

Advances in Food-Induced Anaphylaxis

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Key Points This article is part of the Topical Collection on *Anaphylaxis*

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Key Points

1. Food-induced anaphylaxis is a critical clinical situation that requires an accurate diagnosis and a prompt intervention.
2. Epinephrine (Adrenaline) is the first-line treatment medication along with several support measures.
3. Long-term management includes education and training of the patients, their family and the community in order to avoid recurrent episodes of this life-threatening event.

Opinion statement

Anaphylaxis is a potentially life-threatening severe systemic reaction and food allergy is one of its most frequent causes. Diagnosis of food-induced anaphylaxis requires diagnostic criteria for anaphylaxis based on clinical features and a comprehensive history. Adrenaline is a first-line treatment along with support measures. Epinephrine (adrenaline) is the first choice drug in anaphylaxis because it is the only medication that has been proved to reduce hospitalization and death. Long-term treatment based on an accurate identification of the anaphylaxis trigger, a clear education and training of the patients, their family and the community, under the coordination of a trained allergist, is strongly recommended in order to avoid future events.

Introduction

Anaphylaxis is defined as “a serious life-threatening generalized or systemic hypersensitivity reaction” [1•]. It usually occurs suddenly after contact with an inducing substance. Food allergy is one of the most frequent

anaphylaxis causes. These reactions are mediated by mast cells and circulating basophils, through IgE attached to its surface. A previous sensitization phase to the food is required. On re-exposure to the antigen, IgE

cross-linking on the surface of mast cells and basophils results in the acute release of preformed and newly synthesized mediators, with rapid development of signs and symptoms. Hypersensitivity signs and symptoms develop minutes to 2 h after ingesting the culprit food [2].

Epidemiology

The incidence of anaphylaxis in Europe and the USA has been estimated to range from 3 to 300 per 100,000 persons/year [3]. The lifetime prevalence was estimated between 0.05 and 2 % [4]. As anaphylaxis is an acute condition with long asymptomatic periods, incidence could be an adequate measure of frequency. In a phone survey in the EEUU in adults published by Wood et al., the cumulative prevalence of probable anaphylaxis was 5.1 %, and 1.6 % required a visit to the hospital and were life-threatening [5]. It seems that the incidence of anaphylaxis has increased in the UK, the USA and Australia [6–9]. In contrast, a time trend analysis in the USA showed that the number of ED visits for food anaphylaxis has been stable over time from 2001 to 2009 [9].

Mulla et al. [10] did not find an increase in hospital discharges related to anaphylaxis in Florida, but they confirmed this increase in New York State, suggesting that latitude may have an effect on anaphylaxis. The increased anaphylaxis discharge rate was noted only among young people in New York State (7 % annual increase) while in adults there was a 2 % annual increase. A similar increment was not observed in Florida, which has more hours of sunlight. The effects of sunlight are more commonly observed in the pediatric population and in food anaphylaxis. Another study performed in children in the USA [11] showed that the greatest differences in admissions to the emergency department between northern and southern states were for food anaphylaxis. A study in pediatric hospitals in the USA found that the incidence of food-induced anaphylaxis was 0.31 versus 0.17 per 1000 encounters in the north and south respectively (relative risk 1.81) [12]. In a recent paper from Korea, Kim et al. [13] studied 2814 patients with food-induced anaphylaxis (FIA) and 15,367 people with available serum vitamin D measurements. Differences in FIA incidence and vitamin D levels between regions with low and high solar radiation were found; in the region with lower radiation patients presented more FIA and a lower vitamin D level. A recent systematic review of food allergy in Europe identified a point prevalence of 5.9 %. In contrast, food challenge confirmed that prevalence of food allergy (FA) was around 0.9 % [14].

The youngest children (0–4 years old) presented the highest hospital admission rates for food-induced anaphylaxis. The rate of food-induced anaphylaxis in the groups 5–14 years and 15–29 years is increasing. [15]. According to a recent meta-analysis, the incidence of food-induced anaphylaxis is 0.14 per 100 person-years at all ages, and up to 7 per 100 person-years in the youngest children (0–4 years old) [16].

