

Update on the clinical features of food-induced anaphylaxis

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Food-induced anaphylaxis has become the leading cause of anaphylactic reactions that occur outside hospital. We introduce the present review with a definition of food-induced anaphylaxis, including its prevalence and proposed etiology. Second, we discuss an entity that is increasingly being recognized: exercise-induced food anaphylaxis, which may be triggered by specific foods or at times where no specific food has been identified. Third, we review current attempts to identify specific food antigens that are responsible for anaphylaxis to well-known triggers (i.e. peanut, as well as more unusual antigens). Fourth, we discuss current treatment options available (i.e. patient education, food avoidance, acute symptom recognition, and early use of self-administered epinephrine). Additionally, we discuss outcome data regarding the morbidity and mortality related to food allergy and anaphylaxis. Finally, information regarding experimental immunomodulatory therapy is presented. *Curr Opin Allergy Clin Immunol* 2:211–216. © 2002 Lippincott Williams & Wilkins.

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Introduction

Food-induced anaphylaxis is defined as an immunologically mediated group of symptoms that occur after the ingestion of a food to which the reacting individual has previously been sensitized. The constellation of symptoms typically involves the respiratory, cardiovascular, cutaneous and gastrointestinal organ systems, and can include urticaria, angioedema, dyspnea, wheezing, abdominal pain, choking, acute loss of consciousness, hypotension, and cardiovascular collapse. Of note, there is no consensus in the literature regarding the number or severity of symptoms that are required to make a diagnosis of anaphylaxis. Reported diagnostic criteria vary from generalized urticaria to cardiovascular collapse after ingestion of an offending food. It is therefore important, when reading the literature, to look for the definition being used by the authors of the particular article.

Cianferoni *et al.* [1•] reported an 11-year retrospective review of 113 episodes of anaphylaxis occurring from 1985 to 1996. In that series, 8% of the reactions were attributed to foods, including mustard, mussels, shrimp, soy, peanut, and fish. Those investigators divided the diagnosis into three distinct categories. Classically, anaphylaxis occurs in a monophasic pattern, with complete resolution of symptoms within 2 h of appropriate treatment. A biphasic reaction occurs when there is a recurrence of symptoms 2–72 h after complete resolution of the initial manifestation, without any further exposure to the triggering agent. Finally, protracted anaphylaxis was defined as cardiac or respiratory symptoms, or both, persisting 10 h after the onset of maximal treatment. In patients with a biphasic reaction, extreme bronchospasm and poor response to epinephrine can render treatment and resuscitation difficult. Fatal and near-fatal cases of anaphylaxis to food described by Sampson *et al.* [2] make these points quite emphatically.

The reported prevalence of food-induced anaphylaxis varies on the basis of the country from which the study originated. Anaphylaxis from foods is most commonly reported in westernized countries, accounting for up to one-third to one-half of all cases of anaphylaxis. It is uncommonly reported in nonwesternized countries. Sorensen *et al.* [3] reported a prevalence of 3.2 cases per 100 000 inhabitants per year in Denmark, with a fatality rate of approximately 5%. In a review of medical records from Olmsted County, from inhabitants included in the Rochester Epidemiology Study from 1983 to 1987, Yocum *et al.* [4] reported an incidence of food

anaphylaxis of 21 cases per 100 000 person-years, and an anaphylaxis occurrence rate of 30 per 100 000 person-years. Based on a US population of 270 million, those data would suggest that the incidence of anaphylaxis is 81 000 annually. In that study, 36% of the reactions were due to food, 17% to medications, and 15% to insect stings. Extrapolating these data to the US population would suggest that 29 000 cases of food anaphylaxis occur in the USA each year, resulting in 2000 hospitalizations and 150 deaths.

Brown *et al.* [5•] reported a retrospective review of 142 patients, aged 13 years and older, who presented to an emergency department in Brisbane, Australia, during the years 1998 and 1999. The presentation incidence of anaphylaxis reported was 1 in 439, with a case fatality rate of 0.70%. The etiology of anaphylaxis was recognized in 73% of these cases, with the most common causes being drugs (28%), insect venom (17.5%), and foods (17%). The causative foods identified included fish, seafood, nuts, mango, and lemon.

