

Food Allergy:

Diagnosis, Treatment, Prognosis, and Prevention

Jennifer S. Kim, MD

CME EDUCATIONAL OBJECTIVES

1. Determine the most effective means to obtain historical information that may illuminate foods that are causing an allergic reaction.
2. Discuss the appropriate use and interpretation of available diagnostic tools in the evaluation of food allergies.
3. Assess the currently recommended treatment and prevention of IgE-mediated food allergy.

Jennifer S. Kim, MD, is Assistant Professor of Pediatrics, Northwestern University Feinberg School of Medicine, and Attending Physician, Division of Allergy and Immunology, Children's Memorial Hospital. Address correspondence to: js-kim@childrensmemorial.org.

Dr. Kim has disclosed no relevant financial relationships.

As with most diseases in medicine, a detailed medical history obtained by a skilled and knowledgeable healthcare provider is crucial in reaching a diagnosis of food allergy. Therefore, patient (or parental) perceptions with regards to food allergy are notoriously inaccurate. Parents often have very strongly held beliefs that various foods cause a variety of symptoms, many of which are inconsistent with an immune-mediated process. In fact, when double-blind, placebo-controlled, food challenges (DBPCFCs) are used to establish the diagnosis of IgE-mediated food allergy, only about 40% of patients' histories of food-induced reactions can be verified.¹⁻⁴ Therefore, this article focuses on how to obtain historical highlights and use the available diagnostic tools, as well as treatment and prognosis of IgE-mediated food allergy.

HISTORY

The signs and symptoms of food have been reviewed by Dr. Story in this issue (see page 530). However, other specifications are equally vital in assessing adverse food reactions. In asking "What

happened?" the provider must also ascertain further details.

The Food in Question

What was ingested? What were the ingredients in the dish? How much of the food was ingested? Common things being common, the most likely allergens in children include milk, egg, soy, wheat, peanut, tree nuts (eg, walnut, cashew, almond, pecan), fish (eg, salmon, tuna, catfish, cod), and shellfish (eg, shrimp, crab, lobster). Sesame seed allergy also appears to be recognized increasingly.⁵ Ingredient labels may also be helpful in pinpointing the allergen. It is important to note that soy lecithin and soybean oil are usually tolerated by soy-allergic individuals,⁶ and that refined or highly processed peanut oil has not been shown to contain any detectable allergenic protein.^{7,8}

Potential Cross-contamination

What else was eaten at the same time? What else could have touched the food that was ingested? Hints may include the setting at the time of the ingestion, and whether the ingestion



© 2008/Photos.com, Jupiterimages Corporation

took place outside the home. For example, egg rolls from an Asian restaurant may contain egg, peanut, and/or shrimp. Foods consumed at buffets, ice cream parlors, and bakeries have high potential for cross-contamination.

The Reaction

At what age did the initial reaction occur? What was the timing from the ingestion to the onset of symptoms? Outline the sequence of events, including any medications given and the patient's response. Food allergy in children is most likely to manifest between 1 and 3 years.⁹ Symptoms that occur more than 2 to 3 hours after the ingestion are less likely to be IgE-mediated. Symptoms (eg, hives) that persist for days or weeks without subsequent exposure (to the

food in question) are also not likely to be attributable to food.

Reproducibility

Have subsequent exposures resulted in reactions? Has the child been exposed to the food in question before, and with what kind of frequency? Has the child been exposed to the food after the reaction in question (and in what amount)? What was the response? Immune-mediated reactions are reproducible. Foods such as milk, egg, soy, and wheat that have been tolerated on a regular basis (daily or weekly) for prolonged periods of time (months or years) are less commonly the culprits. However, older children and adults may develop allergy to peanut, tree nuts, fish, or shellfish despite long periods of tolerance. Foods that

have been tolerated subsequently (ie, in a serving size amount) are not likely to be the cause of an immune reaction.

