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The Likelihood of Remission of Food Allergy in Children: When Is the Optimal Time for Challenge?

Robert A. Wood

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Abstract Although diagnostic testing methods for food hypersensitivity have improved over time, both in vivo and in vitro methods are significantly flawed, especially as evidenced by the frequent occurrence of false-positive test results. Because of these limitations, oral food challenge testing remains an essential element in the diagnosis and management of food allergy. In fact, the double-blind, placebo-controlled food challenge remains the gold standard for the diagnosis of food allergy. In this review, we focus on the optimal timing of oral food challenges, especially for patients with a known food allergy, to determine if the food allergy may have been outgrown.

Keywords Food allergy · Oral food challenge · Children · Pediatric · Remission · Food allergy testing · Milk allergy · Egg allergy · Peanut allergy · Tree nut allergy

Introduction

The natural history of food allergy is generally positive in that a large proportion of food allergy is typically outgrown over time. However, this varies dramatically from food to food, and even from patient to patient. It is therefore very important that each patient's care be individualized with regard to the natural course of his or her specific food allergies and the optimal timing of oral food challenges (OFCs) to determine if an allergy has been outgrown. This review describes the means currently available to optimize this important decision process, with the goal being to minimize unnecessary challenges, given their inherent risk, while at the same time using challenges to avoid unnecessary dietary restrictions [1, 2, 3••].

R. A. Wood (✉)
Pediatric Allergy and Immunology,
Johns Hopkins University School of Medicine,
600 North Wolfe Street,
Baltimore, MD 21287, USA
e-mail: rwood@jhmi.edu

Overall Indications for Oral Challenge Testing

There are several reasons that oral challenge testing should be considered, for both clinical and research purposes. As presented in the algorithm in Fig. 1, in the clinical setting, challenges are typically done for three major reasons. First, OFCs are used to establish an accurate diagnosis when the diagnosis is still not clear after performing other standard diagnostic tests, including the history, skin testing, measurement of specific IgE levels, and/or elimination diets. For example, if a patient recently experienced an acute, severe reaction to his or her first peanut exposure and has a strongly positive skin test or markedly elevated peanut-specific IgE level, an OFC to peanut would not be necessary or appropriate [4–15]. In the second scenario, if a patient has a chronic allergic condition, such as atopic dermatitis or allergic gastrointestinal disease, skin tests or specific IgE levels that are not in the diagnostic range, and an unclear response to an elimination diet, one or more challenge tests may be very appropriate.

Third, OFCs are frequently used to determine if a patient with a known food allergy has developed tolerance to that food. For example, in a patient with a known allergy to egg or peanut who has remained reaction free over a period of time and with test results that suggest that the allergy may have been outgrown, a challenge should be considered to determine the degree of tolerance. If a reaction has occurred in the recent past, usually considered to be a minimum of 1 year, especially to a small exposure, an oral challenge