Although numerous foods have been implicated as a cause of anaphylaxis, the most common causative agents mirror the most common food allergies: peanut, tree nuts, shellfish, and fish (Table 1). In recent reports, Bock *et al.* [6••] noted that peanut and tree nuts (walnuts, almonds, pecans, Brazil nuts, hazelnuts, cashews, pistachios, macadamia, pine nuts) account for 92% of all food anaphylactic events. Research is ongoing to define the proteins/antigens that are responsible for immunoglobulin E mediated reactions. Asero *et al.* [7] reported a case of string bean induced anaphylaxis in a 20-year-old woman who developed gastroenteritis and generalized urticaria after ingestion. Those investigators went on to identify a 35-kDa protein in string beans to which the patient had immunoglobulin E reactivity. Goh *et al.* [8] identified a 66-kDa protein (probably secreted by the salivary gland of several species of swallows) that is responsible for anaphylaxis after ingestion of bird's nest soup.

Table 1. Foods reported to be associated with food anaphylaxis

Egg	Milk	Fish	Grape
Peanut	Tree nuts	Shellfish	Beer
Wheat	Soy	Sesame seed	Poppy seed
Mustard	Potato	Rice	Acorn
Buckwheat	Kiwi	Millet	Mango
Persimmon	Garlic	Mushroom	Saffron
Spices	Ackee fruit	Lychee fruit	Ficus carica
Carmine	Fowl	Beef	Pork
Psyllium	Annatto dye	Cabbage	Bird's nest soup
Pea	Beans	Legumes	Banana
Sunflower seed	Avocado	Wine	Sulfites
Nitrate	Nitrite	Pomegranate	Red currant
Snails	Frog	Celery	

The mechanism of action in food anaphylaxis is an immunoglobulin E mediated response, which can occur anywhere from several minutes to hours after ingestion of a protein to which the individual has been sensitized. When food antigens are presented to food-specific immunoglobulin E found on mast cells, a cascade of proinflammatory mediators is released. A dramatic rise in plasma histamine levels may be detected; however, the level is difficult to measure because the peak remains for only a few minutes, and the collection techniques are not readily available. Unlike other anaphylactic reactions, food-triggered anaphylaxis rarely results in an increase in serum or plasma tryptase levels [9]. The reason for this observation is unclear, but it implies that cells other than mast cells may play a more important role. Classically, oral ingestion has been the mode of antigen exposure. A recent report by Tan *et al.* [10] attempted to link severe food allergies/anaphylaxis with cutaneous exposure. Unfortunately, that report does not definitively exclude concurrent oral ingestion in any of the case presentations. Additional study of each of those individuals would be required to provide a truly convincing argument that these minute contact exposures could cause the severe symptoms described.

Although ingestion of a specific food antigen leading to an immunoglobulin mediated anaphylactic response is the usual mechanism of action, a specific entity has arisen with the use of bee pollen as a dietary supplement. Greenberger *et al.* [11•] described a woman with documented seasonal allergic rhinitis and ragweed sensitivity, who developed palmar pruritus, generalized urticaria, acute dyspnea, and throat tightness 1 h after ingesting a fruit smoothie containing bee pollen. Not surprisingly, subsequent analysis of the bee pollen detected ragweed, grasses, tree pollens, and *Alternaria* and *Cladosporium* spp. This case highlights the importance of using caution when ingesting food 'supplements'.

Food-induced anaphylaxis may mimic other presentations, including anaphylaxis to a medication taken concurrently with the meal, scombroid fish poisoning, vasovagal syncope, factitious anaphylaxis, pulmonary embolism, seizure disorder, hereditary angioedema, and possible aspiration. Furthermore, contamination of one food with another food substance (occult peanut exposure in chocolate) or the presence of another agent within a meal may occur. Several reports from Europe have illustrated this scenario with patients who developed anaphylaxis after consumption of fish contaminated with the intestinal parasite *Anisakis simplex*. Dominguez-Ortega *et al.* [12] reported three cases of anaphylaxis due to hypersensitivity to *A. simplex*. In those cases the individuals consumed fish contaminated with the *Anisakis* larva, which secretes an excretory/secretory antigen

that is suspected of being the cause of anaphylaxis. All of the patients had increased immunoglobulin E levels (579–16 540 kU/l), increased *Anisakis*-specific immunoglobulin E levels (15.7–4670 kU/l), negative fish-specific immunoglobulin E, and a positive prick skin test to *Anisakis* extract.

Diagnosis

Diagnosis of food allergy/anaphylaxis revolves around a careful history. When the history indicates an isolated ingestion, a positive prick skin test can provide a straightforward diagnosis. Unfortunately, many episodes occur during the consumption of a meal with multiple foods, which can render the diagnosis more difficult. Careful prick skin testing and eventual food challenges must be employed in order to identify the causative food. If concern over a significant anaphylactic reaction exists, then a diluted skin test extract can be used (1:10 million for example) and up-titrated until a positive response is elicited. Intradermal skin testing for food sensitivity has a very low positive predictive value, and may increase the risk for systemic reaction; it is therefore not recommended at this time. There are a few foods where the use of quantitative RAST (Radioallergosorbent testing) assays may give predictive information obviating the need for food challenge to confirm a diagnosis and provide a measurement that may be followed over time.

