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# Food-Induced Anaphylaxis

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## DEFINITION

Food-induced anaphylaxis (FIA) is a serious allergic reaction that may cause death rapidly in otherwise healthy individuals. There is no universal agreement on its definition or criteria for diagnosis.[1] In 2006 an international task force on anaphylaxis recommended a new working clinical definition of anaphylaxis, which tried to address such issues (Box 1).[2]

**Box 1**

**Clinical criteria for the diagnosis of anaphylaxis**

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, itch or flushing, swollen lips, tongue, or uvula, rhinorrhea, conjunctivitis). And at least one of the following:
   - **a.** Respiratory compromise (eg, dyspnea, bronchospasm, stridor, hypoxia)
   - **b.** Cardiovascular compromise (eg, hypotension, collapse)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   - **a.** Involvement of the skin or mucosal tissue (eg, generalized hives, itch, flushing, swelling)
   - **b.** Respiratory compromise (eg, dyspnea, bronchospasm, stridor, hypoxia)
   - **c.** Cardiovascular compromise (eg, hypotension, collapse)
   - **d.** Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)



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3. Hypotension after exposure to known allergen for that patient (minutes to several hours)

Hypotension for children is defined as systolic blood pressure <70 mm Hg from 1 month to 1 year [<70 mm Hg + (2 × age)] from 1 to 10 years, and <90 mm Hg from 11 to 17 years.

*Data from* Muraro A, Roberts G, Clark A, et al. The management of anaphylaxis in childhood: position paper of the European Academy of Allergology and Clinical Immunology. Allergy 2007;62(8):857–71.

Based on this latest recommendation,[1,3] FIA is diagnosed when

1. Two or more of the following symptoms occur rapidly and acutely after exposure to a likely allergen and:
    - Involvement of the skin or mucosal tissue, respiratory compromise, cardiovascular compromise, persistent gastrointestinal symptoms
2. Hypotension after exposure to known allergen for that patient.

## EPIDEMIOLOGY

The epidemiology of FIA has been difficult to quantify, with estimates varying widely[2]; however, there is general agreement that hospital admissions for FIA have more than doubled in the last decade.[4]

Epidemiologic challenges in determining the burden of FIA has been reviewed[5] and are listed in Box 2.

**Box 2**

**Epidemiologic challenges in determining the burden of food-induced anaphylaxis**

1. Lack of universal consensus on consistent definition to identify anaphylaxis (especially for studies published before the new 2006 guidelines[2])
2. Difficulty in distinguishing anaphylaxis from other disorders
3. Selection bias based on hospital presentation
4. Use of different measures of disease occurrence to estimate disease burden (such as prevalence and incidence)
5. Limited ability of International Classification of Diseases (ICD) 995.6 code (“anaphylactic shock due to adverse food reaction”) to identify specific allergic reactions in the emergency department, as it is not realistic to expect physicians (or health statistics) to code anaphylactic reactions defined as multisystem organ involvement, but not shock, with codes specifically including shock

Bearing in mind the limitation cited in Box 2, it is estimated that the incidence of:

- *Fatal reaction due to FIA* is 1 in 800,000 per year in children and 1 in 4 million for adults
- *Nonfatal reaction due to FIA* is reported to be between 0.5 and 16 cases per 100,000 person-years.[6–9]

These numbers may underestimate the actual burden of anaphylaxis or risk of anaphylaxis in the general population. Indeed it is estimated that 0.1% to 5% of children have a prescription for epinephrine,[10,11] and that in the United States the direct and indirect cost of hospitalization, emergency room visits, epinephrine prescription, and ambulance transport related to FIA is more than $40 million per year, with about 75% of these costs attributable to pediatric patients.[12]

Peanut/tree nuts anaphylaxis is estimated to have a prevalence of 0.25% to 0.95% in the United Kingdom and United States pediatric populations, and appears to be on the increase in the last decade.[13–15] This statistic mirrors the increased prevalence of peanut and tree nut allergy reported in United States children. Peanut allergy recently has been found to be 2.6% in the general population and 22.6% among children sensitized to peanut.[16] In general, the prevalence of adverse reactions to foods is higher in children than in adults; however, allergy to nuts is an important problem in adulthood, the prevalence of allergy to nuts being higher in adults (1.6%) than in children (0.6%).[14] As allergy to nuts persists over the years, these data could reflect a cumulative effect in adults because peanut and tree nut allergy seems to develop early in life, with most affected children in the United States and the United Kingdom developing symptoms before the age of 2 years.[17,18]

Shellfish anaphylaxis has a prevalence of 0.44% in the United States.[19] The consumption of seafood has risen by approximately 50% over the last 40 years, both in the United States and elsewhere,[20] corresponding to an increase in the incidence of seafood allergy over the same period, with significantly lower rates in children compared with adults[19,21] as happens for tree nut and peanut allergy.

## TRIGGERS OF FIA

Food is one of the most common causes of anaphylaxis, with most surveys indicating that food-induced reactions account for 30% to 50% of anaphylaxis cases in North America, Europe, Asia, and Australia,[4,6,7,9,12,22] and for up to 81% of anaphylaxis cases in children.[23,24]

Although a wide range of foods has been reported as the cause of FIA, the most commonly implicated foods worldwide are peanut, tree nuts, milk, egg, sesame seeds, fish, and shellfish[2,3,5,6,9,25,26] in both adults and children (Table 1). However, the individual food allergy varies by culture and population. For example, peanut allergy is one of the most common causes of FIA in the United States, United Kingdom, and Australia, but is rare in Italy and Spain (where consumption of peanut is significantly lower than in the United States) or China (where peanut consumption is similar to that in the United States).[5,6,25,27–30]

Even if prior exposure is necessary for the development of sensitization, 72% patients with peanut and/or tree nut allergy reported symptoms during their first known exposure.[31] These patients may have had previous unknown exposures through breast milk, contamination with other foods, or use of topical products containing food oils (eg, peanut).[32]

Reports of anaphylaxis in exclusively breast-fed babies due to passage of food allergens from the mother to the infant are extremely rare,[33,34] and there are no reports in the literature of fatal FIA in exclusively breast-fed infants.

The spectrum of foods responsible for causing anaphylaxis appears to be broadening, to include fruits and other foods not previously commonly associated with anaphylaxis.

- Asero and colleagues[29] recently reported on a series of 1110 adolescent and adult Italian patients (mean age 31 years, range 12–79 years) diagnosed with food allergy based on history of reaction in the presence of positive skin prick test (SPT) or elevated food-specific serum IgE. Anaphylaxis was reported by 5% of food-allergic individuals, with the most common cause being lipid transfer protein (LTP). LTP is a widely cross-reacting plant pan-allergen. Offending food for LTP-allergic patients was most often peach, but included also other members of the *Rosaceae* family of fruits (apple, pear, cherry, plum, apricot, medlar, almond, strawberry), tree nuts, corn, rice, beer, tomato, spelt, pineapple, and grape.[35–37]
- Recently there have been several case reports of anaphylaxis resulting from ingestion of lupin flour, which is being increasingly used in bakery products in France and Mediterranean countries.[38,39]
- Moreover, some newly described food allergens appear to cause specific clinical subtypes of anaphylaxis.
  - Water-insoluble omega-5-gliadin (Tri a 19) has been identified as a major allergen in Finnish subjects with food-dependent exercise-induced anaphylaxis (FDEIA), with in vitro and in vivo cross-reactivity to rye allergens and barley allergens, but not oat allergens.[40,41]
  - A carbohydrate nonprotein food allergen, galactose-α-1,3-galactose (α-gal), is capable of eliciting delayed systemic symptoms of anaphylaxis, angioedema, or urticaria associated with eating beef, pork, or lamb 3 to 6 hours earlier, and appears to be more common in middle-aged men living in Virginia, North Carolina, Tennessee, Arkansas, and Missouri, as well as in Australia. Given the peculiar geographic distribution and the fact that more than 80% of the patients reported being bitten by ticks, researchers were able to provide evidence that tick (*Amblyomma americanum* or *Ixodes holocyclus*) bites are a (possibly singular) cause of IgE-mediated sensitization to α-gal in these areas of the United States and Australia.[42–44]

