

The National Institutes of Allergy and Infectious Diseases sponsored guidelines on preventing peanut allergy: A new paradigm in food allergy prevention

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ABSTRACT

Peanut allergy is a significant public health problem without proven treatment or cure at present. In 2000, the American Academy of Pediatrics recommended that solid-food introduction be delayed in infants at high risk, including peanut introduction, until age 3 years. In 2008, the American Academy of Pediatrics revised these recommendations based on limited evidence of benefit and, instead, recommended solid-food introduction not be delayed past 4–6 months of life. In 2015, the Learning Early About Peanut Allergy study showed that early peanut introduction (between 4 and 11 months of life) was associated with a significant absolute and relative risk reduction in the development of peanut allergy compared with delayed introduction. Based on these findings, the National Institutes of Allergy and Infectious Diseases sponsored an expert panel to create an addendum to the 2010 Food Allergy Guidelines that specifically focuses on peanut allergy prevention. The addendum recommends that children with severe eczema, egg allergy, or both have peanut introduced as early as 4–6 months of life, after assessment by a trained allergy specialist. For children with mild-to-moderate eczema, peanut can be introduced at ~6 months, without the need for specialist evaluation. For children with no eczema, peanut can be introduced in accordance with family and cultural preferences, without the need for specialist evaluation. Adherence to these clinical practice recommendations can help potentially reduce the number of cases of peanut allergy per year. However, this can only be accomplished with the cooperation of parents and health care providers who adhere to these recommendations.

(Allergy Asthma Proc 38:92–97, 2017; doi: 10.2500/aap.2017.38.4037)

THE CLINICAL PROBLEM

Peanut allergy is a significant public health problem that affects as many as 2% of U.S. children and 3% of Australian 1 year olds.^{1,2} Through use of random-digit telephone surveys, the estimated self-reported prevalence of peanut allergy in the United States tripled within a recent 10-year time frame, although comparative cohort data from two studies on the Isle of Wight indicated that the prevalence of peanut allergy may not have significantly risen in the past 20 years.^{3,4} Peanut allergy is often considered to be severe, associ-

ated with fatality, and may be life-long for some individuals, with <25% expected to regain tolerance.⁵ Multiple investigative treatments are focused on providing susceptible individuals some raised threshold of desensitization, with the possibility of sustained unresponsiveness to peanut exposure in some individuals.⁶ However, there is no definitively proven treatment or cure at present, and, thus, the recommended management is strict avoidance and epinephrine autoinjector carriage.

A BACKGROUND ON PEANUT ALLERGY PREVENTION

The reported rise in the prevalence of peanut allergy has occurred within a period of time in which there has been conflicting guidance regarding primary preventative measures to decrease the risk of developing peanut allergy.⁷ Before the year 2000, there was no guidance that recommended any particular timing of peanut introduction or deliberate strategy to delay introduction to prevent allergic disease. In 2000, the American Academy of Pediatrics published updated infant feeding guidelines that recommend that “solid foods should not be introduced into the diet of high-risk infants until 6 months of age, with dairy products delayed until 1 year, eggs until 2 years, and peanuts, nuts, and fish until 3 years of age” in “infants at high risk for developing allergy, identified by a strong (biparental, parent, and sibling) family history of allergy.”⁸

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No external funding sources reported

M. Greenhawt is supported by grant 1K08HS024599–01 from the Agency for Healthcare Quality and Research; is a panel and coordinating committee member of the NIAID-sponsored Guidelines for Peanut Allergy Prevention; has served as a consultant for the Canadian Transportation Agency and Aimmune Therapeutics; is a member of physician/medical advisory boards for Aimmune, Nutricia, Kaleo Pharmaceutical, Nestle, and Monsanto; is a member of the scientific advisory council for the National Peanut Board; has received honorarium for lectures from Thermo Fisher, ReachMD, and the Kentucky/Pennsylvania/Aspen/New York allergy societies, the ACAAI, the EAACI, and University of California Los Angeles/Harbor Medical Center; and is a member of the Joint Taskforce on Allergy Practice Parameters

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Published online January 24, 2017

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However, as more data from observational cohort studies emerged, the American Academy of Pediatrics reversed this guidance in 2008 (as did the American Academy of Allergy Asthma and Immunology in 2013) and made a passive recommendation that introduction of solid foods not be delayed past 4–6 months of life given “serious questions about the benefit of delaying the introduction of solid foods that are thought to be highly allergic” but not further specifying what was an appropriate timing to introduce such foods, peanut included.⁹ Recently, two studies noted poor adherence with these recommendations. The Infant Feeding Practices II study noted that <0.5% of U.S. infants have peanut introduced by 5 months and <20% by 12 months; and nested data from a 2014 birth cohort study noted only 7% of infants had solid-food introduction by 4 months and 13% by 6 months, with peanut introduction occurring, on average, at 20.2 months.^{10,11} Thus, although there is a paucity of data that monitors adherence as an outcome, analysis of these data would indicate sluggish uptake of the 2008 guidelines.