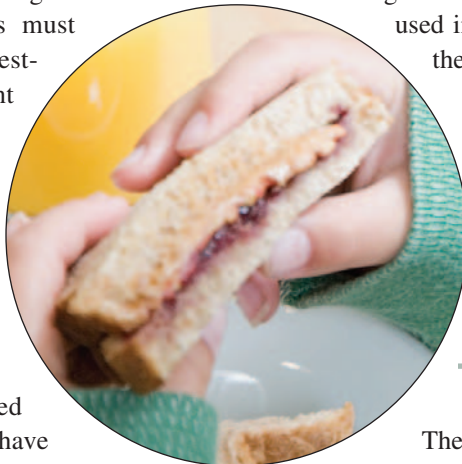
Comorbidities

Is there a history of eczema in the child? Young children with atopic dermatitis are a higher risk of developing food allergy, particularly those infants and toddlers whose skin disease is more severe or recalcitrant to therapy. Generally, the younger the patient and the more severe the atopic dermatitis, the more likely food allergy is to be a causative factor.¹⁰

EVALUATION FOR IMMEDIATE HYPERSENSITIVITY

If the elicited history is suggestive of an immune mechanism, then formal

confirmatory testing may be utilized to establish the presence of IgE to the suspected food allergen. Allergen specific IgE (sIgE) testing may be performed in vivo (skin prick testing) or in vitro. Skin prick tests (SPTs) are typically performed in an allergist's office. Antihistamines must be stopped prior to testing for a sufficient length of time (at least three half-lives) so as to minimize the risk of false-negative results. Different prick/puncture devices are available but the bifurcated needle and lancet have the lowest false-positive rates.¹¹ Food extracts along with positive (histamine) and negative (saline or glycerin) controls are applied to normal-appearing skin. A response of a ≥ 3 mm wheal (associated with a flare; ie, erythema) indicates the presence of sIgE in the setting of a negative saline response. Larger wheal sizes (> 8 to 10 mm) indicate an even greater likelihood of clinical reactivity with ingestion.¹² Intradermal testing is con-



traindicated for food allergens because of its high false-positive rate and risk of systemic reactions.

RAST (radioallergosorbent test) is the colloquial term for an antiquated in vitro method of measuring sIgE. Although this method is no longer used in most laboratories, the name has stuck.

sitization), whether measured in vivo or in vitro, does not automatically indicate disease or clinical relevance in a given patient. Among children who have elevated sIgE to food as measured by ImmunoCAP, Perry et al¹⁸ demonstrated that those without a clear history of a food reaction were more likely to be tolerant to the food in DBPCFCs.

It is important to note that higher sIgE levels do not correlate with severity of reactions; rather, they indicate an increased probability of a food-induced reaction.

The most predictive and most useful method of measuring sIgE is the Phadia CAP system, a fluoroenzyme-immunoassay (FEIA) approved for use by the Food and Drug Administration. This is a quantitative test with a reportable range of 0.1 to 100 kU_A/L. This assay, also referred to as ImmunoCAP, has been used in studies¹³⁻¹⁶ to define diagnostic points for certain foods (see Table).¹⁷ These data curves have been generated for some of the more common food allergens, including egg, milk, peanut, and fish.¹³ It is important to note that higher sIgE levels do not correlate with severity of reactions; rather, they indicate an increased probability of a food-induced reaction. Therefore, the 95% predictive values (see Table) are helpful in determining which patients are at higher risk of developing a reaction with ingestion and in whom oral challenges may not be advisable. On the other hand, there are limitations to this assay as patients (up to 20%, depending on the food) may react to a food despite very low or undetectable levels of food sIgE as demonstrated by oral challenges.¹³ Simply establishing the presence of sIgE against allergens (also called sen-

Therefore, sensitization may be symptomatic (as in food allergy) or asymptomatic (as in food tolerance).

In general, properly performed SPTs to food allergens have a high negative predictive value ($>95\%$),^{19,20} but the positive predictive value is much lower at 30% to 65%.^{3,19-22} Therefore, a positive test indicates sensitization, which may or may not be symptomatic. For example, 8.6% of the U.S. population has positive test responses to peanut,²³ but clinical peanut allergy is estimated to affect 0.4% of the population.²⁴ In other words, for every 100 Americans with positive skin tests to peanut, fewer than 5 have a clinical peanut allergy. Therefore, if testing is undertaken, it must be performed with regard to epidemiology and medical history. Screening for a wide panel of foods can result in unnecessary food avoidance with potentially detrimental effects on childhood growth and development. Increased use of serum tests by primary care providers leaves the allergist the arduous task of determining which positive tests are true or false. Serial food challenges may be required to confirm or refute the presumptive diagnosis. Conversely, the absence of sIgE, in

TABLE.

