

An expanding evidence base provides food for thought to avoid indigestion in managing difficult dilemmas in food allergy

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An increasing prevalence of atopic disease presents us with a growing number of patients in need of expert advice for diagnosis and management of food allergy. As clinicians, our patients are asking us thought provoking questions, such as “Will my child tolerate foods that are labeled ‘may contain an allergen,’ and how do I respond to recent labeling changes?”; “Did eating something while I was breast-feeding cause my child’s allergy?”; and “Will avoiding a food speed my child’s recovery from an allergy, or could it make the allergy worse?” At the same time, rapid advances in our appreciation of allergy testing lead our colleagues to ask, “Why did this child fail a food challenge with negative test results?”; “What should I be telling my primary care colleagues about allergy testing before consultations?”; “How can I best use tests to determine who needs an oral food challenge?”; and “Am I missing anything in regard to keeping my patients safe in regard to anaphylaxis?” Fortunately, an expanding research base and increasing responses from government agencies, industry, and numerous organizations are continuously addressing these needs. Selected issues of note for the allergist are listed in Table I.¹⁻¹⁴ In this essay we present our approaches and suggestions about the common and vexing concerns described above, for which recent advances have modified our approaches.

INTERPRETATION OF TESTS FOR FOOD-SPECIFIC IgE ANTIBODIES

Research advances are redefining the way we interpret skin prick test responses and serum test results for food-specific IgE antibodies. A yes-no interpretation of skin test sizes (eg, a 3-mm or larger wheal) or food-specific serum IgE concentrations (eg, class 2 or above) masks predictive information obtainable when the degree of positive response is considered. The stronger the test response (wheal size or antibody concentration), the more likely there is clinical allergy. For example, serum food-specific IgE antibody concentrations in children about age 5 years that are associated with a high (>90% to 95%) risk of clinical reactions have been calculated to be as follows (Pharmacia CAP System FEIA): 7 kIU/L or greater for egg, 15 kIU/L or greater for milk, and 14 kIU/L or greater for peanut.¹⁻⁵ In contrast, oral food challenges can be considered when serum antibody levels decrease to a range at which about 50% of children this age tolerate the food (eg, ≤ 2 kIU/L for egg, ≤ 2 kIU/L for milk, and ≤ 5 kIU/L for peanut with an unclear past history or < 2 kIU/L if the history of past reactions is more certain).^{3,5} Rational use of these levels to determine the appropriateness (and safety) of challenges must consider the medical history, skin test results,² and the clinical likelihood of a reaction.⁵ For other foods, we do not yet have cutoff levels as helpful as these, but additional research is ongoing to obtain such data.

We have seen clinical errors occur when the tests are overinterpreted or various limitations are not appreciated, such as consideration of the medical history, epidemiology (likely causal foods, cross-reactivity, age, and illness) and test limitations (sensitivity-specificity, technique, and reagents). It must be appreciated that results from studies investigating test utility might not be applicable beyond the specific food and test studied and characteristics of the study population (eg, children).

Use of screening tests to a panel of foods without regard to epidemiology or medical history is not advised. This approach often yields numerous “positive” results without clinical correlation. Increased use of serum tests for screening by primary care doctors often leaves the allergist to evaluate the person who is “allergic to everything.” Avoiding the repercussions of screening will require additional education of us, our primary care colleagues,

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TABLE I. Examples of selected common clinical concerns, with resources containing recent solutions or additional information

Clinical concerns	Examples of issues	Resources, reviews, references
Diagnostic tests	Interpretation	References 1-5
Deciding on and performing oral food challenges	Selection, safety, dosing	References 6-9; instructional manual available from FAAN
Prevention	Pregnancy, lactation, food introduction	References 10-12
Ingredient labeling (FALCPA)	Specifics of legislation and changes	Center for Food Safety and Applied Nutrition (www.cfsan.fda.gov)
School, camp, travel issues, avoidance	Practical advice	FAAN
Prescribing, instructing self-injection of epinephrine, approach to anaphylaxis	Indications, definitions, quandaries	References 13 and 14

This is not meant to be a comprehensive list of all such concerns or references but a starting point for additional reading or a portal to further resources. FALCPA, Food Allergen Labeling and Consumer Protection Act; FAAN, Food Allergy & Anaphylaxis Network (www.foodallergy.org; 800-929-4040).

and our patients. One way to explain the interpretation of tests is to use the term *sensitization* to indicate a positive test result for specific IgE, with the possibility of *symptomatic sensitization* when medical problems are associated with ingestion of the food and *asymptomatic sensitization* when the food is tolerated. A good example to bring home this point derives from a recent US population-based study that showed 8.6% of the population have positive test responses to peanut,¹⁵ but clinical peanut allergy is estimated to affect 0.4%.¹⁶ Asymptomatic sensitization rates could be 95% if medical history is ignored!

