

CME Review

Long-term follow-up of IgE-mediated food allergy: determining persistence versus clinical tolerance

A. Wesley Burks, MD^{*}; and Michael H. Land, MD[†]

^{*} University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

[†] Southern California Permanente Medical Group, San Diego, California

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Learning Objectives:

At the conclusion of this activity, participants should be able to:

- Develop a general approach to re-evaluation of food allergy patients
- Discuss the evidence supporting the use of component-resolved diagnostics in the workup of IgE-mediated food allergy

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Introduction

The practice of allergy and immunology is continually evolving; with recent advances in diagnostic tools, technology, and treatment modalities, clinicians are learning new ways to care for their

Reprints: A. Wesley Burks, MD, Department of Pediatrics, University of North Carolina, 260 MacNider Building CB# 7220, Chapel Hill, NC 27599; E-mail: wburks@email.unc.edu.

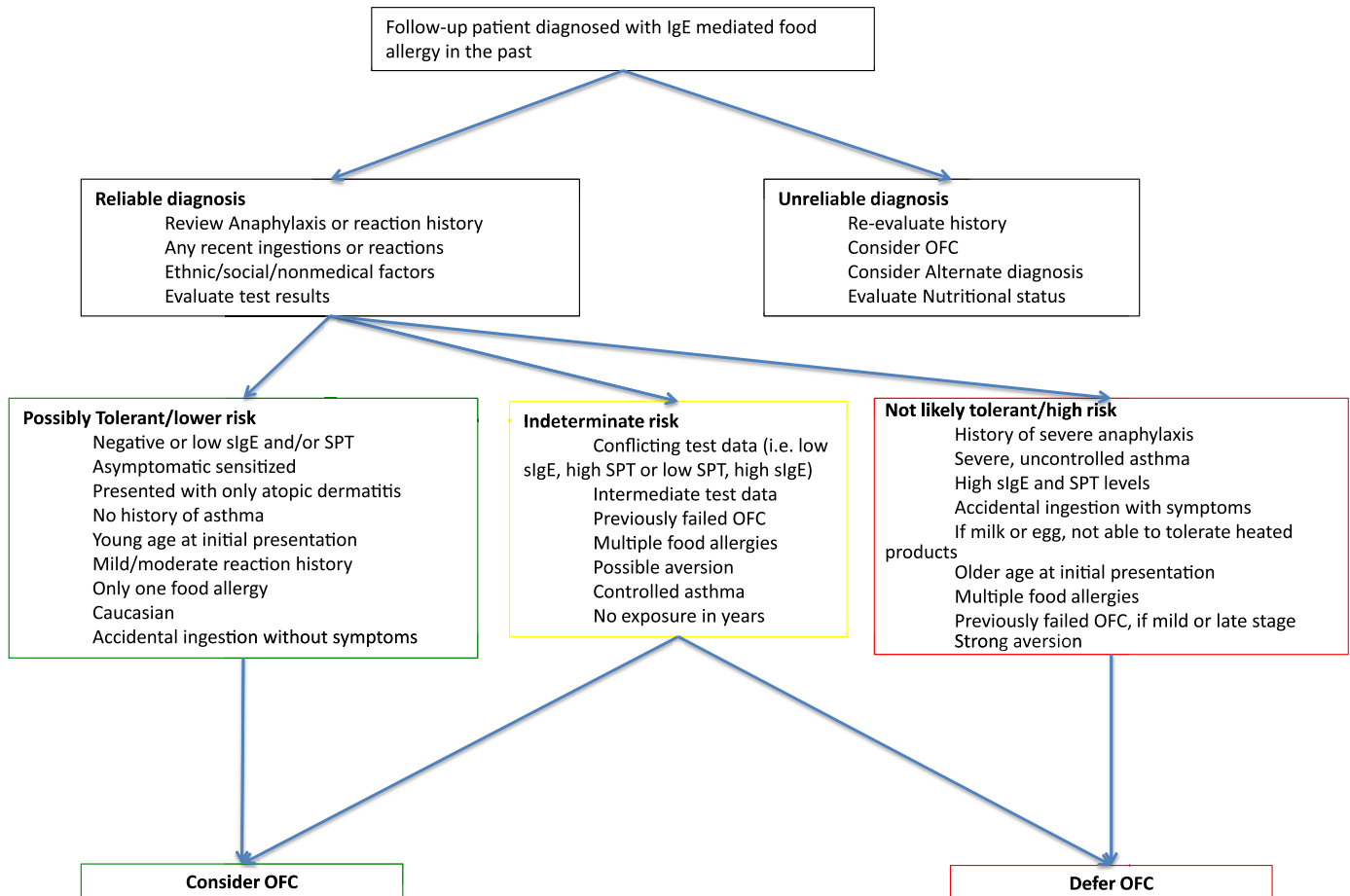


Figure 1. Suggested algorithm for re-evaluation of food allergy to help determine persistence vs tolerance. OFC, oral food challenge; SPT, skin prick test.

patients. As patients' diseases change, clinicians must be willing to change how they manage these patients. In this article, the authors review recent advances in the re-evaluation of known food allergy. This article is not intended to be a comprehensive review of food allergy management, but rather a practical reference for clinicians to review the long-term evaluation of established IgE-mediated food allergy and provide guidance for determining the indication for an oral food challenge (OFC) or continued avoidance. A basic algorithm (Fig 1) may serve as a quick reference for practicing allergists to follow while reviewing this report.