Interpretation of Specific IgE Levels (ImmunoCAP Assay): $>95\%$ PPV¹⁷

Allergen	kU _A /L
Egg	7
Infants ≤ 2 yrs	2
Milk	15
Infants ≤ 2 yrs	2
Peanut	14
Tree nuts	~ 15
Fish	20

the setting of a highly suggestive history, does not necessarily represent the absence of allergy. Thus, the medical history must be considered prior to test selection and interpretation.

THE ROLE OF ORAL FOOD CHALLENGES IN ESTABLISHING THE DIAGNOSIS

Although DBPCFCs are the accepted gold standard of diagnostic modalities for IgE-mediated food allergy, they are time-consuming and impractical in the clinical setting. However, open (or even single-blind) food challenges can be performed in the office provided there are emergency medications, equipment, and trained personnel in place. Given the limitations of available testing as previously outlined, often the best test is to see what happens when the child actually ingests the food, particularly when the history and test results are equivocal. In open challenges, small doses of food are administered to the child in gradually increasing amounts until a full serving of the allergen has been ingested. Each dose administered is preceded by an assessment that includes vital signs and examination of the potential target organs (eg, skin, oral mucosa, lungs). Particular caution must be taken with foods more likely to induce anaphylactic reactions, such as peanuts, tree nuts, and seafood.

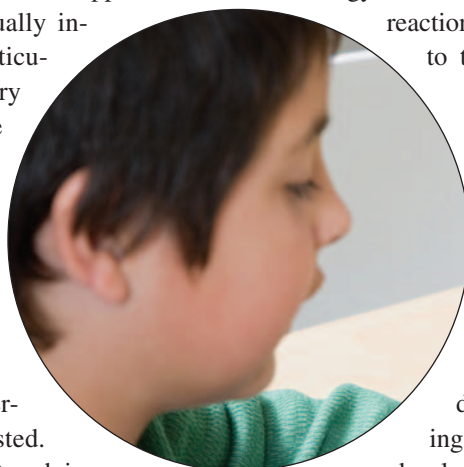
TREATMENT

Elimination of the food allergen is the only proven effective therapy at this time. Strict dietary avoidance is generally recommended once a food allergy is diagnosed. Legislation has facilitated the ability to identify common aller-

gens in foods commercially prepared in the United States. The Food Allergen Labeling and Consumer Protection Act (effective January 2006) mandated labeling in plain English ingredients derived from common allergenic sources (milk, egg, soybean, wheat, peanut, tree nuts, fish, and crustacean shellfish). If the mother is breastfeeding, she must also strictly eliminate the causal foods from her diet. Educational materials are available through the Food Allergy and Anaphylaxis Network or FAAN (<http://www.foodallergy.org>) to help families cope with required dietary and lifestyle changes.

INDICATIONS FOR AUTOINJECTABLE EPINEPHRINE

Children diagnosed with food allergy are at risk of an immediate reaction upon re-exposure to the allergenic food.



Because of the difficulty in predicting which patients will develop anaphylaxis after allergen exposure, it is advisable to prescribe autoinjectable epinephrine to these patients because antihistamines do not block systemic reactions. Special consideration should be given to those at high risk of developing fatal-food anaphylaxis,²⁵⁻²⁶ specifically to those with concomitant asthma and/or peanut or tree nut allergy.

Epinephrine is clearly the treatment of choice for anaphylaxis. In 2006, a universally accepted definition of anaphylaxis was published.²⁷ If exposure to an allergen is suspected, epinephrine should be administered if two or more of

the following occur rapidly after exposure (within minutes to several hours):

- Skin or mucosal involvement (eg, generalized hives or swelling of oral mucosa)
- Respiratory compromise (eg, dyspnea, wheeze, stridor)
- Persistent gastrointestinal symptoms (eg, vomiting)
- Hypotension (eg, hypotonia, syncope)

Certainly, having signs of hypotension (even without accompanying symptoms) is an indication for epinephrine administration, particularly in a child with known food allergy.

