

Peanut Allergy: Changes in Dogma and Past, Present, and Future Directions

Sarah Boudreau-Romano, MD; and Nashmia Qamar, DO, MSci

ABSTRACT

The prevalence of food allergy in the pediatric population, specifically to peanuts, has been rising. Accidental exposure to peanuts in a person who is allergic may have life-threatening consequences. Previous recommendations regarding peanut allergy included a delay in introduction of peanut to infants. However, more recent studies have provided sufficient contrary evidence supporting early introduction of peanuts for prevention of peanut allergy. Therefore, prompt evaluation by a specialist should be considered in infants at high risk of developing peanut allergy. Current treatment is strict avoidance of the allergen; however, future therapies are being sought, including oral immunotherapy, sublingual immunotherapy, and epicutaneous immunotherapy. [*Pediatr Ann.* 2018;47(7):e300-e304.]

Food allergy affects nearly 8% of children according to a recent comprehensive review of food allergy prevalence studies.¹ The prevalence of peanut allergy specifically has doubled in the past 10 years among children in North America.² Peanut allergy is known to be a life-long allergy, with fewer than 25% of children losing their reactivity.³ Exposure to peanuts in a peanut-allergic person, such as through accidental

ingestion or cross-contact, can cause a severe reaction (anaphylaxis), and these reactions can prove to be fatal. In fact, food anaphylaxis directories in the US indicate peanuts as the culprit in 59% of the 63 deaths recorded from 2001 to 2007.⁴ Risk factors for peanut allergy include family history of peanut allergy, personal history of severe atopic dermatitis, and personal history of egg allergy. Male sex, Asian ancestry, African ancestry, and genet-

ics (presence of human leukocyte antigen, familial associations, specific genes) are also risk factors that appear to increase risk of food allergy.¹

A number of theories exist as to the causative factors leading to the increased prevalence of peanut allergy and food allergy in general. In addition to gender, ethnicity, and genetics, other possible risk factors include vitamin D insufficiency, dietary fat, reduced consumption of antioxidants, obesity, increased personal hygiene and cleanliness, and timing and route of exposure.⁵ Timing and route of exposure to allergenic foods is a risk factor that has undertaken a significant paradigm shift over the years. Previously, early infant allergen exposure was thought to be a risk factor for the subsequent development of food allergy, whereas more recently prolonged allergen avoidance has been suspected as playing a causative role. By delaying oral tolerance induction through prolonged avoidance, alternative routes of exposure leading to sensitization are suspected to occur, particularly in those patients with skin-barrier defects such as in atopic dermatitis.¹ This hypothesis has been supported by findings of filaggrin gene loss-of-function mutations being associated with peanut allergy.^{6,7}

Sarah Boudreau-Romano, MD, is an Assistant Professor of Pediatrics. Nashmia Qamar, DO, MSci, is an Assistant Professor of Pediatrics. Both authors are affiliated with the Division of Allergy and Immunology, Department of Pediatrics, Ann & Robert H. Lurie Children's Hospital of Chicago.

Address correspondence to Nashmia Qamar, DO, MSci, Division of Allergy & Immunology, Ann & Robert H. Lurie Children's Hospital of Chicago, 225 E. Chicago Avenue, Box #60, Chicago, IL 60611; email: nqamar@luriechildrens.org.

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Both authors contributed equally to this article and should be considered equal first authors.

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CLINICAL PRESENTATION

Children can present to their physician with symptoms thought to be associated with the ingestion of a particular food. These symptoms can vary widely from nonspecific abdominal discomfort to urticaria or anaphylaxis, and can represent a spectrum of adverse reactions to food from intolerance to immunoglobulin E (IgE)-mediated food allergy. The history of an IgE-mediated allergic reaction usually includes ingestion of the trigger food followed by symptoms within minutes to up to 2 hours after ingestion. The reactions occur reliably every time the food is ingested, although the symptoms can vary with subsequent ingestions. The most common signs and symptoms of IgE-mediated food allergy are listed in **Table 1**.

MANAGEMENT IN THE PEDIATRICIAN'S OFFICE

A patient presenting to their pediatrician's office after experiencing a reaction to peanut-containing food with a history strongly indicative of an IgE-mediated peanut allergy should be given a Food Allergy Emergency Action Plan. The Illinois Food Allergy Emergency Action Plan and Treatment Authorization form is an example of such a plan.⁸ This plan details the signs and symptoms of an allergic reaction and how to treat such a reaction. The patient should be provided with a prescription for an epinephrine auto-injector as well as instructions on when and how it is to be used.

