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A Brief Review on the Update of Food Allergy and Improving Diagnostic Accuracy

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Abstract

There is a growing prevalence of food allergies (FAs) in the urbanized world, and they have a significant impact on the lives of allergy patients and their families. It may be possible to find definitive ways to treat and prevent FAs if we study the risk factors that have contributed to this increase and the immune mechanisms that underlie them. At the moment, peanuts and other allergenic foods can be introduced to the diet during weaning to prevent the development of FAs. Food immunotherapy and biologics are making the transition from lab to clinic, improving diagnosis, management, and support of FA patients. The diagnosis of FA can also have a significant impact on patients and their families, imposing dietary restrictions and social restrictions. Misdiagnosis, however, can result in a potentially life-threatening allergic reaction. An accurate diagnosis of FA is therefore essential. Often, FA sensitization is determined by a combination of clinical history and allergen specific IgE; however, without an allergy history, IgE sensitization tests can be difficult to interpret. Additionally, there are rare cases of clinical FAs without IgE sensitization. Therefore, oral food challenges (OFCs), which are currently the gold standard for diagnosing FAs, are ideal for testing for suspected FAs. Besides providing a brief update on FA, the review discusses the predictive value of different tests used to diagnose FA, discusses implications for therapy and prognosis, and proposes a diagnostic approach for clinical use.

Keywords: Food allergies, Immunoglobulins, Diagnosis, Oral food challenges

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Food Allergies: The Impact

Based on the involvement of IgE in its pathogenesis, FAs can be classified as IgE- or non-IgE-mediated. The present paper focuses on IgE-mediated FAs and some of its diagnostic approaches. About 8% of children in Western countries suffer from FAs, and the number appears to be increasing in other parts of the world, especially in urban areas rather than in rural ones. Following what appears to be a 'second wave of allergy epidemic' following the increase in asthma and respiratory allergy prevalence in previous decades, the prevalence of FA and the number of hospitalizations related to food-induced anaphylaxis have increased over the past decade. Anaphylaxis-related ICU admissions attributed to foods accounted for 34% of cases and 73% of recurrences, according to articles published in several repositories. Even more common is self-reported FA, whose impact is often underappreciated. FA children report multiple FAs, often severe allergies, and carry adrenaline auto-injectors, according to Dr. Gupta and his co-authors. Children of Afro-Caribbean descent are disproportionally affected by FA in Western countries, like the USA and UK. [1]. Uncertainty remains about whether this is related to genetic predisposition in combination with environmental factors related to modern lifestyles, or if cultural background, history of inequality, and access to health care also play a role. Compared to infants born to Australian-born parents, infants born to Asian-born parents had a threefold higher risk of peanut and other FAs. This underscores the rapidity with which these changes take place and the importance of gene-environment interactions that need to be explored in greater depth.

As far as treatment goes, there is no curative treatment for FA, and the mainstay of management is to avoid allergens. Sadly, it is common for patients to suffer acute allergic reactions after accidentally exposing themselves to allergens, and urgent treatment needs to be made available to them. It can result in food insecurity and dietary restrictions due to allergen avoidance. According to a study, 86 percent of mothers who have children with FA avoid food on their own [2]. Researchers found that low calcium intake, asthma, and weight are independently linked to lowered bone mineral density in milk-allergic young adults. Moreover, FA can impair children's quality of life and their mental health. Approximately 50% of children and teenagers with FA experience bullying; mothers with suspected FA have higher state and trait anxiety scores than healthy controls. It is also possible for FA to negatively impact the costs, affecting not only healthcare, but also indirect costs, such as school and work absences, as well as the financial burden on the families themselves, as a result of having to spend more time shopping and find more expensive alternatives to food. All of these factors, along with the hypersensitivity to the culprit allergen, negatively impact FA children and their families, highlighting the need for accurate diagnosis and treatment [3].

Epidemiology: Facts of Food Allergy

Infants and young children are most likely to develop IgE-mediated FA, primarily due to egg and cow's milk allergies that often disappear later in childhood. As opposed to peanut and tree nut allergies, which often present in infancy, peanut and tree nut allergies tend to last longer, which leads to their predominance in older childhood. Despite a lack of data from some countries, FA prevalence varies significantly between countries for a variety of foods. Several recent studies have suggested that FA prevalence varies widely within countries, in part because rural areas have a lower prevalence than urban areas. Differences in the prevalence of the risk factors described below could play a role in explaining these differences [4-6].

