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Food-Induced Anaphylaxis: an Update

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Abstract

Purpose of Review This review aims to provide an update of recent advances in the epidemiology, clinical features and diagnosis, and management of food-induced anaphylaxis (FIA).

Recent Findings Food allergy prevalence and FIA rates continue to rise, but FIA fatalities are stable. Basophil and mast cell activation tests promise more accurate identification of food triggers. Oral, sublingual, and epicutaneous immunotherapy can desensitize a significant portion of subjects. Epinephrine use for FIA remains sub-optimal.

Summary As the burden of food allergy continues to increase, it appears that the corresponding increase in research focused on this epidemic is beginning to bear fruit. The stable number of FIA fatalities in the face of an ongoing epidemic indicates lives have already been saved. The emergence of new diagnostic tests and interventional therapies may transform the management of FIA in the coming years.

Keywords Food allergy · Anaphylaxis · Epinephrine · Peanut allergy · Oral immunotherapy

Introduction

IgE-mediated food allergy is a serious worldwide problem of increasing prevalence. The most feared outcome of food allergy is anaphylaxis: a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergen [1]. While fatalities due to food allergy are quite rare, the constant vigilance and lifestyle modifications necessary for those living with food allergy can have profound effects on quality of life (QoL) [2–5]. Significant unmet needs exist in our abilities to accurately diagnose and manage food-induced anaphylaxis (FIA), but progress has been made in recent years with new diagnostic methods and promising therapeutic options under investigation.

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Epidemiology

Food allergy affects approximately 1 in 13 children and 2 to 3% of adults in the United States (US) [6, 7], while challenge-proven rates reach nearly 10% in Australian children [8]. Lifetime prevalence of anaphylaxis due to all causes is estimated to be between 1.6 and 5.1% in the US [9]. Food is the most common cause of anaphylaxis in children and young adults and about 40% of the US children with food allergy experience severe reactions [10]. An ED visit due to FIA occurs every 6 min on average in the US [11]. Nearly 10% of Australian adolescents with food allergy report symptoms consistent with anaphylaxis annually [12]. A recent prospective study in Denmark found that food was responsible for 61% of anaphylaxis in children and 17% in adults [13•]. In recent years, emergency department visits and hospitalizations due to FIA have increased, but only a single Australian study indicated a parallel rise in fatalities [14–16, 17••, 18, 19].

Fatal Reactions

Turner et al. [20••] reviewed recent reports on food anaphylaxis deaths and illustrated that in the general population the rate of fatal food anaphylaxis (0.03 to 0.3 deaths per million person years in the general population) [21•, 22] is comparable to that of death due to lightning. Even among those with

known food allergy, the rate is about 1 per one million person years, which is orders of magnitude lower than death by accident, murder, or fire (Fig. 1). As such, a diagnosis of food allergy does not significantly affect overall mortality risk, although patients and caregivers still perceive the risk as significant [23]. Rates of fatal food anaphylaxis vary geographically from an estimate of 0.04 per million person years in the US [14] to 0.08 in Ontario, Canada [16], 0.09 in Australia [18], and 0.12 in the United Kingdom (UK) [17••], although reasons underlying this variation are unknown.

The most common food triggers of fatal anaphylaxis worldwide are peanut and tree nuts [20••], while milk is commonly implicated in young children [17••]. This pattern of food triggers has been replicated in most studies from Europe and the US. Regional variations of food triggers exist, with seafood the culprit in up to 50% of deaths in Australia [18]. While egg allergy is very common in young children, it is rarely implicated in deaths [20••].