When indicated, epinephrine is preferably injected intramuscularly in the lateral aspect of the thigh. Higher peak plasma concentration of epinephrine has been demonstrated with injection into the vastus lateralis compared with the deltoid.²⁸ Moreover, the time to peak plasma epinephrine concentration is 8 ± 2 minutes

Elimination of the food allergen is the only proven effective therapy at this time.

after intramuscular injection but much longer (34 ± 14 minutes) after subcutaneous injection.²⁹ Rapid delivery of epinephrine is essential because the median time to respiratory or cardiac arrest in individuals with food-induced anaphylaxis is 30 minutes.³⁰

Antihistamines, beta-agonists, and systemic corticosteroids may be used as adjunctive treatments for anaphylaxis. However, these should not be administered in place of epinephrine, as they have not been proven to reverse respiratory or cardiovascular symptoms. Antihistamines may be tried initially if the symptoms involve only the skin (not including oral mucosa), and the child should be closely monitored for development of more concerning symptoms.

EpiPen and Twinject are both available in two doses: Jr. (0.15 mg) and regular (0.3 mg). The recommended dose for pediatric use is 0.01 mg/kg body weight. For patients near 30 kg (66 lbs) and above, a dose of 0.3 mg is appropriate. For children around 15 kg (33 lbs), 0.15 mg is indicated. For very small children (< 10 kg) and for those weighing between 15 kg and 30 kg, the physician must exercise clinical judgment.³¹ In our practice, children weighing 22 kg (~50 lbs) are graduated from the Jr. to the regular dose.

Even when epinephrine is prescribed, it appears to be underused.³² Demonstration or training is an important factor in encouraging use of epinephrine autoinjectors.³³ Physicians are advised to counsel patients verbally as well as demonstrate use (preferably with a placebo device) of these autoinjectors. Patients and their families should be provided a written plan that clearly outlines when epinephrine should be administered. An example is available online at <http://www.foodallergy.org/downloads/FAAP.pdf>.

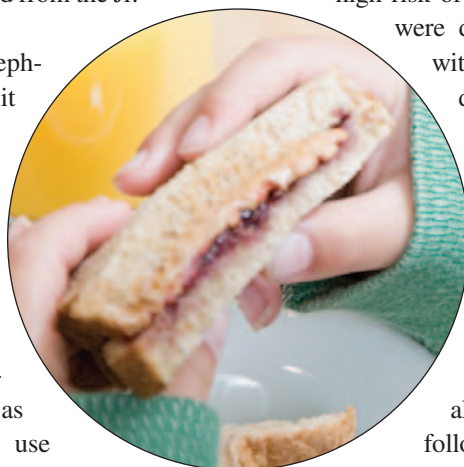
PROGNOSIS

Clinical tolerance can develop over time, more commonly to some foods (milk, egg, soy, wheat) over others (peanut, tree nuts, seafood). Older studies touted an 80% rate of tolerance by ages 3 to 5 years for milk and egg.³⁴ More recent retrospective studies from the Johns Hopkins Pediatric Allergy Clinic revealed that rates of resolution for cow milk allergy are 79% by 16 years³⁵ and for egg allergy 68% by 16 years.³⁶ This may not be reflective of the general community as academic centers may draw patients with more severe and persistent disease. In contrast, only about

20% of young children develop tolerance to peanut,³⁷ and less than 10% outgrow allergy to tree nuts.³⁸

PREVENTION OF ATOPY IN SIBLINGS OR OFFSPRING

Families often ask how allergy can be prevented in future offspring. The American Academy of Pediatrics (AAP) published a clinical report in 2008 with recommendations for those infants at high risk of developing atopy.³⁹ Children at high risk of developing allergy were defined as “infants with at least one first-degree relative (par-



ent or sibling) with allergic disease.” The following recommendations are evidence-based and specific to prevention of atopic dermatitis and food allergy:

1. Exclusive breast feeding for at least 4 months compared with feeding with intact cow milk protein formula decreases the incidence of atopic dermatitis and cow milk allergy during the first 2 years of life.
2. Atopic dermatitis may be delayed or prevented by the use of extensively hydrolyzed or partially hydrolyzed formulas, compared with cow milk formula, in early childhood. Extensively hydrolyzed formulas may be more effective in prevention than partially hydrolyzed but at a significantly higher economic cost.
3. There is no role for soy-based formula in allergy prevention, and amino acid formulas have not been studied with regard to atopy prevention.
4. Solid foods should not be introduced before ages 4 to 6 months. There is insufficient evidence to support dietary intervention before this age.

