

Implementation of Early Peanut Introduction Guidelines: It Takes a Village



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KEYWORDS

• Peanut allergy • Allergy prevention • Food allergy • Food introduction

KEY POINTS

- Early peanut introduction around 6 months of age is thought to help prevent the development of peanut allergy in high-risk infants.
- It is unclear if high-risk infants need to have peanut allergy testing before first ingestion of peanut.
- Implementing new guidelines related to peanut introduction on a national level has been challenging for several reasons.

INTRODUCTION

Food allergy can affect up to 5% of the pediatric population in the United States.¹ There is special interest in peanut allergy because it is rarely outgrown, is most often associated with fatal anaphylaxis,² and has a significant effect on quality of life.^{2,3} Currently, there are no Food and Drug Administration–approved treatment options for peanut allergy, although at least 2 potential treatment options are undergoing clinical trials.⁴ Although these treatment options appear promising, they are not without risk, complication, and cost. Furthermore, they provide no guarantee of complete tolerance to peanut.⁴ Consequently, there has been, and continues to be, great interest in the prevention of peanut allergy.

HISTORICAL PERSPECTIVE

In the late 1990s, partially in response to the growing incidence of food allergy, international organizations released recommendations calling for the avoidance of highly allergenic foods until later in life.^{5,6} These recommendations were based on an assumption of the protective role of exclusive breastfeeding, an understanding of mucosal immunity in allergy development and observations on increased rates of eczema when solid food was introduced before 4 months of age.⁷ However, an

Disclosure Statement: No disclosures.

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Immunol Allergy Clin N Am 39 (2019) 459–467

<https://doi.org/10.1016/j.iac.2019.07.002>

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understanding of the impact of different routes of sensitization (and preference for oral sensitization to precede other routes of sensitization) began to emerge, and new data began to challenge these recommendations. For instance, a compelling study by Du Toit and colleagues⁸ found a pattern in which food allergies were prevalent at a higher rate in London (where peanut avoidance was practiced), compared with Tel Aviv (where peanut consumption began in infancy) in a genetically similar population. In 2008, the American Academy of Pediatrics reversed its original recommendation, indicating the timing of allergic foods should be left up to personal and cultural preferences because there was a lack of evidence to make recommendations in any specific direction.⁹ The American Academy of Allergy and Immunology (AAAAI) and Canadian society made similar reversals in 2013.^{10,11}

The paucity of evidence on the optimal timing of introduction of peanut lead to the Learning Early About Peanut trial (LEAP), a randomized control trial that compared the incidence of peanut allergy in a group of infants who had deliberate early introduction of peanut with a group of infants who delayed introduction of peanut.¹²

LEARNING EARLY ABOUT PEANUT TRIAL

The results of the LEAP trial were published in February 2015. High-risk infants were defined as those with either an egg allergy or moderate to severe atopic dermatitis. All infants had peanut skin prick testing (SPT) at study entry. Infants with an SPT greater than 4 mm were assumed to be allergic to peanut and were excluded from the trial. The remaining infants were separated into a group with no peanut sensitization and those with SPT of 1 to 4 mm. Each group was then randomized into early introduction, which considered of eating 2 g of peanut product in the form of Bamba, 3 times a week or strict peanut avoidance. Infants in the early introduction group had an oral food challenge (OFC) to peanut before beginning peanut introduction at home. At the end of 5 years, all infants who were randomized had an OFC to peanut.¹²

The results of the LEAP trial were compelling, with an overall risk reduction of peanut allergy from 17.2% in the avoidance group to 3.2% in the introduction group. In the group with no peanut sensitization, there was a relative risk reduction of 86% in children who consumed peanut, compared with those who avoided peanut, showing promising primary prevention. In the sensitized group, there was a 70% relative risk reduction in the consuming group compared with the avoiding group, demonstrating secondary prevention.¹² The LEAP-On trial went on to show that infants who consumed peanut in infancy were able to maintain peanut tolerance, even after they stopped regular peanut consumption, demonstrating they had achieved true peanut tolerance.¹³

Although the LEAP trial demonstrated quite robust data, it left many unanswered questions. How frequent was peanut consumption required to obtain the protective effect? Which population would benefit the most from early introduction? Could the infants who were excluded from the study because of large skin test benefit from early introduction? Do infants need to have allergy testing before eating peanut product? Could the results seen in the study be extrapolated to other populations? Essentially, the message behind the LEAP trial was understood, but there was confusion on how to implement the findings in clinical practice.