In addition, patients should be given instructions for strict avoidance of peanuts. Discussions regarding cross-contact and the importance of properly reading ingredient labels are critical. In 2004, the US Food and Drug Administration (FDA) passed the Food Allergen Labeling and Consumer Act, which states that foods containing any of the top eight allergens (milk, egg, wheat,

TABLE 1.

Signs and Symptoms That Can Be Exhibited by a Patient During an IgE-Mediated Allergic Reaction

System Involved	Signs and Symptoms
Skin	Urticaria, pruritic rash, localized or generalized erythema
Gastrointestinal	Nausea, abdominal cramping, emesis, diarrhea
Respiratory	Shortness of breath, repetitive cough, wheeze, chest tightness, difficulty breathing
Cardiovascular	Pallor/cyanotic skin, thready or weak pulse, hypotension, feeling of impending doom, confusion, syncope, shock
Oropharynx	Tongue angioedema, throat tightness/angioedema, throat clearing

Abbreviation: IgE, immunoglobulin E.
Adapted from Boyce et al.³²

fish, shellfish, tree nuts, peanuts, and soy) must declare the presence of those allergens on the product label.⁹ These ingredients must be listed in the ingredient list or after the word “contains” printed immediately after or adjacent to the list of ingredients. Many companies choose to add statements with the phrases “may contain,” “processed in a facility with,” or “may contain traces of.” These statements are voluntary and can be confusing to consumers. In fact, a recent study demonstrated that only 16 of the 186 (9%) food products with “may contain peanuts” labeling actually demonstrated detectable levels of peanuts.¹⁰

Food allergy has a significant effect on a family's lifestyle. Discussing issues like anxiety surrounding food, fear of reactions, and school readiness can be helpful. Referring patients to websites for further education and support, including the American Academy of Asthma Allergy & Immunology (www.aaaai.org), can also be beneficial.

For children with likely peanut allergy based on history and symptoms, a referral to an allergist for more detailed testing, including skin prick testing (SPT) and food-specific IgE testing, is advised. If blood testing for food-specific IgE is performed through the pri-

mary care physician's office, care should be taken to only test for foods to which the history suggests a reaction. Panel testing to foods should be avoided, as this can often lead to overdiagnosis of food allergies and unnecessary avoidance.

MANAGEMENT FOR PEANUT INTRODUCTION

Due to the increase in prevalence of peanut allergy, many parents express concern regarding the prevention of peanut allergy in their infants. This is especially true if there is a family history of a diagnosed peanut allergy. Previous recommendations indicated that delaying exposure to certain allergens, including peanuts, was advisable.¹¹⁻¹³ However, in 2015, the Learning Early About Peanut (LEAP) trial² demonstrated an 11% to 25% absolute risk reduction in the development of peanut allergy in high-risk infants if peanut products were introduced between ages 4 and 11 months, significantly earlier than previously recommended.

After the results of the LEAP trial, the National Institute of Allergy and Infectious Diseases released “Addendum Guidelines for the Prevention of Peanut Allergy in the United States.”¹³ The addendum created three distinct guidelines for infants based on varying risk levels.¹⁴

The first guideline addresses infants with severe eczema, egg allergy, or both (**Table 2**). It has been shown that introduction of peanuts to these infants between the ages of 4 and 6 months is critical to reduce the risk of peanut allergy, but the expert panel recommends strong consideration of evaluation with peanut-specific IgE, SPT, or both prior to peanut introduction. Referral to an allergist is the appropriate next step. If appointment availability or access to an allergist causes a delay to introduction, physicians may consider obtaining peanut-specific IgE through *in vitro* testing, even if SPT is not an option. If the blood test result is <0.35 kUa/L, the risk of a reaction is low enough to warrant either home introduction or supervised in-office feeding. If the peanut-specific IgE results are >0.35 kUa/L, there is a higher likelihood of reaction and referral to a specialist is indicated for further evaluation and SPT.¹⁴

The second guideline addresses infants with mild to moderate eczema. These infants should have peanut-containing food introduced at approximately 6 months of age in forms that are developmentally appropriate and safe (ie, no whole peanuts). This can be done at home with the recognition that fear and anxiety, or a sibling with peanut allergy, may be reasons that families choose to delay introduction and may lead families to request an in-office evaluation or feeding.¹⁴

The third guideline states that parents of infants without eczema or any food allergy can introduce age-appropriate peanut-containing foods freely when developmentally ready for solid food and according to family preferences.

