

STATE-OF-THE-ART REVIEW

Food anaphylaxis

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Clinical and
Experimental
Allergy

Summary

Anaphylaxis is a life-threatening allergic reaction, and food is one of the most common responsible allergens in the outpatient setting. The prevalence of food-induced anaphylaxis has been steadily rising. Education regarding food allergen avoidance is crucial as most of the fatal reactions occurred in those with known food allergies. The lack of a consensus definition for anaphylaxis has made its diagnosis difficult. Symptoms affect multiple organ systems and include pruritus, urticaria, angioedema, vomiting, diarrhoea, abdominal cramps, respiratory difficulty, wheezing, hypotension, and shock. Prompt recognition of anaphylaxis is essential as delayed treatment has been associated with fatalities. Although epinephrine is accepted as the treatment of choice, timely administration does not always occur, partly due to a lack of awareness of the diagnostic criteria. Several novel tools are currently being investigated, which will potentially aid in the diagnosis and treatment of food-induced anaphylaxis.

Keywords anaphylaxis, food allergy, allergic reaction*Submitted 11 October 2006; revised 18 December 2006; accepted 4 January 2007*

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Epidemiology

Anaphylaxis is a 'serious allergic reaction that is rapid in onset and may cause death'. [1] Food is one of the most common inciting allergens, and remains the leading cause of outpatient anaphylaxis in most surveys [2]. Food reactions account for one-third to one-half of anaphylaxis cases in emergency departments in North America, Europe, Asia and Australia [3–5]. In the paediatric population, food reactions account for an even larger fraction of anaphylaxis cases. The Canadian Pediatric Surveillance Program reported that 81% of anaphylaxis cases in children were due to food [6]. Peanuts, tree nuts and seafood, the more persistent food allergies, are the most frequently implicated foods [3]. Fatal food-induced anaphylaxis can occur, and in the United States about 150 food allergy-related deaths are believed to occur each year [3].

Food anaphylaxis affects both sexes equally [7], although there are reports of slightly higher rates in males in Hong Kong [4] and females in Australia [5]. Most cases of anaphylaxis reportedly occur in the home [8, 9]. In a study of self-reported anaphylactic reactions due to foods in the United Kingdom, nearly one-fifth of the reactions in children occurred at school [9].

Interestingly, many of the patients who experience food-induced anaphylaxis are aware of their food aller-

gies. Sixty-six percent of patients in a study from the United Kingdom reported having known of their allergy to the triggering food, however, over half were unaware that the food they were eating contained the allergen [9]. In a United States study, there was a known allergy to the triggering food in 41% of emergency department visits for allergic reactions to foods [10]. Of the 32 food-related fatalities reported by Bock et al. [7], at least 87% of patients had a prior history of reaction to the responsible food allergen. This highlights the importance of allergen avoidance and the fact that more education is necessary.

Food allergens

The prevalence of food allergy is greatest in the first 2 years of life and decreases with age. The most common food allergens causing reactions in children include milk, egg, wheat, soy, peanuts, tree nuts, fish and shellfish. While the majority of children outgrow their allergy to milk, egg, wheat and soy, allergies to peanut, tree nuts, fish and shellfish are often life-long. Although any food can cause anaphylaxis, the most commonly implicated foods for severe allergic reactions are peanuts, tree nuts, fish and shellfish [11].

Dietary factors can influence the prevalence of food allergies in a given population. For example, peanut

allergy is one of the most common food allergies in the United States. However, seafood is a common food allergy in Hong Kong, and sesame is a major food allergen for children in Israel [4, 12].

Although prior exposure is necessary for the development of sensitization, 72% of peanut and/or tree nut allergic patients reported symptoms during their first known exposure [13]. These patients may have had previous unknown exposures through breastmilk, contamination within other foods, or use of topical products containing food oils, e.g. peanut [14].