## Peanut/Tree Nut Anaphylaxis

Peanut and tree nuts are overwhelmingly and disproportionately represented in case series of severe and fatal outcomes, severe allergic reaction, and visits to the emergency department for food anaphylaxis, particularly in United States, Germany, Australia, and the United Kingdom (see Table 1),[4,5,45–48] and allergy to peanut and tree nuts is becoming a significant health problem in many parts of the world.[49] Large surveys indicate that in comparison with other foods, allergic reactions to nuts seem to be particularly severe, with multisystemic or respiratory symptoms in up to 81% of the cases. Some studies indicate that severity of coexisting atopic diseases may be a risk factor in the development of life-threatening allergic reactions to peanut and tree nuts.[50]

Recent advances in allergy sequencing and the availability of platforms for IgE specific for single epitopes of the single allergens have increased our understanding of which epitopes are more important in the triggering of an allergic reaction. Major allergens described for peanut and tree nuts are listed in Tables 2a and 2b. Serologic studies have shown that the diversity of IgE recognition of peanut proteins is associated more with clinical outcome than with recognition of individual allergens.[51] However, some studies suggest having IgE specific to Ara h 2 is associated with more severe (mostly respiratory) symptoms, whereas Ara h 8, a Bet v 1 cross-reactive allergen, more often causes less severe reaction such as oral syndrome.[52] Different food processing methods used in different countries may be

responsible for increased or decreased peanut allergenicity, and consequently peanut allergy prevalence in countries with similar consumption such as China and the United States. Indeed the dry-roasting process (150°C) used in United States enhances the allergenicity of Ara h 1, 2, and 3, whereas boiling (100°C) or frying (120°C) used in China reduces the allergenic properties of these molecules.[30]

One of the most common reported tree nut allergies is that of the cashew. One-third of the patients reacting to cashew nuts are also allergic to pistachios, which belongs to the same botanic family (Table 3). Severe allergic reactions to hazelnuts, including systemic anaphylaxis, have also been described in patients sensitized to Cor a 8 (LTP) and Cor a 9 (11S globulin).[53] In United States children the most common tree nut allergies are walnut, almond, and pecan.[31] Allergic reactions to other nuts such as Brazil nuts, pistachios, macadamia nuts, pine nuts, and coconuts are less common triggers of FIA and have been reported anecdotally.[49] Chestnut allergy is generally observed in the context of latex-fruit syndrome.[54]

Assessment of cross-reactivity among tree nuts is complicated by shared allergens among the nuts and between nuts and other plant-derived foods and pollens. If skin test reactivity is a result of cross-reactivity to pollens, food reactions are typically absent or mild (ie, oral allergy syndrome) (see Tables 2a and 2b).[49] Some nut allergens may be homologous and cause reactions (eg, in pistachio and cashew), whereas others may be homologous but rarely elicit clinical cross-reactivity (eg, proteins in coconut and walnut). Clinical relevant cross-reactivity is estimated to be around 30% to 40%; however, fatal reactions have been described from a first exposure to a nut in patients allergic to other nuts.[55] Hence, considering the potential severity of the allergy and issues with accurate identification of specific nuts in prepared foods, very often a total elimination of the nut family (perhaps with the exception of previously tolerated nuts eaten in isolation) is suggested by most clinicians.[55] Cross-reactions to seeds, such as sesame, mustard, and poppy, have also been reported.[56–64]

Cosensitization to allergenic foods, such as peanut, tree nuts, and seeds (sesame, poppy, and mustard) is common, although clinically significant cross-reacting proteins have not yet been described. Coallergy to peanut and tree nut has been reported as between 23% and 50% in referral populations of atopic patients and 2.5% in unselected populations.[56]

## Seafood

Seafood is a common cause of anaphylaxis, and fatal events have been reported (see Table 1), with a rate of anaphylaxis among sensitized patients of about 20%.[20] Shellfish are a nontaxonomic group that includes crustaceans and mollusks, which are invertebrates, unlike fish (see Table 3). The major shellfish allergen has been identified as tropomyosin, an essential protein in muscle contraction, which is a pan-allergen responsible for in vivo and in vitro cross-reactivity between crustaceans (shrimp, crab, crawfish, lobster), insects (cockroaches), arachnids (house dust mites), and different classes of mollusks (Table 2c).[65]

The situation with fish is less certain, with reports of both polysensitization to multiple species (50%–92% of individuals) and monosensitization to a single fish type. The major allergens responsible for cross-reactivity among noncrustacean fish are the muscular parvalbumins (see Table 2c), pan-allergens resistant to thermal and enzymatic degradation.[65] Canned fish, which is cooked for up to 7 hours under pressure, may be less allergenic; however, anaphylaxis related to canned fish has been reported, so this food is not safe for patients with fish-induced anaphylaxis.[20]

Cross-reactivity between crustaceans and fish has been not reported, so affected individuals are usually advised to avoid either fish or crustaceans; however, up to 50% of individuals may be sensitive to both shellfish and fish.[20]

Despite a generalized belief within the medical community, allergies to shellfish do not increase the risk of reaction to intravenous contrast.[66]

## Milk, Egg, and Soy

In the pediatric population, milk and egg allergy are a frequent cause of anaphylactic reactions.[67,68]

Milk is also the third most common food responsible for fatal or near-fatal food-induced anaphylactic reactions (8%–15% cases),[67–69] and appears to be globally one of the most common causes of anaphylaxis in young children (see Table 1).[28,48,70,71] Acute (IgE-mediated) reactions to milk are caused by various milk allergens mainly belonging to the family of caseins and whey proteins (see Table 2a).[72,73] Cooking diminishes the allergenicity of whey proteins, presumably by denaturation of heat-labile proteins, resulting in loss of conformational epitopes. Children reactive to extensively heated milk (but not egg) are at higher risk for systemic reactions treated with epinephrine than those children tolerant to heated milk but reactive to unheated milk, suggesting a possible correlation between sensitivity toward different epitopes in the allergens and severity of reaction.[74] Indeed the importance of sequential epitope recognition in the persistence of cow's milk allergy has been highlighted in several studies.[75–79] Cooking-induced allergen denaturation may explain why many patients allergic to cow's milk tolerate extensively heated milk.[74,80] Similarly, yogurt cultures, which ferment and acidify milk, contain less intact whey protein, therefore individuals with cow's milk allergy exclusively sensitized to whey proteins may tolerate yogurt-based dairy products.[81] However, in children with near-fatal anaphylaxis it is prudent to avoid all forms of milk even in minor quantities. Mammals that are phylogenetically related have quite similar milk protein expression, hence no mammalian milk (ie, goat, donkey, and so forth) is safe for children with anaphylaxis to milk.[81]