NATIONAL INSTITUTES OF HEALTH GUIDELINES: PUBLICATION OF THE ADDENDUM GUIDELINES FROM THE NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

In response to the compelling data published in the LEAP trial, international experts from pediatrics, allergy/immunology, and dermatology quickly released consensus

guidelines to assist with the implementation of the LEAP data.¹⁴ Subsequently, the National Institute of Allergy and Infectious Diseases (NIAID) released more detailed guidelines that made specific recommendations on peanut introduction and testing based on infant risk factors. These guidelines were published in January 2017 and suggested discussing the introduction of peanut between 4 and 6 months of age after other solid foods are introduced for infants with eczema or egg allergy.¹⁵ The guidelines further recommend that high-risk infants, defined as infants with egg allergy or severe atopic dermatitis, should have allergy testing before peanut introduction. The guidelines did not make specific recommendations for infants who do not have eczema or egg allergy, stating they should introduce peanut according to family and cultural preferences.

Although serum-specific immunoglobulin E (IgE) was not found to be very specific in the LEAP trial or in other trials, the guidelines do include the use of serum-specific IgE as a screening tool in some populations, especially when access to an allergist may be limited. Infants with a negative peanut IgE (<0.10 KU/L) have minimal risk for a systemic reaction to peanut and can introduce peanut at home without evaluation by an allergist. However, any value greater than 0.10 KU/L is not very sensitive and would require referral to an allergist for evaluation.¹⁵

An allergist should evaluate all the high-risk infants (egg allergy or severe atopic dermatitis) who have a serum-specific IgE greater than 0.10 KU/L (when performed) with SPT and OFC. An infant with a peanut SPT less than or equal to 2 has a minimal chance of a systemic reaction and can be instructed to introduce peanut at home. Those with an SPT of 3 to 7 mm warrant further evaluation with an OFC to determine if the infant can tolerate peanut. Infants with an SPT greater than 7 mm have a high likelihood of peanut allergy and should be counseled appropriately. An upper limit of 7 mm was chosen, rather than the 4 mm used in the LEAP trial, based on data from the HealthNuts study, which was a longitudinal, population-based study looking at the incidence of peanut allergy in infants in Australia that included an OFC for all infants.¹⁶

All infants who are considered tolerant to peanut (either by SPT or passed OFC) should be instructed to maintain peanut in their diet 3 times a week in order to ensure continued tolerance to peanut. As part of the NIAID addendum guidelines, specific recommendations were made on how to introduce peanut protein into an infant's diet. Special interest, of course, was given to the prevention of choking. It is imperative that infants are not given peanuts. Instead, they can be offered peanut butter or peanut-flavored snacks. Peanut butter can be mixed with hot water or mixed in a puree to a consistency the infant is used to eating. Two grams of peanut protein is equal to approximately 2 teaspoons of peanut butter or 21 peanut-flavored snacks. Detailed recipes can be found on the NIAID Web site.¹⁵