Clinical features of anaphylaxis

Anaphylaxis, which was first described a century ago [15], encompasses a variety of symptoms and often affects multiple organ systems. Symptoms may include, but are not limited to, pruritus, flushing, urticaria, angioedema, vomiting, diarrhoea, abdominal cramps, respiratory difficulty, wheezing, hypotension, syncope, and shock (Table 1). Less commonly, symptoms of headache, substernal chest pain and seizures may occur [16]. Unfortunately, there have been no consensus criteria for the diagnosis of anaphylaxis, thus contributing to the difficulties in identifying cases and timely initiation of treatment.

In an effort to clarify these issues, an international panel of experts was assembled by the National Institute of Allergy and Infectious Diseases and the Food Allergy & Anaphylaxis Network in two symposia to establish diagnostic criteria that would allow rapid identification of affected individuals (Table 2) [1]. Cutaneous symptoms are the most common, appearing in more than 80% of cases. These cases would be diagnosed using the first criteria listed in Table 2. However, up to 20% of cases do not present with skin findings, particularly in children reacting to foods or insect stings [17, 18]. In these cases, a history of allergy and possible exposure, along with symptoms consistent with the second criteria would establish the diagnosis.

Table 1. Clinical features of anaphylaxis

Cutaneous	Urticaria, angioedema, pruritus, flushing, morbilliform rash
Respiratory	Upper airway – rhinorrhea, congestion, sneezing, stridor, hoarseness Lower airway – cough, wheeze, dyspnea, chest tightness, cyanosis
Cardiovascular	Tachycardia, arrhythmia, syncope, hypotension, shock
Gastrointestinal	Pruritus or edema of the lips/tongue/palate, metallic taste in the mouth, nausea, vomiting, abdominal cramps, diarrhea
Neurologic	Anxiety, headache, seizure, syncope, loss of consciousness
Ocular	Pruritus, conjunctival injection, lacrimation

Table 2. Diagnostic criteria for anaphylaxis [1]

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 (e.g. generalized hives, pruritus, or flushing, swollen lips–tongue–uvula)

And at least one of the following

- a. Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - b. Reduced BP or associated symptoms of end-organ dysfunction [e.g. hypotonia (collapse), syncope, incontinence]
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–mucosal tissue (e.g. generalized hives, itch-flush, swollen lips–tongue–uvula)
 - b. Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - c. Reduced BP or associated symptoms of end-organ dysfunction [e.g. hypotonia (collapse), syncope, incontinence]
 - d. Persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)
 3. Reduced BP after exposure to known allergen for that patient (minutes to several hours)
 - a. Infants and children: low systolic BP (age-specific) or greater than 30% decrease in systolic BP*
 - b. Adults: systolic BP < 90 mmHg or greater than 30% decrease from that patient's baseline

*Low systolic BP for children: 1 month to 1 year <70 mmHg; 1–10 years < [70 mmHg + (2 × age)]; 11–17 years < 90 mmHg.

PEF, peak expiratory flow; BP, blood pressure.

In rare cases, hypotension has been reported to be the primary symptom of anaphylaxis. These situations would satisfy the third criteria if the patient had exposure to a known allergen. Ten percent of cardiovascular anaphylaxis cases are induced by food allergens [19], and 39% of food-allergic reactions have cardiovascular compromise [20].

Although cardiovascular symptoms occur less frequently in food-induced anaphylactic reactions, it is important to recognize the potential complications. Symptoms associated with hypotension can include nausea, vomiting, diaphoresis, dyspnoea, hypoxia, dizziness, seizures and collapse [21]. Fluid extravasation and vasodilatation can lead to a decrease in circulating blood volume of up to 35% within 10 min [22]. In addition, cardiac dysfunction associated with non-specific electrocardiographic changes and normal coronary arteries have been reported [23]. Therefore, aggressive fluid resuscitation, as well as supine positioning and elevation of the legs to prevent pooling of blood in the lower extremities, is recommended. In fact, upright posture has been found to lead to fatalities in cases of food-induced anaphylactic shock [24].