MANAGEMENT AT THE ALLERGIST'S OFFICE

Obtaining a detailed history regarding symptoms, timing, and treatment

required after ingestion of the food or foods in question is critical in the evaluation and management of food allergy. When multiple foods were simultaneously ingested, inquiring about ingredient labels, possible cross-contact, and which foods are currently tolerated by the patient will help identify culprit foods. Paying particular attention to timing of onset and symptomatology will help distinguish between IgE-mediated food allergy and non-IgE-mediated reactions such as food intolerances.

Available tests for diagnosing food allergy include the SPT and *in vitro* serum testing for food-specific IgE. Both skin and food-specific IgE testing are sensitive but not specific, which is why the presence of food-specific IgE must be correlated with a clinical history of reaction to diagnose food allergy. Detection of food-specific IgE alone is termed sensitization and does not necessarily equate to food allergy. The high false-positive rates of SPT make it imperative to carefully consider which foods should be investigated through SPT. Suspect foods identified as positive on SPT are also investigated via *in vitro* allergen-specific IgE testing. This testing allows for monitoring of levels over time to determine the possibility of the resolution of food allergy. In the case of peanut *in vitro* allergen-specific IgE testing, newer component testing evaluates for pure allergen proteins and can correlate to likelihood of clinical reactivity. The peanut proteins rAra h1, rAra h2, and rAra h3 are associated with likelihood of systemic, immediate reactions to peanuts. The protein rAra h8 is cross-reactive to Bet v1 (birch pollen), which is associated with less severe pollen-food syndrome (also known as oral allergy syndrome). Allergists may also consider testing to tree nuts as it is estimated that between 25% and 40% of people allergic to peanuts are also allergic to tree nuts.¹⁵

In some instances an oral food challenge may be necessary, either to establish the diagnosis of food allergy or to determine the development of tolerance to a particular food. Oral food challenge is the gold standard in diagnosis of food allergy and involves ingestion of increasing “doses” of the food in question to reach a standard serving size. It is safe to perform challenges in an outpatient setting if performed by skilled personnel with access to epinephrine, antihistamines, corticosteroids, and intubation equipment in the event of airway compromise.

Once the diagnosis of food allergy has been made, the mainstay of treatment is strict avoidance of the food. It is the role of the allergist to provide families with tools and resources to create safe eating environments for patients, including the prevention of accidental ingestion through label reading and avoidance of cross-contact. Providing families with a Food Allergy Emergency Action Plan and instructions on when and how to use the prescribed epinephrine auto-injector is of critical importance. This is of particular importance given that delayed administration of epinephrine has been associated with poor outcomes in food-induced anaphylaxis.^{15,16}

As mentioned previously, in the first guideline, applying LEAP study findings to clinical practice is particularly important in the infant age group. Should an infant present to an allergist with severe eczema, egg allergy, or both, evaluation of sensitization to peanuts with SPT and/or *in vitro* allergen-specific IgE testing will likely be performed. Based on these results, the allergist may consider proceeding to oral food challenge either at home or in clinic. After a successful oral challenge, the family is encouraged to continue inclusion of peanut-containing products in the infant's diet so as to maintain tolerance to peanuts. Expediting referral to an al-

TABLE 2.

Summary of Guidelines for the Prevention of Peanut Allergy

Guideline	Infant Criteria	Recommendation	Age of Peanut Introduction
1	High risk: severe eczema, egg allergy, or both	Strongly consider evaluation including peanut-specific immunoglobulin E and/or skin prick test; if necessary try oral food challenge Based on test results, introduction of peanut-containing foods	4-6 months
2	Medium risk: mild to moderate eczema	Introduce peanut-containing foods	Around 6 months
3	No eczema or any food allergy	Introduce peanut-containing foods	Age-appropriate or developmentally appropriate and in accordance with family preferences

Adapted from Togias et al.¹⁴

lergist is preferred given the findings of significant reduction in subsequent development of clinical reactivity to peanuts based on earlier introduction of peanut-containing foods.^{2,14}

FUTURE THERAPIES

Therapies that are actively under investigation are largely allergen specific. These include oral immunotherapy (OIT), sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT). Regardless of the route used, immunotherapy involves exposure to increasing doses of specific allergen over time. It is known to induce allergen-specific regulatory T cells and suppress T-helper 2 cell responses. It also results in increases in immunoglobulin G4 antibodies, decreased mast cell and basophil activation, and mediator release.¹⁸

OIT is prepared by mixing the allergenic food into a vehicle and ingesting it in gradually increased doses. OIT dosing protocols vary substantially but most include a dose-escalation phase, followed by gradual dose build-up, and lastly a prolonged maintenance phase.^{18,19} In those patients who tolerate OIT, significant desensitization has been observed.²⁰⁻²⁵ Desensitization is considered a change in the thresh-

old dose of food allergen necessary to cause a reaction and is dependent on consistent ongoing exposure to the food. In contrast, the term “sustained responsiveness” has been used to describe no increase in reactivity to the allergen after a period of avoidance. However, after a period of discontinuing treatment (typically 4-8 weeks), studies have shown that there is a lack of sustained unresponsiveness in the majority of treated patients.²⁶⁻²⁸ Adverse reactions to OIT are common and can include oral pruritus and transient abdominal pain, but are typically mild and respond to oral antihistamines.