Fatal reactions to egg are rare, but have been reported.[22] Food-dependent, exercise-induced anaphylaxis with egg as the trigger has also been reported.[82] Five major allergenic proteins from the egg of the domestic chicken (*Gallus domesticus*) have been identified, and are designated Gal d 1 to Gal d 5. Most of the allergenic egg proteins are found in egg white. Although ovalbumin (OVA) is the most abundant protein in hen's egg white, ovomucoid (OVM) has been shown to be the dominant allergen in egg. Egg-specific IgE molecules that identify sequential or conformational epitopes of OVM and OVA can distinguish different clinical phenotypes of egg allergy. It has been shown that patients with egg allergy with IgE antibodies reacting against sequential epitopes tend to have persistent allergy, whereas those with IgE antibodies primarily to conformational epitopes tend to have transient allergy. Studies have shown that ingestion of raw or undercooked egg may trigger more severe clinical reactions than well-cooked egg.[83] Manufactured food products often contain trace amounts of egg lecithin as emulsifiers, but ingestion of trace amounts of egg lecithin is probably insufficient to elicit allergic reactions.[84]

Although severe soy allergy reactions have been reported, they are quite rare and far less common than milk allergy (see Table 1).[85,86] The specificity of soy allergens is variable and complex. As many as 28 different soy proteins have been recognized as being allergenic; however, only a few are considered major allergens. Gly m 5 and Gly m 6 account for about 30% and 40% of the total seed proteins, respectively, and have been shown to be a potential indicator for severe allergic reactions to soy (see Table 2a).[87] Most individuals with anaphylaxis induced by cow's milk allergy tolerate soy if such patients have no IgE to soy.[81]

Clinical cross-reactivity between peanut and soy, both legumes, is extremely rare despite the high degree of cross-sensitization, and is estimated to be less than 7%.[37,88,89]

## RISK FACTORS

The major risk factor for FIA appears to be food allergy. Indeed the majority of patients with fatal or near-fatal FIA are known to be allergic to the food that caused the anaphylactic reaction.[2,28,67,90] The severity of previous allergic reaction is not predictive of the severity of future allergic reaction, as the experience accumulated with food challenge and reports on fatal FIA seems to indicate.[68,91] Therefore it is not surprising that recent National Institutes of Health (NIH) guidelines for the management of food allergy encourage clinicians to consider prescribing an epinephrine autoinjector for all patients with documented IgE-mediated food allergy reactions, because it is impossible to predict the severity of any subsequent reactions with accuracy.[45] The group at highest risk of FIA are young male children, while among adults women are at higher risk. Overall the group at highest risk for fatal anaphylaxis is young adults.[23,28,29,67,71,92] Among patients with food allergy, those at highest risk[45,67,68,93] are those with a history positive anaphylaxis, those with asthma (risk increases with the severity of asthma),[46,92] those with allergy to peanut, tree nuts, and shellfish, and adolescents.

Several factors can contribute to lower the “threshold” for anaphylaxis, possibly by increasing the allergen uptake (ie, exercise, alcohol, drugs that increase gastric pH) or by enhancing the inflammatory response (ie, febrile illness, asthma exacerbation, or nonsteroidal anti-inflammatory drug use); hence the unpredictability of future reaction.[94]

Higher income, living in an area with low sun exposure, and possible low level of vitamin D may predispose individuals to develop anaphylaxis.[95,96]

## PATHOGENESIS

FIA is a typical IgE-mediated allergic reaction, being immediate, reproducible, and readily diagnosed by detection of food-specific IgE. FIA is initiated by the engagement of allergen-specific IgE antibody with its high-affinity receptor (FcεRI) that is expressed on mast cells and basophils. When a specific antigen binds the IgE linked to the FcεRI it determines a receptor cross-link and consequent release of preformed mediators (histamine, tryptase, carboxypeptidase A, proteoglycans, and some cytokines) and newly synthesized ones (leukotrienes, bradykinins, cytokines including tumor necrosis factor α, and platelet-activating factor [PAF]).[97,98] Ultimately, these mediators cause the characteristic clinical features of anaphylaxis, including vasodilation, angioedema, bronchoconstriction, and increased mucus production (Table 4).[99–101]

Even if initially it was thought that mast cells were the principal effector cells in IgE-mediated acute reaction, further studies have shown that basophils also play a major role in acute food allergy symptoms. Indeed patients with food allergy have higher rates of spontaneous release of histamine from basophils, which normalizes after the offending food has been removed from the diet. Furthermore, normal serum tryptase levels (a specific marker of mast cell activation) in patients with FIA have been reported, suggesting an involvement of histamine release from tryptase-negative cells such as basophils. Moreover, in a peanut anaphylaxis animal model the combined deficiency of mast cells and phagocytes, but not mast cells and basophils, averted nearly all clinical and physiologic signs of anaphylaxis, suggesting that other cells of the innate immune system may play a role in anaphylaxis.[102]

Histamine is one of the major preformed mediators released by mast cells and basophils, and can induce most of the characteristics of anaphylaxis when administered intravenously to humans and laboratory animals (see Table 4).[99] However, even the strongest inhibitors of histamines are not sufficient to block or reverse anaphylaxis, suggesting other mechanism may also be involved.[103,104] In the past few years, PAF has emerged as a major player in the propagation of anaphylaxis. PAF is a preformed mediator released by mast cells, monocytes, and tissue macrophages during anaphylaxis, and is capable of activating mast cells in the lung and peripheral blood but not in the skin.[105] Higher levels of PAF and lower levels of its metabolizing enzyme (PAF acetylhydrolase) have been found by Vadas and colleagues[106,107] to correlate with the severity of the anaphylactic attack. Recently, Arias and colleagues[108] showed that a molecule that blocks PAF prevents severe anaphylactic reactions and, when combined with antihistamines, abolishes nearly all signs of anaphylaxis. In a mouse model of peanut anaphylaxis it has been shown that peanut may contribute to induce anaphylactic shock by causing activation of the complement cascade and relative production of C3a, which stimulates macrophages, basophils, and mast cells to produce PAF and histamine.[109]

Patients with the lowest serum angiotensin-converting enzyme concentrations were also more likely to develop life-threatening pharyngeal edema in peanut-induced FIA, suggesting that this complication may be partly mediated by bradykinins.[50]

The intrinsic properties of the food allergens may contribute to whether the allergen favors allergic immune responses. Indeed, relatively few foods (egg, milk, peanut, tree nuts, fish, shellfish) account for most of the allergic reactions.[110] Characteristics common to major food allergens are that they are water-soluble glycoproteins, are 10 to 70 kDa in size, and are relatively stable to heat, acid, and proteases. To elicit a sustained immune response, the immunogenic molecule should ideally stimulate both T and B cells. The portion of the immunogenic molecule that binds specifically with membrane receptors on T or B cells is called an epitope, which can be sequential or conformational. Sequential epitopes are determined by contiguous amino acids, whereas conformational epitopes contain amino acids from different regions of the protein that are in close proximity because of the folding of the protein. Conformational epitopes can be destroyed with heating or partial hydrolysis, which alters the tertiary structure of the protein, hence they are less stable, heat/enzyme labile, and often cause less severe reactions especially when cooked.[83]

In addition, the presence of immunostimulatory factors in the food may also contribute to such sensitization. For example, the major glycoprotein allergen from peanut, Ara h 1, is not only very stable and resistant to heat-digestive enzyme degradation but also acts as a Th2 adjuvant, due to the expression of a glycan adduct.[111,112]

