

# Food-induced anaphylaxis

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## Purpose of review

Food-induced anaphylaxis is the leading single cause of anaphylaxis treated in emergency departments and increasing in prevalence.

## Recent findings

Food allergy is an increasing problem in westernized countries around the world, with a cumulative prevalence of 3–6%. Peanut, tree nuts, and shellfish are the most commonly implicated foods in anaphylaxis, although milk is a common trigger in children. Asthmatics, adolescents, and those with a prior reaction are at increased risk for more severe reactions. Most first reactions and reactions in children most commonly occur at home, whereas most subsequent reactions and reactions in adults occur outside home. Studies on schools have identified inadequate management plans and symptom recognition whereas those on restaurants report lack of prior notification by allergic individuals and lack in staff education. Epinephrine, although underutilized is the drug of choice with multiple doses needed in up to one-fifth of reactions. Diagnosis is currently based on convincing history and allergy testing supported by elevated serum tryptase, if available. Long-term management includes strict avoidance and emergency action plan.

## Summary

With a growing population of food-allergic children and adults, markers to predict which individuals are at increased risk for anaphylaxis as well as new therapies are vigorously sought.

## Keywords

anaphylaxis, diagnosis, epinephrine, food allergy, management

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## Introduction

This review summarizes how common food-induced anaphylaxis is, how it presents, which are the common trigger foods, who are at risk, and where and why reactions occur. The diagnosis, natural history as well as acute and long-term management will also be reviewed.

## How common is food-induced anaphylaxis?

Anaphylaxis has been recently defined by an expert panel as ‘a serious allergic reaction that is rapid in onset and may cause death’ [1]. Food-induced anaphylaxis is the leading single cause of anaphylaxis treated in emergency departments (EDs) in the USA, especially in childhood [2–4]. Food allergy is an increasing problem in westernized countries around the world, with a cumulative prevalence of 3–6% [5\*]. On the basis of the study by Yocum *et al.* [6], it has been estimated that there are close to 30 000 food-induced anaphylactic reactions treated in EDs and 150–200 deaths in the United States each year [3]. Extrapolations from a recent ED data from The National Electronic Injury Surveillance System (NEISS) predict about 14 000 ED visits annually [7]. The latest estimations using data from two large ED-based cohort

studies and the National Hospital Ambulatory Medical Care Survey (NHAMCS) suggest nearly 90 000 ED visits for anaphylaxis annually [8]. Food-related anaphylaxis and admissions increased in the UK (1990–2004) and in Australia (1993–2003) [9,10]. However, food-induced anaphylaxis mortality rates, based on death certificates, were recently shown to remain stable between 2000 and 2009 in Australia [11\*].

## How does food-induced anaphylaxis present?

The majority of reactions manifest within 1 h of exposure, but the onset of symptoms may occur a few hours after exposure to the food allergen, possibly related to a less severe reaction or delayed absorption of the food [3]. The symptoms are most commonly seen in the skin (urticaria, angioedema, pruritus, flushing) and respiratory tract (cough, difficulty breathing, wheezing) in about 80% of cases [4] (Table 1) [12]. The cardiovascular system is less often affected than in anaphylaxis of other causes [13], especially in children [4].

The clinical presentation including the onset of symptoms, clinical severity, and sequence of symptom progression can differ between individuals and between

reactions in the same individual and is likely dependent on the amount of food ingested, consumption of food to an empty vs. full stomach, concurrent illness, exercise, consumption of alcohol or medications, menstruation, among others [14,15]. Exercise and intake of nonsteroidal medications increase intestinal uptake of food allergens [16]. Food-dependent, exercise-induced anaphylaxis occurs when ingestion of food occurs within 2–4 h of exercise. Symptoms do not occur in the absence of exercise.