Definition and Epidemiology

The term *food allergy* has been defined as “an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food” by a recent expert panel sponsored by the National Institute of Allergy and Infectious Disease.¹ This definition encompasses many conditions that are subtypes of food allergies, such as food protein-induced enterocolitis syndrome, eosinophilic esophagitis, delayed anaphylaxis to mammalian meat (IgE to galactose- α -1,3-galactose), severe atopic dermatitis from food allergy, and food-dependent exercise-induced anaphylaxis, which is not the topic of this review. Instead, the authors focus on food-induced anaphylaxis, a common type of IgE-mediated food allergy characterized by immediate local and/or systemic symptoms, such as urticaria, angioedema, flushing, vomiting, shortness of breath, wheezing, and respiratory distress.

This topic is of particular importance to allergists because the incidence of food allergies may be continually increasing and

clinicians likely will be faced with an increased volume of patients who need to be followed long term.² Recent estimates on the prevalence of food allergies have ranged from 3% to 8% of the general population.^{3–5} The long-term assessment of patients with established food allergy also depends on which food is involved. Patients allergic to milk, egg, soy, and wheat are more likely to eventually tolerate these foods compared with those allergic to peanuts and tree nuts.¹ These differences between the likelihood of natural tolerance development should be taken into account when assessing each patient.

Evaluation of the Patient

It cannot be overly emphasized that the approach to follow-up of each patient must begin with confirmation of a correct diagnosis of IgE-mediated food allergy. Careful review of the patient's inciting reactions, dose of exposure, timing, symptoms, and test data (skin prick and specific IgE) can solidify the diagnosis and affect decisions on whether to challenge a patient. For example, patients who have had severe anaphylaxis with the first or second exposure to a food (particularly to a small amount) should be approached differently (perhaps more conservatively) than patients who had worsening of mild eczema when a food was regularly consumed. Also, it is important to distinguish patients who have oral allergy syndrome, food protein-induced enterocolitis syndrome, eosinophilic esophagitis, and other forms of food allergy, because these disorders are approached differently. Patients who have never had a food exposure but have asymptomatic sensitization to a food also are a dilemma, because they

Table 1

Factors influencing the re-evaluation of patients with known food allergy at annual follow-up

Factors	Consider testing	Consider deferring testing
Prior skin test	small/negative	large
Prior serum IgE	low/undetected	high
Recent reaction	none for >12 mo	within past 12 mo
Recent exposure without reaction	yes	no
Importance of food to nutrition	very important	not important
Patient willing to eat if able to	not averse	averse
Time from last surveillance test	>2–3 y	<1 y
Asthma history	negative history	positive history or uncontrolled
Food in question	milk, egg, wheat, soy	nuts, fish, shellfish
Complicated medical history	none	pregnant, heart disease, β -blocker use, cannot stop antihistamines
Number of food allergies	1	multiple
Initial presenting reaction	mild	severe

might not truly have a food allergy. Once a patient is determined to have a solid diagnosis of IgE-mediated food allergy, the long-term management would be to determine whether that patient is developing tolerance to the food and should be offered a supervised OFC or advised to continue strict avoidance.

Frequency of Follow-up

As recent guidelines have noted, there is insufficient evidence to indicate an optimal interval for re-evaluation of a patient with a known food allergy. What is often performed in the clinical setting is a re-evaluation of milk, egg, soy, or wheat allergy yearly and peanut, tree nut, fish, and shellfish allergy every 2 to 3 years.¹ This surveillance approach should be combined with several factors to determine whether retesting should be performed or deferred until a later date (Table 1). Of particular importance is whether a patient has interest in even trying to consume the food. If there is a natural aversion to the food despite data indicating that a challenge is indicated, then testing is not necessary. A typical example is a child who has been diagnosed with peanut allergy as an infant but has always regarded peanut as a “poison.” When retesting shows skin and serum test reactions to be negative and the patient is offered an OFC, that patient may have no interest in trying the food and would choose to defer until a later time. This patient would not require re-evaluation testing if the challenge is refused regardless of the results.