SIBLINGS WITH PEANUT ALLERGY

The guidelines make no recommendations regarding testing infants who have older siblings with peanut allergy. Previous studies have shown that a family history of a sibling with a peanut allergy may slightly increase the risk of peanut allergy.^{17–19} However, these studies have several inherent flaws, primarily reliance on self-report or evidence of sensitization to define allergy. Others have noted that siblings of children of peanut allergy are more likely to avoid peanut or to be mislabeled as peanut allergic, potential risk factors for peanut allergy.²⁰ Gupta and colleagues²¹ suggested that siblings of peanut-allergic children did not have a higher incidence of peanut allergy, when allergy was defined as clinical reactivity and sensitization, but were more likely to have

evidence of peanut sensitization. Although it is unclear if the potential increased risk of peanut allergy in siblings of children with peanut allergy is genetic²² or related to environmental responses,²¹ their risk of clinically insignificant sensitization is high. Furthermore, other risk factors, such as egg allergy or eczema, seem to be more significant risk factors for the development of peanut allergy. Many believe the slightly higher risk of peanut allergy in siblings of peanut-allergic children is mitigated by earlier peanut introduction. Therefore, screening for peanut allergy is not necessary when an infant has a sibling with peanut allergy and can actually lead to unnecessary delay and food avoidance.

Requiring allergy testing for all infants who have a sibling with peanut allergy, the vast majority of whom would be able to safely tolerate peanut, does not make sense from a public health perspective. However, when allergy testing is available, it can be offered to caregivers who are uncomfortable introducing peanut without testing. Many families are comfortable introducing without testing, especially when the risks are explained. However, in this author's experience, some families refuse to introduce peanut without testing, especially if they have witnessed another child have anaphylaxis to peanut. In these situations, providing allergy tests for reassurance, and OFC when testing is positive, is sometimes necessary to introduce peanut into an infant's diet. However, it is important to note that testing is not required in this situation and counseling against the need for testing is always an option.

Some families have chosen to become strictly peanut-free after 1 member develops a peanut allergy and struggle with the recommendation to keep peanut a regular part of another infant's diet. In these cases, the author recommends that peanut either be introduced into the diet away from home if the child frequents another caregiver's home regularly or be introduced into the home in a safe location for the purpose of remaining in the tolerant child's diet. Especially for infants with a risk factor for developing a peanut allergy, it is important to highlight the recommendation to maintain peanut in the infant's diet.

BREASTFEEDING

Many countries have changed policies to include proactive peanut introduction between 4 and 6 months of age based on the LEAP data. However, others have questioned the wisdom of these global changes, especially when considering developing countries, which may have different risk factors, such as malnutrition and human immunodeficiency virus. To date, all studies have been conducted in developed countries. Levin and colleagues²³ advise the risks associated with weaning be balanced against the risk of developing a peanut allergy and encourage recommendations be country specific. It is important to note, however, that in the studies that have been done investigating early introduction of allergenic foods, the introduction of peanut did not hinder breastfeeding rates or duration.^{12,13,24}

BARRIERS TO IMPLEMENTATION

Although the NIAID guidelines were published in 2017, bringing the guidelines into widespread clinical practice has been met with several barriers. In a survey conducted 3 months after the guidelines were released (and 26 months after the LEAP data were published), Greenhawt and colleagues²⁵ found that caregivers and expectant caregivers were very hesitant to adopt these recommended changes, with only 30% of nationally surveyed participants indicating a willingness to introduce peanut to an infant around 6 months of age. The survey conducted was a nationally represented (other than age, gender, and marital status) sample of 1000 expectant caregivers and

1000 new caregivers (mean age, 30.1%; 99.6% women and 79% married). Approximately half of the sample agreed that the timing of food introduction could influence the development of food allergy. However, nearly 40% preferred to wait until after 11 months of age to introduce peanut, and more than half preferred allergy testing and OFC after 11 months of age. Interestingly, respondents with a family history of peanut allergy, including other children with food allergy, did not have any increased willingness to introduce peanut early.²⁵

The hesitation to adopt new guidelines likely goes beyond family preferences and extends to physician knowledge and comfort. Abrams and colleagues²⁶ surveyed allergists, pediatricians, and family practitioners on approach to an infant at risk of developing peanut allergy and found that pediatricians and family practitioners were unclear on the risk factors for infants at high risk of developing peanut allergy, citing a sibling with a peanut allergy as the most important risk factor. In this study, only 24.6%, 3.95%, and 4.22% of allergists, pediatricians, and family practitioners, respectively, recommended preemptive testing for infants with severe eczema before peanut introduction. In an abstract presented at the AAAAI in 2018, the author's group described difficulty in getting pediatric colleagues to refer to a designated early introduction of peanut clinic, designed to address the need to test and challenge high-risk infants in a timely manner, and how the use of a quality improvement algorithm helped to address the difficulty.²⁷