SLIT involves delivering the protein sublingually in a liquid form. It is hypothesized that SLIT uses exposure to tolerogenic antigen-presenting cells in the oral mucosa.²⁹ Studies directly comparing SLIT and OIT retrospectively are sparse. In a recent double-blind, placebo-controlled trial comparing peanut SLIT and OIT, the OIT group had a greater dose threshold upon rechallenge than the SLIT group; however, adverse reactions were more common in the OIT group.³⁰

EPIT uses patch technology to deliver allergen directly to the skin. The allergen-containing patch is designed to activate dendritic cells in

the skin. This activation creates an overall downregulation of effector cell responses leading to desensitization to the allergen. A recent multicenter, randomized controlled trial of EPIT for the treatment of peanut allergy using a skin patch containing peanut IgE proved to be safe and showed moderate treatment response.^{30,31}

CONCLUSIONS

Given the increasing prevalence of food allergy, specifically peanut allergy, developing strategies to aid in evaluation, management, and prevention of the development of peanut allergy is of utmost importance. Although numerous studies are currently examining the safety and efficacy of various forms of immunotherapy for treatment of peanut allergy, applying new evidence regarding primary prevention of peanut allergy would be most advantageous. Findings from the LEAP study have led to a shift in recommendations from prolonged avoidance of peanuts to earlier introduction of peanuts being a primary method of prevention of peanut allergy. Referral to an allergist for further evaluation and management may be of direct benefit, particularly in cases where infants are at high risk of developing food allergies.