Factors associated with fatal FIA have been identified through case series (Table 1) but, as discussed later in this text, severity of individual reactions cannot be accurately predicted. Sampson et al. noted delay in epinephrine administration beyond 30 min from reaction onset in fatal but not near-fatal FIA in their landmark 1992 report [24]. This association with delayed epinephrine use has been observed in numerous subsequent studies [16, 18, 25, 26]. Improved rates of epinephrine autoinjector (EAI) prescriptions have been documented [17••] and a corresponding increase in use of epinephrine could plausibly explain the discordance between rising FIA rates and stable fatality rates. However, fatalities do occur despite rapid administration of epinephrine [25, 28] and clinical trial evidence that epinephrine can prevent fatalities is absent [29] for ethical reasons. Rates of FIA and hospitalization are highest among infants and young children, yet fatalities are very rare at these ages, while adolescents and young adults in the second and third decade of life are overrepresented in series of FIA deaths [14, 17••, 18, 19]. Prior reactions to foods are commonly noted, but are not always severe [17••], possibly related to the age at the time of the reactions. Asthma has been noted in 70 to 75% of fatalities in recent series [17••, 18] and even greater proportions of earlier series [24–26, 30, 31]. Severe respiratory symptoms predominate in fatal FIA, with cardiovascular comprise occurring secondarily as a result of respiratory failure [32]. While intuitively this association should inspire more aggressive asthma treatment in patients with food allergy, asthma control has not been clearly proven to affect risk of death [20••]. Other fatality risk factors include use of alcohol or recreational drugs [18] and upright posture [27], while evidence is inconsistent for associations with African American [19] or UK-resident South Asian race [17••], multiple food allergies, and acute illness [33].

Non-Fatal Reactions

Patterns of food triggers for non-fatal anaphylaxis mirror those for fatal reactions, with peanuts and tree nuts predominating while milk is common in infants and younger children [13•, 15, 34–36]. Food was the most common specified trigger for anaphylaxis leading to PICU admission in North America from 2010 to 2015, with peanut (45%), tree nuts/seeds (19%), and milk (10%) as the main culprits [37]. Nut allergy was associated with triple the likelihood of anaphylaxis compared to other food allergies in Australian adolescents [12]. More severe reactions to milk and egg are associated with persistent allergy into adolescence instead of resolution by school age [38, 39]. Regional variations in patterns are noted, with peanut strikingly uncommon in Portugal [40] and walnut and pine nut common in South Korea [41]. Another Korean study listed seafood, meat, and grains including wheat as more common triggers than nuts [42]. There is evidence in Western countries that ethnicity may affect risk of anaphylaxis. Patients of Asian ethnicity are disproportionately affected [15, 35, 37]. While Hispanics have the lowest rates of FIA, their rates of ED and hospital visits for FIA are increasing rapidly [15, 34].

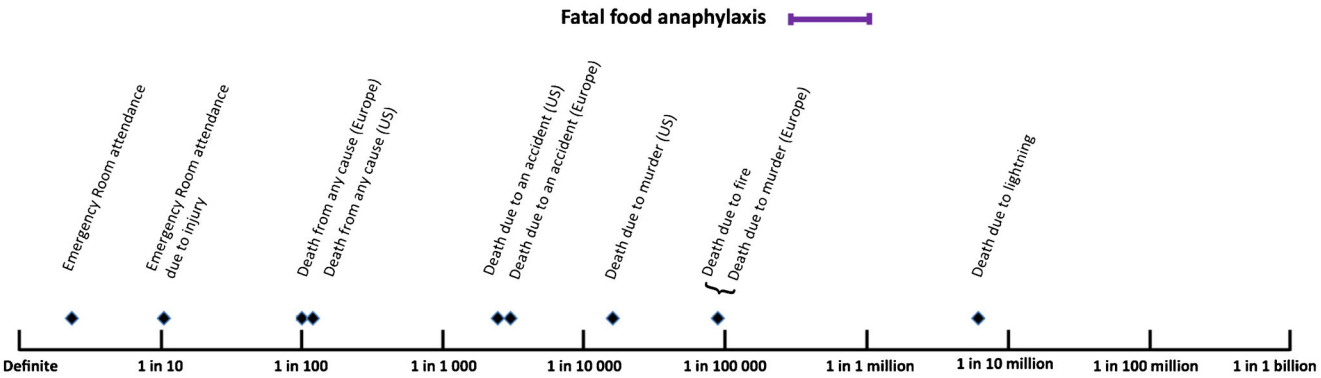

Fig. 1 Annual incidence of fatal anaphylaxis among food allergic individuals. Estimate of fatal FIA for individuals with food allergy is the 95% confidence interval of fatal food anaphylaxis risk derived from the systematic review of Umasunthar et al. [22]. Figure modified with permission from Turner et al. *J Allergy Clin Immunol Pract*. 2017; 5(5):1169–1178