Features of anaphylaxis differ between children and adults [17]. Whereas adults reported severe symptoms, including cardiovascular collapse more often, severe abdominal pain, hives, rhinitis, conjunctivitis, flushing was reported more often in children [18]. Among the pediatric population, hives and vomiting were more commonly documented in infants, and wheezing and stridor more frequently in preschool-aged children [19<sup>\*</sup>]. Adolescents reported subjective symptoms such as trouble swallowing and difficulty breathing more often. The rate of anaphylaxis in infants is unknown, but it is likely underdiagnosed because the presentation may be atypical and nonspecific in infants including lethargy, cyanosis, fussing, irritability, and seizures, and some signs are otherwise common in infants (drowsiness, regurgitation) [20]. Their inability to report subjective symptoms and infrequent blood pressure measurements [19<sup>\*</sup>] further complicate diagnosis.

Late-phase reactions typically develop within 8 h of resolution of the initial reaction but may occur up to 72 h later [21]. These late phase reactions have been reported in 3–20% of anaphylactic reactions of all causes [22,23] but in only 2% of anaphylaxis induced by foods during in-patient oral food challenges [24<sup>\*</sup>]. Previous studies have suggested orally administered allergen, delayed onset of initial symptoms (>30 min), prior  $\beta$ -blockade, and a delay in the administration, an inadequate amount or the requirement of larger doses of epinephrine as risk factors [22]. The mechanisms of biphasic reactions are largely unknown [25].

### Key points

- Food-induced anaphylaxis is the leading single cause of anaphylaxis treated in emergency departments and increasing in prevalence.
- Asthmatics, adolescents, and those with a prior reaction are at increased risk for more severe reactions.
- Epinephrine, although underutilized is the drug of choice with multiple doses needed in up to one-fifth of reactions.
- Markers to predict which individuals at increased risk for anaphylaxis as well as new therapies are vigorously sought.

### Who is at risk?

The majority of patients with food-induced anaphylaxis have a prior history of a reaction to foods [18,26,27]. Among children with a known food allergy, 16–18% developed a reaction at school [28,29], and 60% of those with a known peanut allergy had an accidental peanut exposure in 5 years [30]. However, also patients without a known allergy may be at risk for food-induced anaphylaxis. Among peanut-allergic and tree nut-allergic reactions, 25% occurred in patients without a known allergy [29].

Patients with asthma and adolescents are at increased risk for severe food anaphylaxis [3,31–33]. Although data have not been reproduced, the severity of co-existing other atopic diseases has also been associated with likelihood of developing life-threatening allergic reactions to peanut and tree nuts [34]. It has been appreciated that reactions generally worsen as children get older and with development of asthma [35]. Adolescents and young adults are also at higher risk as they engage in risky behaviors and often deny symptoms [36]. Furthermore, use of  $\beta$ -blockers, angiotensin-converting enzyme (ACE) or monoamine oxidase inhibitors, or tricyclic antidepressants may diminish the efficacy of epinephrine or increase the severity of anaphylactic reactions [35,37].

**Table 1 Clinical presentation of food-induced anaphylaxis**

Cutaneous	Pruritus, urticaria, flushing, morbilliform rash, angioedema
Ocular	Pruritus, eye lid edema and erythema, conjunctival injection and tearing
Respiratory tract	
Upper respiratory	Nasal and ear itching, rhinorrhea, sneezing, congestion
Laryngeal	Throat pruritus and/or tightness, stridor, hoarseness, dysphonia, barking cough
Lower respiratory	Cough, wheezing, difficulty breathing, chest tightness, cyanosis
Gastrointestinal	
Upper GI	Pruritus and or edema of the lips/mouth/tongue, metallic taste, dysphagia
Lower GI	Nausea, vomiting, crampy abdominal pain, diarrhea
Cardiovascular	Tachycardia, arrhythmia, dizziness, syncope, chest pain, hypotension, shock
Neurologic	Anxiety, headache, seizure, altered consciousness
Other	Urinary/fecal incontinence, diaphoresis, lower back pain and uterine contractions in women, sense of 'pending doom'

GI, gastrointestinal. Adapted with permission from [12].

Although the allergy tests correlate with the risk of reactivity to foods, they do not correlate with the severity of reactions. However, recognition of more numerous IgE-binding epitopes by patients' specific IgE antibodies increases the likelihood of a more severe reaction [38]. It has also been shown that ACE concentrations are significantly lower in peanut-induced and tree nut-induced anaphylactic reactions, which progressed into severe pharyngeal edema [34].