It is likely that eczema is the strongest risk factor for FA, particularly early-onset and severe eczema [5]. For many years, these findings have been consistently reported in both population-based studies and allergy clinics; however, the mechanism behind the association is unclear [6-8]. In the absence of pre-existing oral tolerance to food allergens, a damaged skin barrier resulting from eczema may allow food allergens to penetrate the skin, resulting in food sensitization and allergy. It is possible that both eczema and FA are associated with genetic or environmental risk factors [9].

The identification of factors that can be modified to prevent FA has been of great interest. A number of factors, including vitamin supplements, fish oil, probiotics, and timing of introduction of allergenic foods, have been investigated in observational studies and randomized controlled trials [10-12]. In the section on FA prevention, these are further described. FA risk has also been associated with factors such as pet dogs and older siblings who may be exposed to more microbes.

Pathophysiology and Mechanism of Food Allergy

Type I hypersensitivity underlies IgE-mediated FAs. The underlying immune mechanisms of FA must be understood in order to prevent and reduce its impact [3, 13]. B cells produce antibodies in response to food allergens by coordinating T cell production. Neeland characterized the immune signatures of IgE-sensitive infants using mass cytometry for immunoprofiling of peanut allergies and tolerances [14]. Peanut-allergic infants were more likely to have activated B cells and memory CD4+ T cells, as well as increased levels of TNF-alpha and CD19hiHLA-DRhi, while peanut-sensitized tolerant infants were less likely to have CD4+ naive T cells and more likely to have plasmacytoid dendritic cells [15-18]. The TH2A cells, a new subset of Th2 cells typical of highly allergic patients, were described by authors like Wambre as diminishing after allergen-specific immunotherapy. According to Weissler and his coauthors, both allergic and non-allergic individuals have a stable T regulatory response, with the former exhibiting a Th2- and the latter a Th1-skewed response [19]. In peanut-allergic patients. There is a strong convergent selection of peanut specific T cell receptors among effector T cells in patients with peanut allergies, as well as an imbalance between effectors and regulatory T cells. Ruiter and his colleagues studied the T cell receptors repertoire of CD154+CD4+ memory T cells and found that peanut-associated clones were much more numerous among effector T cells [20-23]. Peanut-specific IgE levels were correlated with Th2 cytokine expression in patients with a more reactive Th2 effector phenotype.

There is still a puzzling discrepancy between the presence of allergen specific IgE in the body and clinical reactivity to food despite recent studies shedding light on antibodies and allergies. In the germinal center, Tfh13 cells have been identified as a new subset of T follicular helper cells. The Tfh13 cell line is characterized by a distinct transcription factor profile that includes BCL6 and GATA-3, as well as the production of IL-4 and IL-13 [24-27]. Anaphylaxis to allergens can be induced by Tfh13 by producing high-affinity IgE. IgG1+ cells have switched indirectly to IgE+ cells to produce this high-affinity IgE. The IgA molecule does not depend on germinal centers, Tfh, or T follicular regulatory cells like IgG and IgE, which are dependent on germinal centers and Tfh cells. According to Hoh and his co-authors, peanut-allergic individuals can develop somatic hypermutation and class switch recombination that led to increased affinity for allergens in the gut, thus emphasizing the importance of gut-associated lymphoid tissues in FA [28-32] (Figure 1).

Besides its intrinsic characteristics, such as its affinity for allergens, glycosylation of IgE can affect its ability to activate effector cells. According to a recent study, peanut allergy subjects had higher sialic acid levels in total IgE than non-atopic subjects and desialylation of IgE reduced effector cell degranulation, leading to anaphylaxis, opening a new area for intervention in allergy-related diseases, such as FA [34-36].