Table 1 Factors associated with risk of fatal food-induced anaphylaxis

Allergens—increased risk [20••]	Allergens—decreased risk [20••]
Peanut	Egg
Tree Nuts	Soy
Milk (infants/children) [17••]	
Seafood [18]	
Patient factors—increased risk	Patient factors—decreased risk
Asthma [17••, 18, 24–26]	
Known food allergy [17••, 18] (prior reactions not always severe)	
Adolescent or young adult age [14, 17••, 18, 19]	Infancy or early childhood
Other factors—increased risk	
Delay in epinephrine use [16, 18, 24–26]	
Upright/change in posture [17••, 18, 27]	
Alcohol/recreational drug use [18]	

Clinical Presentation and Diagnosis

Anaphylaxis is a clinical diagnosis with rapid onset after allergen exposure of symptoms affecting the skin and mucous membranes (urticaria, angioedema, pruritus, flushing), respiratory tract (cough, shortness of breath, wheezing, stridor), gastrointestinal (GI) tract (abdominal pain or vomiting), and/or cardiovascular system (light-headedness or syncope) [1]. Diagnostic criteria include rapid onset of symptoms and either mucocutaneous involvement after possible allergen exposure plus respiratory compromise and hypotension; involvement of two or more systems rapidly after exposure to a likely allergen; or hypotension after exposure to a known allergen [1]. In FIA symptoms typically occur within minutes to a few hours of ingestion, with cutaneous symptoms (typically urticaria) most common and usually associated with respiratory (cough, wheeze, stridor) and/or GI symptoms (abdominal pain, vomiting) [34]. The diagnosis of anaphylaxis is often missed, in part because of wide variation in clinical symptoms and a plethora of potential underlying causes and triggers [43•].

FIA is much more likely to include respiratory symptoms than hypotension as prominent clinical features, and most deaths are due to respiratory arrest, with cardiovascular collapse occurring as a late result of respiratory collapse [17••, 31]. While this may be due to comorbid asthma, many food allergic patients without a diagnosis of asthma also have bronchial hyperreactivity that may predispose to severe reactions [44, 45]. Presentation may also vary by age, with infants experiencing hives and vomiting, young children presenting with wheezing and stridor, and adolescents reporting "difficulty breathing" or "trouble swallowing" [34].

Anaphylaxis is under-diagnosed, with as few as 13% of children and 6% of infants that meet criteria receiving the diagnosis at the time of ED discharge [34]. Infants and younger children are unable to describe symptoms and some potential indications of reaction overlap with normal behavior (e.g., crying, irritability, drooling). Adolescents often fail to recognize symptoms as anaphylaxis, with less than half of anaphylactic reactions being self-identified as such in a recent Australian study [12]. Lack of cutaneous symptoms has been identified as a factor leading to failure to recognize and promptly treat anaphylaxis, with resulting poor outcomes [25].

Two atypical forms of FIA should also be mentioned: food-dependent exercise-induced anaphylaxis (FDEIA) and delayed anaphylaxis to red meat due to allergy to galactose-apha-1,3-galactose (α-gal). In FDEIA, patients can tolerate both the culprit food (most commonly wheat) and exercise separately, but if the food is eaten within several hours of exercise, the result may be anaphylaxis [46]. In alpha-gal allergy, first described in 2009 [47], the allergen is not a protein but rather a sugar moiety present in all non-primate mammalian tissues and reactions may be idiosyncratic. The presentation typically involves delayed onset (3 to 6 h post-ingestion) of severe cutaneous symptoms [48] and sensitization has been linked to tick bites [49, 50]. A recent report indicates a prominence of abdominal symptoms and more rapid onset among rural South African patients [51].

