

Advances in Food Allergy

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KEYWORDS

- Food allergy • Biomarkers • Component-resolved testing • Oral challenge
- Peanut allergy • Oral immunotherapy • Sublingual immunotherapy
- Epicutaneous immunotherapy

KEY POINTS

- Improvements in component-resolved testing, biomarkers, and immunoglobulin G 4(IgG4)/IgE ratios may improve practitioner's ability to discriminate between patients who are food sensitive but can tolerate food, and patients who are truly food allergic.
- Studies in oral immunotherapy, sublingual immunotherapy, and epicutaneous immunotherapy show promising results as potential treatment options for food allergy.
- Changes in guidelines regarding the early introduction of foods, particularly peanuts, as well as additional investigations into adjunctive therapies, may help prevent food allergies.

INTRODUCTION

The subject of food allergy continues to gain considerable interest due, in part, to the clinical challenge it presents in diagnosis, treatment, and management. Given its potential to cause life-threatening anaphylactic reactions and its impact on quality of life and health care systems, increasing attention has been directed toward strategies to prevent food allergies, including analysis of populations, genotype, and phenotype risk factors, and timing of the introduction of foods. This article reviews some of the recent advances in the diagnosis, treatment, and prevention of food allergy.

ADVANCES IN DIAGNOSIS

Making the diagnosis of any type of allergy requires the combination of appropriate symptomatic patient history with a positive test for immunoglobulin E (IgE) to relevant antigens. When testing for food-specific IgE either by skin or by serum, the practitioner faces a similar dilemma to testing for other allergens, the dilemma that a positive test indicating sensitization does not necessarily translate to clinically relevant allergy.¹ This reality poses a diagnostic challenge to the provider and sows confusion in the patient who has difficulty reconciling a positive test result to a food he/she consumes

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without difficulty. In other situations where the test is equivocal or does not meet the threshold to comfortably recommend strict avoidance of the food in question, oral food challenges are employed to determine clinical reactivity, which carry a real risk of potential harm to the patient. When the patient under evaluation is a child, parents also seek to answer the questions of whether the food allergy will be of limited duration or lifelong, whether reactions will be mild or severe, and even whether siblings might develop the same allergy. Improvements in diagnostic testing seek to discriminate between those truly allergic and those merely sensitized without risk of clinical reaction with the goal of reducing the number of oral food challenges needed, as well as predicting duration and severity of food allergy.

Genetic biomarkers may provide 1 method of improving diagnostic accuracy. In a study by Martino and colleagues,² 58 food-sensitized patients ages 11 to 15 months and 13 nonallergic controls underwent skin prick testing, specific IgE testing, oral food challenges, and genome-wide DNA methylation profiling of their blood monocytes. Using 96 DNA methylation sites identified from the study group, these biomarkers were used to successfully predict the clinical reactivity and outcomes of oral food challenges with an accuracy of almost 80% (79.2%), surpassing predictive accuracy of both skin prick tests and specific IgE tests.² Further development of such biomarkers has the potential to provide clinically useful diagnostic assays to determine which patients are allergic versus sensitized and decrease the need for oral food challenges.

Other possibilities at improving diagnostic accuracy include component-resolved testing and the presence of IgG4 or blocking antibodies. Component-resolved testing is a diagnostic test similar to specific IgE testing, but involves measuring IgE antibodies to specific allergenic molecules that comprise the foods, rather than the crude food extract.¹ In a study of 108 peanut-allergic, 77 peanut-sensitized, and 43 nonallergic/nonsensitized children by Santos and colleagues,³ assays of specific IgE and IgG4 to peanut and its components were performed. Although peanut-allergic patients had higher levels of specific IgE to peanut and the components Ara h 1, Ara h 2, and Ara h 8, this did not fully explain the clinical differences in reactivity.³ However, 2 peanut component patterns emerged; all patients sensitized simultaneously to Ara h 1 and to Ara h 2 had peanut allergy, while all patients monosensitized to Ara h 1 were only peanut sensitized.³

Peanut IgG4 levels were 1.6-fold higher in peanut-sensitive patients without clinical allergy, but no significant differences between the levels of specific IgG4 to peanut components were seen, except for Ara h 2-specific IgG4, which was higher in peanut-allergic patients. However, the ratio of peanut-specific IgG4 to peanut-specific IgE was 8 times higher in sensitized but tolerant patients, compared with peanut-allergic patients.³ When the ratio of IgG4 to peanut components was examined, differences between peanut-sensitive but tolerant and peanut-allergic patients became even larger, with the IgG4/IgE ratio to Ara h 1 (18.8-fold, $P = .05$), Ara h 2 (100-fold, $P = .004$), and Ara h 3 (7-fold, $P = .016$).³ Overall, although the absolute levels of specific IgG and IgE to peanut and its components individually did not fully account for clinical differences in reactivity between peanut-allergic and peanut-sensitive/tolerant patients, the ratios between these 2 antibodies for peanuts and its components did.