## DIAGNOSIS

### Clinical

Anaphylaxis remains first and foremost a clinical diagnosis. A good history remains the most powerful tool that physicians have to confirm both a history of FIA and the food trigger. Indeed anaphylaxis occurs soon after food ingestion (see Box 1), and patients themselves often notice the relationship with the eliciting food. However, the patient's own perceptions and knowledge may influence history, so the physician has to ensure correct compilation of the history. Thus a systematic review of all patient's symptoms, patient's diet, and the last meal before the reaction are a highly useful first step. As described in Box 1, anaphylaxis is characterized by a combination of cutaneous, respiratory, cardiovascular, and gastrointestinal factors. The presence of all of these symptoms need to be asked of patients and parents, because patients may only initially remember or mention the more

severe or obvious ones. Reactions of skin and mucosal involvement such as urticaria, angioedema, itch, rhinorrhea, and conjunctivitis present in a high percentage (70%–98%) of patients, especially in young children.[35,48,56,113] However, anaphylaxis without skin or mucosal involvement have been described, and relying solely on skin manifestation may delay the diagnosis and could be fatal for the patient.[68] Perhaps because the gastrointestinal mucosa is the location of exposure in FIA, immediate gastrointestinal hypersensitivity is commonly seen as a manifestation of anaphylaxis.[27,90] Abdominal pain and vomiting is common especially in children, and can be the primary manifestation of anaphylaxis with only minimal involvement of other organs.[23,48,71] Cardiovascular symptoms can rapidly cause the death of the patient, and need to be recognized at an early stage. Close monitoring of blood pressure with the correct cuff size for age is essential in all patients with suspected or ongoing anaphylaxis. However, cardiovascular symptoms are much less common in FIA compared with other types of anaphylaxis, and are rarely found in isolation from respiratory arrest. In infant and preschool children, reactions tend to be less likely to involve the cardiovascular system.[23,48,71] Respiratory manifestation such edema of the glottis and asthma are the primary cause of death in patients with FIA and need to be treated aggressively, especially in asthmatic patients.[67–69]

The time from ingestion of food to the onset of FIA symptoms is usually on the order of minutes, and almost never occurs after 2 hours from ingestion of the triggering foods.[91] In small children timing can help to differentiate between anaphylaxis and food protein–induced enterocolitis (FPIES), a non-IgE–mediated food allergy that typically begins later than 1.5 hours after ingestion.

Additional elements of clinical history can be helpful. Knowing the quantity necessary to trigger a reaction is helpful in evaluating risk of anaphylaxis for trace amounts of foods and the severity of anaphylaxis.

One area of considerable controversy in the literature is the true frequency of biphasic reactions during anaphylaxis. In a biphasic reaction, symptoms of the initial reaction resolve but are followed by new symptoms without any further allergen exposure, and are never more severe than the first manifestation. The true incidence of biphasic reaction and prevention measures is not known. Published reports suggest that biphasic reactions occur in 5% to 28% of anaphylaxis cases, with the highest incidence in FIA. However, in children undergoing oral food challenge (OFC) reactions are extremely rare.[85,114] There is also conflicting evidence about whether administration of steroid or epinephrine can prevent a biphasic reaction.[114]

When history is not convincing, other diseases that may mimic FIA have to be considered (Box 3), and laboratory evaluation in the acute phase may be important. Especially important in the differential diagnosis of FIA are the restaurant syndromes and toxic reactions due to fish intake (see Box 3 and Table 5).

**Box 3**

**Differential diagnosis of food-induced anaphylaxis**

1. Vasovagal reactions
2. Non-IgE–mediated food allergy
    a. FPIES
3. “Flush” syndrome
    a. Carcinoid

- **b.** Postmenopausal
- **c.** Chlorpropamide alcohol
- **d.** Medullary and thyroid carcinoma
- **e.** Autonomic epilepsy

4. "Restaurant syndromes"
   - **a.** Monosodium glutamate
   - **b.** Sulfites
   - **c.** Scombroid
5. Other shock
   - **a.** Hemorrhagic
   - **b.** Cardiac
   - **c.** Endotoxic
   - **d.** Monoclonal gammopathy (paroxysmal hyperpermeability)
6. Syndromes with excessive endogenous production of histamine
   - **a.** Mastocytosis
   - **b.** Urticaria pigmentosa
   - **c.** Basophil leukemia
   - **d.** Promyelocytic acute leukemia
   - **e.** Hydatid cyst
7. Nonorganic syndromes
   - **a.** Panic attack
   - **b.** Munchausen
   - **c.** Vocal cord dysfunction
   - **d.** Hysteric bolus
8. Miscellaneous
   - **a.** Hereditary angioedema
   - **b.** Anaphylaxis due to progesterone
   - **c.** Urticaria vasculitis
   - **d.** Pheochromocytoma
   - **e.** Hyper-IgE syndrome
   - **f.** Neurologic diseases (seizures, stroke)
   - **g.** Pseudoanaphylaxis
   - **h.** Red man syndrome (vancomycin)

## Laboratory Studies

At present, there is no laboratory test that reliably confirms cases of FIA. Indeed histamine and tryptase serum levels are less helpful in FIA than in other types of anaphylaxis. Serum histamine levels are elevated only for 30 to 60 minutes after the onset of reaction, so they are very rarely measured. The most commonly assessed mediator in clinical practice is tryptase, whose blood levels peak 1.5 hours after the onset of symptoms and are measurable for up to 5 hours. However, in FIA tryptase is less commonly elevated than in other types of anaphylaxis.[114] Other laboratory tests may be important in ruling out nonanaphylactic causes of symptoms, as shown in Box 4.

**Box 4**

**Examinations in cases of nonconvincing anaphylaxis**

Blood Tests

Serum histamine (within 1 hour)

Tryptase (within 5 hours)

$CH_{50}$, C1 esterase → Hereditary angioedema

IgA, IgM, IgG immunoelectrophoresis → monoclonal gammopathy

Cardiac enzymes → cardiac ischemia?

Serotonin → carcinoid syndrome?

Urine

Histamine

5-Indoleacetic acid, vanillylmandelic acid, catecholamines → carcinoid syndrome, pheochromocytoma

Other

Blood pressure monitoring

Electrocardiogram

Echocardiogram

Chest radiograph

Liver ultrasound examination

Parasites in feces

Diagnosis of the food allergen that caused anaphylaxis is the most important step in preventing future reaction; hence referral to an allergist is essential for the appropriate workup. Food allergy diagnosis is made primarily on the history and on a few tests done to confirm the history. An SPT examines for the presence of food protein–specific IgEs, having a positive predictive accuracy of about 50% that the patient will react to the tested food. The larger the size of wheal on SPT, the more accurate is such a predictive value; however, negative predictive values are in excess of 95%. Furthermore, the age of the patient, previous exposure reactions to the food, and the type of food change the predictive value for a wheal size. An alternative method to detect food protein–specific IgE is by in vitro methods (FEIA-CAP or “RAST test”). Some clinicians may prefer to use in vitro testing when there is persistent dermatographism (rare) in the few weeks following an anaphylactic shock (ie, mast cell refractory period), severe eczema, or when the patient is on

antihistamines. Indeed in all these conditions skin tests may not be reliable. Similar to SPT, a cutoff value can be developed for predicting 50% to 95% of who will react to foods. SPT or levels of specific IgE give only an indication of the likelihood of clinical reactivity; however, individual results do not provide prognostic information or distinguish between likelihood of mild or severe reaction.[51,76,98,114,115] Recently, peptide microarrays have been developed for large-scale epitope mapping, with small quantities of serum allowing large-scale study to compare levels of IgE and their affinity toward specific epitopes of different allergens.[51,72,73,116–122] So far no single informative epitope that reliably distinguishes between the different phenotypes of milk, egg, or peanut allergy has been identified because of the heterogeneity of epitopes recognized by subjects within the different phenotypes. The number of epitopes recognized, rather than recognition of specific epitopes, might be more predictive of clinical features of food allergy.[15] However, the overlap in the number of epitopes recognized in different clinical group does not allow its clinical use.[51,72,73,116–122]

### Oral Food Challenges

OFC are the key to establishing the identity of specific food triggers. The most rigorous method is double-blinded and placebo-controlled (DBPC), but single-blind (patient) and open challenges can be performed. The least time-intensive procedure is the open challenge. With a previous history of anaphylaxis they are not needed, and they can be very dangerous if history and allergy evaluation are concordant. OFC may be needed years after the anaphylactic reaction has occurred in order to establish the possible development of tolerance, especially in children. In such highly selected cases, they should be performed in the hospital setting with an intensive care unit readily available, and should be started from allergen doses of less than 100 mg of protein.[123]

## TREATMENT

### Epinephrine

Intramuscular injection of epinephrine into the vastus lateralis muscle (lateral thigh) is the life-saving treatment in cases of FIA as well as for all types of anaphylactic reactions. All other treatments such as antihistamines, glucocorticoids, and β-agonists, either alone or in combination, are to be considered ancillary in the treatment of anaphylaxis.