A recent study by Gupta et al⁶ examined factors that were associated with the development of tolerance to foods in a cohort of 40,104 children, of which 1,245 had outgrown their food allergies. Factors that were significantly associated with tolerance development included a mild to moderate reaction history, having only 1 food allergy, presenting with only atopic dermatitis, having a white vs black ethnicity, and presenting at a younger age rather than at an older age with the first reaction. Patients who have these factors

may benefit from more frequent testing rather than delaying for longer periods.

Testing Modalities

Most clinicians use skin prick test (SPT) reactions and allergen-specific serum IgE (sIgE) levels in the diagnosis of IgE-mediated food allergy and for re-evaluation testing. Although neither test is superior to the other, the use of 1 modality or the 2 modalities in combination may aid in the decision to perform an OFC. In the initial diagnosis of food allergies, SPTs have a low sensitivity and low positive predictive value compared with OFCs. However, in a patient with a confirmed diagnosis of food allergy, SPTs have high negative predictive values and high sensitivity. The sIgE levels also have comparable sensitivity to SPTs with regard to OFC outcomes.¹ It is important to keep in mind that the decision points for foods are food specific and need to be applied to only those foods. Atopy patch testing, total sIgE, intradermal testing, and IgG levels to foods are not recommended tests for re-evaluation of known food allergy. Ultimately, the OFC is the best testing modality to help clinicians make a diagnosis of tolerance or persistence.

Using Test Data

A recurring theme of this article is that no single test can be used alone to predict tolerance. Using sIgE and SPT data are helpful in the decision-making process, but it is necessary to emphasize the importance of taking multiple factors together to decide to perform an OFC or recommend avoidance. Later in this article, the authors review studies that present positive and negative decision points (positive and negative predictive values) for passed or failed OFCs. These are calculated variables that depend on sensitivity, specificity, and prevalence. To briefly review the reader, the positive predictive value is the probability that a positive result is correct, or true, and the negative predictive value is the probability that a negative result will be true. Thus, when reviewing decision points such as a 95% positive predictive point for a failed OFC, one would consider a sIgE level higher than the cutoff to have a 95% probability of a true positive (failed) OFC. Hence, a 50% negative decision point would suggest that a level below the cutoff would have a 50% probability of a true negative (passed) OFC.

Taking a Patient-Centered Approach

When re-evaluating a patient with a known food allergy, it is crucial to take into consideration individual nonmedical patient factors before making the decision to perform testing. Table 2 presents a list of these factors. First, determine whether there is a desire to introduce the food into the diet if the patient were to pass an OFC. As stated earlier, some children have a natural aversion to a food, and even if they were to have the opportunity to eat the food, they would refuse. This is often encountered in the setting of an OFC when a child refuses to eat the food and an OFC is inconclusive from failure to progress. Knowing beforehand that this might occur would prevent unnecessary scheduling and use of resources. Second, cultural and dietary factors also influence the decision on performing testing or an OFC. Some families and cultures may have ethnic foods or geographic preferences that

Table 2

Nonmedical patient-specific factors influencing the decision to re-evaluate

Aversion	patients may have no desire to eat the food even if they have the opportunity
Cultural and dietary factors	vegetarians may have no desire to introduce egg, fish, or shellfish in the diet, whereas families of fishermen may have a strong desire to introduce fish or shellfish into the diet of a fish-allergic child
Family members with medical problems	having a sibling with the same food allergy may lead some families to defer an oral food challenge in a child who may be developing tolerance to avoid accidental exposure to the sibling; in families in which a specific food is important to ingest (peanut or proteins in diabetic siblings), there may be a strong desire to introduce a food

Table 3

Suggested cutoff values for specific foods predicting positive and negative oral food challenge results

Food	SPT (mm) ~95% positive	Food-specific IgE (kU _A /L)	
		~95% Positive	~50% Negative
Milk	≥8	≥15 ≥5 (if <1 y old)	≤2
Baked milk			
Milk IgE			≤5
Casein IgE			≤0.94
Egg white	≥7	≥7 ≥2 (if <2 y old)	≤2
Baked egg			
Egg IgE	≥15 ^a	≥10	≤2.5
Ovomucoid IgE		≥50	≤0.35 ^b
Peanut	≥8	≥14	≤2 with/≤5 without history of peanut reaction
Ara h 2 IgE		≥0.35	

Abbreviation: SPT, skin prick test.

^aApproximately 60% positive decision point.^bApproximately 90% negative decision point.

would increase or decrease the desire to introduce a particular food. An example of this might be a fisherman's family who has a child allergic to fish and would have a strong desire to evaluate for tolerance development, whereas a family of vegetarians or vegans would likely have no desire to introduce fish into the diet. Third, family members with medical problems may influence the desire to challenge or not. This is particularly relevant in siblings who have the same food allergy, but one sibling may be developing tolerance, whereas the other one does not. Some families may have no desire to introduce the food into one child but not the other for fear of accidental exposure.