Table 3. Risk factors for severe anaphylaxis

Peanut or treenut allergy
Concurrent asthma
Adolescent age
Delayed or no administration of epinephrine

Onset of symptoms

The onset of symptoms from food-induced anaphylaxis is variable, ranging from within seconds to a few hours after exposure to the causal food allergen. While the majority of reactions manifest within 1 h of exposure, a slower onset of symptoms correlates with less severe reactions [3]. Reactions to ingested allergens, such as foods, have a slower onset than injected allergens. Fatal reactions due to foods can occur within 25–35 min of ingesting the triggering food allergen [25]. In contrast, median time intervals for fatal anaphylaxis to medications and insect venom are shorter, ranging from 5 to 12 min.

Children vs. adults

Features of anaphylaxis have been recently noted to differ between children and adults [18]. Paediatric cases are more often triggered by foods, while drugs and insect venom are more common triggers for adults. In Lee and Greenes's [8] report of 108 anaphylaxis episodes in children, nearly half were due to a food allergen trigger. Twenty-seven percent involved tree nuts, 24% involved peanuts, and 16% were due to seafood. In fact, fatal food-allergic reactions affect younger people more often than fatal insect sting or drug reactions [25], which may be explained by the presentation of food allergies at an earlier age.

Although generalized allergic reactions occur more commonly in children, adults more often experience anaphylaxis [5]. More than 90% of adults have cutaneous symptoms with anaphylaxis; this rate is lower in children (~80%) [18]. Children more often experience respiratory symptoms, whereas adults are more frequently affected by cardiovascular compromise [18]; this may be due to their increased age and a higher frequency of co-morbid conditions.

Modifying factors

Asthma has been shown to be a risk factor for more severe anaphylaxis [7]. The prevalence of asthma among those who have anaphylaxis ranges from 19 to 37% [2, 4, 10, 18]. In one study in Australia, the prevalence of asthma is higher in children with anaphylaxis as compared to adults (36.8% vs. 23.2%) [18], and this rate was significantly higher than the background prevalence of paediatric asthma in the same area (17.5%). In a study of fatal food

allergic reactions, the majority of patients had underlying asthma [7] (Table 3).

Other factors have been reported to affect anaphylaxis. Food associated, exercise-induced anaphylaxis occurs in susceptible individuals when they ingest the triggering food within 2–4 h of exercise. Symptoms do not occur in the absence of exercise or if the food was not ingested before exercise. Females are more commonly affected, and the majority of cases occur in individuals <30 years of age [3]. Alcohol, aspirin, β -blockers, angiotensin converting enzyme inhibitors, monoamine oxidase inhibitors, tricyclic antidepressants and concurrent infection are additional factors that may increase the severity of anaphylactic reactions or diminish the efficacy of epinephrine [25, 26]. Therefore, avoidance of these medications in patients at high risk for anaphylaxis would be recommended, if possible.

Differential diagnosis

Since food-induced anaphylaxis can affect almost any organ system, its symptomatology overlaps with many illnesses. Cutaneous symptoms may be a result of acute or chronic urticaria, and respiratory features may be similar to asthma exacerbations, foreign body aspiration (especially in children) and vocal cord dysfunction. Food poisoning, in particular from scombroid fish, may present with symptoms similar to those of food-induced anaphylaxis. Some cases of vasovagal reaction, panic attack, mastocytosis, carcinoid syndrome, pheochromocytoma, C1 esterase inhibitor deficiency and serum sickness can be confused with anaphylaxis as well [27].

Biphasic reactions

Biphasic reactions are defined as a recurrence of symptoms after resolution of the initial presentation. The rate of biphasic reactions has been reported to range between 3% and 20% in adults [4, 28–31]. One paediatric study noted that 6% of anaphylaxis cases progressed to a biphasic reaction [8]. Biphasic reactions have been reported to occur in up to 25% of fatal or near-fatal food reactions [32]. The triggering foods have mainly been nuts and seafood [33].

The severity of the late-phase symptoms is highly variable, being either more or less severe than the initial symptoms [33]. Unfortunately, the onset of the late-phase response is also highly variable, ranging from 1 to 78 h, with the majority occurring within 8 h of the initial presentation [33]. There is no consensus on optimal observation time following the initial reaction; recommendations range from 4 to 24 h [17, 33, 34].