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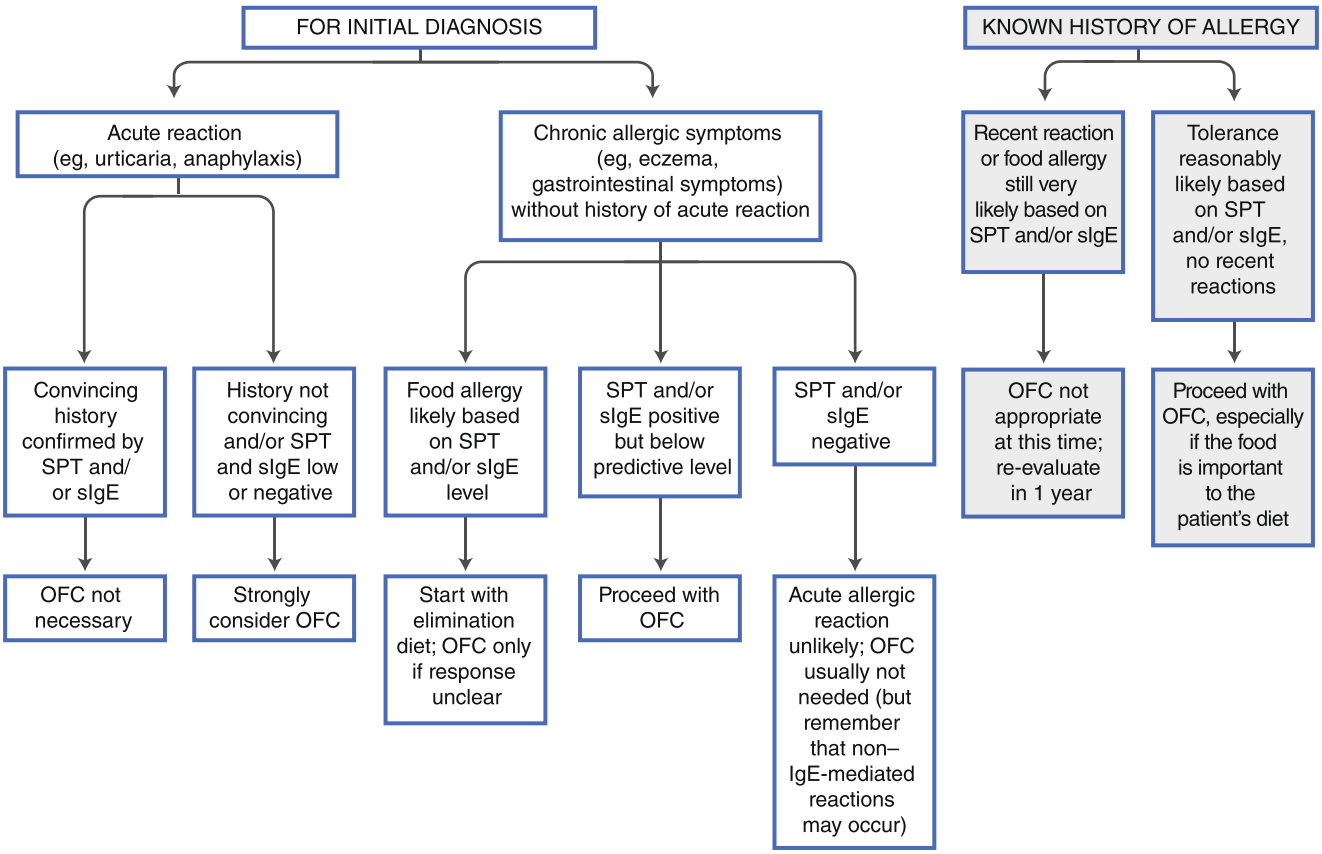

Fig. 1 Oral food challenge (OFC) decision making. Assessments to determine timing of challenges should be based on a detailed history, skin prick test(s) (SPT), and specific IgE level(s) (sIgE). OFCs are likely to be needed in one of three common clinical scenarios. The *shaded boxes* are most relevant to this review regarding the timing of challenge in patients with known food allergy

usually would not be necessary. On the other hand, even if the test results suggest an ongoing allergy, if there has been an accidental exposure without a reaction, especially to a larger exposure, a challenge would be very appropriate.

Although the goal of every challenge is the demonstration of complete tolerance, even if a reaction occurs in the challenge, that information can still be used to guide the patient and family regarding the approach to the diet (e.g., the need for strict avoidance of the problem food, or possibly some liberalization of the diet). This may be especially the case for milk and egg allergy, for which it has been shown that many children can tolerate the extensively heated form of milk or egg even though they are still reactive to the uncooked or less-heated form of the food [16, 17].

The data obtained from failed OFCs may also help the physician counsel patients regarding the risks they may encounter with accidental exposures [18]. This would particularly be the case if a patient experienced a significant reaction with a very small challenge dose. However, challenges typically do not provide information that will accurately predict the risk or extent of future reactions because challenges are conducted by giving gradually increasing doses of the food and are normally stopped at the first sign of a reaction, after which medications are immediately administered. Therefore, this will not typically mimic the real world, in which a single large dose may be ingested, early signs of a reaction may not be recognized, and medications may not be readily available. Therefore, we never do challenges for the primary purpose of determining the risk of future reactions or to inform the development of a specific action plan for treating future reactions.