Another common pitfall in regard to IgE-mediated illnesses is the assumption that a negative test result indicates no allergy. Although higher than we might have anticipated from our own experiences, Roberts and Lack² reported 13% of children with a negative skin test response to peanut had reactions on challenges. Similar results (15% to 20% false-negative) are reported for undetectable (CAP-System FEIA <0.35 kIU/L) serum IgE concentrations to peanut, milk, or egg.⁵ Our suggestion is to use both skin prick and serum tests to confirm lack of sensitization, but in the context of high suspicion and negative commercial test results, skin prick testing with fresh food might increase sensitivity and provide additional insight before consideration of physician-supervised oral challenges.¹⁷ The clinical pearls regarding test interpretation all focus on one theme: consider the history before test selection and interpretation and proceed with caution (eg, physician-supervised food challenges and not introduction at home if there is a strong suspicion of clinical allergy, even with negative test results).

USING FOOD CHALLENGES

Food challenges are practical to undertake in the office setting with certain guidelines and precautions and are the accepted gold standard for the confirmation or refutation of histories of adverse food reactions.^{4,6-8,18} They can be administered openly, single blind, or double blind with placebo control. In many situations food challenges are undertaken to eliminate incriminated foods that are highly unlikely to cause symptoms. It is reasonable and practical to challenge foods in an office or clinic if they have never

and are not likely to produce severe systemic reactions in the individual being evaluated. The usual exceptions are peanut, tree nuts, and seafood that have caused systemic symptoms in the past. Although not typical anaphylaxis, food challenges for children with enterocolitis syndrome might induce severe symptoms (hypotension) and are also best undertaken in a more controlled setting.⁹ Single-blind and double-blind challenges are extremely helpful for proving that certain symptoms are not food related. Examples include behavioral reactions attributed to sugar and dyes (for which grape juice is a useful vehicle and placebo). Food challenge in patients with eosinophilic esophagitis and eosinophilic gastroenteropathy are more difficult to interpret because symptoms might be subtle and of gradual onset, and biopsies are often required to determine the true outcome.

PRESCRIBING DIETARY AVOIDANCE: IMPLICATIONS

What are the benefits of strict dietary avoidance? Improvement in chronic allergic conditions, avoidance of anaphylaxis, and possibly allergy prevention and recovery. What are the risks of dietary avoidance? Nutritional and social consequences. However, parents often inquire about issues regarding sensitization and tolerance. For example, if a child truly tolerates milk and egg in baked goods with no chronic disease but reacts to less cooked and larger amounts, should the baked forms be allowed in the diet? Of course, doing so carries a risk for a reaction if a larger amount is encountered, but is there an immunologic price to pay?

Although there is a notion that strict avoidance speeds recovery and delayed introduction of foods prevents allergy, various studies are modifying our understanding of this dogma and changing how we might present dietary information to parents. For example, recurrence of peanut allergy has been noted when tolerated ingestion was not continued.^{19,20} One study showed no causal relationship of maternal ingestion of peanut during pregnancy or lactation on outcome of peanut allergy in young children, whereas skin exposure was implicated.²¹ However, at least one case report implicated oral exposure in boosting

food allergy.²² Studies in murine models indicate that depending on dosing of allergen (amount and frequency), sensitization or tolerance (or a state of desensitization) might be induced,²³⁻²⁵ and continued oral exposure might also tolerate.²⁶ Lack of oral exposure with repeated skin exposure can also sensitize.²⁷ Infants are not mice, but assessment of the risks and benefits of diet avoidance are becoming more complex and less certain. Perhaps tolerated exposure speeds, rather than hinders, recovery from an allergy for some children.

Similarly, when a food to which test results were positive is removed from the diet of a child who has tolerated the food without anaphylaxis, usually suggested for remediation of a chronic atopic disease, there is a risk of eventual acute and more severe allergic reactions if re-exposure occurs before resolution of the allergy.²⁸ Although the frequency of this occurrence is not well documented, it is a risk that should be considered when recommending dietary avoidance and discussed in assessments of risks and benefits. The notion that avoidance might in some circumstances be counterproductive is an additional argument to avoid screening tests that can lead to avoidance of a tolerated food. Can we feel comfortable allowing a child to eat a food to which he or she had a positive test result but seems to tolerate? We explain this situation to parents by offering the observation that after a negative oral food challenge result, recurrence of reactions to a food incorporated into the diet has not been reported.