Clinical Course

The clinical course of FIA varies, but usually includes rapid onset of symptoms and rapid resolution after treatment. In a recent cohort study of pediatric hospitalizations for FIA, symptoms resolved while in the ED 92% of patients and inpatient interventions were needed in only 16% of patients, most commonly albuterol administration in those with a history of asthma [52]. One can reasonably assume that most of these patients were admitted despite symptom resolution to monitor for biphasic reactions, which occur in about 4.6% of anaphylactic reactions overall and less frequently in FIA [53]. The disproportion between admissions and need for interventions likely reflects the lack of clear predictors for biphasic reactions [53, 54]. A recent analysis found that prior anaphylaxis, unknown inciting trigger, and delayed epinephrine increased risk of biphasic reactions [54]. Identification of further factors could help distinguish which patients need prolonged observation after resolution of symptoms and which can be safely discharged after shorter observation periods.

Tryptase in FIA

The diagnosis of anaphylaxis is clinical, and laboratory tests are not included in diagnostic criteria. Serum tryptase has been used to confirm mast cell activation in anaphylaxis triggered

by venom [55] and drugs [56]. Such elevations have not been seen consistently in fatal or near-fatal FIA [24], although tryptase elevation was noted in 6 of 8 fatal food reactions in one early study [57]. A recent prospective study showed that tryptase levels increased from baseline and peaked at 2 h in positive peanut challenges in adults [58•]. Levels rose by a median of 78% among patients with anaphylaxis, but remained in the normal range (≤ 11.4 ng/mL) for 10 of the 14 anaphylactic reactions and all non-anaphylactic positive reactions. The increases seen were significantly larger than inter-day variation in baseline levels. Severe anaphylaxis occurred in all four cases where tryptase rose above normal. These findings may not be generalizable to children or infants, especially considering that baseline levels are elevated in infants, more so in those with atopy [59, 60]. Other investigators have observed smaller peaks in tryptase during food-induced reactions as opposed to allergens delivered rapidly and directly into the systemic circulation (anesthetics, intravenous drugs, venoms) [61]. It remains unclear whether the smaller rise in tryptase during FIA is due to slow allergen absorption, differences in patterns of mast cell activation and secretion (e.g., mucosal GI tract mast cells secreting tryptase into GI lumen), or lower tryptase content in mucosal mast cells [62]. Basophils contain much less tryptase than mast cells [63], so it has also been proposed that basophil activation may play a more prominent role in food-induced reactions [24].

Identification of Food Triggers

The clinical determination of food allergy as the cause of anaphylaxis is generally suggested by the history and confirmed with documentation of sensitization to the suspected food trigger with skin-prick testing and/or serum food-specific IgE measurement [64]. Predictive cutoff values for skin-prick test wheal size [65–67] and serum food-specific IgE [68–72] have been established for many foods. Skin testing can be performed safely even in patients with prior episodes of FIA. Broad panels of food-specific IgE testing are not recommended due to poor specificity leading to overdiagnosis [73]. The basophil activation test (BAT) and component-resolved diagnostics have shown promise in predicting the likelihood of reactivity to foods, especially when traditional tests are inconclusive [74, 75]. However, the BAT is limited by the requirement for fresh blood and the fact that 10 to 15% of patients have uninterpretable results due to basophils unresponsive to IgE-mediated stimuli. Santos et al. recently described a novel mast cell activation test (MAT) using LAD2 mast cells and patient plasma, which allows for use of stored samples [76]. The MAT was not as sensitive as the BAT, but did allow for conclusive results in subjects with nonresponsive basophils. A separate report by Bahri et al. found that MAT, using human blood-derived mast cells (hMCs) cultured from peripheral blood precursors, outperformed conventional tests and BAT, with patterns of MAT reactivity correlating with reaction phenotypes upon peanut oral food challenge (OFC) [77•]. Another emerging diagnostic tool is a recently developed nanoallergen platform, which has been used to identify immunogenic epitopes on the major peanut allergen Ara h2 and may further improve diagnostic precision [78••].