Specific Challenge Considerations

In the clinical setting, decision making about challenges is based on three key criteria:

- The chances of success. We typically recommend food challenges for younger children when odds of a successful challenge are 50% or greater for that particular food, and consider challenges with lower odds of success as children grow older, especially for foods that are harder to avoid or more important to the diet. For example, we would not typically do a food

challenge in a 2-year-old with peanut allergy with a 10% to 20% chance of success but would recommend such a challenge in a teenager with the same test results who has been reaction free for the past decade.

- The potential for risk. Unfortunately, although certain criteria will help predict the odds of a successful challenge, no test results accurately predict challenge risk. In addition, even though the food was previously associated only with chronic symptoms (e.g., eczema), OFCs performed after a period of elimination could result in acute and severe reactions [19, 20]. It is also important to recognize that different patients and families may have widely varying tolerance for risk, with some being very comfortable with the risks that a challenge entails and others being anxious to the point at which they may decide to defer a challenge until success is almost guaranteed.
- The preferences of the patient and family and the importance of the food to the diet. For example, we typically would be much quicker to do an OFC to a major food item, such as milk, egg, or wheat, even if the chances of success are less because it would be so advantageous to be able to reintroduce that food into the diet. It is also very important to recognize that a food that might be unimportant to one family might be extremely important to another. For example, one family may not care if fish or lentils are ever introduced into the diet, whereas for another family practicing a vegetarian diet, these might be extremely important foods.

Given these key considerations, I believe that my key role as the food allergy specialist is to provide my best estimate for the chance of a successful challenge and the potential for risk and then let the family decide whether a challenge to that particular food makes sense to them. We rarely pressure a child or family to do a challenge unless we believe that the child's quality of life or nutritional status is being adversely affected by unnecessary food avoidance. One final consideration is that OFCs are most appropriate when the food is likely to become part of the diet, as food allergy may occasionally recur after a negative challenge if the family practices continued avoidance or infrequent ingestion [21]. Although this has been demonstrated only for peanut, the same scenario is likely with other foods, especially those that may be difficult to incorporate into the diet.

Determining if an Allergy Has Resolved

Children should be evaluated at regular intervals to determine if a food allergy has been outgrown. This is usually done yearly; however, longer or shorter intervals may be more appropriate in some situations. As examples, a young child with a reaction to fruit might be evaluated every 6 months, and an older child with persistent peanut or tree nut allergy may not need any repeat testing after the first few years if there is no indication of improvement.

Decisions regarding the appropriate timing of OFCs should be based on a combination of in vitro testing (specific IgE levels), skin prick testing, and information on accidental exposures. The optimal method of monitoring specific food allergies has not yet been determined, and various approaches can be used. We primarily use the clinical history and IgE testing (using the ImmunoCAP [Phadia AB, Uppsala, Sweden] method) to follow patients in our clinic. We generally do not perform repeat skin testing, as we believe it does not change our management in most cases. However, other centers routinely use skin testing in making decisions about whether or not to proceed to an oral challenge, and this information could be very helpful in select patients.

As noted above, if accidental ingestions have occurred without reaction, a challenge should be considered even if the test results suggest that the child is still allergic. The history of ingestion—with or without a reaction—is always the most valuable information, as both skin and serologic tests are frequently inaccurate. If the patient has clearly reacted in the past or had a previous failed OFC, the food has been successfully avoided, and there is no interim history to suggest a recent reaction, then we recommend the following food-specific re-evaluation. If there is no history of reaction, or the history suggests that the food has been previously tolerated, the paradigm is completely different, given the inherent inaccuracy of food allergy test results. In these cases, challenges should be pursued much more liberally.