Depending on their immune response to T- and B-cells as well as antibodies, allergic or sensitized people have varying responses to the effector cell response. Hemmings and his co-authors published a study in which IgE specific to Ara h 2 inhibited IgE binding and caused mast cell degranulation to be greater than that specific to Ara h 6 [37-39]. The results indicate that, although both Ara h 2 and Ara h 6 are major allergens in peanuts, Ara h 2 is the dominant allergen, despite their sequence and structural similarities. As a result of the effector cell response to allergen, phenotypes of food-allergic patients can be identified who might require specialized treatment, like allergen-specific immunotherapy. The differences in clinical reactivity to baked eggs were explained by changes in basophil reactivity rather than changes in the T-cell compartment in a study of egg-allergic children [40, 41]. At baseline and at different time points during peanut oral immunotherapy (OIT), Patil et al. assessed basophil responses to Ara h 2. Based on basophil sensitivity, which is determined by the concentration at which basophils react, the patients who responded and sustained unresponsiveness after 3 months of OIT were distinguished

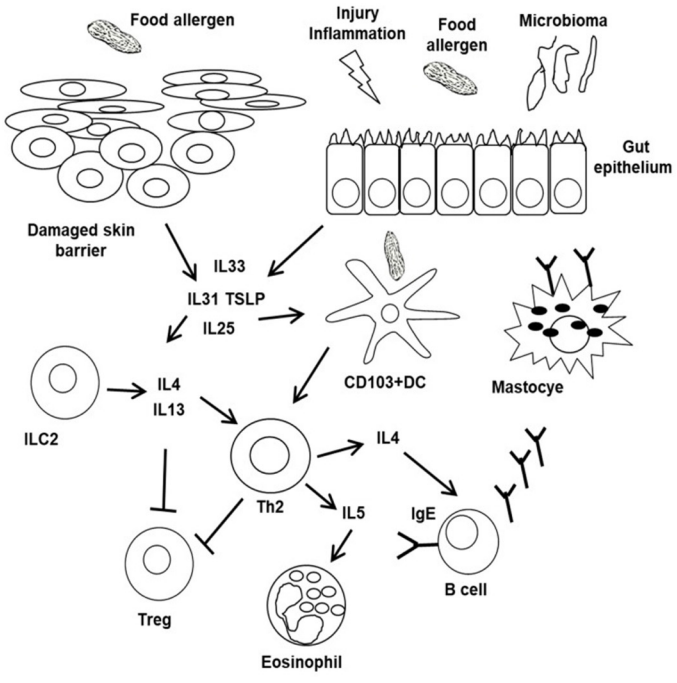

Figure 1: Main mechanisms by which the breakdown of tolerance to food antigens [33].

from those who experienced transient desensitization and whose basophil response to Ara h 2 rebounded after discontinuing OIT [3, 42, 43].

In conclusion, improving diagnostics and patient care for FA patients and their families depends on understanding the immune mechanisms behind FA and oral tolerance, and identifying targets for definitive treatment [44-47].

Evaluation and Diagnosis for Food Allergies

Patients and their families are often restricted in their diets and limited in their social and family activities when diagnosed with FAs. An allergic reaction, however, may result from a misdiagnosis. It's crucial to get the food allergy diagnosis right, so it's crucial to get it right the first time [48]. Clinical history is crucial to accurate diagnosis, and when symptoms are mediated by IgE after ingesting a particular food, the diagnosis can be fairly straightforward. An allergenic food should be consumed in an age-appropriate amount without causing complications if there is no clear history of allergic reaction [49-52].

For an IgE-mediated FA to be diagnosed, a skin prick test (SPT) or serum IgE must be performed. FAs can occur without IgE sensitization as well as with IgE sensitization. It is often best to diagnose allergies by combining history with allergen specific IgE; however, interpreting IgE sensitization tests can be challenging without a clear history of allergic reaction. In order to test suspected FAs, an OFC is ideal [53]. The question remains: how can we improve our diagnosis of patients before referring them to OFCs, since OFCs are time consuming and can cause unpredictable allergic reactions?

Basophil activation test

In contrast to tests that quantify the level of IgE, the basophil activation test (BAT) provides a result that is more closely tied to the patients' phenotype because it considers all characteristics of IgE and possibly interfering antibodies [55]. A roadmap for bringing the BAT into clinical practice and its diagnostic utility have been discussed elsewhere. SPT and sIgE are not as specific as BAT, and when BAT is positive, FA can be diagnosed. According to a discovery cohort, BAT to peanut had a 96% specificity and a 100% specificity. Using the same methodology as in this study, a large number (n = 981) of BATs of participants in the Learning Early About Peanut Allergy (LEAP), Persistence of Oral Tolerance to Peanut (LEAP-On), and Peanut Allergy and Sensitization studies confirmed that BAT had high specificity (98.5%) in diagnosing peanut allergies [56-58].