Recommending an OFC or Continued Avoidance

Re-evaluation of patients with known food allergy relies on a careful history and confirmation of the underlying diagnosis, evaluating factors that may increase the risk of a failed challenge, determining whether testing is indicated and performing the tests, and taking into account nonmedical patient-specific factors that may defer testing altogether. Figure 1 outlines a basic algorithm that can assist in this type of assessment.

Recent data on the use of SPTs and sIgE levels on OFC outcomes in several different food allergies has been published and are reviewed below for milk, egg, and peanut and presented in Table 3. Within the past 5 to 10 years, component-resolved diagnostic tests for peanut and the use of ovomucoid and casein IgE levels in egg and milk allergies have been used more in clinical practice.

Cow's Milk

In recent years, Sampson⁷ and Sampson and Ho⁸ established parameters that have been widely used and considered to be the recommended decision points for predicting positive or negative OFC reactions in children with food allergies. In studies from 1997 and 2001 involving serum samples from patients with food allergy (n = 196 in the first study, n = 100 in the second study), the 95% predictive decision point for a positive (failed) OFC for milk was determined to be 15 kU_A/L.^{7,8} A 2009 work group report on OFC testing also presented this “cutoff” level as a recommended 95% predictive decision point at which patients have a greater chance for a positive OFC result.⁹ A negative decision point for a 50% pass rate is generally regarded to be a milk IgE level lower than or equal to 2 kU_A/L based on work performed by Perry et al.¹⁰ In children younger than 1 year, Garcia-Ara et al¹¹ analyzed 170 patients with cow's milk allergy and found that the 95% predictive decision point for a positive OFC was 5 kU_A/L.

The utility of the SPT as a predictor of a positive OFC was studied by Sporik et al¹² in 339 challenges to cow's milk, and they found that the 95% predictive decision point was an 8-mm skin wheal.¹²

Recent studies from Wood et al¹³ in the Consortium for Food Allergy Research, including the primary author of this review, analyzed data from a multicenter cohort of 244 children with milk allergy in an observational study of milk and egg allergy.¹³ The study found that baseline characteristics of milk IgE, milk SPT, and severity of atopic dermatitis were the most predictive factors of resolution of milk allergy over a 5-year period. Of patients with a baseline milk IgE lower than or equal to 2.0 kU_A/L, a milk SPT wheal smaller than or equal to 5 mm, or mild or absent atopic dermatitis, more than 70% of patients had resolution of their milk allergy at 5 years. In addition, when using all 3 variables, the investigators developed a composite scoring system that could be individualized to a specific patient. An online Web-based calculator is available to assist clinicians in counseling patients (<http://www.cofargroup.org>).

Baked Cow's Milk Products

In 2008, Nowak-Węgrzyn et al¹⁴ reported their findings of a prospective study to evaluate the ability of children with milk allergy to tolerate extensively heated milk products. Based on their previous findings that children who outgrew their milk allergy had antibodies directed against conformational epitopes¹⁵ and high temperatures could destroy conformational epitopes, they sought to determine whether highly heated or baked milk products would be tolerated. The study of 100 children with milk allergy indicated that approximately 75% of them tolerated heated or baked milk. The subjects were challenged with a muffin and then a waffle (both considered “baked milk”), each containing 1.3 g of milk protein. At the time, their data suggested that a milk-specific IgE level lower than or equal to 5 kU_A/L would predict a 90% chance of tolerating heated milk. They found that 100% of patients with an undetectable milk sIgE level (≤0.35 kU_A/L) and a SPT wheal smaller than or equal to 5 mm tolerated heated milk (n = 6).

A subsequent study by the same group published in 2011 examined the long-term effects of children with milk allergy who were tolerant of baked milk and their likelihood of developing tolerance to unheated milk. They challenged 65 children with baked milk tolerance and 23 with baked milk reaction to various forms of heated and unheated milk products and found that 60% of patients who were tolerating baked milk eventually tolerated unheated milk over a 3-year period, whereas only 9% of patients with a baked milk reaction were able to tolerate unheated milk. A comparison group of 60 matched subjects who were not challenged with baked milk to evaluate the natural development of milk tolerance eventually tolerated milk after 3 years (22% of patients). This finding suggests that clinicians should identify patients with milk allergy who tolerate baked milk and continue to follow these patients closely, with the hope that they may develop tolerance sooner than patients who do not tolerate baked milk.¹⁶

In determining the challenge criteria for baked milk, in addition to data from the 2008 study¹⁴ that suggested a milk sIgE level lower than or equal to 5 kU_A/L as the lower cutoff point, new data from the same group published in 2012 suggested a casein IgE level lower than or equal to 0.94 kU_A/L as the negative decision point for passing a baked milk OFC.¹⁷ In this analysis, Caubet et al¹⁷ evaluated 225 patients for tolerance to baked milk by studying baseline IgE levels specific to casein, cow's milk, and β-lactoglobulin. It was determined that casein IgE levels had significantly greater accuracy compared with milk and β-lactoglobulin IgE levels.