Cow's Milk and Egg

IgE-mediated allergies to milk and egg are usually lost gradually throughout childhood and adolescence [22–30]. We retest yearly with IgE (ImmunoCAP) testing. The IgE level and the rate of decline are useful predictors of challenge outcome. We usually offer challenges to milk and egg when the specific IgE level is less than or equal to 2 kU/L, which gives the patient an approximately 50% chance of passing the challenge in our patient population [13]. However, positive predictive values for both specific IgE and skin prick testing may vary depending on the population studied [31]. In addition, lower cutoffs may be necessary for children younger than 2 years of age, and we are happy to challenge at higher values depending on the age of the child, the overall IgE profile, and family preference. For example, even if there is only a 10% chance of success, it may be more reasonable to proceed

with a challenge in a 12-year-old than a 2-year-old, and in a patient who demonstrates overall higher IgE levels. An IgE level of 3.5 kU/L may be very different in a child with a history of severe reactions and no other elevated food-specific IgE results compared with the highly atopic child who has markedly elevated IgE levels to many foods.

As noted above, recent evidence has also demonstrated that a substantial number of children with milk and egg allergy—overall at least 50%—can tolerate these foods in an extensively heated form, such as cupcakes, muffins, or even pizza [16, 17], even though they are still reactive to whole egg (e.g., scrambled) or uncooked dairy products (e.g., cheese or yogurt). Whether allowing this less strict avoidance alters the natural course of allergy remains unclear, but most data suggest that it may help hasten the development of tolerance to the uncooked variety of the food. This is completely contrary to the longstanding recommendation that strict avoidance is more likely to lead to outgrowing an allergy.

Non–IgE-mediated food allergy, which is probably more common with milk than any other food, tends to be outgrown more quickly than IgE-mediated allergies [32]. Therefore, a careful challenge is warranted by the age of 2 to 3 years—or after 2 to 3 years of avoidance in disease of later onset—if there have been no recent reactions from accidental exposures. Reintroduction of food in food protein–induced enterocolitis syndrome (FPIES) in particular is associated with significant risk. Challenges in patients with FPIES who had severe reactions upon presentation should only be performed under close supervision in a hospital setting, with an intravenous catheter in place.

Peanut

We recommend repeat testing yearly with ImmunoCAP testing. Patients with peanut IgE levels less than or equal to 2 kUA/L should be offered a supervised challenge [14, 15, 33, 34]. If negative, the patient should be advised to ingest the nut at least once per week. The optimal amount of nut that patients should eat monthly is not known. We therefore suggest that patients ingest a serving (e.g., the amount in a peanut butter sandwich or nut-containing candy bar). Patients should be observed for at least another year to ensure that there are no recurrent symptoms. In patients with persistent allergy, especially if the CAP-FEIA remains unchanged for several years, testing can be performed less frequently over time.

Tree Nuts

Tree nut allergies are not typically outgrown, but this does occur in about 10% of patients [35]. This appears to be especially likely in those with low specific IgE levels and in those who are not truly allergic to more than one or two tree nuts. We therefore typically recommend challenges with tree nut–specific IgE levels less than 5 kU/L and no recent reactions. Whereas some families prefer to avoid all tree nuts, others may choose to sort out those that are tolerated even though the child is still avoiding other tree nuts.

Wheat

A wheat-specific IgE level predictive of clinical reactivity has not been determined due to poor performance characteristics of the IgE assay for this allergen [7, 8]. Proposed challenge decision points range from 20 to 100 kU/L. In one survey, 60% of patients with a wheat IgE level less than 20 kU/L passed their challenges and 50% of those with a wheat IgE level less than 50 kU/L passed [36]. Peak wheat-specific IgE has some predictive value in determining the age at which tolerance develops, and higher levels may indicate risk of persistent allergy [36].

We suggest that patients with wheat allergy or sensitization undergo serial oral challenges to wheat at least every 2 years in the absence of an interval history of symptoms triggered by an exposure. Additional variables to take into consideration before proceeding with the challenge include the wheat-specific IgE level and how it compares with the level at the time of the last challenge, the result of the last challenge (e.g., did the reaction occur at the beginning or near the end of the challenge, and what was the severity of the reaction?), and the age of the child (e.g., resolution may occur at later ages but is more likely to occur in a 2-year time span in a younger child).