These recommendations do not apply to those patients who have already developed an atopic disease such as atopic dermatitis or food allergy.

SUMMARY

Primary care providers are advised to refer to an allergist those children in whom they suspect a food allergic reaction. Approximately 6% of U.S. children have food allergy, although many more parents will present with concerns of a food-induced condition. At higher risk are young children with atopic dermatitis. Generally, the stronger the test response (wheal size or sIgE concentra-

Even when epinephrine is prescribed, it appears to be underused.

tion), the more likely there is to be clinical allergy. However, testing must be applied judiciously. Most importantly, the medical history must be considered in order to interpret test results appropriately. Avoidance of the offending food allergen is currently the only way to prevent reactions. Because exposures and reactions can occur unexpectedly, patients and their families must be prepared to treat symptoms quickly with intramuscular epinephrine in the lateral thigh. Hopefully, additional treatment options will become available in the near future to ease the anxiety and fearfulness that parents and patients face on a daily basis. Until then, healthcare providers are urged to demonstrate the correct administration of autoinjectable epinephrine using a placebo device and review the technique with families on an ongoing basis.

REFERENCES

1. May CD. Objective clinical and laboratory studies of immediate hypersensitivity reactions to foods in asthmatic children. *J Allergy Clin Immunol*. 1976;58(4):500-515.