In a recent study of CMA, BAT to cow's milk was found to have 100% sensitivity and 100% specificity, which was the highest diagnostic performance of BAT. However, only 41% of the children studied had IgE to cow's milk, 5% had non-IgE-mediated CMA, and 54% were neither sensitized nor allergic, thereby contributing to BAT's excellent discriminatory ability. According to another study, BAT to egg was able to distinguish between different phenotypes of egg allergy, similar to what had previously been shown for baked milk allergy and tolerance [60]. Compared with baked egg tolerant patients, patients reactive to baked egg had a higher proportion of activated basophils following stimulation with egg (at 10 and 100 ng/ml concentrations). Children who are multi-sensitized to tree nuts and sesame are undergoing new studies on BAT. BAT to tree nuts had an area under the ROC curve varying from 0.78 for pecans to 0.97 for cashews in the "Nutcracker" study. The same group reported a study of BAT to sesame that showed an area under the ROC curve of 0.86 [61].

Compared to sIgE, BATs are more accurate for peanuts and hazelnuts based on Ara h 2 and Cor a 9/Cor a 14. The Pronuts study found that BAT to Ara h 2 was more accurate than BAT to Ara h 2 alone in diagnosing peanut allergy, and a Dutch study showed that stimulating basophils with both Ara h 2 and Ara h 6 increased the BAT sensitivity to 79%, as compared to 72% with Ara h 2 alone and 74% with Ara h 6.73 As a result, the BAT can be combined with individual allergens to provide a better diagnostic tool for peanut allergy [62]. Moreover, BAT to Pru p 3 has shown superior results for peach allergy to BAT to peach extract, possibly due to cross-reactive allergens present in the extract and Pru p 3 being the primary sensitizer in peach allergies in Southern Europe, as well as the primary inducer of effector cell activation. After initial studies by Commins and his coauthors show basophil activation coinciding with allergic reactions to alpha-gal during OFC to red meat, Mehlich and his coauthors showed that BAT can be used

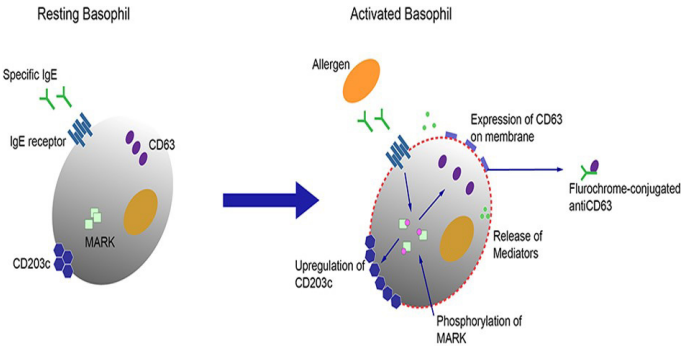

Figure 2: BAT principle – At a resting mode, the activation marker CD203c is expressed at low levels, but upon activation it is rapidly up-regulated [65].

as a diagnostic tool for detecting clinically relevant alpha-gal or pork kidney sensitization. BAT can also be used ad hoc to diagnose allergy to unusual allergens, such as beer or cannabis, as recently reported [63, 64] (Figure 2).

Skin Prick Test and Specific IgE to Allergen Extracts

Diagnostic methods for detecting specific IgE (sIgE) antibodies in food are skin prick testing and specific IgE (sIgE) levels. SPT whale diameters greater than the negative controls are considered positive results, or sIgE concentrations greater than 0.35 kU/L. Although a positive result alone indicates sensitization, it does not necessarily indicate FA. SPT and sIgE have a high sensitivity and negative predictive value (NPV) when used at a cutoff of 3 mm and 0.35 mm. However, they have a low specificity and positive predictive value (PPV), so overdiagnosis may occur. An increased likelihood of clinical allergies is associated with a larger SPT wheal size and/or a higher sIgE. Thus, 95% PPVs can increase specificity, but reduce sensitivity [66] (Figure 3).

In spite of their usefulness in diagnosing FAs, these cutoffs have many limitations. Despite elevated SPT and sIgE results, patients can tolerate food despite these tests alone not being definitive. As a result of differences in patient populations and disease prevalence, diagnostic cutoff values have varied widely across studies [48, 68]. There is limited information about the SPT and sIgE thresholds in children under 2 years old. Furthermore, reaction thresholds or severity are not predicted by positivity levels. The final category is the intermediate range of results, or results between NPV and PPV, which are difficult to diagnose and often require an OFC (Table 1).