While history and testing often suffice to establish a diagnosis of FIA and confirm the food trigger, OFC (specifically double-blind placebo-controlled food challenge or DBPCFC) is the gold standard for diagnosis of food allergy and may be performed safely in the office of experienced allergists [64]. OFC is often done when history and initial tests are inconclusive or to assess for the development of tolerance. Detailed instructions for the safe performance of OFCs have been published by a workgroup report of the AAAAI [79] and will be updated in the near future. With the recent recommendation for early peanut introduction [80] based on the results of the landmark LEAP study [81], the need for OFCs in infants has greatly increased and practical guidance has been published [82]. For standardized OFCs performed in research settings, the PRACTALL guidelines offer strict parameters for OFC protocols [83]. OFCs are associated with improved food allergy specific health-related quality of life and reduced parental burden [84]. However, OFCs are not risk-free. There has been a single death reported as a result of an OFC, which occurred in a 3-year-old boy after baked milk OFC [85•], and other reactions have been severe enough to require hospitalization and intensive care support [86, 87]. While OFC remains the gold standard for confirming a diagnosis of food allergy, the high specificity in vitro tests such as the BAT and MAT may allow more accurate diagnosis with fewer OFCs and therefore less risk in the future.

Predicting Reaction Severity

Much effort has been expended in the attempt to identify factors that predict severe food-induced reactions and better risk-stratify patients. Such factors may be specific to the trigger (higher risk with peanut, tree nuts, shellfish, milk, and wheat; lower risk with egg and soy) or the patient (higher risk with past anaphylactic reactions, increased age, asthma, allergic rhinitis) [86, 88•, 89]. Reaction outcomes are also influenced by treatment decisions such as timing of epinephrine administration.

Allergen-specific skin-prick test wheal size and serum IgE can suggest the likelihood of reaction upon ingestion [64], and component-resolved diagnostics may further improve diagnostic accuracy [75, 90, 91]. However, such markers do not reliably predict reaction severity. Analysis of 583 entry DBPCFCs for highly sensitized subjects in a phase 3 peanut OIT study showed no association between markers of peanut sensitivity (peanut SPT mean wheal diameter, peanut-specific IgE, or Ara h2-specific IgE) and severity of reaction [92]. Another recent study found that although several factors were

independent predictors of severity (age, SPT, eliciting dose (ED), allergen-specific IgE, reaction time, and severity of accidental reaction), even in combination, they explained less than 25% of the variance, leaving reaction severity largely unpredictable [93]. BAT has correlated with reaction severity in some studies [90, 94] but not others [95, 96]. The MAT as performed by Santos et al. also showed some predictive value regarding severity of OFC reactions, with excellent sensitivity and NPV but poor PPV [76].

Given the inability of individual markers to predict reaction severity, more comprehensive predictive models have been studied. Sugiura et al. developed promising models to stratify risk for egg, wheat, and milk OFCs with predictive scores that incorporate factors such as age, allergen-specific or component-specific IgE levels, total IgE < 1000, and complete allergen avoidance [97–99]. Chinthrajah et al. proposed a clinical severity scoring system for peanut allergy with scores ranging from 1 to 6 based on threshold of sensitivity combined with a severity clinical indicator meant to indicate a reaction severe enough that most clinicians would treat with epinephrine [100]. Machine learning procedures then determined that the BAT (ratio of CD63+ basophils after stimulation with peanut vs. anti-IgE) was most predictive of severe reactions, and developed an algorithm incorporating threshold BAT values and clinical factors (history of exercise-induced asthma and FEV1/FVC ratio below 80%). Validation of all these models in further studies will be needed before widespread application. It is important to note that severity as predicted by each of these models is actually a composite measure of both reaction severity and reaction threshold. While intuitively a severe reaction that occurs at a low dose indicates more severe allergy than if the same reaction occurs at a much higher dose, the evidence for correlation between threshold dose and reaction severity is lacking [93, 101, 102].

Management of FIA

Acute Management

Successful management of anaphylaxis requires rapid recognition followed by prompt removal of any suspected triggers, rapid assessment of circulation, airway, breathing, skin, and weight [103]. Patients should be placed in a supine position unless doing so worsens respiratory status, as upright posture has been associated with poor outcomes [27]. Epinephrine is the first-line treatment for anaphylaxis and should be administered intramuscularly without delay in the mid-outer thigh at a dose of 0.01 mg/kg utilizing the 1:1000 formulation (max dose of 0.5 mg) or an epinephrine autoinjector (EAI) [104–106]. EAIs have long been available in 0.15 and 0.3 mg doses. The need for a 0.1 mg EAI has been recognized [107], and the first such product is now available for use in infants. In a canine anaphylaxis model, epinephrine had no therapeutic effect when administered after shock fully developed [108]. Such studies cannot be done in humans for ethical reasons, but anaphylactic deaths are clearly associated with delay in epinephrine administration [24, 31].