There is no consistent constellation of symptoms that predicts the development of a biphasic response, although a recent report from Hong Kong noted that respiratory

features appeared less commonly in those with biphasic anaphylaxis [4]. Studies suggest that delayed administration, inadequate dosing, or a need for large doses of epinephrine are risk factors for biphasic reactions [33].

Near-fatal/fatal food anaphylaxis

Although fatalities occur in <1% of cases of anaphylaxis, there is room for improvement in outcomes for a disease that is preventable and treatable. In a study of 202 cases of fatal anaphylaxis in the United Kingdom, 45 cases were caused by food, and another 18 were reported to be possibly due to food [25]. Thus, food allergens accounted for up to 30% of fatal cases of anaphylaxis, with over half associated with nuts. One-third of cases occurred at home, 25% in restaurants and 15% at school or work.

Commercially prepared foods accounted for 68% of nut reactions [25]. In all of these cases, the patient had prior reactions to the triggering food. The severity of subsequent reactions cannot be predicted based on history alone, as most prior reactions were not as severe. In this study, eight (4%) patients received epinephrine within 30 min of the onset, but still had a fatal reaction.

The time interval between ingestion of the food allergen and fatal collapse has been reported to be approximately 25–35 min (range: 10 min to 6 h) [25]. Fatal food reactions are also more commonly associated with asthma or respiratory symptoms than with shock, in contrast to insect sting or medication reactions. Interestingly, a study of fatal and near-fatal food reactions reported that all children with non-fatal reactions had cutaneous symptoms, however, only one child with fatal anaphylaxis had skin findings [17]. Similarly, there is a paucity of cutaneous symptoms in fatal anaphylaxis due to allergen immunotherapy, with only 29% of fatal cases having any cutaneous signs [35].

Another study of fatal anaphylaxis to foods in the United States by Bock et al. [7] demonstrated that the majority of their 32 cases involved adolescents and young adults. All but one individual had a known allergy to the food causing the fatal reaction. Reactions to peanuts and tree nuts accounted for 94% of these fatalities. In addition, except for one case, all the patients for whom data were complete had a history of asthma. Ninety percent did not have epinephrine available at the time of the reaction; therefore, at least some of these fatalities may have been avoided if proper treatment was administered in a timely manner.

Serum tryptase has not been found to be elevated in most cases of food-induced anaphylaxis, contributing to some of the diagnostic difficulties [17]. However, Vadas et al. examined another potential marker of severe anaphylaxis. In an abstract, the authors reported that the mean serum platelet-activating factor acetylhydrolase (PAF-AH) activity in eight cases of fatal peanut anaphylaxis

was significantly lower as compared with those with peanut allergy, non-fatal anaphylaxis, and healthy controls, suggesting that low levels of PAF-AH may be a marker for more severe food-induced anaphylaxis [36].

Diagnostic tests

In addition to the lack of universally accepted diagnostic criteria for anaphylaxis, there is no reliable laboratory test for diagnosing anaphylaxis. In a study of 97 emergency room patients with anaphylaxis, 42% had increased plasma histamine and 21% had increased serum tryptase [37]. Although elevated plasma histamine levels were found in more cases, histamine has a very short half-life so elevations will be transient and can easily be missed. Urinary histamine and its metabolites, however, are elevated for longer periods and may be useful [38].

Furthermore, serum tryptase is not generally increased in food-induced anaphylaxis [17], and would therefore be a poor biomarker for diagnosis. This may be a temporal issue since anaphylaxis to food allergens can develop more slowly and may be biphasic, hence preventing timely measurement of a peak serum tryptase level [39]. Other mechanisms suggested to explain the inability to detect elevated tryptase include the distribution of tryptase into the gut lumen rather than in the circulation or the activation of basophils instead of mast cells [39].

Alternative biomarkers would be useful for the diagnosis of food-induced anaphylaxis. PAF-AH and mast cell carboxypeptidase are currently being investigated [36, 40]. Ongoing work with peptide microarray immunoassay technology has also shown promise in the diagnosis of food allergy. Greater epitope diversity, as detected by microarray immunoassay, has been shown to correlate with increased severity of clinical reactions to peanut (Fig. 1) [41]. Whether these new diagnostic tools can alter our management of patients with food-induced anaphylaxis remains to be seen.