Oral food challenges are relatively contraindicated in instances in which there is a clear history of anaphylaxis, or when the suspected food is commonly associated with anaphylaxis. In cases in which the history is not diagnostic, however, the 'gold standard' for diagnosis remains a double-blinded, placebo-controlled food challenge. Extreme caution must be exercised, and these challenges should only be performed in a controlled clinical setting where emergency resuscitation equipment and staff are readily available. A recent case report of anaphylaxis during a double-blind, placebo-controlled challenge to corn, reported by Tanaka *et al.* [13•], illustrates the potential risks and adverse outcomes even in patients in whom the suspected food is not usually associated with anaphylaxis. Those investigators reported the case of a 44-year-old woman with the history of reactions to oral ingestion of corn ranging from oral tingling to pruritus, urticaria, vomiting, diarrhea, and difficulty breathing. Four episodes required treatment in an emergency room setting. During her challenge she developed symptoms of erythematous sclera, nasal congestion, and generalized urticaria after the ingestion of the third dose of corn (16 g). She initially responded well to diphenhydramine; however, after 15 min she developed hypotension, tachycardia, vomiting, and wheezing. She was then treated with epinephrine and intravenous steroids, and her symptoms resolved.

Food-associated, exercise-induced anaphylaxis

Romano *et al.* [14•] reported clinical and laboratory findings in 54 patients with exercise-induced anaphylaxis, with both specific-food and nonspecific-food triggers. In the first instance, there is often an identified food sensitivity by prick skin test or radioallergosorbent test. This would support the presence of an immunoglobulin E mediated response. There is a distinct subset of patients who clearly have exercise-induced anaphylaxis associated with food, but for whom no specific food has been identified as the precipitating substance. Although the exact mechanism is unclear in either case, several hypotheses have been proposed. The first hypothesis is that patients have a lower mast cell threshold for mediator release. This is suggested by the fact that increased serum histamine and increased eosinophilic cationic protein have been isolated in patients after oral food challenges and exercise. Second, there is an increased distribution of food allergens with exercise after ingestion because of increased splanchnic blood flow, leading to mast cell degranulation. This action may be potentiated by nonsteroidal anti-inflammatory agents that cause an increase in digestive tract permeability, thus allowing greater absorption of more intact food antigen. Finally, autonomic dysfunction and the ability of gastrin to cause increased cutaneous mast cell mediator release may also play a role.

Although the precise role of exercise in food-dependent, exercise-induced anaphylaxis has yet to be determined, case reports continue to arise. Longo *et al.* [15] described a patient who had immunoglobulin E mediated anaphylaxis after ingestion of snail and subsequent exercise. That patient also had comorbid house dust mite sensitivity. Unlike the patient described by Peroni *et al.* [16] (discussed below), this patient had consumed snails repeatedly in the past without difficulty; however, he had never exercised after their consumption. In order to confirm the role of exercise, a specific food challenge to snail without exercise was performed and was negative, and an isolated exercise challenge was negative. The patient declined the specific food followed by exercise challenge because of concern over a severe reaction occurring; however, the presence of a positive Clinical Assay Pharmacia radioallergosorbent test to snail and the supportive past history made the diagnosis highly probable.

Similarly, Aihara *et al.* [17] presented a unique case of dual food intake leading to food-specific, exercise-induced anaphylaxis. The patient underwent an intricate series of challenges to wheat, umeboshi (pickled Japanese plums), and exercise. The patient ate each item separately followed by exercise without difficulty;

however, when he consumed both items and exercised, symptoms of anaphylaxis recurred (i.e. stridor; dyspnea; itching of the eyes, nose, and ears; generalized urticaria; and a 40% drop in his forced expiratory volume in 1 s from baseline). Cholinergic anaphylaxis was excluded by a hot bath without symptoms. The clinicians went on to show an in-vitro decrease in basophil histamine release by 50% after cromolyn administration. Additionally, the patient underwent an in-vivo cromolyn challenge of 100 mg orally at 4 h and at 30 min before ingesting both foods and exercising, and had no symptoms of anaphylaxis. It is unclear whether cromolyn is clinically significant, because several studies have indicated that waiting 4 h after ingestion of an offending food before exercise may prevent anaphylaxis altogether.