Risk factors

Risk factors for food-induced anaphylaxis are poorly understood. Fatalities have been linked to peanut or tree nut allergy, presence of asthma (particularly severe

or poorly controlled asthma), delay or no administration of epinephrine, upright (rather than supine) position during a reaction with hypotension, and age, with teenagers and young adults at highest risk (related to age-associated risk-taking behavior?). For example, in patients who presented severe anaphylaxis during food oral immunotherapy studies, risk factors included lack of compliance with asthma control medications, uncontrolled asthma, and being a teenager, fasting, exercise, denial of symptoms, and delay in looking for help [17].

Teenagers frequently present risk-taking behavior with disease denial or non-compliance with treatment (e.g., not carrying an epinephrine auto-injector). Restrain from eating certain foods is difficult for them [18]. Elderly patients with cardiovascular and pulmonary co-morbidities presented more hospitalizations, prolonged hospital stays and fatalities [19, 20•].

Most cases of fatal food anaphylactic reactions are preceded by prior reactions. In a longitudinal study of 80 children with 116 systemic food allergy reactions seen in the Emergency Department, Vetander et al. confirmed that the severity of reactions is variable, and it is difficult to predict severity of subsequent reactions [2, 21]. However, a history of anaphylaxis is a risk factor for fatal food severe allergic reactions [22, 23].

In food dependent, exercise-induced anaphylaxis (FDEIA) exercise is a co-factor, but the ingestion of some food with alcohol or medications such as nonsteroidal anti-inflammatory drugs seems to increase food absorption, inducing more severe reactions. In a recent published study, Brockow et al. describe oral gluten flour challenge in 16 patients that presented wheat-dependent exercise-induced anaphylaxis (WDEIA). They tried to establish the amount of gluten required to induce symptoms, and correlated these results with allergologic parameters and plasma gliadin levels. Oral food challenges (OFCs) with increasing amounts of gluten alone, or combined with cofactors, were performed. The cofactors acetyl salicylic acid plus alcohol and exercise increased plasma gliadin levels. In some patients, symptoms developed without exercise [24].

Specific triggers

The most frequent anaphylaxis inducers include foods, drugs, and stinging insects; and their relative importance varies with age and region studied. Food allergy is the most frequent cause of anaphylaxis in children, teenagers and young adults [25]. In a study in adults with new-onset food allergy, the disease usually began among 10 and 30 years old; almost half of the patients presented anaphylaxis. Fish, shellfish, soy, tree nuts, and peanuts were the most frequent inducers, but many other foods were implicated [26]. A variety of other foods, including egg, wheat, sesame, food additives, and spices, have also been associated with anaphylactic reactions [2].

For young children, egg and cow's milk are very common food allergy triggers. Although 3 out of 4 children with cow milk allergy tolerate milk in baked forms, those who are reactive to baked milk presented a higher risk of severe and protracted anaphylaxis [27].

Grabenhenrich et al. recently published data from the European Anaphylaxis Registry. Between July 2007 and March 2015, 1970 anaphylaxis patients younger than 18 years old were described. Foods were the most frequent triggers (1291 patients). Until 6 years old, foods were the predominating elicitors reported (88 %). Cow's milk and hen's egg were the most frequent elicitors

reported in the first 2 years. Most of the reactions to cashew and hazelnut occurred in the preschool-aged children. Peanut was an elicitor for anaphylaxis from infancy to young adulthood [28].

Within the last decade, the development of antibodies to a carbohydrate moiety on proteins inducing anaphylactic and hypersensitivity reactions were described. A novel IgE antibody against a mammalian oligosaccharide epitope, galactose- α -1,3-galactose ("alpha-gal") was identified, which is related to hypersensitivity reactions to cetuximab, a chimeric epidermal growth factor receptor inhibitor that is being used to treat cancer. This reaction appeared during the first infusion. Alpha-gal is part of the heavy chain of cetuximab. Bites from the lone star tick were linked to the presence of IgE to alpha-gal. Specific IgE to alpha-gal increased following documented tick bites and staining of the gastrointestinal tract of *Ixodes ricinus* showed the presence of galactose- α -1,3-galactose. Alpha-gal is also a blood group substance of no primate mammals. Some of the affected patients reported hypersensitivity and anaphylactic reactions that began 3–6 h after eating red meat. Since then, beef, lamb, and pork have been shown to contain the alpha-gal allergen and to induce such delayed anaphylaxis. The delay is likely due to the time it takes for antigen digestion and/or processing. This specific IgE has been demonstrated in adults and in children with this entity [29].