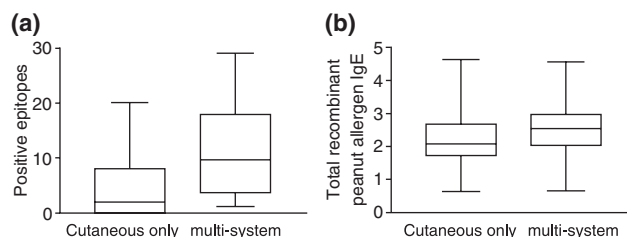


Fig. 1. Individuals with a history of more severe peanut-induced reactions recognize more peanut allergen epitopes. (a) Individuals with a history of cutaneous symptoms ($n = 14$) recognize fewer epitopes (median, 2; range, 0–20) compared with those with a history of reactions involving multiple organ systems ($n = 24$; median, 9.5; range, 1–29; $P < 0.01$). (b) The same patients have similar recognition of recombinant peanut allergens [41].

Treatment of food-induced anaphylaxis

Epinephrine

The primary treatment for anaphylaxis is epinephrine (Fig. 2). Studies have shown that intramuscular administration in the lateral thigh achieves higher and faster peak plasma concentrations than injection in the deltoid either by subcutaneous or intramuscular administration [42]. No human trials have been performed to determine the optimal dosage of epinephrine in cases of anaphylaxis, however, it is recommended that patients receive 0.01 mg/kg up to 0.5 mg. In severe reactions, intravenous administration may be necessary. In extremely severe cases of collapse where epinephrine and fluids are not effective, vasoconstrictors such as vasopressin may be required [23].

Although the treatment of choice for anaphylaxis is clear, it is not always utilized. For example, in a study in Hong Kong, 67% cases of anaphylaxis treated in emergency departments were given epinephrine [4], and an Italian study reported that only 15% of anaphylaxis cases admitted to the hospital were treated with epinephrine [20]. Differences in the treatment of children and adults also have been noted. In a study from Australia, only 26.3% of the children with anaphylaxis received epi-

nephrine. A higher proportion received epinephrine if cases were stratified into severe anaphylaxis (39.3%) [18]. In comparison, more than half of the adults presenting with anaphylaxis in the same geographic location received epinephrine (57%) [5].

Similar results are seen when looking specifically at food allergic reactions. A multi-centre study of US emergency department visits for food allergies revealed that 22% of anaphylaxis cases were treated with epinephrine [10]. In a prospective survey of food allergic individuals in the United Kingdom, 32% adults and 11% of children experiencing food reactions and who had self-injectable epinephrine available used it at the time of the reaction [9]. Overall, underutilization of epinephrine for the treatment of food-induced anaphylaxis by healthcare workers and patients/caregivers is a major problem and appears to be more pronounced in paediatric cases.

Corticosteroids

Corticosteroids may have a role in preventing or ameliorating biphasic or protracted anaphylaxis, however, there are contradictory studies regarding their effectiveness [33]. One study found that treatment with corticosteroids was not effective in preventing biphasic reactions [30],