### Which foods?

Peanut, tree nuts, fish, and shellfish are the most commonly implicated foods in anaphylaxis, although milk is a common trigger in children (Table 2) [18,32,33,39\*,40–43]. In addition, lipid transfer protein has been reported as the most common food to induce anaphylaxis in southern Europe [40]. Galactose-alpha-1,3-galactose ( $\alpha$ -gal), a carbohydrate commonly expressed on nonprimate mammalian proteins, has been identified as a trigger in late-onset anaphylaxis or urticaria [44\*\*].

Most of the anaphylactic reactions occur to ingested food allergens; however, reports on anaphylaxis to inhaled food allergens have been reported including fish, shellfish, seeds, soybeans, cereal grains, egg, milk, and other foods in the form of allergen flour in the air and vapors during cooking or roasting [45]. However, skin exposure to or inhalation of peanut butter did not result in systemic or respiratory reactions in highly peanut-sensitized children [46].

Most known food allergens are proteins that are resistant to enzymatic digestion and heat, and therefore, the allergenicity of food can be modified by the degree of enzymatic digestion and heating [25]. Underdigestion of food proteins places patients with food allergy at a higher risk for more severe allergic reactions [47,48]. In wheat-dependent, exercise-induced anaphylaxis, exercise induces the activation of tissue transglutaminase. This results in generation of high molecular weight complexes of omega-5 gliadin, a wheat allergen, that bind IgE with

increased intensity leading to activation of mast cells and anaphylaxis [49]. Heating egg and milk proteins results in tolerance by 70–75% of patients who otherwise react to nonheated egg or milk, which is likely due to modification of the protein structure [50,51]. Children reactive to extensively heated milk (but not egg) were at higher risk for systemic reactions treated with epinephrine than those children tolerant to heated milk but reactive to unheated milk [50,51].

### Where and why do food-induced anaphylactic reactions occur?

Most reactions in children occur at home, whereas most reactions in adults occur in restaurants followed by home and work or school [39\*,41]. Among peanut-allergic and tree nut-allergic reactions in the USA, most (76%) first reactions occurred at home, whereas most subsequent reactions occurred outside home [29]. In the UK, nearly one-fifth of the reactions in children occurred at school [18]. Commercial catering accounted for 68% of nut reactions [52].

Most peanut and tree nut reactions at school occurred in the classroom and were due to craft projects using nuts or celebrations such as birthdays. A number of reactions also occurred in the playground or on school trips, among others [53]. Multiple studies have identified inadequacies in management plans and in symptom recognition in schools [54\*\*].

Among reactions in food establishments, most occurred in Asian food restaurants, ice cream parlors and bakeries/doughnut shops, and desserts were a common meal course [55]. Half of the patients with known allergy did not give prior notification of their allergy to the staff; in the majority of reactions someone in the establishment would have known that nut was an ingredient. Twenty percent of the reactions resulted from food in a buffet, or a food bar, or due to skin contact or inhalation. Survey of staff individuals (managers, waiters, chefs) indicated that there was a false sense of security among them: one in

**Table 2 Foods implicated in anaphylaxis**

Authors	Population	No. of study participants	Country	Most common foods (% of reactions)
Banerji <i>et al.</i> [39*]	Adults	802	USA	Shellfish 21%, peanut 15%, tree nuts 15%, fruits and vegetables 13%, fish 9%
Asero <i>et al.</i> [40]	Adults	58	Italy	LTP 33%, shrimp 17%, tree nut 16%, legumes 7%, seed 3%
Rudders <i>et al.</i> [41]	Children	658	USA	Peanut 23%, tree nuts 19%, milk 19%, fruits and vegetables 9%, shellfish 7%
Jarvinen <i>et al.</i> [32]	Children	95	USA	Peanut 25%, milk 19%, tree nut 13%, nut 4%, wheat 9%, fish/shellfish 3%, soy 2%, seed 2%
Colver <i>et al.</i> [42]	Children	229	UK, Ireland	Peanut 21%, tree nut 16%, milk 10%, egg 7%
Oren <i>et al.</i> [43]	Mixed age	19	USA	Peanut, tree nut
Uguz <i>et al.</i> [18]	Mixed age	126	UK	Peanut ~25%, tree nut ~25%, milk 10%, egg ~5%
Moneret-Vautrin <i>et al.</i> [33]	Mixed age	107	France	Tree nut 15%, peanut 13%, shellfish 10%, lupine flour 9%, wheat 7%