Diagnosis

The diagnosis of food-induced anaphylaxis requires diagnostic criteria for anaphylaxis. Physical examination is usually not helpful, unless the examination is performed during an acute reaction. However, findings of other allergic diseases may help guide toward the diagnosis [19].

The diagnosis of FIA should be considered when some typical skin symptoms (e.g., hives, angioedema) and/or respiratory (wheezing, dyspnea) and/or hypotension with associated symptoms (hypotonia, syncope) are present shortly after food ingestion (from minutes to several hours) [2]. Anaphylaxis is a protean condition as it can occur without mucocutaneous involvement, with the presence of two of the following: cardiovascular, respiratory and/or gastrointestinal symptoms arising shortly after exposure to a potential inciting agent. Circulatory collapse and complete airway obstruction can be fatal. Up to 90 % of anaphylaxis patients have urticaria/angioedema [30].

Children with food-induced anaphylaxis present more frequent respiratory and less frequently cardiovascular involvement than adults. Fatality is mostly due to respiratory compromise in children versus cardiovascular collapse in adults [31]. In infants and very young children, cutaneous, GI, and respiratory symptoms are most common. Usually 80–90 % of patients with anaphylaxis have the characteristic cutaneous symptoms (e.g., urticaria, angioedema). In a recently published anaphylaxis registry study from Europe done in patients younger than 18 years, most common symptoms during the first decade of life were vomiting and cough, whereas later in life subjective symptoms (nausea, throat tightness, and dizziness) were prevalent. The skin was involved in 92 %, and the respiratory tract in 80 % of the children. Cardiac and circulatory symptoms were less frequent (41 %) and dizziness, hypotension, and collapse predominated in adolescence [28].

Initially, symptoms may present as urticaria or vomiting. Progression of symptoms to include other organ systems should be monitored with caution, as severe anaphylaxis can take place in a few minutes. The lack of cutaneous symptoms can cause a delay in recognition and treatment. It is important to recognize subtle symptoms of anaphylaxis, such as cough or voice changes (Table 1). [19].

The history is of paramount importance for identifying the culprit food. This goal can be difficult when multiple foods are involved. Timing of the reaction and ingredient information is crucial to identify the culprit food. In the context of a suggestive history, in vivo or in vitro tests are helpful for confirming the diagnosis.

Skin testing

Skin prick tests (SPT) are useful to demonstrate specific IgE to food purified extracts or fresh foods by means of a lancet. A positive result should be considered if wheal size is at least 3 mm or more after 15–20 min of puncture [19, 32]. When commercial extracts are not available, fresh products (particularly fruits, vegetables and milk) are preferred. Although skin tests have high sensitivity and low specificity, they are simple and cheap tests to detect sensitization but not necessarily true allergy [32]. This testing can give false negative results in children less than 4 to 6 months of age or if histamine blocking medications are being taken [19].

SPT should be carried out only for doubtful food allergens, and results must be compared with patient's history in order to reduce overdiagnosis and excessive dietary restrictions. Therefore, extensive panel testing should be avoided. When a patient has negative SPT, other diagnostic tests, such as serum sIgE measurement and/or oral food challenges (OFCs) should be carried out before the introduction of the suspected food into the diet [33].

Table 1. Clinical features of food-induced anaphylaxis

- 1- Onset of symptoms from minutes to several hours after culprit food ingestion.
- 2- Up to 90 % of patients have cutaneous and/or mucosal compromise (e.g., generalized hives, pruritus, swollen lips-tongue-uvula)
- 3- Respiratory involvement (cough, voice changes, rhinorrhea, nasal congestion, dyspnea, bronchospasm, stridor, hypoxemia, reduced PEF) in 80 % of children and main cause of fatality in this age group. Risk of death is higher in asthmatics. Adults have less respiratory compromise than children (45 %).
- 4- Hypotension with associated symptoms (hypotonia, syncope, and tachycardia) is less frequent in very young children and dizziness, hypotension and collapse are predominant in adolescents and adults. Fatality is mostly due to cardiovascular collapse in adults.
- 5- Upper gastrointestinal symptoms (nausea, vomiting) are usually present at the start of anaphylaxis whereas lower GI symptoms (diarrhea, abdominal pain) can appear later on.
- 6- Nonspecific symptoms: urinary incontinence, anxiety, headache, confusion, sudden behavioral changes (in young children: crying, becoming irritable and stop playing)