Specific IgE to Allergen Components

Using component-resolved diagnostics (CRD), IgE is measured

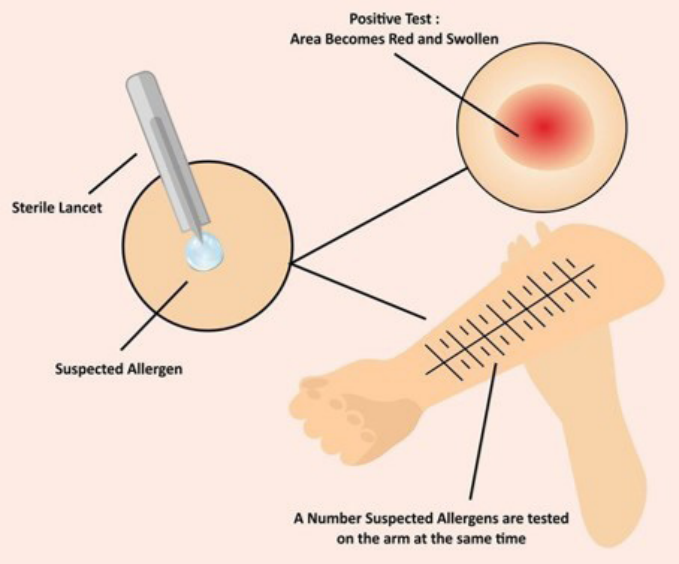

Figure 3: SPT – An accurate method to test individual substances for an allergic reaction [67].

against specific proteins in a food. The objective of this testing is to determine if clinically significant sensitization exists in comparison with cross-reactivity that is clinically irrelevant [69-71]. It is far more likely that storage seed proteins (such as Ara h 2) will be associated with clinical reactivity. A pollen-food allergy syndrome is associated with pollen-cross-reactive components such as profilins, Bet v 1 homologs, and PR-10. Pollen cross-reactivity and systemic reactions can be associated with the lipid-transfer proteins family and less so with PR-10.

In CRD, IgE is measured against specific proteins in a food. This test is intended to determine whether there is clinically significant sensitization compared to clinically irrelevant cross-reactivity. Among storage seed proteins (such as Ara h 2), true clinical reactivity is far more likely to be observed [72]. Pollen-cross-reactive components such as profilins, Bet-v 1 homologs, and PR-10 are associated with pollen-food allergies. Pollen cross-reactivity and systemic reactions can be associated with lipid-transfer proteins and PR-10.

Peanut allergy is largely predicted by antibodies against Ara h 2 (storage protein) and to a much lesser extent by antibodies against Ara h 1, Ara h 3, Ara h 6, and Ara h 9. Ara h 8 is a Bet-v 1 homolog and indicates pollen-food allergy. Ara h 2 cutoffs vary widely by study, as they do for sIgE to total peanut extract (0.35-42.2 kU/L had 90% - 95% PPV). In order to determine who should undergo an OFC, a sensitization profile can be used.

Resolution, severity, and threshold

Food allergies remain a mystery when it comes to immune mechanisms. It is more common for milk and eggs to be outgrown during childhood than other foods. As a way to predict allergic resolution, it has been shown that sequential testing over time is a prognostic factor for future oral tolerance [73]. It was found by Kim and co-authors that sIgE levels to egg and milk at the time of first reaction were significant prognostic factors in predicting future oral tolerance. Clinical tolerance was significantly associated with an increase in sIgE levels to egg and milk in another study.

When children have a confirmed IgE-mediated allergy, the decision to help assess tolerance is often based on an OFC, which remains the gold standard for allergy diagnosis. Rechallenging a patient at the right time is important, but difficult to standardize [74]. Researchers found that teenage children were three times more likely to develop anaphylaxis than younger children during OFCs, as well as a small but significant relationship between peanut SPT size and anaphylaxis. A study by Santos found higher peanut sIgE levels in children with severe peanut allergies compared to those with mild-to-moderate reactions. High-risk OFC can be avoided by identifying patients at higher risk of severe reactions, and the BAT can detect severe reactions in peanut-allergic children with 97% specificity and 100% sensitivity. It was found that patients with lower thresholds of reactivity during OFC were more likely to have basophil activation to peanut in vitro, which could be used to identify those patients who are more likely to react to peanuts and should be avoided during an OFC. Other studies have shown that BAT is associated with threshold dose or severity of peanut allergy reactions [75].