There are no absolute contraindications to epinephrine use in anaphylaxis but adverse events range from accidental self-injection (often from use of live epinephrine instead of training device and rarely significant) [109] to cardiac events including stress (Takotsubo) cardiomyopathy [110] and myocardial infarction (usually in the setting of underlying coronary artery disease) [111]. It may be difficult to differentiate such events attributable to epinephrine from allergic vasospastic angina (Kounis syndrome), a rare complication of anaphylaxis that results from inflammatory cytokines released by mast cells [112]. Cardiac events and epinephrine overdose in general occur more commonly with IV than IM administration [113]. Shaker et al. published a recent review of epinephrine adverse events and also used computer simulation and Markov modeling to predict epinephrine-associated death in 0.07% of recipients [114]. The model is limited by the accuracy or lack thereof of the FDA reports of epinephrine AEs on which it is based. The authors also noted that with an assumed 10-fold increased risk of fatal anaphylaxis from epinephrine non-use, simulated anaphylaxis fatalities would increase from 226 to 1090 annually, clearly illustrating that the risks of non-use outweigh the risks associated with epinephrine. Their literature review led them to recommend use of IV epinephrine only in cases refractory to IM epinephrine (due to increased risk of adverse cardiac events), vigilance to ensure proper dosing with the IV (1:10,000) versus IM (1:1000) formulations of epinephrine, awareness of the potential cardiac risk in patients presenting with cardiac manifestations, and advising families to be sure they use their training device when practicing epinephrine administration.

High-flow oxygen (8–10 L/min via face mask) and intravenous fluid resuscitation (10 to 20 mL/kg 0.9% saline over 5–10 min) should be administered when indicated [103]. Continuous monitoring of vitals including pulse oximetry is indicated and if necessary appropriate cardiopulmonary resuscitation should be initiated. Adjunctive medications such as antihistamines and glucocorticoids should not be used prior to or instead of epinephrine [103]. Because of the risk of biphasic or protracted anaphylaxis, prolonged observation is recommended [1, 103].

A recent case report documented near-fatal anaphylaxis to milk in a 15-year-old that seemed to improve only after placement of a nasogastric tube and gastric drainage despite prompt, aggressive treatment with multiple doses of intramuscular epinephrine followed by continuous intravenous infusion, intubation and respiratory support and IV fluid resuscitation [115]. While gastric drainage is not part of the recommended management of anaphylaxis, cessation of exposure to the inciting trigger (e.g., stop the infusion of an intravenous

drug) is recommended. If ingested food remains in the stomach and absorption is ongoing, then gastric drainage may halt ongoing allergen exposure. Many allergists view emesis in patients with FIA as a positive occurrence often followed by subsequent improvement, presumably for the same reason. While a single case report is not sufficient evidence to change practice, perhaps such maneuvers should be considered in severe reactions with poor response to standard treatment.

Long-Term Management

Outside the acute setting, management of FIA focuses on prevention of future reactions and proper treatment of reactions that occur despite prevention efforts. Written anaphylaxis or food allergy action plans should be provided. Patients should be referred to an allergist for confirmation of the trigger and education on allergen avoidance and management of reactions [103]. Overall rates of allergist referral and EAI prescription fulfillment are low after anaphylaxis, with only 29% of patients following up with an allergist within 1 year and only 46% filling an EAI prescription, but these rates are higher for FIA (39.8% for allergist follow-up and 69.4% filling EAI prescription) [116]. From 2005 to 2014 EAI, dispensation rates increased by 38% for adults after FIA, while rates for children did not increase but have always been high (84%). Patients and/or caregivers should be trained in use of EAIs, and clinicians should be aware that periodic repeat training is necessary as misuse is common [117] and knowledge of proper use may be lost with time [118]. Proper education on food avoidance is necessary as reactions may occur due to misreading of labels, cross-contamination, cross-reactivity (e.g., pistachio ingestion in patient with cashew allergy), and even intentional exposure. Many schools have implemented peanut-free policies, but there is no evidence to date that these effectively reduce risk and QoL is not improved by such policies [119].