Food allergen specific serum IgE

A careful history is very important for the interpretation of food allergen testing. In order to find causal allergens, serum sIgE testing is an important diagnostic tool that can help to identifying them. There are several testing techniques (e.g., ImmunoCAP™, Immulite™) and positive and negative predictive values have been published [19]. Large panels of food allergen testing are not recommended, because they can result in false positives and unnecessary dietary restrictions of safe foods [19].

sIgE testing can be useful in patients with a high degree of clinical suspicion but negative SPT responses, when SPTs are not possible due to active antihistamine therapy, and in case of moderate-to-severe skin disease, or dermatographism [34]. The clinician should be informed that a negative sIgE do not exclude clinical allergy and other tests, such as SPTs and/or OFC to the suspected food should be justified [34].

Component-resolved diagnostics

Component-resolved diagnostics (CRD) is a promising tool that uses allergenic proteins rather than whole allergens. However, only a small number of foods have been incorporated into CRD testing for example, in the diagnosis of peanut sensitivity [34]. Since the clinical utility of CRD has not been completely clarified, even in peanut sensitivity, it is not routinely recommended in clinical practice [34]. When histamine blocking medications are being taken, this method could be particularly useful.

Oral food challenges (OFC)

Undoubtedly, OFCs should be considered in the IgE-mediated food allergy diagnosis. There are various methods of testing: open (unmasked), single-blind with or without placebo, and double-blind, placebo-controlled food challenges (DBPCFC). Despite the fact that DBPCFC is a labor and time-consuming procedure, it is the gold standard method to diagnose food allergy whereas single-blind and open OFCs are most frequently used in clinical practice. In all types of challenges, graded dosing OFCs are recommended [34].

An open OFC is an unblinded feeding of the suspected food and is the most cost- and time-efficient type of OFCs, but they have the highest risk for bias mainly in older children with some subjective symptoms like pruritus without rash or abdominal pain [34]. OFCs should be used to determine clinical reactivity when the history is not clear and results of sIgE testing (SPT or sIgE) are negative or positive but with less than predictive cutoffs for the culprit food. OFCs can also be useful in confirming the development of oral tolerance during the follow-up of patients with diagnosed FA [34].

Basophil activation test

Some products of mast cell activation (such as total tryptase) can be measured in some special laboratories as markers of anaphylaxis although these methods have several clinical limitations. The peak tryptase level should be compared with the baseline value to confirm anaphylaxis [35].

Treatment and prevention

Emergency treatment of anaphylaxis

Epinephrine (Adrenaline)

Anaphylaxis is a critical allergic reaction that is rapid in onset and may be fatal. International guidelines [1•, 20•, 36] concluded that intramuscular (IM) epinephrine (adrenaline) is the first-line therapy in anaphylaxis because it is the only medication that decreases hospitalizations and death. Its vasoconstrictor effects can prevent and relieve airway edema, hypotension, and shock; its chronotropic and inotropic effects ameliorate cardiac output, and its beta-2 agonist activity produce bronchodilatation [20•, 37].

Fleming et al. demonstrated that early treatment of FIA with epinephrine was associated with significantly lower risk of hospitalization, compared with people with initial injection in an Emergency Department [38]; however, in a large number of deaths related to anaphylaxis, only 23 % of patients received epinephrine before cardiac arrest [39]. Despite there are not absolute contraindications to epinephrine, delayed application by underestimation of symptoms, perceived contraindications (pregnancy, older age or cardiovascular disease) or inappropriate management by the physician is frequent [20•, 40].

Aqueous epinephrine, 1:1000 dilution (1 mg/mL), 0.2–0.5 mL (0.01 mg/kg in children, max. 0.3 mg; 0.3–0.5 mg for adults), should be injected intramuscularly into the anterior-lateral thigh every 5–15 min, if necessary [19]. Kids between 10 and 25 kg should receive a 0.15 mg dose when using adrenaline auto-injectors whereas a 0.3 mg dose should be used for patients more than 25 kg [36]. The use of intravenous, subcutaneous or inhaled adrenaline in the treatment of anaphylaxis is not recommended and must be given only by physicians with experience like critical care doctors and with patient monitoring by means of EKG, pulse oximetry and blood pressure [36].