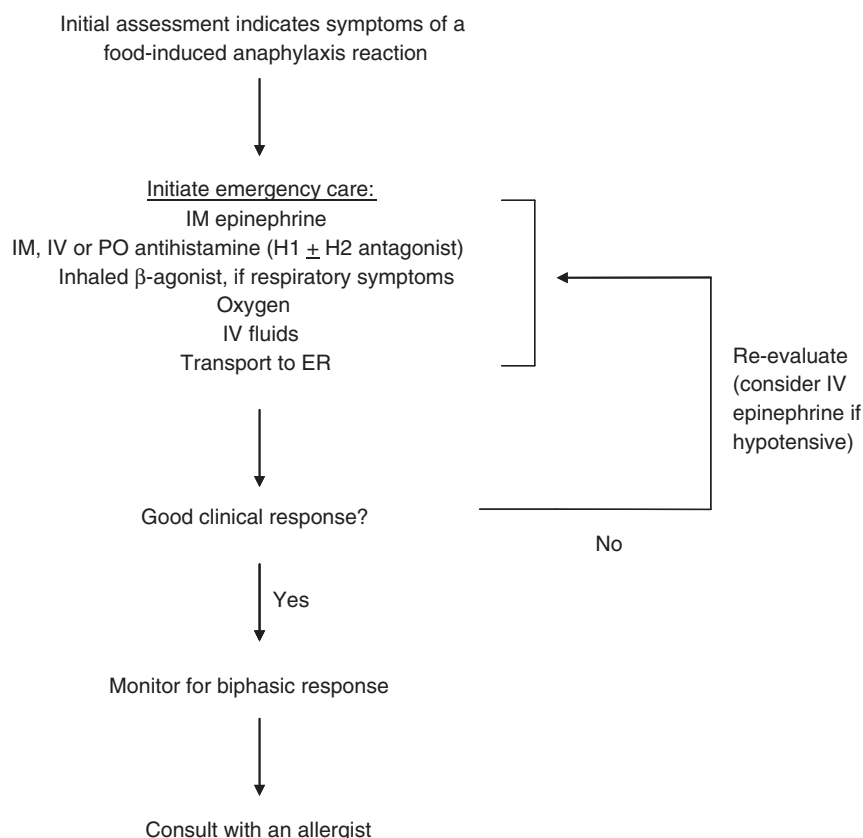


Fig. 2. Treatment algorithm for acute food-induced anaphylaxis.

whereas another study demonstrated that corticosteroids prevented or reduced the severity of the late response [29]. While far from definitive, these findings suggest that corticosteroids may be beneficial in some cases of anaphylaxis and are unlikely to have any adverse consequences.

Antihistamines

Antihistamines are effective for the treatment of cutaneous symptoms, such as pruritus and urticaria, but not for respiratory symptoms, gastrointestinal symptoms or shock. While serum histamine peaks early in anaphylaxis, it quickly returns to baseline even with persistent symptoms, suggesting that the post-reaction timing of antihistamine administration will reduce their effectiveness. Animal studies have not shown a significant effect of antihistamines in the treatment of anaphylactic shock [43, 44]. Therefore, antihistamines (H1 and H2 antagonists) are considered second-line treatment for anaphylaxis. Finally, the onset of action of antihistamines is 1–2 h, which is slow in comparison to the progression of anaphylactic symptoms.

Additional treatment measures

Other considerations include aggressive fluid resuscitation and supine positioning and elevation of the legs to enhance cardiac preload in cases of anaphylactic shock [23]. The upright position promotes blood pooling in the lower extremities and has contributed to fatalities [24]. Supplemental oxygen and β -agonists should be used to treat respiratory symptoms. Glucagon has potent inotropic and chronotropic actions and may be beneficial for the treatment of anaphylactic shock in patients who are on chronic β -blockers if other treatments are ineffective [45].

Outpatient follow-up

Patients who have had a food-related anaphylactic reaction should be referred for evaluation and management by an allergist. Identification of the offending foods and education regarding avoidance measures are important in preventing future reactions. Current diagnostic tests for food allergies include skin prick testing and measurement of serum-specific IgE antibodies. Although both tests have excellent negative predictive values, positive test results are not always an indication of clinical reactivity. Therefore, positive tests must be interpreted in conjunction with convincing histories of allergic reactions, and in some cases confirmed by oral food challenges.

The importance of examining all the ingredients of foods to be consumed cannot be overemphasized, as the majority of fatal food reactions occur in individuals who are aware of their allergy, but unaware that the allergen is

contained in commercially prepared foods [25]. Recently, new labelling laws went into effect in the United States that should facilitate this process as less complicated terminology is required on all packaging labels [46]. In addition, patients should be given guidance for managing their food allergies outside the home, such as in schools or restaurants, as not everyone may be educated about food allergies. Contamination of cookware and serving utensils or hidden ingredients in sauces are often not appreciated by cooking and serving staff and can pose a risk for food-allergic individuals.