Implications for therapy

As FA treatments become more prevalent, diagnostic testing becomes even more important. These implications are evident in at least four areas, with others likely to follow. In the first place, it would be wrong to begin treatment on a patient who is not allergic to the medication. A clinician must therefore be certain of the diagnosis before offering treatment. Even if a patient does not have a clinical history or OFC, for example in a patient with an Ara h 2 level >100 kUA/L and a peanut SPT wheal of 15 mm, treatment should not be considered without clinically responsive patients [76].

As a second reason, since peanut OIT and epicutaneous immunotherapy (EPIT) are designed to prevent allergic reactions to small, accidental peanut exposures, treatment should only be offered

Table 1: Diagnostic cutoffs for specific IgE and SPT with 95% positive predictive NPV, Negative predictive value; PPV, positive predictive value. These numbers were derived from uncooked milk and direct egg and do not apply to baked milk or baked egg [48].

Foods	Specific IgE		SPT
	95% PPV	50% NPV	95% PPV
Cow's milk*	15 kU/L (32 also reported) Infants ≤2 y: 5 kU/L	2 kU/L	≥8 mm Infants ≤2 y: 6 mm
Egg*	7 kU/L Infants ≤2 y: 2 kU/L	2 kU/L	≥7 mm Infants ≤2 y: 4-5 mm
Peanut	15-34 kU/L	2 kU/L if history of reaction; 5 kU/L is no history of reaction	≥8 mm Infants ≤2 y: 4 mm
Fish	20 kU/L	-	
Tree nuts	20 kU/L	-	≥8 mm for walnut ≥12 mm for cashew
Sesame	50 kU/L (86% PPV)	-	≥8 mm

to patients at risk of reacting to these minute amounts [77]. It is unreasonable to expect that a patient would benefit from treatment if their peanut threshold without treatment exceeds 500 mg, or even 300 mg as recommended in AR101. The expense and inconvenience of a long-term treatment is not worth the risk, even if the risk is small.

It would be ideal to measure treatment response without repeating OFCs. EPIT and other treatments in development cannot know without OFCs whether a patient is responding to treatment, as opposed to OIT, where you can at least know the patient is tolerating peanuts. Also, this information is important for patients transitioning from treatment to a dietary form of the food to maintain their desensitization, or for patients wanting to know if they need to continue treatment. It would be tremendously valuable to have a surrogate for OFCs in this context [78].

Treatment

Allergen avoidance

The only way to manage FA in the absence of effective treatment was to avoid allergens and provide appropriate emergency medication. FA avoidance is onerous for patients and their families and often fails, with 10% of patients experiencing allergic reactions each year [79]. Allergic individuals and their families are also subjected to multiple pressures due to allergen avoidance, as well as food manufacturers, restaurants, and public places such as schools and planes. The labeling of precautionary allergens is generally voluntary and inconsistent across industries, making it confusing for patients and caregivers [80].

In addition to their limited availability in high-income countries, diverse national regulations in prescribing, and high cost, adrenaline auto-injectors are difficult to administer to patients at risk of anaphylaxis. Patients and staff both make mistakes in using adrenaline auto-injectors when prescribed, and half of them carry them at all times. When there are two allergic siblings in the same school or household but managed differently, it is problematic to meet the needs of both those receiving immunotherapy and those who continue to avoid allergens strictly [81].