Egg White

In addition to studies of milk allergy, Sampson⁷ and Sampson and Ho⁸ analyzed patients with egg allergy in 1997 and 2001. Data

from the studies of predictive sIgE levels (cited earlier) suggested that a 95% predictive decision point for a positive OFC reaction to egg would be an egg white IgE level of at least 7 kU_A/L, whereas data from Perry et al¹⁰ suggested that a 50% predictive decision point for a negative OFC would be lower than or equal to 2 kU_A/L.¹⁰ These decision points also were included in the 2009 work group report on OFCs.⁹ In children younger than 2 years with egg allergy, the predictive decision point for a positive OFC reaction was 2 kU_A/L in a study of 58 children with egg allergy.¹⁸ Sporik et al¹² also determined an SPT wheal of at least 7 mm to be the 95% positive predictive point for a failed OFC to egg.

A recent natural history study by Savage et al¹⁹ sought to identify the proportion of children with egg allergy who developed tolerance over time and identify predictors of the tolerance. The investigators reviewed 881 patients with egg allergy who went on to develop tolerance or continued to have persistent egg allergy. A Kaplan-Meier analysis predicted resolution of the egg allergy in 4% by 4 years of age, 12% by 6 years, 37% by 10 years, and 68% by 16 years. The patients who had persistent egg allergies generally had higher egg IgE levels, additional atopic diseases, and the presence of additional food allergies. Of note, this was a highly selected cohort from a tertiary center and most patients had multiple food allergies. Therefore, these data may be applicable to only certain populations of patients in clinical practice.

Highly Heated (Baked) Egg

The standard of care in patients with egg allergy until recent years has been to recommend strict avoidance of all egg-containing products. Attention has been drawn to component-resolved diagnostic testing with a focus on ovomucoid IgE. As the dominant allergen in egg white, ovomucoid is considered relatively heat stable and retains solubility with extensive heating, whereas ovalbumin, the most abundant protein in egg white, is sensitive to heat denaturation.²⁰ Clinically, this property is analogous to casein (heat stable) and whey (heat sensitive) in milk allergy.¹⁴

Recent investigations have suggested that approximately 75% of patients with egg allergy tolerate highly heated or baked egg products.^{20–22} In the clinical setting, not all patients who present with an egg allergy have previously ingested baked egg, which provides clinicians the opportunity to add a previously restricted food into the diet.

Ando et al²³ followed 108 children with egg allergy who were challenged to raw and heated egg and found that the egg white IgE level was helpful in diagnosing allergy to raw egg white, with a positive decision point of 7.4 kU_A/L (based on 95% specificity) and a negative decision point of 0.6 kU_A/L (based on 95% sensitivity). The ovomucoid IgE level was superior in determining a reaction to heated egg, with a positive decision point of 10.8 kU_A/L and a negative decision point of 1.2 kU_A/L. In their study, 38 of 108 patients reacted to heated egg, whereas 29 reacted only to raw egg white and 41 were tolerant. In this study, the heated egg was prepared in plain form (liquid egg white heated to 90°C for 60 minutes), which differs from other studies that have incorporated the highly heated egg in a wheat-based baked product (ie, a muffin or waffle) to create a food-matrix effect.

Another study on tolerance of extensively heated egg by Lemon-Mule et al²⁰ involved challenging 117 children with egg allergy to a muffin and waffle initially, followed by scrambled egg or French toast, in patients with baked egg tolerance. The investigators found that 27 of 117 reacted to heated egg, whereas most patients tolerated heated or regular egg (64 tolerated heated egg and 23 tolerated regular egg). Probability curves from this group found the ovomucoid-specific IgE level had a 90% positive predictive value at a level of 50 kU_A/L and a 90% negative predictive value at an undetectable ovomucoid IgE level. An egg white SPT wheal of 15 mm

was 60% predictive, whereas a negative egg white SPT result had a lower than 5% risk for a positive OFC.²⁰

Lieberman et al²² in the same group performed 100 consecutive OFCs to baked egg in children with egg allergy and found that 66% of patients tolerated baked egg. Patients who passed the OFC had a median egg white IgE level of 2.81 kU_A/L, whereas patients who failed the OFC had a median egg white IgE level of 5.85 kU_A/L. Their median wheal sizes were identical, and ovomucoid IgE levels were not measured. This group's predictive values provided an 89% negative predictive value at an egg white IgE level of 2.5 kU_A/L and a 60% positive predictive value at an egg white IgE level of 10.0 kU_A/L.