THE LEARNING EARLY ABOUT PEANUT ALLERGY STUDY AND LEVEL I EVIDENCE OF PRIMARY AND SECONDARY PEANUT ALLERGY PREVENTION

In 2008, Du Toit *et al.* published the results of a provocative observational study of Ashkenazi Jewish children who lived in London, England, and Tel Aviv, Israel. In this study, surveys were used to determine the prevalence of peanut allergy in two cohorts of >5000 children in each city. The prevalence of peanut allergy in London, where, at the time, the standard recommendation was peanut avoidance until age 3 years, was 10-fold higher than in Israel, where peanut was introduced in the first year of life. The only significant factor noted to explain the difference in the rates of peanut allergy was the timing of introduction.¹² Although this study could not imply causality that early introduction was associated with a lower prevalence of peanut allergy, it did generate the hypothesis behind the Learning Early About Peanut Allergy (LEAP) randomized controlled study. In the LEAP study, 640 infants, ages 4–11 months, with either moderate-to-severe eczema, egg allergy, or both were randomized to early peanut introduction at enrollment versus deliberate delayed introduction until the age of 5 years. The participants were skin tested at study entry, with those having peanut skin prick tests >4 mm excluded due to a high likelihood of preexisting peanut allergy. The participants were stratified by skin prick test size (0 mm versus 1–4 mm) and then randomized to either early versus delayed peanut introduction. All early peanut introductions were initially done as an open challenge under medical supervision.

The study subjects were then followed up through age 5 years, when both groups underwent supervised open peanut challenge.¹³

Overall, peanut allergy developed in 3.2% of the early introduction group compared with 17.2% in the avoidance group ($p < 0.001$; absolute risk reduction [ARR], 14; number needed to treat, 7.1). However, the differences were more pronounced within the groups stratified by skin testing. Within the group with negative skin tests, 1.9% in the early introduction group versus 13.7% in the avoidance group developed peanut allergy ($p < 0.001$; ARR, 11.8%; number needed to treat, 8.4). Within the group with positive skin test results, 10.6% in the early introduction group versus 35.3% in the avoidance group developed peanut allergy ($p < 0.001$; ARR, 24.8; number needed to treat, 4), which demonstrated that there was heterogeneity of the treatment effect. A subsequent study of these children, ages 5–6 years, in which all the participants avoided peanut for a year, revealed three new cases of peanut allergy developed in each group, a nonsignificant difference. No fatalities occurred, and no significant differences between the groups in the rate of adverse events were observed. The trial, furthermore, demonstrated that oral food challenge of infants was both safe and feasible. Nutritional assessment of these infants noted no significant differences in the duration of breast-feeding between the groups, micronutrient intake, growth parameters, or percentage of calories from protein. Interestingly, the early introduction group was noted to have significantly lower consumption of chips and/or salty snacks, high-fiber bread, juices, and condiments.^{13,14}

CHANGES TO THE INFANT FEEDING POLICY: THE NATIONAL INSTITUTES OF ALLERGY AND INFECTIOUS DISEASES SPONSORED PEANUT ALLERGY PREVENTION GUIDELINES

The LEAP trial provided level I evidence that peanut can be introduced in children at high risk (defined as having either severe eczema and/or egg allergy) between 4–11 months of life.¹³ The trial was enormously successful and demonstrates the tremendous potential for both primary and secondary peanut allergy prevention. Based on the LEAP study results, there has been strong consensus that a more-specific recommendation could be made as to when to introduce peanut and strengthen the current guidance to not delay solid-food introduction past 4–6 months of life.¹⁵ In the summer of 2015, a multinational group of Allergy, Pediatric, and Dermatology societies issued a Consensus Communication, which echoes the sentiment that the result of the LEAP study indicated that early peanut introduction in such infants at high risk is safe and should be encouraged, which follows the protocol in the LEAP

Table 1 Summary of addendum guidelines

Addendum Guideline No.	Infant Criteria	Recommendations	Earliest Recommended Age of Peanut Introduction
1	Severe eczema, egg allergy, or both	Strongly consider evaluation by sIgE and/or SPT, and, if necessary, oral food challenge; based on the test results, introduce peanut-containing foods	4–6 mo
2	Mild-to-moderate eczema	Introduce peanut-containing foods	~6 mo
3	No eczema or any food allergy	Introduce peanut-containing foods	Timing of introduction is age appropriate and in accordance with family preferences and cultural practices

sIgE = *Specific immunoglobulin E*; SPT = *skin prick test*.