Food immunotherapy

A decade after its first RCT demonstrated its efficacy, food immunotherapy (FIT) is recognized by national and international guidelines as the first established treatment for FA. There is evidence that oral FIT can be effective for children with milk, egg, peanut, and wheat allergies, although desensitization rates for wheat allergy are lower. PALISADE, the largest oral FIT study to date, found that 67.2% of participants achieved the primary endpoint of passing 600 mg dose at the exit DBPCFC after receiving 300 mg peanut protein dose. It has also been confirmed recently in a placebo-controlled study that peanut oral IT (POIT) significantly reduces the risk of reaction after accidental exposure to peanut (placebo group, 24 reactions in 14 patients; active group, eight reactions in five patients; $p < 0.001$). Nevertheless, the recent safety meta-analysis, which looked into 12 POIT studies, estimated that the risk of anaphylaxis while on POIT is over three times higher compared with peanut avoidance (RR, 3.12, 95% CI 1.76 - 5.55) and the risk of adrenaline use is over twice as high (RR, 2.21; 95% CI 1.27 - 3.83) [82]. As a result, FIT research is currently focused on answering crucial questions concerning how to increase the safety of FIT by selecting well-tolerated, effective formulations, routes, and doses, adding adjuvants at the beginning of the treatment, and identifying patients who are more likely to benefit from it. In addition to oral FIT, sublingual IT and EPIT are two alternative routes that have been researched. Despite a favorable safety profile and few reports of systemic allergic reactions, their efficacy is lower [83]. The modest level of desensitization predisposes sublingual IT and EPIT for use in individuals not tolerating OIT. It may also be the case that longer treatment duration is necessary to achieve results comparable with OIT. The other main need is understanding long-term treatment outcomes.

The result of FIT differs from natural outgrowing of FA despite its efficacy in desensitizing to the culprit food. The treatment may provide a margin of protection in case of accidental exposure and introduce certain amounts of the food into regular diet, but the long-term effects are uncertain, with 70 percent of successfully desensitized individuals losing tolerance after avoiding for a short period of time. There is no clear explanation as to why post-IT tolerance is lost despite similar immunologic responses with FA resolution (e.g. decrease in specific IgE concentration and rise in specific IgG4) [84]. Because at least half of the patients fail to maintain unresponsiveness after FIT, the question about the frequency of food consumption remains. A Spanish SEICAP study found that eating an egg twice a week was sufficient to maintain tolerance. Over the median 6.5-year observation period, only a quarter of children who completed milk OIT returned to milk avoidance diets [85]. In terms of continued peanut consumption, 64% of previous peanut IT participants ingested peanuts daily and another 25% less frequently. Even at this late stage of desensitization, allergic reactions including airway involvement were still observed.

Prevention

Although considerable progress has been made in identifying FA risk factors, prevention recommendations are still limited. There are few known risk factors that are easily modifiable. To date, the most modifiable factors have not been found to be effective in preventing FA in clinical trials [86-88]. FA and Anaphylaxis Guidelines Group of the European Academy of Allergy and Clinical Immunology conducted a systematic review and identified 41 randomized controlled trials. In most of these studies, FAs were avoided in the diet, vitamin supplements (maternal and infant), fish oil, probiotics, prebiotics, symbiotics, and hydrolyzed formulas were not found to prevent FA. Although many of these interventions appear to be effective, the authors also noted that most of the evidence surrounding them remains highly uncertain. As a result of insufficient diagnostic criteria, high loss to follow-up, potential confounding, and lack of blinding, many of the trials were at risk of bias [89-91].

In spite of the fact that some FA risks are already established at birth, to date no effective preventative strategies have been developed that can be applied during pregnancy. Currently, peanuts are the only intervention widely recommended to reduce FA risk in infants [90-92]. A large, high-quality randomized controlled trial in high-risk infants conducted in the UK - a country with a relatively high prevalence of FA - largely supports this recommendation. It is less clear whether these findings apply to countries with a low prevalence of peanut allergies. According to meta-analyses of multiple trials, early introduction of egg to the infant diet reduces the risk of egg allergy, although the extent of the reduction appears to be less than for peanut allergy.

Conclusion

A growing number of allergic patients and their families are suffering from FAs, a major public health issue in urbanized areas. In order to treat and prevent FA, it is imperative to investigate the risk factors that have contributed to this increase and their underlying mechanisms. FAs can also be accurately diagnosed with the help of clinical history. Allergy tests can help diagnose FAs and reduce the number of OFCs. It has a high sensitivity for SPT and sIgE, and a high

specificity for CRD and BAT. It is possible to improve the accuracy of FA diagnosis by combining tests, such as using CRD and BAT sequentially after detecting allergen specific IgE with SPT or sIgE. Whenever equivocal results result from combining tests or when not all tests are available, it is necessary to conduct OFCs to confirm or exclude FA diagnosis. Providing a tailored management plan to patients and their families has become increasingly important with the new treatments available.

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Conflict of Interest

None.

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