LTP, lipid transfer protein. Adapted with permission from [12].

four believed that consuming a small amount of allergen or removing an allergen from a finished meal is well tolerated, 35% thought that fryer heat would destroy allergens, and half of them considered that a buffet is well tolerated if kept 'clean' [56].

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### What happens in fatal food-induced anaphylaxis?

The rate of fatal anaphylaxis due to foods is rare but probably underreported [57\*\*]. The risk of a fatal outcome has been estimated less than 1 per million population per year [57\*\*] or less than 1 per 20 million population per year in children [58]. In the UK, food allergens were responsible for up to 30% of fatal cases of anaphylaxis [52].

Unfortunately, most life-threatening, near fatal, and fatal anaphylaxis is unpredictable. The most common risk factors are (poorly controlled) asthma, failure to identify a known food allergen in the meal, and previous allergic reactions to the food in question [26,42,52,59,60]. The most cases of fatal food-induced anaphylactic reactions are associated with peanut and tree nuts, with milk, egg and seafood responsible for the rest [26,52]. Adolescents and young adults are the peak age group at risk [26,52].

Most fatal and near-fatal reactions due to foods occurred within 30 min of ingesting the triggering food allergen [35,60]. The time from the ingestion of the food allergen to the fatal collapse was approximately 25–35 min (range 10 min to 6 h) in one study [52]. Both biphasic and protracted courses have been reported in fatal and near-fatal anaphylaxis [60]. Fatal food reactions are more commonly associated with asphyxia, which is in contrast to insect sting or medication reactions that present with cardiovascular shock. Missing cutaneous symptoms may be a risk factor for fatal anaphylaxis [60]. An upright position is associated with fatalities due to reduced venous return, and it is recommended to stay in a supine position during treatment of anaphylactic reaction [35] unless prevented by profuse vomiting.

Lack of timely treatment with epinephrine is a significant risk factor for a fatal food-induced anaphylaxis [26,52,59,60], although fatalities have also been reported after timely administration of epinephrine [52]. One out of six with fatal outcome received epinephrine in 30 min vs. six out of seven with a near-fatal outcome [60]. No or late administration of epinephrine was seen in 22/32 with fatalities [26].

Vadas *et al.* [61] reported that the mean serum platelet-activating factor acetylhydrolase (PAF-AH) activity was significantly lower in patients with fatal peanut anaphylaxis as compared with those with peanut allergy or

nonfatal anaphylaxis, suggesting PAF-AH as a potential marker for more severe food-induced anaphylaxis.

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### How to make a diagnosis of food-induced anaphylaxis?

Making a clinical diagnosis of food-induced anaphylaxis can be challenging if there is no known history of food allergy or cutaneous involvement is lacking [37]. Furthermore, the fact that many foods are usually consumed at the same time may obscure identification of the triggering allergen. The diagnosis can also be difficult to make because of transience of symptoms due to endogenous production of catecholamines or prehospital administration of medications.

Currently, total tryptase level is the most commonly measured marker to establish a diagnosis of anaphylaxis. Tryptase levels increase immediately, peak at 1–2 h and return to baseline 24 h after complete resolution of symptoms. Levels are ideally obtained within 3 h of onset of symptoms and serial measurements may help establish a diagnosis of anaphylaxis [62]. Lack of tryptase elevation is commonly seen in food-induced anaphylaxis [60,63], which may be due to slow onset of reactions or because mucosal mast cells and basophils, the major players in food-induced anaphylaxis, contain less to no tryptase as compared with skin mast cells [25]. Another laboratory marker of anaphylaxis is serum histamine which peaks at 10 min and disappears in 60 min and is therefore not a practical marker. Urinary histamine metabolites remain elevated for up to 24 h and may be helpful in establishing the diagnosis. Among other mast cell mediators, chymase, and mast cell carboxypeptidase A3 may be other potential markers of anaphylaxis [64].