study.¹⁶ This document was intended as a placeholder while more formal and specific guidelines by individual societies were being developed. To help accomplish this, the National Institutes of Allergy and Infectious Diseases (NIAID) appointed an expert panel to synthesize the evidence that involves early peanut introduction and to create the recently published addendum to the 2010 Food Allergy Guidelines.¹⁷ These NIAID-sponsored guidelines contain the following three addendum recommendations:

1. Infants with severe eczema, egg allergy, or both should have introduction of age-appropriate peanut-containing food as early as 4 to 6 months of age to reduce the risk of peanut allergy.
2. Infants with mild-to-moderate eczema should have introduction of age-appropriate peanut-containing food at ~6 months of age, in accordance with family preferences and cultural practices, to reduce the risk of peanut allergy.
3. Infants without eczema or any food allergy may have age-appropriate peanut-containing foods freely introduced in the diet, together with other solid foods, and in accordance with family preferences and cultural practices Table 1.

Importantly, these guidelines also contain a list of multiple age-appropriate forms of peanut for introduction in infants; whole peanut is not to be used because it is a choking hazard. Furthermore, infants should also be tolerating at least a few other foods in the diet before peanut introduction is attempted; peanut is not recommended to be an infant's first food. For these guidelines,¹⁸ the high-risk criteria used in the LEAP study¹³ remain largely the same. (Fig. 1) Egg allergy is defined by egg sensitization in an infant with known symptomatic ingestion to egg. In defining severe eczema, the emphasis for severity was placed on chronic, recalcitrant

disease in which control has not been achieved despite stringent emollient use and escalating doses of topical corticosteroids or calcineurin inhibitors. Former criteria of a biparental family history of eczema, featured in the 2000⁸ and 2008⁹ infant feeding guidelines and multiple prevention trials, were not considered.

There is an algorithm in the guidelines to assist providers in assessing those infants in the highest-risk group in recommendation no. 1. For this group, it is recommended that a trained specialist evaluate these children before peanut introduction occurs and strongly considers peanut skin testing (Fig. 2). The algorithm recommends that infants with 0–2 mm skin tests have peanut introduction at home, infants with 3–7-mm skin tests have peanut introduction under observation in the specialist office,¹⁹ and infants with ≥8 mm skin prick tests avoid peanut due to a high likelihood of a preexisting allergy, and undergo ongoing yearly assessment. Some providers may still elect to perform in-office introduction in infants with skin prick tests ≥8 mm, depending on the provider and parent preference because some children with larger skin prick tests may benefit from peanut introduction. For addendum recommendation nos. 2 and 3, the expert panel recognized that children with lesser eczema severity (or no eczema) also would likely benefit from early peanut introduction and recommends peanut be introduced at ~6 months in accordance with family practices and cultural preferences. For addendum recommendation nos. 2 or 3, there is no recommendation for these children to have consultation with a trained specialist before peanut introduction as long as the family is comfortable and introduction can be achieved at home. Providers also have the option to follow the algorithm used in addendum recommendation no. 1 for these infants in addendum recommendation nos. 2 or 3.



Figure 1. Addendum guideline high-risk definitions.

The expert panel also understood that not all infants may necessarily have access to a trained allergy specialist and may be seen by their pediatrician, family physician, or a dermatologist instead. To minimize a delay in peanut introduction for children who will likely have negative skin testing results, testing for peanut-specific immunoglobulin E (sIgE) may be the preferred initial approach in certain instances. If this level is <0.35 KU/L (the lower limit of reporting), then these infants are highly unlikely to have peanut allergy and can have introduction at home.⁵ If the level is ≥ 0.35 KU/L, then it is recommended that these infants be referred to an allergy specialist for further evaluation. For nonspecialists who do provide initial assessment for these children, food allergen panel testing or the addition of sIgE testing to other foods besides peanut is not recommended due to poor positive predictive value, and this is emphasized in the guidelines.¹⁸

IS THERE EVIDENCE THAT SUPPORTS EARLY INTRODUCTION OF OTHER FOODS?

The NIAID-sponsored addendum guidelines¹⁸ are only presently addressing the protective benefits of

early peanut introduction. Similar trials to the LEAP study¹³ have been conducted for egg, although not with as much success or clarity in the findings. A recent meta-analysis that evaluated primary prevention of food allergy pooled the results of these five egg studies and found that there was a net protective benefit against developing egg allergy associated with early introduction of egg at 4–6 months (relative risk, 0.56; $p = 0.009$; ARR, 24 cases per 1000).²⁰ However, only the trial by Natsume *et al.*,²¹ analyzed in this meta-analysis, actually noted any significant benefit. The egg trial by Bellach *et al.*²² noted a nonsignificant trend toward a lack of benefit as well as a high rate of severe reactions in some children who were introduced to egg early and who had positive egg white serum-sIgE at the start of the trial. Thus, the picture is not as clear for egg, although these data certainly support the 2008 American Academy of Pediatrics recommendations to delay any solid-food introduction past 4–6 months.⁹ It is anticipated that these recommendations for egg may be updated in the near future. There are no randomized trials for early milk introduction, although a large Israeli observational study noted that infants exposed to cow's milk in the first 21 days of life (in-