In animal models and in humans, injected epinephrine rapidly reverses anaphylaxis, because is an agonist for the adrenergic receptors (α-1, β-1, β-2).[3,67–69,101,103,114,124] In humans, prospective controlled studies on the use of epinephrine during an acute anaphylactic event have not been done, for obvious ethical reasons; however, retrospective studies have shown convincingly that lack of treatment with epinephrine within a few minutes of the beginning of the symptoms is one of the major risk factors for death from FIA.

There is wide agreement that the optimal method of administration of epinephrine is intramuscular, as subcutaneous injection can lead to local vasoconstriction with possible delayed absorption, and decreased peak levels, while the intravenous route lacks an established dosing regimen, is prone to dosing errors, is difficult to perform rapidly, and can induce lethal arrhythmias.

In cases of profound hypotension or failure to respond to intramuscular epinephrine, intraventricular epinephrine should be used while patients have continuous cardiac monitoring in place.[15,23,48,70,115,120,121,125]

The recommended dose for intramuscular epinephrine injection 1:1000 solution (1 mg/mL) is from 0.01 mg/kg to a maximum of 0.3 mg in children and 0.5 mg in adults. Commercially available prefilled syringes for autoinjection are available in strengths of 0.15 and 0.3 mg.

The most recent guidelines from the NIH recommend switching to the 0.3-mg dose at approximately 25 kg (55 lbs) because of the risk of underdosing above this weight if the smaller dosage is used, even if the package instruction recommends the switch at 30 kg. For children who have asthma or other additional risk factors for fatality from anaphylaxis, switching to the higher dose at a lower weight might be considered. The same guidelines recommend the use of the 0.15-mg auto-injector for patients weighing down to 10 kg. In practice, self-injected epinephrine is prescribed even to smaller otherwise healthy infants, because the risks of overdose with autoinjector use is weighed against the demonstrated difficulty encountered by professionals and nonprofessionals with correctly and promptly drawing up a correct-for-age dose of epinephrine into the syringe. The dose may be repeated at intervals of at least 5 minutes if necessary. World Health Organization (WHO) and Anaphylaxis Canada recommend the availability of 1 dose for every 10 to 20 minutes of travel time to a medical emergency facility, and most guidelines recommend the prescription of 2 doses, as in some cases of anaphylaxis one dose may not be enough.[15,23,48,70,115,120,121,125]

Ideally epinephrine autoinjectors are prescribed on discharge from the emergency room after management of anaphylaxis, or following consultation with a pediatrician or pediatric allergist for suspected food allergy. Despite universal recommendations for the use of epinephrine in anaphylaxis, it is actually uncommonly used in home or emergency room treatment of FIA, and most patients with a history of anaphylaxis will discontinue its use within a few years of the anaphylactic episode, perhaps because patients perceive epinephrine as a dangerous medication or patients and practitioners do not think their symptoms are severe enough to merit epinephrine.[68,114,126] In general, it is recommended that epinephrine be given to food-allergic children at the first signs of a systemic reaction, before life-threatening symptoms such as respiratory distress and hypotension develop, as those symptoms may be harder to reverse and may cause permanent damage to the subjects (cerebral hypoxia). Patient with history of life-threatening reaction have to be instructed to recognize the early symptoms of anaphylaxis (Box 5).

**Box 5**

**Early symptoms of anaphylaxis**

Itch of scalp, palms of hands, or soles of feet extending to acoustic meatus, lips, genital area

Diffuse erythema

Oral or pharyngeal itch

Nasal congestion

Subjective sensation of throat tightness

Changes in the tone of voice: hoarseness

Swelling of lips and tongue

## H1 Antihistamines

H1 antihistamines are inverse agonists at the H1 histamine receptor in that that they bind the receptor in its inactive state, preventing signaling through the receptor. H1 antihistamines are the most commonly used medications in the treatment of anaphylactic episodes both in the hospital and outpatient setting. Although H1 antihistamines decrease skin symptoms (itch, flush, urticaria) and nasal symptoms (rhinorrhea, congestion), they do not prevent or

treat life-threatening manifestations of anaphylaxis such as airway obstruction, wheeze, or hypotension. Hence they are considered secondary medications for the treatment of anaphylaxis, and their use in the outpatient setting is controversial. Indeed, even if the most recent practice parameter suggests that they may have utility for "control of cutaneous and cardiovascular manifestations" of anaphylaxis, others recommend against their use because of their potential for both delaying life-saving therapy and causing dangerous side effects such sedation (which could make assessment of the progression of anaphylaxis difficult), neurotoxicity such as seizure, and potentially fatal QT prolongation. If antihistamines are used for children, the dose should be 1 mg/kg up to 50 mg, whereas for adults the dose is 25 to 50 mg, whether given intramuscularly, intraventricularly, or by mouth.[3,68,114]

### H2 Antihistamines

Like H1 antihistamines, H2 antihistamines are inverse agonists that preferentially bind to the inactive state of the receptor. The H2 receptor participates in the anaphylactic response, and even if theoretically blockade of this receptor may have an additive effect with the H1 antihistamines, their efficacy has been only suggested and not proved in cases of any kind of anaphylaxis including FIA. The most recent United States practice parameter for anaphylaxis states "an H2 antagonist added to the H1 antagonist may be helpful in the management of anaphylaxis." If used, ranitidine can be given intraventricularly or intramuscularly at 1 mg/kg in children and 12.5 to 50 mg in adults. Infusion of cimetidine should be done slowly to prevent hypotension.[3,68,114]

### Glucocorticoids

Like antihistamines, the efficacy of glucocorticoids in the treatment of anaphylaxis has not been proved in a randomized, double-blind, placebo-controlled trial, but is widely used in the emergency room and outpatient settings. The onset of action of glucocorticoids is slow, occurring hours after administration, and it is well known that pretreatment for 48 hours with glucocorticoids prevents the late-phase response to allergen challenge; it does not affect the acute-phase response. Glucocorticoids can cause significant adverse events if used long term, but short-term use is generally much safer and mostly limited to mood changes, increase in peripheral blood concentration of glucose, and occasional high blood pressure. Their use may reduce the biphasic reaction but, given the rarity of such reactions, a double-blind placebo-controlled study to prove such an effect is difficult to realize.[3,68,114]

### β-Agonists

β-Agonists may be used as an adjunct to epinephrine for the treatment of wheeze, but should not replace epinephrine because they lack the widespread effects of epinephrine and do not effectively treat angioedema.[3,68,114]

### Others

β-Blockers are associated with anaphylaxis that is difficult to treat in adults. If the patient is taking β-blockers, glucagon can be useful.