Because food-specific, exercise-induced anaphylaxis has increased in prevalence, attempts to identify specific antigens have also increased. ω -5 Gliadin has been shown to be the major allergen associated with wheat-dependent, exercise-induced anaphylaxis. In addition, Palosuo *et al.* [18] identified allergens in rye and barley that cross-react with the wheat ω -5 gliadin: Rye γ -70 and γ -35 secalins, and barley γ -3 hordein.

Finally, there may be comorbid pollen sensitization. Romano *et al.* [14•] describe nine out of 14 patients who developed tomato-dependent, exercise-induced anaphylaxis, who also had seasonal allergic rhinitis to grasses that cross-react with tomato.

The concept of comorbid pollen sensitization and food anaphylaxis is not limited to exercise provocation. Several case reports were published during the past year that link aeroallergen sensitivity with anaphylaxis after food ingestion. Peroni *et al.* [16] presented a case of anaphylaxis after snail ingestion in a 12-year-old girl who was receiving house dust mite immunotherapy. This patient had significant levels of immunoglobulin E that had cross-reactivity to both house dust mites (*Dermatophagoides pteronyssinus* and *D. farinae*) and snail.

Gandolfo *et al.* [19] reported a case of a 35-year-old female who had developed anaphylaxis to fresh figs after aeroallergen-stimulated sensitivity to *Ficus benjamina*. The patient had a history of palpebral angioedema, ocular pruritus, watery eyes, and dry cough after repeated exposure to *F. benjamina* in her home. She subsequently developed an anaphylactic reaction that consisted of palatine pruritus, sneezing, nasal obstruction, sore throat, sibilant dyspnea, cough, and bilateral palpebral angioedema after ingestion of a single fig. Those investigators went on to identify two immunoglobulin E specific antigens in *F. benjamina* (35 kDa and 19 kDa) and a cross-reacting immunoglobulin E specific antigen in fresh figs (35 kDa).

Treatment

Treatment of food-induced anaphylaxis continues to revolve around the basic principles of food avoidance, education to reduce the chances of accidental ingestion, and emergency rescue treatment after ingestion. Once the causal food or foods have been identified, patients and their families need extensive education regarding food avoidance. Of the common foods that cause anaphylaxis, many are also common ingredients in a host of commercially prepared foods. Extreme caution must be taken, especially when foods may be processed and handled in noncommitted factories (i.e. peanuts may run through the same processing line as other 'nonpeanut containing' foods). In addition, food labeling continues to be confusing for many patients. For instance, milk may appear as whey, casein, or caseinate derivatives, among others. Fortunately, a growing body of reference and educational materials are available at various advocacy groups, such as the Food Allergy and Anaphylaxis Network (www.foodallergy.org). Information regarding occult exposures, recipes, and laminated cards that list the myriad of names and labeling information for foods can be provided.

Acute treatment for food anaphylaxis is no different from that for anaphylaxis of other causes. Proper identification of symptoms and correlation to a history of ingestion warrant rapid intervention. The prompt use of intramuscular epinephrine continues to be the most important medical intervention. Supportive care including oxygen, inhaled bronchodilators, and intravenous corticosteroids and fluids may also be required. Given that early administration of epinephrine in food-induced anaphylaxis continues to have the most significant impact on morbidity and mortality, it is imperative that patients, families, and other caregivers be familiar with the use of self-injected epinephrine. Lee and Greenes [20] reported an association between the delay in administration of epinephrine and an increase in biphasic anaphylactic reactions. In that study, they reviewed 108 pediatric cases of anaphylaxis, and found a 6% incidence of a biphasic response.

Morbidity and mortality

Bock *et al.* [6••] reviewed 32 fatal cases reported to a national registry. In that series, a questionnaire was used to determine the cause of anaphylaxis and the patients were stratified into two groups. In group 1, the causative food was peanut in 67% and tree nuts in the remaining 33%. In group 2, the information available was less complete; however, 55% were probably related to peanut, 27% to tree nuts, and 9% to fish and milk. Unfortunately, most of the individuals did not have epinephrine available at the time of their fatal reaction, despite the fact that all but one of them were known to have food allergy before the fatal events. Furthermore,

all but one was also known to have asthma. That review highlights the extreme importance not only of education regarding food avoidance, but also of education regarding a proper action plan in the event of a reaction, including the proper use of self-administered epinephrine, ensuring immediate availability of epinephrine at all times, and instructing all those involved in care regarding the proper administration techniques.