REFERENCES

1. Sicherer SH, Sampson HA. Food allergy: epidemiology, pathogenesis, diagnosis, and treatment. *J Allergy Clin Immunol*. 2014;133(2):291-307. doi:10.1016/j.jaci.2013.11.020.
2. Du Toit G, Robert G, Sayre PH, et al.; LEAP Study Team. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med*. 2015;372:803-813. doi:10.1056/NEJMoa1414850.
3. Peters RL, Allen KJ, Dharmage SC, et al.; HealthNuts Study. Skin prick test responses and allergen-specific IgE levels as predictors of peanut, egg, and sesame allergy in infants. *J Allergy Clin Immunol*. 2013;132:874-880. doi:10.1016/j.jaci.2013.05.038.
4. Bock SA, Munoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001-2007. *J Allergy Clin Immunol*. 2007;119:1016-1018. doi:10.1016/j.jaci.2006.12.622.
5. Lack G. Update on risk factors for food allergy. *J Allergy Clin Immunol*. 2012;129:1187-1197. doi:10.1016/j.jaci.2012.02.036.
6. Brown SJ, Asai Y, Cordell HJ, et al. Loss-of-function variants in the filaggrin gene are a significant risk factor for peanut allergy. *J Allergy Clin Immunol*. 2011;127:661-667. doi:10.1016/j.jaci.2011.01.031.
7. Asai Y, Greenwood C, Hull PR, et al. Filaggrin gene mutation associations with peanut allergy persist despite variations in peanut allergy diagnostic criteria or asthma status. *J Allergy Clin Immunol*. 2013;132:239-242. doi:10.1016/j.jaci.2013.03.043.
8. Illinois State Board of Education. Illinois Food Allergy Emergency Action Plan And Treatment Authorization. https://www.isbe.net/Documents/food_allergy_emer_action_plan.pdf#search=emergency%20action%20plan. Accessed June 27, 2018.
9. Food Allergen Labeling and Consumer Protection Act of 2004. 21 USC § 108-282 (2004).
10. Remington BC, Baumert JL, Marx DB, Taylor SL. Quantitative risk assessment of foods containing peanut advisory labeling. *Food Chem Toxicol*. 2013;62:179-187. doi:10.1016/j.fct.2013.08.030.
11. American Academy of Pediatrics Committee on Nutrition. *Pediatric Nutrition Handbook*. Elk Grove Village, IL: American Academy of Pediatrics; 2004.
12. Fiocchi A, Assa'ad A, Bahna S; Adverse Reactions to Foods Committee; American College of Allergy, Asthma and Immunology. Food allergy and the introduction of solid foods to infants: a consensus document. Adverse Reactions to Foods Committee, American College of Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol*. 2006;97:10-20.
13. [No authors listed.] American Academy of Pediatrics. Committee on Nutrition. Hypoallergenic infant formulas. *Pediatrics*. 2000;106(2 Pt 1):346-349.
14. Togias A, Cooper SF, Acebal ML, et al. Addendum guidelines for the prevention of peanut allergy in the United States: report of the National Institute of Allergy and Infectious Diseases-sponsored expert panel. *J Allergy Clin Immunol*. 2017;139(1):29-44. doi:10.1016/j.jaci.2016.10.010.
15. Sicherer SH, Munoz-Furlong A, Godbold JH, Sampson SA. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow up. *J Allergy Clin Immunol*. 2010;125(6):1322-1326. doi:10.1016/j.jaci.2010.03.029.
16. Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med*. 1992;1:380-384. doi:10.1056/NEJM199208063270603.
17. Pumphrey RS. Lessons for the management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy*. 2000;30(8):1144-1150.
18. Keet CA, Wood RA. Emerging therapies for food allergy. *J Clin Invest*. 2014;124:1880-1886.
19. Jones SM, Burks AW, Dupont C. State of the art on food allergen immunotherapy: oral, sublingual, and epicutaneous. *J Allergy Clin Immunol*. 2014;133:318-323. doi:10.1016/j.jaci.2013.12.1040.
20. Varshney P, Jones SM, Scurlock AM, et al. A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. *J Allergy Clin Immunol*. 2011;127(3):654-660. doi:10.1016/j.jaci.2010.12.1111.
21. Skripak JM, Nash SD, Rowley H, et al. A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. *J Allergy Clin Immunol*. 2008;122(6):1154-1160. doi:10.1016/j.jaci.2008.09.030.
22. Longo G, Barbi E, Berti I, et al. Specific oral tolerance induction in children with very severe cow's milk-induced reactions. *J Allergy Clin Immunol*. 2008;121:343-347. doi:10.1016/j.jaci.2007.10.029.
23. Martorell A, De la Hoz B, Ibanez MD, et al. Oral desensitization as a useful treatment in 2-year-old children with cow's milk allergy. *Clin Exp Allergy*. 2011;41(9):1297-1304. doi:10.1111/j.1365-2222.2011.03749.x.
24. Pajno GB, Caminiti L, Ruggeri P, et al. Oral immunotherapy for cow's milk allergy with a weekly up-dosing regimen: a randomized single-blind controlled study. *Ann Allergy Asthma Immunol*. 2010;105(5):376-381. doi:10.1016/j.anai.2010.03.015.
25. Salmivesi S, Korppi M, Makela MJ, Paasilta M. Milk oral immunotherapy is effective in school-aged children. *Acta Paediatr*. 2013;102(2):172-176. doi:10.1111/j.1651-2227.2012.02815.x.
26. Vickery BP, Scurlock AM, Kulis M, et al. Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy. *J Allergy Clin Immunol*. 2014;133:468-475. doi:10.1016/j.jaci.2013.11.007.
27. Narisety SD, Frischmeyer-Guerrero PA, Keet CA, et al. A randomized, double-blind, placebo-controlled pilot study of sublingual versus oral immunotherapy for the treatment of peanut allergy. *J Allergy Clin Immunol*. 2015;135:1275-1282.
28. Gorelik M, Narisety SD, Guerrero AL, et al. Suppression of the immunologic response to peanut during immunotherapy is often transient. *J Allergy Clin Immunol*. 2015;135:1283-1292. doi:10.1016/j.jaci.2014.11.010.
29. Akdis CA, Barlan IB, Bahceciler N, Akdis M. Immunological mechanisms of sublingual immunotherapy. *Allergy*. 2006;61 (suppl 81):11-14.
30. Wood RA. Food allergen immunotherapy: current status and prospects for the future. *J Allergy Clin Immunol*. 2016;137:973-982. doi:10.1016/j.jaci.2016.01.001.
31. Jones SM, Sicherer SH, Burks AW, et al., Consortium of Food Allergy Research. Epicutaneous immunotherapy for the treatment of peanut allergy in children and young adults. *J Allergy Clin Immunol*. 2017;139:1242-1252. doi:10.1016/j.jaci.2016.08.017.
32. Boyce JA, Assa'ad A, Burks W, 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(suppl 6):S1-S58. doi:10.1016/j.jaci.2010.10.007.

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