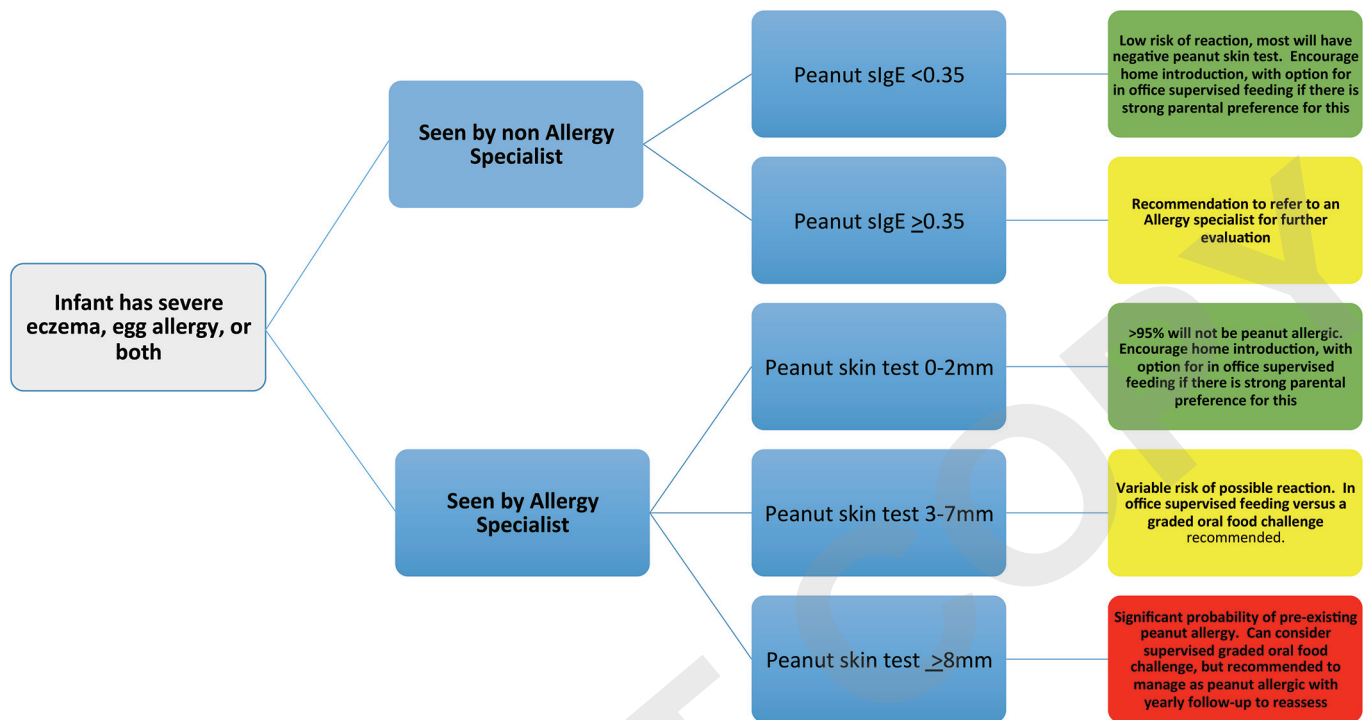


Figure 2. Algorithm for the evaluation of children with severe eczema and/or egg allergy before peanut introduction.

cluding as supplementation) had a 19.3-fold lower odds of developing milk allergy compared with infants exposed between 105 and 194 days of life).²³ A recent meta-analysis noted that there was no protective benefit against the development of food allergy from the use of partially or extensively hydrolyzed cow's milk formula in children at risk for the development of food allergy.²⁴

CONCLUSION

Feeding guidance regarding when to introduce peanut into the diet of an infant has changed. New research that shows that early introduction of peanut-containing product at ~4–6 months of life (after a few other foods have been introduced into the infant's diet) is associated with a significantly reduced risk of such infants who develop peanut allergy. This practice is safe and feasible. Adherence to these clinical practice recommendations is an amazing opportunity to help potentially reduce the number of cases of peanut allergy per year. However, this can only be accomplished with the cooperation of parents and health care providers, who adhere to these recommendations. For the time being, the NIAID-sponsored guidelines¹⁸ do not address the benefits of early introduction of other foods, although growing evidence exists that supports a benefit for early egg introduction.

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