The comorbid association of asthma can make the treatment of an anaphylactic episode markedly more difficult to treat. Pumphrey and Nicholls [21] reported a case study of a 12-year-old boy with a history of anaphylaxis, severe asthma, and markedly elevated serum immunoglobulin E to milk (>100 kU/l), who had a rapid onset of severe asthma symptoms after accidental ingestion of milk. He was given epinephrine within 15 min, a second dose 5 min later, and a third dose by paramedics on the way to the hospital. His bronchospasm ultimately responded to aminophylline in the hospital; unfortunately, however, he sustained fatal cerebral anoxia. Those authors stress the importance of good baseline control of asthma with minimal routine use of inhaled short-acting β -adrenergic agonist, especially in patients with histories of anaphylaxis and food allergy.

Proper instruction and education in the use of self-administered epinephrine continues to be a major stumbling block in the treatment of anaphylaxis. A study by Sicherer *et al.* [22] reported several unsettling features. A total of 101 families of food-allergic children were evaluated, who had previously been prescribed self-administered epinephrine. Those investigators found that 86% reported that they carried epinephrine with them at all times; however, only 71% of the group had epinephrine with them at the time of the visit. Of this group with epinephrine, 10% had medication, which had expired, leaving only 55% of the total group with appropriate epinephrine at the time of the visit. For school-aged children in that study, 77% had the medication available at school, and 81% of those stated that the school knew the indications for administration. Only 32% of the participants were able to demonstrate proper use of the device. This was later correlated to the fact that, after enrolling 29 attending pediatricians into the study, only 24% of them gave written instructions concerning indications for use, and only 18% of the pediatricians were able to demonstrate correct usage of at least one device (EpiPen, EpiE-Z pen; Dey, Napa, California and Ana-Kit; Bayer Corporation, Spokane, Washington). (Neither EpiE-Z pen nor Ana-Kit are currently available). Furthermore, evaluation of 17 pediatric residents revealed that 65% were familiar with EpiPen and 36% were able to demonstrate correct usage. Only one resident was familiar with Ana-Kit. Overall,

this underscores the importance of proper education regarding the use of self-administered epinephrine, for both the physician in practice and patients and families, in order to ensure the timely and proper administration of epinephrine.

Unsworth [23] reported concern regarding the over-prescription of epinephrine syringes because of the potential adverse effects when they are used incorrectly, including excessive patient confidence leading to a delay in treatment, improper administration techniques, and the possibility for overdose and death. As previously mentioned, the physician should address all of these points during the evaluation of food allergy and anaphylaxis.

Future advances in treatment

As with other allergic disorders, immunotherapy is currently under investigation as a modality for treatment of food allergy and anaphylaxis. Bannon *et al.* [24] have reported the possible role of site-directed mutagenesis of the allergen identified complementary DNA clones of the three major peanut antigens – Ara h 1, Ara h 2, and Ara h 3 – in peanut immunotherapy. The goal of this research is to provide a hypoallergenic protein that is a poor competitor for peanut-specific immunoglobulin E *in vivo*, but that still confers the ability to stimulate T-cell proliferation. Current murine models are promising.

Frossard *et al.* [25] reported a murine model of food allergy in which the administration of carrageenan (a high-molecular-weight, galactose-based polysaccharide) prevented anaphylaxis by inducing oral tolerance and the induction of lymphocyte anergy. In that study, young mice were fed either carrageenan or 0.01 mg/ml β -lactoglobulin, or both, for 5 days before oral sensitization with β -lactoglobulin and cholera toxin. The mice were then given an oral challenge of β -lactoglobulin and rated on a symptom score for anaphylaxis. The results showed a significant decrease in anaphylaxis in mice given both carrageenan and β -lactoglobulin (6.3% versus 53% in mice without pretreatment) after β -lactoglobulin challenge. One of the proposed mechanisms of action is a modification in the way that macrophages present antigen after exposure and uptake of carrageenan. The implications for human studies revolve around supplementing the food of young infants with high-molecular-weight polysaccharides to induce oral tolerance, while avoiding the potential side effect of colitis associated with higher doses of carrageenan.

Conclusion

Food-induced anaphylaxis continues to be the leading cause of anaphylaxis in the USA. As our understanding of the mechanisms of action involved in the immune response to foods improves, new treatment options will

become available. Current trials are underway to evaluate the usefulness of blocking the action of food-specific immunoglobulin E, and may provide a tool to decrease the incidence of anaphylaxis, especially after accidental exposures. Until a reliable preventive treatment is available, education regarding strict food avoidance, early recognition of symptoms, and the prompt treatment of anaphylaxis, including emergent administration of intramuscular epinephrine, remains the most important clinical response to food-induced anaphylaxis.

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- of special interest
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