Soy

We recommend repeat evaluation yearly with CAP-FEIA testing. Soy allergies are generally outgrown more quickly than those to egg or milk [37]. Challenge can be offered when the results of in vitro testing have reached low levels, although these are not as well-defined as for the previous foods, and the situation is probably similar to that for wheat. Clinicians also must recognize that soy IgE levels and skin test results may by artificially elevated in patients with peanut allergy, which makes these tests even more difficult to interpret.

Other Foods

Yearly in vitro testing of other foods is our general recommendation. As mentioned previously, repeat evaluation can be less frequent with time if there is minimal evidence of improvement over several years, especially to other food allergies that may be less likely to resolve over

time, including seeds, fish, and shellfish. The limited data available suggest that sesame allergy, similar to peanut and tree nut allergies, is more likely to persist, with a reported rate of resolution ranging from 20% to 30% [38, 39].

Potential for Improved Diagnostic Testing

Given that OFCs are expensive, time consuming, and potentially risky, better diagnostic tests for food allergy certainly would be of great value. Fortunately, it does appear that improved testing is on the horizon, at least for some foods. These methods are based primarily on serologic testing for allergen epitopes and/or specific food protein components.

In fact, IgE molecules are not equally pathogenic, and IgE directed against certain types of epitopes or allergen components may be associated with more persistent or severe allergy [40–43, 44•, 45]. The food-specific IgE tests that are currently available do not distinguish among IgE molecules directed toward different epitopes or allergen components. In one study on milk allergy, it was found that two specific IgE-binding regions were recognized by most older children with persistent allergy, but none of the younger children [40]. A similar analysis was performed in subsequent studies of IgE- and IgG-binding epitopes on β- and κ-casein in cow's milk–allergic patients [41]. Three IgE-binding regions on β-casein and six on κ-casein were recognized by patients with persistent cow's milk allergy, but not by those with transient allergy. A third study found that patients with persistent cow's milk allergy had higher levels of IgE to linear (primary sequence) epitopes (rather than tertiary or conformational epitopes) from α-s1-casein and β-casein than children who achieved tolerance [42]. In a study of peanut allergy, researchers analyzed IgE binding of eight sequential epitopes of the major peanut allergens, Ara h 1, 2, and 3, and found that 93% of patients with clinical reactivity to peanut recognized at least one of the immunodominant epitopes of Ara h 1 or 2, in contrast to 12% of peanut-tolerant individuals with IgE sensitization [43]. Furthermore, reactive patients recognized a greater number of epitopes than tolerant patients.

Another approach is referred to as component-resolved diagnosis, which is based on the recognition that certain food proteins are more consistent with true food allergy—and a higher rate of failed food challenges—while others may represent less important food components. This is especially true for certain plant food proteins, such as peanut, that are homologous to plant aeroallergens, in which case this cross-reactivity can lead to significant overdiagnosis of food allergies. The component-resolved diagnostic approach seeks to improve test specificity through recognition and assessment of this cross-reactivity and co-sensitization. For example, a 2010 study examining true peanut allergy versus sensitization without clinical allergy revealed that IgE binding to Ara h 2 was the most predictive of true allergy, compared with IgE binding to other peanut allergens [44•]. Another study using a microarray with recombinant wheat seed and grass allergens was able to distinguish baker's asthma, food allergy to wheat, and grass pollen allergy more clearly than was possible using crude extracts of wheat or grass allergen extracts [45].

These technological advances likely will result in the development of improved clinical tests, including both epitope-specific and component-based IgE quantitation, with the hope being that they will provide more precise identification of patients who are more likely to have true and/or persistent food allergy. It is also hoped that this type of testing will more accurately determine which patients should undergo oral challenges. At present, component-based testing for peanut allergy is widely used in Europe and recently received US Food and Drug Administration approval for potential introduction into the US market.

Conclusions

The diagnosis and management of food allergy is complex, especially because most of the available diagnostic tools are of limited accuracy. Only the OFC is considered truly accurate, but these tests are limited by their potential risk. Taken together, it is essential that each patient be provided with a detailed, individualized approach to his or her management to monitor the disease over time and determine when tolerance to a specific food has developed.

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