Two recent studies by Santos and colleagues⁴ have evaluated the usefulness of the basophil activation test (BAT) in discriminating between clinically-allergic and tolerant but sensitized patients, as well as predicting the threshold and severity of response to peanut oral food challenges. In the first study, 43 peanut-allergic, 36 peanut-sensitized but tolerant, and 25 nonallergic children underwent skin prick testing, specific IgE

(sIgE) testing to peanut and its components, and BATing. The BAT in peanut-allergic children showed a peanut dose-dependent upregulation of CD63 and CD203c that was not demonstrated in peanut-sensitized but tolerant ($P < .001$) and nonpeanut-sensitized nonallergic children ($P < .001$). Four BAT diagnostic cutoffs showed 97% accuracy, 95% positive predictive value, and 98% negative predictive value, and when combined in a 2-step approach with either skin prick testing or specific IgE testing to Ara 2, reduced the number of food challenges by 97%.⁴ In the second study, 124 children underwent skin prick testing, specific IgE testing to peanut and its components, and BAT on the day of an oral food challenge to peanut.⁵ The study found that patients with a BAT ratio of CD63 peanut/anti-IgE levels of 1.3 or greater had an increased risk of severe reactions (relative risk [RR], 3.4; 95% confidence interval [CI], 1.8–6.2), and those with a CD-sens value of 84 or greater had an increased risk of reacting to 0.1 g or less of peanut protein (RR, 1.9; 95% CI, 1.3–2.8).⁵

As far as clinic practice, there are no current guidelines or recommendations as to whether component-resolved testing for foods, specific IgG4 levels, or BAT should be ordered. However, these tests can potentially be helpful in guiding clinical decision-making as long as the provider understands that these tests are helpful at making predictions, not definitive determinations at this point in time. Component-resolved testing is not yet available for many foods, while specific IgG4 and BAT may not be widely available anymore. In addition, many insurers consider these tests to be experimental, so if the provider decides to utilize them, the potential costs of each of these tests should be discussed with the patient.

ADVANCES IN TREATMENT

The current mainstay of treatment for food allergy is avoidance and elimination of the allergic food[s] from the patient's diet. Investigation into potential treatments for food allergies has been promising and includes studies into protocols for oral immunotherapy (OIT), sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT). These protocols, however, are not widely available, and food-allergic patients follow the current standard treatment—avoidance and use of auto-injectable epinephrine with accidental exposures. Other adjuvant therapies, such as Chinese herbal therapy and the use of probiotics, aimed at more general alterations in the immune system, have also received some attention as potential treatments for food allergy, but there are few published sound clinical trials evaluating these.

Oral immunotherapy protocols vary widely in food type used, dosing, and timing of escalation, but essentially all involve mixing the allergic food into a vehicle and consuming it in a sequential, incrementally progressive fashion until a set maintenance dose is reached.⁶ In general, oral immunotherapy protocols include an initial dose escalation performed over the course of 1 day, with an minute dose (eg, 0.1 mg of food protein), rapidly increased by doubling doses to a maximum but still subthreshold level of food protein (10–25 mg), in an attempt to identify a dose that be safely given at home.⁶ Then a build-up escalation phase is performed with increasing larger doses given every 1 to 2 weeks in the provider's office, with considerable differences in administration between protocols. In between escalation doses in the practitioner's office, the patient continues to take the daily home doses, until a predetermined maintenance dose is reached. There is no set standard for length of escalation (a few months to years) and maintenance dose (300 mg to over 4000 mg of food protein), depending on which food item is used or protocol is being followed.⁶

Although these protocols offer potential treatment options to food-allergic patients, they are limited in that not all patients can tolerate them. Additionally, these protocols

are not widely available, are difficult to perform, and appear to induce a transient desensitization of the allergic food rather than the preferred longer-term tolerance. Adverse reactions are also commonly seen in these protocols, with the most common symptoms being oral pruritus and abdominal pain.⁶ Some protocols utilize pretreatment with H1 antihistamines, H2 antihistamines, or both, but there is no standard or recommended premedication regimen, and not all protocols use premedication. The protocol withdrawal rates range from 10% to 36%, with the most common adverse event leading to treatment or protocol cessation being abdominal pain and intolerable chronic gastrointestinal symptoms.⁶

SLIT protocols for food allergy are similar in nature to protocols performed for inhalant allergy, in that the allergen is administered in a liquid form, held under the tongue for roughly 2 minutes, and then swallowed. However, sublingual immunotherapy protocols for foods differ in that there tends to be a much more extended period of escalation than for inhalant allergens, and the range of starting dose (usually in micrograms) to maintenance dose (1–10 mg of food protein) is much greater than what is typical with inhalant protocols.⁶ Few studies on sublingual immunotherapy for foods have been published, but overall, most sublingual trials seem to have fewer reported adverse events. However, the effects on induced desensitization and elevation of food thresholds to reactivity with food sublingual protocols do not seem to be as great when compared with food oral immunotherapy.⁶