Despite these preventive measures, accidental exposures to food allergens still occur. Therefore individuals should be instructed in the use of self-injectable epinephrine, and an individualized emergency plan should be in place. Although the importance of these recommendations is recognized, few patients receive prescriptions for self-injectable epinephrine upon discharge from emergency departments after experiencing anaphylaxis. In a multicentre emergency department study, only 16% of patients who had food allergic reactions were discharged with a prescription for self-injectable epinephrine [10]. Furthermore, only 12% were referred for allergy evaluation. Several studies have investigated the frequency of self-injectable epinephrine prescriptions given by emergency department staff for anaphylaxis management and have had similarly disappointing results, with rates ranging from 0% to 38% [5, 47, 48].

In addition to prescribing self-injectable epinephrine, it is important to educate patients on its proper use and reinforce the importance of having it available at all times, as delayed administration is associated with an increased risk of fatal reactions. Sicherer et al. [49] demonstrated that although 86% of parents with food allergic children reported carrying self-injectable epinephrine at all times, only 71% had the device during the study visit, and only one-third were able to correctly demonstrate its use. A survey of parents found that psychological factors, such as empowerment by the physician, also correlate with increased parental comfort in EpiPen[®] (Dey, L.P., Napa, CA, USA) use [50]. In 16–36% of anaphylaxis reactions, a second dose of epinephrine is required [9, 51, 52]; therefore carrying multiple doses of epinephrine may be advisable.

Patients and their families are not the only caregivers who lack proficiency in the use of self-injectable epinephrine. Interestingly, less than half of general paediatricians in the study were able to correctly demonstrate its use [49]. Educating the families is key, but it is not effective when even physicians do not know how to use autoinjectors correctly.

Currently, suboptimal dosing choices are available for self-injectable epinephrine. As there are only two dosing options available (ideal for body weights of either 15 kg or ≥ 30 kg), physicians are faced with the dilemma of

choosing which to prescribe for children who are <15 kg or who are between 15–30 kg [53]. Dispensing needles and syringes to allow for more accurate dosing is not practical given the inconsistencies in how quickly doses can be drawn up by parents, as well as their ability to draw up the correct dose [54]. The length of the autoinjector needle becomes another important factor in adults, especially if overweight, because the needle may not be long enough to penetrate the fat layer and reach the intramuscular space. This is further compounded in women, who have more subcutaneous fat than men [55].

Another barrier to the administration of epinephrine is the concern that patients or parents may have regarding the use of needles. Therefore, alternatives to injectable epinephrine are now under investigation. The use of metered dose inhalers for the administration of epinephrine has been shown to be suboptimal because of the high number of inhalations required and the unpleasant taste of the drug [56]. More recently, sublingual epinephrine has been showing promise. In a validated rabbit model, 40 mg of sublingual epinephrine resulted in peak plasma concentrations and time to peak levels that were not significantly different from 0.34 mg epinephrine administered intramuscularly [57]. Human trials are needed to confirm the suitability of sublingual epinephrine for the treatment of anaphylaxis.

Natural history of food allergy

The persistence of food allergy is variable, and depends on the specific food allergen. Approximately 85% of children with cow's milk allergy will become tolerant by 8.6 years of age [58], and about 66% of those with egg allergy will become tolerant by age 5 years [59]. In contrast, only 20% of children with peanut allergy and 9% with tree nut allergy will develop tolerance [60, 61]. Currently, there are no reliable predictors to determine when and in whom this will occur, hence, periodic follow-up with measurement of serum specific IgE levels and prick skin testing can help determine when oral food challenges would be appropriate. Predictive values for serum food-specific IgE levels and prick skin testing have been published for the major food allergens (Table 4) [62–66]. In addition, the rate of

decrease in food specific IgE levels over time has been shown to have predictive value [67].

Even for those who demonstrate tolerance by double-blind, placebo-controlled food challenge, recurrence of allergy has been reported to occur in 8% of peanut allergic individuals [68]. This risk may be higher for those who continue to avoid peanut after having negative food challenges, and therefore regular consumption is recommended for these individuals to confirm and maintain a tolerant state.