In 2013, Bartnikas et al²⁴ reviewed 1,186 patients who had ovomucoid IgE levels tested, among whom 169 patients had baked egg OFCs. Of the 169 patients, 142 passed the baked egg OFCs. The investigators found that egg white SPT and egg white IgE were superior to ovomucoid IgE in their analysis, with greater than 90% predictive values for passing baked egg OFCs at an egg white IgE level of 6 kU_A/L, an ovomucoid IgE level of 0.35 kU_A/L, and an egg white SPT wheal of 11 mm. This group concluded that the ovomucoid IgE level could aid in predicting the outcome of a baked egg OFC but that the egg white SPT reaction and egg white IgE level were superior.²⁴

Taken together, these studies raise important conclusions regarding the management of patients with egg allergy. First, it is clear that most patients with egg allergy tolerate baked egg. Second, owing to this phenomenon, identifying these patients among those with egg allergy may define a clear “second phenotype” of egg allergy (the “baked egg tolerant”) that is more likely to develop tolerance and could benefit from more frequent follow-up. Third, although there is a role for ovomucoid IgE levels in predicting OFC outcome, the utility of this must be taken together with other patient factors, egg white SPT, egg white IgE, and the clinical history.

Peanut

An area of great interest in recent years has been the use of component-resolved diagnostics in the diagnosis and management of peanut allergy. Before the advent of this technology, clinicians relied on peanut-specific IgE levels and peanut SPT. As mentioned earlier, investigations by Sampson and Ho⁸ in 1997 and 2001 using sIgE levels to predict OFC outcomes also examined peanut-specific IgE. The 95% positive predictive point for peanut IgE was 14 kU_A/L. A 50% negative predictive point was determined by Perry et al¹⁰ to be a peanut IgE level lower than or equal to 2 kU_A/L with a history of clinical reactivity and a peanut IgE level lower than or equal to 5 kU_A/L with no history of clinical reaction. Sporik et al¹² also determined a 95% positive predictive point for peanut SPT wheal to be at least 8 mm.

The major peanut component allergens include Ara h 1, 2, and 3, which are seed storage proteins that are stable to heating. Ara h 8 is a Bet v 1 (major allergen in birch pollen) homolog and is a labile protein, which is associated with mild or no symptoms. Ara h 9 is a stable lipid transfer protein that is associated with more severe symptoms but more commonly seen in the Mediterranean regions.^{25–27} Much attention has been given to sIgE antibodies recognizing Ara h 2 and Ara h 6 (an Ara h 2 homolog), with most studies performed in children, suggesting that the diagnosis of clinical peanut allergy was correlated to the presence of IgE to Ara h 2.^{28–31}

As clinicians begin to use these component-resolved diagnostics, it is important to ask oneself 2 key questions when approaching a patient: (1) Does this patient need component-resolved tests to further the management of the disease? (2) Does this patient have an important ethnic or geographic background that might influence the interpretation of the testing? The first question must take into account the clinical history, prior

testing, and factors described earlier regarding the indications for an OFC. For example, a patient who has had clear life-threatening anaphylaxis to peanut and has a high peanut IgE would not require component testing because it likely will not change management. Patients who are not candidates for an OFC may not require testing, because it will not affect their outcome. The second question considers data from a study by Vereda et al³² who analyzed sIgE levels to Ara h 1, 2, 3, 8, and 9 and birch and grass allergens in populations from the United States, Spain, and Sweden. Of note, the data on American patients were taken from a tertiary center and those on Spanish patients were from 2 allergy clinics, and the Swedish patients were part of a birth cohort. These selected cohorts may limit the interpretation of data by the practicing allergist. The investigators found that the American patients most frequently had IgE antibodies to Ara h 1, 2, and 3 and often presented with severe symptoms, whereas the Spanish patients had IgE to these 3 components less frequently but were more often sensitized to Ara h 9 and typically became allergic to peanut after developing plant-derived food allergies. The Swedish patients had greater sensitization to Ara h 1, 2, and 3 but also had the highest sensitization rates to Ara h 8 (the Bet v 1 homolog). Also notably, the Spanish and Swedish patients developed peanut allergy more often after 2 years of age, whereas the American patients developed peanut allergy after approximately 1 year of age.³² These differences in geographic and ethnic backgrounds further emphasize the importance of taking a patient-centered approach to the re-evaluation of peanut allergy.

Nicolaou et al²⁸ examined data from 81 children from the United Kingdom with peanut sensitization but not necessarily clinical allergy who underwent OFCs and had levels of peanut IgE and IgE to Ara h 1, 2, 3, 8, and 9. The study found that 29 of 81 patients were allergic to peanut, whereas 52 were tolerant of peanut, 80 had sIgE to Ara h 2, and 66 had sIgE to all components. The investigators calculated a positive predictive point for an Ara h 2 IgE level of 0.35 kU_A/L, with 96% sensitivity and 100% specificity, and correctly classified 97% of patients with true peanut allergy. Lieberman et al,³³ in the United States and Sweden, analyzed data from 167 patients who underwent peanut OFCs and had IgE to peanut and Ara h 1, 2, 3, and 8. They determined that peanut IgE was the most sensitive test (93%) to detect peanut allergy, but IgE to Ara h 2 was the most specific (92%) and had the best positive predictive value (94%) at a level of at least 0.35 kU_A/L.