In a 2015 double-blind placebo-controlled trial of 21 patients comparing peanut SLIT and OIT dosing protocols, subjects were escalated to a maintenance dose of 3.7 mg in the SLIT group or 2000 mg in the OIT group.⁷ Repeat food challenges were performed after 6 and 12 months of maintenance in both groups. Subjects passing oral food challenges at 12 or 18 months were taken off treatment for 4 weeks and rechallenged. Only 16 of 21 subjects completed the study. Adverse reactions were more common with OIT group, and study discontinuation was generally secondary to gastrointestinal symptoms. All 16 subjects had a greater than tenfold increase in challenge threshold, but threshold elevation was significantly greater in the OIT group compared with that in the SLIT group (141- vs 22-fold).⁷ Sustained unresponsiveness was found in only 4 subjects at study completion.⁷

Although studies have demonstrated that skin is a potential route of sensitization in food allergy, it appears it may also be a route of desensitization. Although there are few published studies evaluating EPIT, this technique involves applying an antigen-containing patch to the skin, and there is currently a phase 3 EPIT trial ongoing for peanut and a phase 1/2 EPIT trial for milk underway. The mechanism of action appears to be the activation of skin Langerhans cells with downstream systemic suppression of effector cell responses.⁸ There is only 1 fully published EPIT trial that enrolled 18 children with milk allergy in a double-blind placebo-controlled study for 3 months.⁹ The oral food challenge threshold after 3 months of treatment showed a trend to desensitization but was not statistically significant.⁹

ADVANCES IN PREVENTION

Although advances have been made in diagnostic techniques and in treatment, a great deal of attention has also been given to preventing the development of food allergies, with much of the attention given to peanut allergy. There is an association of the development of food allergies to atopic dermatitis, and it is thought that cutaneous exposure can serve as a route of sensitization to food allergens, especially if there is disruption of the skin barrier as in the case of atopic dermatitis.^{10–12} In a 2015 study comparing peanut protein levels in household dust to skin prick testing, higher levels

of peanut protein containing dust increased the odds of peanut sensitization and likely allergy, particularly in households with children with a history of atopic dermatitis.¹³

As it is becoming clearer that sensitization occurs through the cutaneous route, ways to prevent the development of clinical food allergy have turned toward the timing of the introduction of food through the oral route. The LEAP study (Learning Early About Peanut allergy) published in 2015 has since changed guidelines regarding the method of evaluation and timing of introduction of peanut-containing food items in high-, moderate-, and low-risk infants.^{14,15} The LEAP study randomly assigned 640 high-risk infants (high risk meaning those with severe eczema, egg allergy, or both) to either consume or avoid peanut-containing food items until 5 years of age. At the end of the study, the prevalence of peanut allergy in those infants with an initial negative skin prick test to peanut was 1.9% in the consumption group and 13.7% in the avoidance group; the prevalence of peanut allergy in those infants with a positive skin test was 10.6% in the consumption group and 35.3% in the avoidance group.¹⁴ This led to the 2017 publication of a guideline addendum from the National Institutes of Allergy and Infectious Diseases,¹⁵ which stated

Infants with severe eczema, egg allergy, or both have introduction of age-appropriate peanut-containing food as early as 4 to 6 months of age. Other solid foods should be introduced before peanut-containing foods to show that the infant is developmentally ready. Evaluation with peanut-specific IgE measurement, SPTs, or both be strongly considered before introduction of peanut to determine if peanut should be introduced and, if so, the preferred method of introduction.

Infants with mild-to-moderate eczema should have introduction of age-appropriate peanut-containing food around 6 months of age, in accordance with family preferences and cultural practices. Other solid foods should be introduced before peanut-containing foods to show that the infant is developmentally ready. These infants may have dietary peanut introduced at home without an in-office evaluation. However, some caregivers and health care providers may desire an in-office supervised feeding, evaluation, or both.

Infants without eczema or any food allergy have age-appropriate peanut-containing foods freely introduced in the diet together with other solid foods and in accordance with family preferences and cultural practices.

In addition to the early introduction of foods, some studies have looked at introducing prebiotics, probiotics, and other nutritional supplements in an attempt to prevent the development of food allergies or conditions associated with food allergy, such as atopic dermatitis. A meta-analysis of 29 randomized trials evaluating the effects of probiotics administered to pregnant women, breast-feeding mothers, and/or infants demonstrated that probiotics reduced the risk of eczema when taken by women during the third trimester, when taken by breast-feeding mothers, and when given to infants, but there was no demonstrable effect on other allergic conditions and the certainty in the evidence grading was low.¹⁶ Another randomized trial of 414 infants in a prebiotic formula group, 416 infants in a regular formula group, and 300 breast-fed infants demonstrated significantly decreased development of atopic dermatitis in the prebiotic formula group compared with the regular formula group (5.7% versus 9.7%) at 12 months of age.¹⁷ However, this effect has not been demonstrated to persist beyond 1 year of age.

Overall, there have been a significant number of studies looking at methods to improve diagnosis, treatment, and prevention of food allergies. Undoubtedly in the

next few years, not only will additional clinical diagnostic tests become more widely available to aid in the differentiation between food-allergic and sensitive but tolerant patients, but methods of desensitization, such as epicutaneous immunotherapy, will become more viable alternatives to avoidance. As the general understanding of food allergy improves, strategies for the prevention of food allergy will become more successful.

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