Oral food challenges are the gold standard for the diagnosis of food allergy but may elicit severe anaphylactic reactions including those requiring treatment with multiple doses of epinephrine [24\*,65]. Therefore, presumptive diagnoses are more often made based on a convincing clinical history of anaphylaxis within 2 h of ingestion of a particular food allergen and detection of food allergen-specific IgE. Unfortunately, these tests are not always sensitive or highly specific [25].

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### How to manage a food-induced anaphylactic reaction?

The mainstay of treatment of any anaphylactic reaction is the timely administration of epinephrine. Various reports on food-induced anaphylaxis occurring in the community have identified underutilization of epinephrine. Epinephrine was administered in 25–44% of severe reactions or anaphylaxis [27,39\*,41]; however, 12–19% of food-induced anaphylactic reactions may require more than

one dose of epinephrine [18,32,39\*,41,43]. Most second doses were administered by healthcare professionals, with favorable outcomes; milk, egg, and peanuts were most common triggers and asthma was predisposing factor [32]. Adjunctive therapies include H1-antihistamine, which may relieve skin symptoms and rhinorrhea, H2 blockers, oxygen, bronchodilators, and corticosteroids, given with the goal of preventing or ameliorating a late phase reaction although their role here has not been proven.

### What is the natural history and long-term management?

The persistence of food allergy is variable and depends on the specific food allergen. Cow's milk allergy will be outgrown in 64% by age 12 years [66], egg allergy in 37% by age 10 years [67], and wheat allergy in 65% by 12 years [68]. In contrast, only 20% of children with peanut allergy and 9% with tree nut allergy will develop tolerance [69,70]. The rate of decrease in food-specific IgE levels over time has been shown to have predictive value [71].

All patients with food allergy, and especially food-induced anaphylaxis, should be educated about the signs and symptoms of anaphylaxis and the correct use of an epinephrine auto-injector together with written instructions on its proper administration into the lateral thigh intramuscularly and an anaphylaxis treatment plan. Otherwise healthy young children who weigh 10–25 kg (22–55 lb) should be prescribed auto-injectors with 0.15 mg of epinephrine and those who weigh approximately 25 kg (55 lb) or more should be prescribed auto-injectors with 0.30 mg of epinephrine [72]. For children who weigh less than 10 kg (22 lb), the risks and benefits of delay in dosing and dosing errors when an ampule/syringe/needle is used against accepting nonideal auto-injector doses should be weighed. Prospective studies are needed to establish rational guidelines for prescribing one or more doses for a growing number of food-allergic patients.

Currently, the only treatment for food-induced anaphylaxis is strict dietary avoidance. Educating the patient regarding dietary avoidance of the food allergen(s) includes stressing the importance of constant reading of package labels and advisory labeling, and asking questions regarding the food to be consumed. Effective care also requires a comprehensive management approach involving schools, camps, and other youth organizations, and education of supervising adults with regard to recognition and treatment of anaphylaxis. A medical identification bracelet or necklace is also recommended.

Development of therapies to prevent the food-induced anaphylaxis is a vigorous research area. Promising therapies under investigation are both allergen specific and

nonspecific, including humanized monoclonal anti-IgE antibodies and Chinese herbal medications, as well as oral, sublingual, and cutaneous immunotherapy (desensitization). They also include use of mutated recombinant proteins, co-administered with heat-killed *Escherichia coli* and peptide immunotherapy [73\*\*].

### Conclusion

Food-induced anaphylaxis is the leading single cause of anaphylaxis treated in EDs. With a growing population of food-allergic children and adults, markers to predict which individuals are at increased risk for anaphylaxis as well as new therapies are vigorously sought.

### References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 272–273).

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