Additional potentially life-saving supportive measures include placing the patient in a supine position to maximize cardiac return, administering oxygen if needed, and giving intraventricular fluids if hypotension develops.[3,68,114]

## PREVENTION OF ANAPHYLAXIS AND FATAL ANAPHYLAXIS

Until recently the only proven prevention strategy for FIA has been food elimination in subjects with a history of food allergy to a specific food. To facilitate allergen avoidance in the United States the Food Allergen Labeling and Consumer Protection Act was enacted in

2005 to publish help on food labels to prevent accidental exposure to foods for the 8 most common food allergens (milk, egg, peanut, tree nuts, fish, shellfish, soy, and wheat). Similar legislation has been introduced in Japan, Europe, and Australia. All patients at risk for anaphylaxis must be trained to identify relevant food allergens on the labels, and written instruction should be given.[115,124]

Even if a correct diagnosis is made, accidental exposure and recurrence of anaphylaxis induced by the same or different foods are frequent in subjects with FIA. Indeed most patients who died of anaphylaxis knew they were allergic to the food that eventually killed them.[67–69,126] All patients with a history of anaphylaxis or at high risk of anaphylaxis should be taught to recognize early symptoms (see Box 5) and be taught the use of autoinjectable epinephrine with written and verbal instruction immediately after the diagnosis of anaphylaxis is made. All patients at risk of anaphylaxis should leave the clinician's office or the hospital with a written plan indicating clearly the food allergies, the dose of epinephrine to be used, and symptoms that should induce epinephrine use.[1,3]

In a recent report, Pumphrey and Gowland[68] noted that more than half FIA-related deaths occurred in patients whose previous reactions had been so mild that it was unlikely that a doctor would have recommended they should carry self-injectable epinephrine. Indeed recent NIH guidelines for food allergy management encourage clinicians to consider prescribing an epinephrine autoinjector for all patients with food allergy having IgE-mediated reactions, based on the fact that it is impossible to predict the severity of any subsequent reactions with accuracy (Box 6)[45] WHO and Anaphylaxis Canada recommend the availability of 1 dose for every 10 to 20 minutes of travel time to a medical emergency facility.

**Box 6**

**Epinephrine autoinjector (or 2-dose prescription) NIH food allergy guidelines 2010**

All patients experiencing anaphylaxis should be provided directly with an epinephrine autoinjector or, if this is not possible, with a prescription (recommended prescription is for 2 doses of epinephrine), and advised to fill it immediately.

Other patients who should be prescribed an epinephrine autoinjector include:

1. Patients with a history of a prior systemic allergic reaction
2. Patients with food allergy and asthma
3. Patients with a known food allergy to peanut, tree nuts, fish, and crustacean shellfish (ie, allergens known to be associated with more fatal and near-fatal allergic reactions)
4. In addition, consideration should be given to prescribing an epinephrine autoinjector for all patients with food allergy having IgE-mediated reactions because it is impossible to predict the severity of any subsequent reactions with accuracy

*Data from* Boyce JA, Assa'ad A, Burks AW, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol 2010;126(Suppl 6):S1–58.

More recently oral immunotherapy has been proved to be effective in the short term in preventing anaphylaxis attributable to several foods such as milk, hazelnut, and eggs.[127]

Moreover, a unique combination of Chinese herbs, Zhi Fu Zi (Radix Lateralis Aconiti Carmichaeli Praeparata) and Xi Xin (Herba Asari), could also help with the induction of tolerance.[127]

## FOOD-DEPENDENT EXERCISE-INDUCED ANAPHYLAXIS

Exercise-induced anaphylaxis (EIA) is a particular type of anaphylaxis that occurs while performing intense exercise. It is estimated that 5% to 15% of anaphylactic episodes are caused by or are associated with exercise. EIA may occur independently of food ingestion (pure EIA) or in close time relationship with food ingestion (30% to 50% of EIA).[128] Food-dependent exercise-induced anaphylaxis (FDEIA) is diagnosed when anaphylactic episodes occur only when exercise follows food ingestion (up to 6 hours, usually within 1–3 hours), and is otherwise well tolerated. The most common foods reported in adults with FDEIA include crustacean shellfish, celery, cheese, tomatoes, and alcohol. In adults with FDEIA about 75% are female. Fifty percent report seasonal allergic rhinitis and 19% report asthma.[129] In children, FDEIA may be more frequent in teenage males and in association with wheat allergy.[130] Water-insoluble omega-5-gliadin (Tri a 19) has been identified as a major allergen in Finnish subjects with FDEIA.[40,41] However, a long list of foods including many vegetables (ie, celery), cereals, milk, eggs, and meat has been reported as a cause of FDEIA.[14,131,132] Clinical presentations of FDEIA include pruritus, urticaria, angioedema, flushing, shortness of breath, dysphagia, chest tightness, syncope, profuse sweating, headache, nausea, diarrhea, colicky abdominal pain, throat closing, and hoarseness.[128]

FDEIA can manifest in teen years or adulthood in subjects without any prior history of food allergy. In patients with suspected FDEIA, SPT to foods ingested prior to the exercise can identify the offending food, although negative allergy test results do not rule out FDEIA. Suspected FDEIA is one of the few situations for which a large panel of food skin tests needs to be performed if the meal eaten before the exercise included many ingredients. A food challenge followed by exercise on a treadmill may be necessary to confirm the diagnosis in selected cases. Food challenges in FDEIA are a high-risk procedure, as the dose of food and intensity of exercise required to induce a reaction cannot be well controlled, and severe anaphylactic reactions have been reported.[133] A positive challenge provides definitive diagnosis. However, a negative challenge does not rule out FDEIA because the intensity of exercise might have not been well reproduced, or because of the potential necessary association of additional cofactors, such as pollen exposure or concomitant ingestions of drugs such as nonsteroidal anti-inflammatory drugs or, in women, the concomitant presence of menses.[133] Management of FDEIA includes prompt treatment with epinephrine during an acute episode.

To prevent FDEIA, the following strategies are recommended: (1) avoidance of exercise within 4 to 6 hours following the incriminated food ingestion; (2) avoidance of exercising alone or in hot or humid weather or during pollen allergy season; and (3) carrying emergency medications. Patients with FDEIA often have environmental allergies to pollens, and one of the major challenges is to distinguish between FDEIA and exercise-induced asthma especially in those subjects in whom FDEIA is associated with dyspnea or wheezing. Elevated serum tryptase levels have been reported in subjects with FDEIA following an acute episode, and can be helpful in determining the diagnosis.[128]

## SUMMARY

FIA is a serious allergic reaction that may cause death rapidly in otherwise healthy individuals. There is no universal agreement on its definition or criteria for diagnosis.

Food is one of the most common causes of anaphylaxis, with most surveys indicating that food-induced reactions account for 30% to 50% of anaphylaxis cases in North America, Europe, Asia, and Australia, with up to 81% of anaphylaxis occurring in children.

Although a wide range of foods has been reported as a cause of FIA, the most commonly implicated foods worldwide are peanut, tree nuts, milk, egg, sesame seeds, fish, and shellfish, in both adults and children.

Allergens and patients' characteristics are probably important in determining an anaphylactic reaction. The major risk factor for FIA appears to be food allergy, in particular for those with asthma with allergy to peanut, tree nuts, and shellfish, adolescents, and young adults. The severity of previous allergic reaction is not predictive of the severity of any future allergic reaction. The only life-saving treatment for anaphylaxis is allergen avoidance and intramuscular epinephrine injection if an anaphylactic event occurs. All patients at risk for FIA should be provided with an anaphylaxis plan that indicates allergen and treatment modalities, as well as with self-injectable epinephrine.