2. Burks AW, Mallory SB, Williams LW, Shirrell MA. Atopic dermatitis: clinical relevance of food hypersensitivity reactions. *J Pediatr*. 1988;113(3):447-451.
3. Bock SA, Atkins FM. Patterns of food hypersensitivity during sixteen years of double-blind, placebo-controlled food challenges. *J Pediatr*. 1990;117(4):561-567.
4. Sampson HA. Immunologically mediated food allergy: the importance of food challenge procedures. *Ann Allergy*. 1988;60(3):262-269.
5. Cohen A, Goldberg M, Levy B, Leshno M, Katz Y. Sesame food allergy and sensitization in children: the natural history and long-term follow-up. *Pediatr Allergy Immunol*. 2007;18(3):217-223.
6. Bush RK, Taylor SL, Nordlee JA, Busse WW. Soybean oil is not allergenic to soybean-sensitive individuals. *J Allergy Clin Immunol*. 1985;76(2 Pt 1):242-245.
7. Teuber SS, Brown RL, Haapanen LA. Allergenicity of gourmet nut oils processed by different methods. *J Allergy Clin Immunol*. 1997;99(4):502-507.
8. Martín-Hernández C, Bénet S, Obert L. Determination of proteins in refined and nonrefined oils. *J Agric Food Chem*. 2008;56(12):4348-4351.
9. Kulig M, Bergmann R, Klettke U, Wahn V, Tacke U, Wahn U. Natural course of sensitization to food and inhalant allergens during the first 6 years of life. *J Allergy Clin Immunol*. 1999;103(6):1173-1179.
10. Guillet G, Guillet MH. Natural history of sensitizations in atopic dermatitis. A 3-year follow-up in 250 children: food allergy and high risk of respiratory symptoms. *Arch Dermatol*. 1992;128(2):187-192.
11. Nelson HS, Rosloniec DM, McCall LI, Iklé D. Comparative performance of five commercial prick skin test devices. *J Allergy Clin Immunol*. 1993;92(5):750-756.
12. Hill DJ, Hosking CS, Reyes-Benito LV. Reducing the need for food allergen challenges in young children: a comparison of in vitro with in vivo tests. *Clin Exp Allergy*. 2001;31(7):1031-1035.
13. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol*. 2001;107(5):891-896.
14. Boyano Martínez T, García-Ara C, Díaz-Pena JM, Muñoz FM, García Sánchez G, Esteban MM. Validity of specific IgE antibodies in children with egg allergy. *Clin Exp Allergy*. 2001;31(9):1464-1469.
15. García-Ara C, Boyano-Martínez T, Díaz-Pena JM, Martín-Muñoz F, Reche-Frutos M, Martín-Esteban M. Specific IgE levels in the diagnosis of immediate hypersensitivity to cows' milk protein in the infant. *J Allergy Clin Immunol*. 2001;107(1):185-190.
16. Clark AT, Ewan PW. Interpretation of tests for nut allergy in one thousand patients, in relation to allergy or tolerance. *Clin Exp Allergy*. 2003;33(8):1041-5.
17. Sampson HA. Update on food allergy. *J Allergy Clin Immunol*. 2004;113(5):805-19.
18. Perry 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(1):144-149.
19. Bock SA, Buckley J, Holst A, May CD. Proper use of skin tests with food extracts in diagnosis of hypersensitivity to food in children. *Clin Allergy*. 1977;7(4):375-383.
20. Sampson HA, Albergo R. Comparison of results of skin tests, RAST, and double-blind, placebo-controlled food challenges in children with atopic dermatitis. *J Allergy Clin Immunol*. 1984;74(1):26-33.
21. Sampson HA, Scanlon SM. Natural history of food hypersensitivity in children with atopic dermatitis. *J Pediatr*. 1989;115(1):23-27.
22. Burks AW, James JM, Hiegel A, et al. Atopic dermatitis and food hypersensitivity reactions. *J Pediatr*. 1998;132(1):132-136.
23. Arbes SJ, Gergen PJ, Elliott L, Zeldin DC. Prevalences of positive skin test responses to 10 common allergens in the US population: results from the third National Health and Nutrition Examination Survey. *J Allergy Clin Immunol*. 2005;116(2):377-383.
24. Sicherer SH, Muñoz-Furlong A, Sampson HA. Prevalence of peanut and tree nut allergy in the United States determined by means of a random digit dial telephone survey: a 5-year follow-up study. *J Allergy Clin Immunol*. 2003;112(6):1203-1207.
25. Bock SA, Muñoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol*. 2001;107(1):191-193.
26. Shimamoto SR, Bock SA. Update on the clinical features of food-induced anaphylaxis. *Curr Opin Allergy Clin Immunol*. 2002;2(3):211-216.
27. Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol*. 2006;117(2):391-397.
28. Simons FE, Roberts JR, Gu X, Simons KJ. Epinephrine absorption in children with a history of anaphylaxis. *J Allergy Clin Immunol*. 1998;101(1 Pt 1):33-37.
29. Simons FE, Gu X, Simons KJ. Epinephrine absorption in adults: intramuscular versus subcutaneous injection. *J Allergy Clin Immunol*. 2001;108(5):871-873.
30. Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy*. 2000;30(8):1144-1150.
31. Simons FE, Gu X, Silver NA, Simons KJ. EpiPen Jr versus EpiPen in young children weighing 15 to 30 kg at risk for anaphylaxis. *J Allergy Clin Immunol*. 2002;109(1):171-175.
32. Uguz A, Lack G, Pumphrey R, et al. Allergic reactions in the community: a questionnaire survey of members of the anaphylaxis campaign. *Clin Exp Allergy*. 2005;35(6):746-750.
33. Kim JS, Sinacore JM, Pongracic JA. Parental use of EpiPen for children with food allergies. *J Allergy Clin Immunol*. 2005;116(1):164-168.
34. Sampson HA. Food allergy. Part 1: immunopathogenesis and clinical disorders. *J Allergy Clin Immunol*. 1999;103(5 Pt 1):717-728.
35. Skripak JM, Matsui EC, Mudd K, Wood RA. The natural history of IgE-mediated cow's milk allergy. *J Allergy Clin Immunol*. 2007;120(5):1172-1177.
36. Savage JH, Matsui EC, Skripak JM, Wood RA. The natural history of egg allergy. *J Allergy Clin Immunol*. 2007;120(6):1413-1417.
37. Skolnick HS, Conover-Walker MK, Koerner CB, Sampson HA, Burks W, Wood RA. The natural history of peanut allergy. *J Allergy Clin Immunol*. 2001;107(2):367-74.
38. Fleischer DM, Conover-Walker MK, Matsui EC, Wood RA. The natural history of tree nut allergy. *J Allergy Clin Immunol*. 2005;116(5):1087-1093.
39. Greer FR, Sicherer SH, Burks AW; American Academy of Pediatrics Committee on Nutrition; American Academy of Pediatrics Section on Allergy and Immunology. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics*. 2008;121(1):183-191.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.