New therapies under investigation for food allergy

Recombinant food proteins are being investigated for use in allergen specific treatment of food-induced anaphylaxis. Modified peanut allergens, in which the primary sequence of IgE-binding epitopes of peanut is altered to decrease IgE-binding capacity, have been engineered. These recombinant proteins stimulate T cells from peanut allergic individuals to proliferate, but have greatly reduced IgE-binding capacity as compared with wild-type peanut protein [69, 70]. Heat-killed *Escherichia coli* producing recombinant peanut proteins have been shown to have protective effects in a murine model of peanut anaphylaxis [71]. The proposed mechanisms involve T-helper type1 (Th1) cytokines and/or T regulatory cells suppressing Th2 cell activation and mast cell/basophil mediator release on re-exposure to antigen [72, 73].

The use of food allergen peptide immunotherapy has also shown promise. These peptide fragments contain T cell epitopes, but are not of sufficient length to cross-link IgE and therefore, cannot trigger mast cell or basophil activation. A preliminary study using pepsin-digested peanut peptides showed the ability to induce IFN- γ (Th1 cytokine) in a concentration-dependent manner [74].

Immunostimulatory sequences (ISS), such as CpG oligodeoxynucleotides, bound to proteins can act as adjuvants to switch to a Th1 response [75]. Although there are no published studies for food allergy, immunotherapy with ISS in combination with Amb a 1, the major ragweed allergen, was found to promote Th1 responses and reduce allergenicity in mice, rabbit and primates [76]. A similar approach is being investigated in a murine model of peanut-induced anaphylaxis.

Table 4. Predictive values of specific IgE and prick skin testing for selected food allergens

	~50% react [63]	~95% react [62, 63]	~95% react (≤ 2 years of age) [64–66]
Milk	sIgE = 2 kIU/L	sIgE = 15 kIU/L SPT = 8 mm weal	sIgE = 5 kIU/L SPT = 6 mm weal
Egg	sIgE = 2 kIU/L	sIgE = 7 kIU/L SPT = 7 mm weal	sIgE = 2 kIU/L SPT = 5 mm weal
Peanut	sIgE = 2 kIU/L (convincing history) sIgE = 5 kIU/L (unconvincing history)	sIgE = 14 kIU/L SPT = 8 mm weal	– SPT = 4 mm weal

sIgE, food specific IgE level; SPT, skin prick test – dependent upon extracts and technique utilized.

Treatment with anti-IgE antibodies has been investigated in a double-blind, randomized, dose-ranging trial in 84 patients with a history of peanut allergy [77]. Patients who received the highest dose (450 mg) of anti-IgE, HU-901, monthly for 4 months had a significant decrease in symptoms with peanut challenge as compared with the placebo group. The median threshold of sensitivity to peanut increased from less than one peanut to almost nine peanuts. Therapy was well-tolerated. However, while 25% of patients were able to tolerate over 20 peanuts following therapy, another 25% failed to develop any change in tolerance to peanut after treatment. Recently, investigation of another anti-IgE preparation, omalizumab, has been at least temporarily discontinued.

Alternative approaches are currently under investigation. Traditional Chinese Herbal Medicine formula, FAHF-2, was shown to protect peanut-sensitized mice from anaphylaxis. Treated mice had no signs of anaphylaxis after peanut challenge, but all sham-treated mice had severe symptoms of anaphylaxis [78]. The clinical effects were associated with decreased peanut-specific IgE levels and Th2 cytokine production. The protective effects of FAHF-2 were demonstrated to last up to 6 months post-therapy, which represents about 25% of the life-span of the mouse [79].

Conclusion

Food-induced anaphylaxis is a disease that is well-known and has been studied for many years. However, the lack of consensus in the definition of anaphylaxis has made its diagnosis and treatment challenging. The fatalities related to anaphylaxis and the increased incidence of emergency department visits highlights the fact that there remains much to be learned. Ongoing research seeks to improve diagnostic tools and determine predictors of anaphylaxis risk. Novel treatments are currently being tested and show promise in the prevention and management of food-related allergic reactions.

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