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**Table 1**

Most common cause of FIA

| Food | Type of Anaphylaxis | % | Country | Refs. | Age | Food | Type of Anaphylaxis | % | Country | Refs. | Age |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Peanut | Fatal | 42 | Australia | 38 | Peds and adults | Egg | Fatal | 2 | UK | 68 | Peds and adults |
| | | 62 | USA | 69 | Peds and adults | | ED/Hospital | 9 | Australia | 38 | Peds and adults |
| | | 53 | USA | 67 | Peds and adults | | | 9 | Israel | 70 | Peds |
| | | 19 | UK | 68 | Peds and adults | | | 2 | USA | 48 | Peds |
| | ED/Hospital | 23 | Australia | 38 | Peds and adults | | Registry | 7 | Germany | 47 | Peds |
| | | 0 | Israel | 70 | Peds | | Allergy office | 11 | Italy | 71 | Peds |
| | | 10 | Italy | 23 | Adults | | | 7 | Spain | 28 | Peds |
| | | 22 | USA | 48 | Peds | | | 0 | Italy | 29 | Adults |
| | Registry | 22 | Germany | 47 | Peds | Vegetables | Fatal | 2 | UK | 68 | Peds and adults |
| | Allergy office | 0 | Italy | 71 | Peds | | ED/Hospital | | | | |
| | | 0 | Spain | 28 | Peds | | Registry | 10 | | 47 | Peds |
| | | 3 | Italy | 29 | Adults | | Allergy office | 4 | Italy | 71 | |
| Tree nuts | Fatal | 28 | USA | 69 | Peds and adults | | | 3 | Italy | 29 | Adults |
| | | 25 | USA | 67 | Peds and adults | Fruit | Fatal/near fatal | | | | |
| | | 19 | UK | 68 | Peds and adults | | ED/Hospital | 13 | Israel | 70 | Peds |
| | ED/Hospital | 16 | Australia | 38 | Peds and adults | | | 8 | USA | 48 | Peds |
| | | 23 | Israel | 70 | Peds | | Registry | 4 | Germany | 47 | Peds |
| | | 18 | USA | 48 | Peds | | Allergy office | 11 | Italy | 71 | Peds |
| | Registry | 25 | Germany | 47 | Peds | | | 8 | Spain | 28 | Peds |
| | Allergy office | 13 | Italy | 71 | Peds | | | 31 | Italy | 29 | Adults |
| | | 16 | Spain | 28 | Peds | Cereal | Fatal/near fatal | | | | |
| | | 19 | Italy | 29 | Adults | | ED/Hospital | | | | |
| Fish | Fatal | 14 | Australia | 38 | Peds and adults | | Registry | 2 | Germany | 47 | Peds |
| Shellfish | | 3 | USA | 69 | Peds and adults | | Allergy office | 5 | Italy | 71 | Peds |
| | | 6 | USA | 67 | Peds and adults | | | 5 | Italy | 29 | Adults |

| Food | Type of Anaphylaxis | % | Country | Refs. | Age | Food | Type of Anaphylaxis | % | Country | Refs. | Age |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 4 | UK | 68 | Peds and adults | Soy | Fatal/near fatal | | | | |
| | ED/Hospital | 34 | Australia | 38 | Peds and adults | | ED/Hospital | 4.5 | Israel | 70 | Peds |
| | | 30 | Italy | 23 | Adults | | | 10 | Italy | 23 | Adults |
| | | 5 | USA | 48 | Peds | | Registry | 1 | Germany | 47 | Peds |
| | Registry | 5 | Germany | 47 | Peds | | Allergy office | | | | |
| | Allergy office | 30 | Italy | 71 | Peds | | | | | | |
| | | 22 | Spain | 28 | Peds | | | | | | |
| | | 18 | Italy | 29 | Adults | | | | | | |
| Milk | Fatal | 3 | USA | 69 | Peds and adults | | | | | | |
| | | 12 | USA | 67 | Peds and adults | | | | | | |
| | | 12 | UK | 68 | Peds and adults | | | | | | |
| | ED/Hospital | 8 | Australia | 38 | Peds and adults | | | | | | |
| | | 39 | Israel | 70 | Peds | | | | | | |
| | | 0 | Italy | 23 | Adults | | | | | | |
| | | 18 | USA | 48 | Peds | | | | | | |
| | Registry | 9 | Germany | 47 | Peds | | | | | | |
| | Allergy office | 22 | Italy | 71 | Peds | | | | | | |
| | | 47 | Spain | 28 | Peds | | | | | | |
| | | 0 | Italy | 29 | Adults | | | | | | |

*Abbreviations:* ED, emergency department; Peds, pediatric patients.

**Table 2a**

Allergen described in egg, cow's milk, soy, peanut

| Allergen Name | Allergen Common Name | Clinical Relevance | Allergen Name | Allergen Common Name | Clinical Relevance |
|---|---|---|---|---|---|
| Hen's egg (*Gallus domesticus*) | | | Peanut (*Arachis hypogea*) | | |
| Gal d 1 | Ovomucoid | | Ara h 1 | Seed storage proteins | Heat stable |
| Gal d 2 | Ovalbumin | Major allergen | Ara h 2 | Seed storage proteins | Heat stable, associated with anaphylaxis |
| Gal d 3 | Ovotransferrin/conalbumin | | Ara h 3 | Seed storage proteins | |
| Gal d 4 | Lysozyme | | Ara h 4 | Seed storage proteins | |
| Gal d 5 | α-Livetin | Bird-egg syndrome | Ara h 5 | Profilin (Bet v 2 like) | Cross-reactive with other plants; little clinical relevance |
| Cow's milk | | | Ara h 6 | Seed storage proteins | Homology with Ara h 2. Allergy persists |
| *Bos d 8* | α−, α.2-n, β-, γ1, γ2 γs K-casein | Major allergen, heat stable | Ara h 7 | Seed storage proteins | |
| *Bos d 4* | α-Lactalbumin | Major allergen, heat sensitive | Ara h 8 | Bet v 1 family (PR-1 O, Bet v 1 like) | Responsible for cross-reactivity with birch pollen analogues |
| *Bos d 5* | β-Lactoglobulin | Major allergen, heat sensitive | Ara h 9 | LTP | Low prevalence of recognition in USA and north Europe; more common in south Europe |
| *Bos d 7* | Immunoglobulin | | Ara h 10 | Oleosin plant lipid storage bodies | |
| *Bos d 6* | BSA | Cross-reactivity with beef | Ara h 11 | Oleosin plant lipid storage bodies | |
| Soybean (*Glycine max*) | | | | | |
| Gly m 1 | LTP | | | | |
| Gly m 2 | Defensin | | | | |
| Gly m 3 | Profilin | | | | |
| Gly m 4 | Bet v 1 family (PR-1 O, Bet v 1 like) | Cross-reactive with birch/ peanut, mild oropharyngeal reaction | | | |
| Gly m 5 | Vicilin | Severe reaction | | | |
| Gly m 6 | Legumin | Severe reaction | | | |

*Abbreviations:* BSA, bovine serum albumin; LTP, lipid transfer protein.