In further studies examining the ability of sIgE to Ara h 2 to predict symptomatic peanut allergy, investigators from different groups were not as convinced that sIgE to Ara h 2 was clearly advantageous in correctly diagnosing peanut allergy without an OFC. Keet et al³⁰ retrospectively reviewed 60 American patients with peanut sensitization, 26 of whom had failed OFCs and 35 had passing OFCs. Their data demonstrated that Ara h 2 was the most commonly recognized peanut component in patients with failed OFCs and had a diagnostic sensitivity of 96% and a specificity of 54%; however, IgE to Ara h 2 misclassified 26% of patients at a level of 0.23 kU_A/L and 21% of patients at a level of 0.35 kU_A/L.³⁰ Lopes de Oliveira et al³¹ evaluated the predictive ability of peanut and component IgE levels in diagnosing peanut allergy in 61 German patients undergoing a peanut OFC. Thirty-four patients had peanut allergy. They found that 94% of patients with peanut allergies had IgE to Ara h 2, but that 26% of sensitized but tolerant patients also had IgE to Ara h 2.

Conclusion

Food allergy is a growing medical problem that will continue to be a major part of allergy practices for years to come. Establishing a diagnosis is critical to accurately counsel patients on appropriate dietary restrictions and lower the risk for life-threatening

anaphylaxis. The long-term follow-up of patients with established food allergy is challenging for different reasons. The heterogeneity of food allergy does not promote the use of protocols to manage disease as in other specialties such as cardiology, oncology, or endocrinology. Therefore, it is difficult to standardize therapy or long-term management of these patients.

The use of component-resolved diagnostic testing is likely to provide clinicians with additional tools in the re-evaluation of patients with food allergy. For milk and egg, the emergence of a new phenotype of patient who tolerates highly heated or baked goods is likely to decrease unnecessary restrictions and may direct more frequent follow-up visits to ultimately allow such patients to tolerate unheated milk or egg. The use of Ara h 2–specific IgE levels may be beneficial in the assessment of patients with peanut allergy. For all 3 of these foods, more studies are needed and in the near future will be informative to the field regarding the utility of component-resolved tests. Until there is a viable active treatment for food allergy, regular follow-up and re-evaluation can help identify patients who could naturally develop tolerance.

References

- [1] Boyce JA, Assa'ad A, Burks AW, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol*. 2010;126:S1–58.
- [2] Sicherer SH, Munoz-Furlong A, Godbold JH, Sampson HA. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. *J Allergy Clin Immunol*. 2010;125:1322–1326.
- [3] Rona RJ, Keil T, Summers C, et al. The prevalence of food allergy: a meta-analysis. *J Allergy Clin Immunol*. 2007;120:638–646.
- [4] Sicherer SH. Epidemiology of food allergy. *J Allergy Clin Immunol*. 2011;127:594–602.
- [5] Gupta RS, Springston EE, Warrier MR, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics*. 2011;128:e9–e17.
- [6] Gupta RS, Lau CH, Sita EE, Smith B, Greenhawt MJ. Factors associated with reported food allergy tolerance among US children. *Ann Allergy Asthma Immunol*. 2013;111:194–198 e4.
- [7] Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol*. 1997;100:444–451.
- [8] Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol*. 2001;107:891–896.
- [9] Nowak-Węgrzyn A, Assa'ad AH, Bahna SL, Bock SA, Sicherer SH, Teuber SS. Work Group report: oral food challenge testing. *J Allergy Clin Immunol*. 2009;123:S365–S383.
- [10] Pery TT, Matsui EC, Kay Conover-Walker M, Wood RA. The relationship of allergen-specific IgE levels and oral food challenge outcome. *J Allergy Clin Immunol*. 2004;114:144–149.
- [11] Garcia-Ara C, Boyano-Martinez T, Diaz-Pena JM, Martin-Munoz F, Reche-Frutos M, Martin-Esteban M. Specific IgE levels in the diagnosis of immediate hypersensitivity to cows' milk protein in the infant. *J Allergy Clin Immunol*. 2001;107:185–190.
- [12] Sporik R, Hill DJ, Hosking CS. Specificity of allergen skin testing in predicting positive open food challenges to milk, egg and peanut in children. *Clin Exp Immunol*. 2000;30:1540–1546.
- [13] Wood RA, Sicherer SH, Vickery BP, et al. The natural history of milk allergy in an observational cohort. *J Allergy Clin Immunol*. 2013;131:805–812.
- [14] Nowak-Węgrzyn A, Bloom KA, Sicherer SH, et al. Tolerance to extensively heated milk in children with cow's milk allergy. *J Allergy Clin Immunol*. 2008;122:342–347. e1–e2.
- [15] Vila L, Beyer K, Jarvinen KM, Chatchatee P, Bardina L, Sampson HA. Role of conformational and linear epitopes in the achievement of tolerance in cow's milk allergy. *Clin Exp Immunol*. 2001;31:1599–1606.
- [16] Kim JS, Nowak-Węgrzyn A, Sicherer SH, Noone S, Moshier EL, Sampson HA. Dietary baked milk accelerates the resolution of cow's milk allergy in children. *J Allergy Clin Immunol*. 2011;128:125–131 e2.
- [17] Caubet JC, Nowak-Węgrzyn A, Moshier E, Godbold J, Wang J, Sampson HA. Utility of casein-specific IgE levels in predicting reactivity to baked milk. *J Allergy Clin Immunol*. 2013;131:222–224 e1–e4.
- [18] Boyano-Martinez T, Garcia-Ara C, Diaz-Pena JM, Martin-Esteban M. Prediction of tolerance on the basis of quantification of egg white-specific IgE antibodies in children with egg allergy. *J Allergy Clin Immunol*. 2002;110:304–309.
- [19] Savage JH, Matsui EC, Skripak JM, Wood RA. The natural history of egg allergy. *J Allergy Clin Immunol*. 2007;120:1413–1417.
- [20] Lemon-Mule H, Sampson HA, Sicherer SH, Shreffler WG, Noone S, Nowak-Węgrzyn A. Immunologic changes in children with egg allergy ingesting extensively heated egg. *J Allergy Clin Immunol*. 2008;122:977–983 e1.