Regarding avoidance diets for prevention, most studies show a protective effect on atopy of exclusive breastfeeding (for at least 3-4 months),^{10,11} but the effect on atopy of lactation diets and selection of specific solid foods for introduction to the infant is still unclear. For example, delayed introduction of allergens (eg, egg and milk) was associated with increased atopy in one study,²⁹ although it is difficult to eliminate possible bias of reverse causation. Although the American Academy of Pediatrics recommended numerous suggestions for avoidance of major allergens to prevent allergy,¹² more recent recommendations from Europe have been less draconian.¹⁰ Although it remains uncertain whether low-level oral exposure (eg, oral or through breast milk) is sensitizing or tolerizing, for certain foods and certain clinical circumstances, it seems clear that there are dietary options to be discussed with families. It is apparent that genetics, environment, and timing-route-dose of exposure interact toward allergy outcomes. For now, parents can be told that we do not have proof that they caused their child's allergy through diet selection, and a more expanded risk and benefit discussion about avoidance is justified.

INSTRUCTING PATIENTS ABOUT DIETARY AVOIDANCE AND TREATMENT

The Food Allergen Labeling and Consumer Protection Act, effective January 2006, is changing the way we instruct patients about dietary avoidance. Although a roll-out period of up to 2 years might be needed, major

allergens (milk, egg, wheat, soy, peanut, tree nuts, and seafood) will be disclosed on packaged foods in plain English. We will eventually stop counseling for these foods in regard to terms that are scientific (eg, *casein*) or ambiguous (eg, *natural flavor*). However, for now, the law only applies to the listed major allergens. If a patient is reactive to other foods (eg, sesame or garlic), they might need to call manufacturers to ascertain ingredients when terms such as *spices* or *flavors* are used. In addition, provisional labeling remains ungoverned. Many patients ask us to okay their ingestion of foods that "may contain" an allergen. Although an argument from a patient might be compelling ("I tolerated this brand dozens of times"), we have no direct way to monitor the risk and generally do not overturn the companies' warnings. We suggest avoidance and calling the company for more information to make personal decisions. A current lack of scientifically sound and legislatively agreed upon thresholds of allergen contamination in regard to labeling will continue to hinder clear and simple instructions about the selection of safe products.

Concern about casual contact with allergens through touching or inhalation permeates instructions for allergen avoidance and increases anxiety. Studies and clinical experiences indicate that significant reactions from touch are unlikely³⁰ and that inhalation reactions usually require specific circumstances that allow food particles to become airborne in large amounts (eg, cooking and powdered foods), leading to reactions typical of nonfood inhalational allergen exposures.³¹ Young children could be at special risk for transfer of allergen into the mouth (sucking), and all age groups must be well educated about avoidance of oral exposures (eg, shared drinking cups-straws, utensils, cross-contact in food preparation, and passionate kissing). When a family has what appears to us to be undue concern for casual contact given the child's allergy profile, we find it helpful to remind them that skin tests did not invoke a systemic reaction. We can perform a touch challenge with the food (eg, a dab of peanut on the arm wiped away in a minute), which might need to be performed in a blinded fashion.³⁰

Teens and young adults are at particular risk for fatal food-induced allergic reactions.³² We believe that it is important to meet often with them to review the serious nature of a food-induced allergic reaction, the precautions needed for effective allergen avoidance, and the importance of being prepared to treat a reaction. Education of their friends is crucial because many accidents occur when they are away from home. The areas to emphasize repeatedly with patients-families are that they be trained to use self-injectable epinephrine, practice using the device, carry it at all times, educate others about treatment, and notify friends and food service establishments about the allergy and wear medical identification jewelry.^{13,14}

CONCLUSIONS

Recent studies have improved our ability to diagnose and manage food allergy but must be applied judiciously

in the context of a clinical history. Recent clinical and laboratory studies are challenging our notions of avoidance in regard to sensitization, tolerance induction, and allergy prevention. Although this has complicated our view of risks and benefits for allergen avoidance strategies, we await more research for confidently recommending specific strategies. Until better treatment and cures are available, education is key to increase patient safety, and policy changes have helped us toward these ends. The Food Allergy and Anaphylaxis Network is a tremendous resource for all types of educational programs.

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