With increased research on interventional therapies for food allergy, there is hope that long-term management in the future will include treatment to induce desensitization and lower the risk of future reactions. Oral, epicutaneous, and sublingual immunotherapy have all shown promise in achieving desensitization to foods, and any significant increase in reactivity threshold induced is likely to be clinically relevant. A recent analysis estimated that an increase in peanut threshold of reactivity from ≤ 100 to 300 mg would reduce the risk of reaction to contaminated cookies, ice cream, doughnuts/snack cakes, and snack chip mixes by over 95% [120••]. There is also evidence that desensitization decreases the severity of subsequent reactions upon exit DBPCFC [121]. There is some evidence that oral immunotherapy (OIT) may improve food-specific QoL [122, 123]. However, this evidence may be exaggerated by lack of confirmatory DBPCFC prior to initiation of OIT. It remains to be seen if findings will be similar in patients with challenge-proven allergy undergoing OIT. OIT may also be cost-effective, but may actually increase the total number of anaphylactic reactions to foods [124]. It is conceivable that the predictability of reactions occurring after OIT dosing may lead to less patient and caregiver stress than anaphylaxis after unpredictable accidental ingestion, which often occurs despite constant vigilance on the part of patients and caregivers [125]. No deaths have been attributed to OIT to date, but one school-age boy in Japan suffered respiratory arrest during milk OIT resulting in ventilator dependence (Personal correspondence, Motohiro Ebisawa, MD, Ph.D). Products for both peanut OIT and epicutaneous immunotherapy are currently undergoing phase 3 clinical trials with hopes of commercial availability in the future. In the meantime, these promising interventional therapies should remain reserved for research settings.

Shaker and Greenhawt recently analyzed two strategies utilized at times for peanut allergy: avoidance of products with precautionary allergen labeling and EAI administration for peanut allergen ingestion even when symptoms were not present [126]. Their analysis found that neither strategy was cost-effective, but that low-dose (1.5 mg) peanut threshold challenge was cost-effective to facilitate consumption of products with PAL, which may then lead to improved QoL.

Epinephrine Use and Underuse

Despite guideline recommendations and the well-documented association between delay in epinephrine use and poor outcomes, epinephrine remains underutilized for FIA in all settings worldwide [13•, 127–131]. While allergists have been critical of underuse of epinephrine by first responders and emergency departments [132, 133], we also fail to administer epinephrine in many cases of anaphylaxis. Noone et al. noted the use of epinephrine in 39% (29 of 74) of positive DBPCFCs performed as screening for food allergy therapy trials [134]. While their study did not focus on anaphylaxis, the two reactions deemed severe (2.7% of total reactions) and 75% of those deemed moderate (34% of total reactions) received epinephrine. It is interesting to note that virtually all patients in this study (97%) reported GI symptoms, typically subjective abdominal discomfort. In van der Valk et al.'s recent retrospective study of open and DBPC OFCs performed in children at three tertiary care centers in the Netherlands [135], epinephrine was given to only 39% of children (32 of 83) who met the EAACI criteria for anaphylaxis [106]. This study included OFCs done in clinical settings and research settings, with the use of epinephrine significantly higher (71%) in the clinical group than the research group (16%). This difference was driven by a parallel disparity in epinephrine use between patients with skin plus GI symptoms (22% treated with epinephrine, much more common in the research group) as opposed to skin plus respiratory symptoms (70%

treated with epinephrine, much more common in the clinical group). This implies that allergists' use of epinephrine in FIA may be influenced by the clearly documented risk associated with respiratory symptoms and the previously discussed view of GI symptoms as potentially positive, especially emesis.

Epinephrine is also underutilized for reactions during OIT, and this is important to note as epinephrine use has been used as a surrogate for OIT-induced anaphylaxis rates [136–139]. The largest OIT safety analysis to date estimated that epinephrine was warranted but not given for 9% of OIT AEs [88•], illustrating both the underuse of epinephrine and the resulting limitations of its use as a surrogate for anaphylaxis during OIT.