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**Table 2b**

Allergens described in legumes, tree nuts, and seeds

| Allergen Name | Allergen Common Name | Clinical Relevance | Allergen Name | Allergen Common Name | Clinical Relevance |
|---|---|---|---|---|---|
| Pea (*Pisum sativum*) | | | Sesame | | |
| Pis s 1 | Vicilin | | Ses i 1 | S albumin | |
| Pis s 2 | Convicilin | | Ses i 2 | S albumin | |
| Green bean (*Phaseolus vu/garis*) | | | Ses i 3 | 7S globulin | |
| Pha v 3 | nsLTP type 1 | | Ses i 4 | Oleosin | |
| Hazelnut (*Corylus avellana*) | | | Ses i 5 | Oleosin | |
| Cor a 1 | PR-10 (Bet v 1 homologous) | | Ses i 6 | Basic subunit of 11S globulins | |
| Cor a 2 | Profilin | | Ses i 7 | Basic subunit of 11S globulins | |
| Cor a 8 | PR-14 (LPT) 9 | | Lupine (*Lupinus angustifolius*) | | |
| Cor a 9 | Globulin (11S) | | Lup an 1 | β-Conglutin (vicilin) | |
| Cor a 11 | Vicilin (7S) | | Lentil (*Lens culinaris*) | | |
| Chestnut (*Castanea sativa*) | | | Len c 1 | γ-Vicilin subunit | |
| Cas s 5 | Chitinase Ib | | Len c 2 | Seed specific | |
| Cas s 8 | PR-14 (LPT) | Oral allergy syndrome | Len c 3 | nsLTP type 1 | |
| Brazil nut | | | Cashew (*Anacardium occidentale*) | | |
| Ber e 1 | Albumin (2S) | Anaphylaxis | Ana o 1 | Vicilin (7S) | |
| Ber e 2 | Legumin (11S) | Anaphylaxis | Ana o 2 | Legumin (11S) | |
| | | | Walnut (*Juglans regia*) | | |
| | | | Jug r 1 | Albumin (2S) | |
| | | | Jug r 2 | Vicilin (7S) | |
| | | | Jug r 3 | PR-14 (LTP) | |
| | | | Jug r 4 | Legumin (11S) | |

## Table 2c

Allergens in seafood

| Allergen Name | Allergen Common Name | Clinical Relevance |
|---|---|---|
| Fish | | |
| Baltic cod (*Gadus callarias*), Atlantic cod (*Gadus morhua*), Atlantic salmon (*Salmo salar*), edible frog (*Rana esculenta*) | | |
| Gad c 1 | Parvalbumin | Anaphylaxis cross-reactivity among multiple fish |
| Gad m 1 | | |
| Sal s 1 | | |
| Ran e 1 | | |
| Shellfish | | |
| Greasyback shrimp (*Metapenaeus ensis*), brown shrimp (*Penaeus aztecus*), black tiger shrimp (*Penaeus monodon*), shrimp (*Penaeus indicus*), Crab (*Charybdis feriatus*), lobster (*Homarus americanus*, *Panulirus stimpsoni*), squid (*Todarodes pacificus*), Snail (*Helix aspera*), abalone (*Haliotis midae*) | | |
| Met e 1 | Tropomyosin | Anaphylaxis cross-reaction with multiple shellfish and with house dust mite |
| Pen a 1 | | |
| Pen m 1 | | |
| Pen i 1 | | |
| Cha f 1 | | |
| Hom a 1 | | |
| Pan s 1 | | |
| Tod p 1 | | |
| Hel as 1 | | |
| Hal m 1 | | |
| Shrimp (*Penaeus indicus*) | | |
| | Myosin light chain | Anaphylaxis |
| Black tiger shrimp (*Penaeus monodon*), shrimp (*Penaeus indicus*) | | |
| | Sarcoplasmic calcium- binding protein | |
| Black tiger shrimp (*Penaeus monodon*) | | |

## Table 3

Family of most common allergenic foods: peanut, tree nuts, and seafood

| Family | Species | Common Name | Common Cause of Anaphylaxis | Uncommon Cause of Anaphylaxis |
|---|---|---|---|---|
| Leguminoseae | *Arachis hypogea* | Peanut | + | |
| Betulaceae | *Corylus avellana* | Hazelnut | + | |
| Anacardiaceae | *Anacardium occidentale* | Cashew | + | |
| | *Pistacia vera* | Pistachio | + | |
| Juglandaceae | *Juglans regia* | Walnut | + | |
| | *Carya illinoinensis* | Pecan nut | | + |
| Rosaceae | *Prunus dulcis* | Almond | | + |
| Lecythidaceae | *Bertholletia excelsa* | Brazil nut | + | |
| Fagaceae | *Castanea sativa* | Chestnut | | + |
| Pinaceae | *Pinus pinea* | Pine nut | | + |
| Proteaceae | *Macadamia intergrifolia* | Macadamia nut | | + |
| Palmaceae | *Cocos nucifera* | Coconut | | + |
| Arthropods | Crustaceans | Crab, rock lobster, prawn, shrimp Shellfish | + | |
| Mollusks | Gastropods | Abalone, snail, whelk | | + |
| | Bivalves | Clam, oyster, scallop, mussel, cockles | | + |
| | Cephalopods | Squid (cuttlefish), octopus | | + |
| Chordate | Teleosts | Tuna, salmon, carp, trout | + | + |

*Data from* Lopata AL, O'Hehir RE, Lehrer SB. Shellfish allergy. Clin Exp Allergy 2010;40(6):850–8; and Crespo JF, James JM, Fernandez-Rodriguez C, et al. Food allergy: nuts and tree nuts. British J Nutr 2006;96(Suppl 2):S95–102.

## Table 4

Mediators involved in anaphylaxis

| Mediators | Effects | Clinical Manifestation |
|---|---|---|
| Histamine | Agonist of H1 and H2 receptors, which causes increase in the vascular permeability, vasodilation, contraction of smooth muscle cells, increase in exocrine gland secretion, and irritation of sensory nerves | Urticaria, angioedema, asthma, hypotension, abdominal cramps, diarrhea |
| Lipooxygenase pathway products<br>$LTB_4$<br>$LTC_4$<br>$LTD_4$ | Chemotaxis<br>Contraction of smooth muscle cells, increase in vascular permeability, increase in exocrine gland secretion (goblet cells) | Biphasic reaction, asthma, hypotension |
| Cyclooxygenase<br>$PGD_2$<br>$PGF_{2a}$<br>$TXA_2$ | Vasodilation, contraction of smooth muscle cells, coronary vasoconstriction, increase in exocrine gland secretion (goblet cells) | Asthma, hypotension, heart ischemia |
| PAF | Induction of arachidonic acid metabolites | Asthma, hypotension |
| Chemotactic factors for eosinophils and neutrophils | Tissue infiltration and activation of eosinophils and neutrophils | Possible role in biphasic or prolonged reactions |
| Tryptase | Activates complement through $C_3$<br>Cut fibrinogen<br>Activates kallikrein | No clear physiologic role |
| Kininogenase of mast cells and basophil kallikrein | Activation of contact system, release of kinins | No clear physiologic role |
| Chymase | Degrades neuropeptides<br>Conversion of angiotensin I to II | Hypotension and inhibition of neuropeptides |
| Heparin | Inhibition of coagulation, plasmin, kallikrein and complement | Possible anti-inflammatory role |

*Abbreviations:* LTB, leukotriene B; LTC, leukotriene C; LTD, leukotriene D; PAF, platelet-activating factor; PGD, prostaglandin D; PGF, prostaglandin F; TXA, thromboxane A.

## Table 5

Adverse reactions to seafood generated by different triggers

| | Symptoms | Time of Reaction |
|---|---|---|
| **Bacteria** | | |
| *Aeromonas*, *Listeria*, *Salmonella*, *Vibrio*, *Klebsiella pneumoniae*, *Proteus morganii* | Cutaneous, gastrointestinal, and neurologic (headache) | Minutes to several hours |
| Viruses | | |
| Rotavirus, astrovirus, hepatitis A, small round viruses, etc | Gastrointestinal | Hours |
| Parasites | | |
| Anisakis | Respiratory distress | Minutes to several hours |
| Toxins | | |
| Algae toxins | | |