- [21] Des Roches A, Nguyen M, Paradis L, Primeau MN, Singer S. Tolerance to cooked egg in an egg allergic population. *Allergy*. 2006;61:900–901.
- [22] Lieberman JA, Huang FR, Sampson HA, Nowak-Wegrzyn A. Outcomes of 100 consecutive open, baked-egg oral food challenges in the allergy office. *J Allergy Clin Immunol*. 2012;129:1682–1684 e2.
- [23] Ando H, Moverare R, Kondo Y, et al. Utility of ovomucoid-specific IgE concentrations in predicting symptomatic egg allergy. *J Allergy Clin Immunol*. 2008;122:583–588.
- [24] Bartnikas LM, Sheehan WJ, Larabee KS, Petty C, Schneider LC, Phipatanakul W. Ovomucoid is not superior to egg white testing in predicting tolerance to baked egg. *J Allergy Clin Immunol*. 2013;1:354–360.
- [25] Asarjoj A, Nilsson C, Lidholm J, et al. Peanut component Ara h 8 sensitization and tolerance to peanut. *J Allergy Clin Immunol*. 2012;130:468–472.
- [26] Krause S, Reese G, Randow S, et al. Lipid transfer protein (Ara h 9) as a new peanut allergen relevant for a Mediterranean allergic population. *J Allergy Clin Immunol*. 2009;124:771–778 e5.
- [27] Javaloyes G, Goikoetxea MJ, Garcia Nunez I, et al. Pru p 3 acts as a strong sensitizer for peanut allergy in Spain. *J Allergy Clin Immunol*. 2012;130:1432–1434 e3.
- [28] Nicolaou N, Murray C, Belgrave D, Poorafshar M, Simpson A, Custovic A. Quantification of specific IgE to whole peanut extract and peanut components in prediction of peanut allergy. *J Allergy Clin Immunol*. 2011;127:684–685.
- [29] Dang TD, Tang M, Choo S, et al. Increasing the accuracy of peanut allergy diagnosis by using Ara h 2. *J Allergy Clin Immunol*. 2012;129:1056–1063.
- [30] Keet C, Johnson K, Savage J, Hamilton RG, Wood RA. Evaluation of Ara h 2 IgE thresholds in the diagnosis of peanut allergy in a clinical population. *J Allergy Clin Immunol*. 2013;1:101–103.
- [31] Lopes de Oliveira LC AM, Brill M, Schultz G, et al. The value of specific IgE to peanut and its component Ara h 2 in the diagnosis of peanut allergy. *J Allergy Clin Immunol*. 2013;1:394–398.
- [32] Vereda A, van Hage M, Ahlstedt S, et al. Peanut allergy: Clinical and immunologic differences among patients from 3 different geographic regions. *J Allergy Clin Immunol*. 2011;127:603–607.
- [33] Lieberman JA, Glaumann S, Batelson S, Borres MP, Sampson HA, Nilsson C. The utility of peanut components in the diagnosis of IgE-mediated peanut allergy among distinct populations. *J Allergy Clin Immunol*. 2013;1:75–82.