1 antihistamines (*i.e.* diphenhydramine – 1 mg/kg up to 75 mg) and H_2 antihistamines (*e.g.* 4 mg/kg up to 300 mg of cimetidine) may be more effective than either administered alone[37]. Patients at risk for food anaphylaxis should be provided with liquid forms of these preparations for immediate use if an inadvertent ingestion is suspected. Many 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 β-adrenergic agent (*i.e.* albuterol) is recommended intermittently or continuously, depending upon the patient's symptoms and the availability of cardiac monitoring. Hypotension may be severe and prove 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.

Long-term management of food anaphylaxis

The life-threatening nature of anaphylaxis makes prevention the cornerstone of therapy. The central focus of prevention necessitates

appropriate identification and complete dietary avoidance of the responsible food allergen. Certain factors place some individuals at increased risk for more severe anaphylactic reactions: (i) history of a previous anaphylactic reaction; (ii) history of asthma, especially if poorly controlled; (iii) allergy to peanuts, nuts, fish, and shellfish; and (iv) patients on β-blockers or ACE-inhibitors. Education is imperative to ensure the patient and the family understand how to avoid all forms of the food allergen and the potential severity of a reaction if the food is inadvertently ingested. In addition, patients at risk for food anaphylaxis should carry medical information concerning their condition, *e.g.* Medic Alert® bracelet, emergency medications, and a treatment plan with them at all times. This information may be life-saving, since it can expedite the diagnosis and appropriate treatment of a patient experiencing an anaphylactic reaction.

Future management of food anaphylaxis

An attempt to 'desensitize' patients with peanut anaphylaxis with standard immunotherapy was found to have an unacceptable risk:benefit ratio[38,39]. Consequently, new strategies are being investigated to 'desensitize' food-allergic patients. A trial of anti-IgE therapy for the treatment of patients with peanut anaphylaxis is underway in the US. In addition, new immunotherapeutic approaches utilizing 'engineered' recombinant peanut proteins, overlapping peptides of peanut allergens, and the addition of oligodeoxynucleotide immunostimulatory sequences to peanut proteins have all appeared promising for reversing peanut anaphylaxis in our murine model of peanut allergy (Li *et al.* in press). While the aetiology of the apparent increase in atopy and food allergy in Westernized countries remain unknown, it is hoped that safe, efficacious forms of immunotherapy will be available within the next decade to treat food anaphylaxis.

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