Support measures

Adjunctive treatment includes elimination of allergen exposure and call for help; positioning the patient on the back with lower extremities elevated, sitting up if he/she has dyspnea and reclining on the left side with lower extremities elevated in pregnant patients. Supplemental oxygen should be provided by face mask and in patients with cardiovascular instability intravenous crystalloids (20 mL/kg) should be administered; inhaled short-acting beta-2 agonists when the patient has bronchoconstriction and nebulized budesonide when laryngeal stridor is present are also recommended [36].

Cutaneous symptoms can be mitigated by the use of oral H1 and H2 antihistamines and oral or systemic glucocorticosteroids may be used to diminish the risk of late-phase symptoms particularly in patients with asthma, only after first- and second-line interventions have been used [36].

Patients with respiratory symptoms should be observed for 6–8 h, and those who show hypotension require close monitoring for 12–24 h before discharge.

Long-term treatment of anaphylaxis

After a critical episode of anaphylaxis, a long-term treatment strategy should be planned. Campbell has showed that the intervention of an allergy/immunology specialist helps in the accurate diagnosis in patients referred after treatment for anaphylaxis [41] and this intervention reduces the risk of anaphylaxis requiring hospitalization [42].

Patients should be educated on allergen avoidance. An allergy specialist can assist to recognize food triggers and to supply strategies in food avoidance [36]. As anaphylactic reactions frequently occurs in the community (schools, restaurants, bakeries, fast-food stores) and mainly at school or kindergarten (16–22 % of reactions) patients and their caregivers should be provided with exhaustive information on food allergen avoidance and trained in early recognition of symptoms and treatment of allergic reactions before arriving to the ED. The European Academy of Allergy and Clinical Immunology (EAACI) Food Allergy and Anaphylaxis Guidelines for managing patients with food allergy is proposed to educate patients and families in order to attenuate the impact of this problem in the community [43••].

Since anaphylaxis is a long-lasting condition, it is necessary to balance safety and limitations to normal activities since we could affect the quality of life of patients and parents. When kids, parents and caregivers have the responsibility to provide a safe environment, but when they become adolescents, and start to select foods outside home they should take responsibility for carrying their auto-injectable epinephrine (EAI). At this age death by anaphylaxis becomes more frequent [36].

An exhaustive educational package should include the provision of strategies in order to avoid the dangerous food at home and at places where the patient has social activities, an intensive training on how and when emergency medication should be used and other advices [35, 43••]. Educational programs are more effective by using a written action plan [36]. At secondary school, peers of students with food allergies should be educated in prevention and management of critical situations, avoiding bullying associated with this type of allergies [43••].

Early administration of adrenaline is the first action in the treatment of anaphylaxis. Before discharge, an adrenaline auto-injector should be prescribed with clear instructions for patient and caregivers about the need of permanent carrying and advice on which situation and how to use it [36]. Despite the fact that EAI's are unavailable in many countries, they still remain under-prescribed and under-used in others. In a recent publication only 11 % of patients with a confirmed anaphylaxis reported EAI's had been used in their last episode, and 52 % of the patients referred that they never received an EAI prescription [44].

Psychological approach and methods to control anxiety in patients and families should be part of the educational training in order to improve the outcomes in patients and give them the best possible quality of life.

Summary

Food-induced anaphylaxis (FIA) is a critical situation that usually occurs in varied places where the patients live, study, work and travel. Unfortunately often not only patients but also caregivers and occasional people cannot help

patients to resolve this clinical emergency, but sometimes doctors are not suitably trained in the recognition and management of this clinical emergency.

Anaphylaxis diagnosis is based on clinical signs and symptoms. It is most common in children, especially in very young people and any food is capable to triggering anaphylaxis, although more commonly milk, peanuts, tree nuts, eggs and fish are involved. Allergy tests are usually helpful in the accurate identification of the trigger. Adrenaline is the first-line treatment and other actions (calling for help, removing the trigger, correct positioning of the patient, supplemental oxygen, crystalloids and additional medications) are necessary in order to achieve the control of the situation. Before discharge, patients and caregivers should receive a comprehensive assessment in order to prevent futures reactions, and an adrenaline auto-injector should be prescribed if necessary, depending on availability.

Treatment of food-induced anaphylaxis is not different from that other causes, but it is necessary to focused on the prevention and education for patients, their families and all the levels of the society.

Compliance with Ethical Standards

Conflict of Interest

Dr. Héctor Badellino declares that he has no conflict of interest. Dr. Edgardo Jares declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of major importance

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