However, allergists do not always underutilize epinephrine. Analysis of entry DBPCFCs for a phase 3 peanut OIT study revealed that of 583 North American participants, only 28 (5%) were deemed to meet NIAID-FAAN criteria for anaphylaxis, but 240 (41%) were treated with epinephrine [92]. Only 3% of the reactions were graded as severe. In the European challenges of the same study, only 15% were treated with epinephrine despite overall similarity of reaction severity, indicating a possible geographic variation in epinephrine use [140].

Better understanding of why epinephrine is underused may allow better understanding of how best to increase appropriate administration of epinephrine. Documented reasons for parental non-use of EAIs include failure to recognize anaphylaxis, unavailability of the EAI, fear of EAI use, waiting for more symptoms, and/or uncertainty whether EAI use was needed [141]. Supervised parent/child epinephrine EAI administration during OFC reactions increased parental confidence in multiple domains relating to EAI use for anaphylaxis [142], but it remains unproven whether or not this will translate to higher rates of EAI use in practice. Online educational programs have shown promise in improving knowledge in parents and caregivers of children with food allergy [143], but this may or may not improve epinephrine use. Social media is another potentially powerful tool for influencing food allergy management, but it is likely underutilized [144]. An analysis of the cost-effectiveness of bystander epinephrine in community anaphylaxis estimated the cost of preventing one venom-associated death using bystander epinephrine to be $71,519 [126]. Given that anaphylaxis fatality rates are comparable for venom and foods [20], this may be a cost-effective approach to prevent food allergy deaths as well. Unassigned stock epinephrine was used in 68% of 31 cases in the first 2 years after implementation of a stock epinephrine program in a large school district in Texas, often for adolescents with known food allergy but no assigned epinephrine [145]. Most likely, a multi-pronged approach including education of patients and caregivers, first responders, ED providers, and allergists will need to be combined with improved availability of epinephrine (including use of bystander or stock epinephrine) to maximize appropriate and timely epinephrine use.

Table 2 Future needs in FIA diagnosis and management

Diagnosis
Better awareness and recognition of anaphylaxis among patients, first responders, and physicians
Improved tools for confirming/ruling out foods as triggers
Better ability to risk stratify patients and predict reaction severity
Management
Increased rates of prompt epinephrine use
Wider availability of EAIs, including unassigned EAIs
Ongoing development of and clarification of the role of emerging interventional therapies (OIT, SLIT, EPIT)

Conclusion

Food-induced anaphylaxis continues to be a significant public health problem, and many related needs remain unmet. It remains difficult to predict which patients will suffer the most severe reactions, epinephrine remains underutilized, and the only approved management strategy is strict avoidance and preparation to treat reactions when they occur. Future needs in the area of FIA diagnosis and management are listed in Table 2.

However, there are numerous reasons for optimism. Despite increasing rates of food allergy and ED visits and hospitalizations for FIA, fatalities due to food allergy are not increasing. As early peanut introduction becomes more widely implemented, we may begin to see decreasing rates of peanut allergy in the future. The diagnostic toolbox for identifying allergic triggers and predicting reaction severity continues to expand with component-resolved diagnostics, basophil and mast cell activation tests, and multifactorial algorithms. Progress has been made in making stock or bystander epinephrine more readily available to treat FIA that occurs in schools and other public places. Potentially even more impactful are emerging interventional therapies including oral, sublingual, and epicutaneous immunotherapy as well as biologic therapy targeting Th2 inflammation. With continued improvements in our understanding of food allergies and anaphylaxis we should expect that the progress made so far to continue and improve life for those affected by food-induced anaphylaxis.

Compliance with Ethical Standards

Conflict of Interest Dr. Parrish reports personal fees and non-financial support from Pharmacy Times Continuing Education, non-financial support from DBV Technologies, and non-financial support from Aimmune Therapeutics, outside the submitted work. Dr. Kim declares that she 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.

References

Papers of Particular Interest, Published Recently, Have Been Highlighted as:
- • Of Importance,
- •• Of Major Importance

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