Even when guidelines are followed and high-risk infants are appropriately referred for allergy evaluation, performing OFC when needed can be difficult. Stukus and colleagues²⁸ described the implementation of these guidelines in clinical practice and found that 40% of infants who were told to return for an OFC were lost to follow-up. When infants were challenged on the same day as SPT, a resolution was more likely to be established.

UNANSWERED QUESTIONS

Testing Requirements

Many controversies remain regarding early peanut introduction. Perhaps the most pressing issue is the question of which patients, if any, require testing before introduction. The NIAID addendum guidelines call for testing of high-risk infants, as previously described. Other countries, such as the United Kingdom and Australia, did not include the need for allergy testing in their revised national guidelines.^{29,30} Australia's guidelines do not make any recommendations for testing, instead suggesting that all infants be fed peanut in a graded manner around 6 months of age.²⁹ The United Kingdom has a similar policy as Australia, but does note that allergy referral can be considered for high-risk infants (but should be considered against the potential for delayed introduction).³⁰

Concerns about testing relate to the capacity of allergists' to meet the demand. In the HealthNuts study, an estimate of 11% of infants would have met the inclusion criteria of moderate to severe eczema or egg allergy by 6 months of age. With an expected 300,000 births each year, this would equate to 33,000 referrals to allergy for allergy testing. Based on the LEAP trial, approximately 4488 infants would require OFCs. Koplin and colleagues³¹ used these data to estimate the feasibility of implementing the LEAP data and concluded there would not be enough allergists in Australia to perform the necessary OFC to adequately implement the NIAID guidelines.

The idea to forgo testing comes from the observation that reactions in the infant population are usually mild. When examining the reactions at baseline OFC in the LEAP data, all the reactions were mild and able to be treated with antihistamine alone. Furthermore, Koplin and colleagues³¹ described reactions to first peanut introduction

in the HealthNuts study and found there were no anaphylactic reactions in the group that introduced at home. Most of the 150 reactions occurring in the 400 OFC conducted in the office were mild and required either no treatment or treatment with antihistamines. However, there were 6 cases of anaphylaxis that occurred in both high-risk and low-risk infants.³¹

Because systemic reactions requiring epinephrine are rare in the infant population, some believe the requirement for allergy testing before introduction may be leading to an unnecessary delay in peanut introduction and overburdening limited allergy resources. However, others argue that although systemic reactions are rare, they do still occur. On a population level, if all infants are told to introduce peanuts without testing, it is inevitable that some infants will have systemic reactions that families may be unprepared to handle. Not only can this be dangerous for the infant but also it may inadvertently lead to a hesitation to introduce peanut. In a simulated model, Shaker and colleagues³² found that a no-screening approach was more cost-effective than a screening approach in implementing early peanut introduction, but also led to a greater number of peanut-allergic reactions.

At this time it is unknown if there is a need to screen every high-risk infant and the best screening method. Furthermore, it is unclear if the current screening recommendation is creating a delay in peanut introduction or overburdening the capacity of allergists. However, there have not been any reports indicating an inability to adequately test and challenge high-risk infants. On the contrary, it is far more likely that high-risk infants are being underreferred for allergy evaluation and consequently may not be discussing peanut introduction.³³ It is possible, as the guidelines become more engrained in the culture, that a greater number of high-risk infants will be identified and referred. Given the current reluctance to adopt the new guidelines, there is a concern that primary care providers would be reluctant to encourage early peanut introduction in high-risk infants without prior testing. Further recommendations should take into account primary care physician willingness to comply with the recommendation.

It is desirable to identify the infants who would attain the highest yield from evaluation by an allergist. Other evaluation methods should also be considered based on the availability of allergist, family preferences, and community comfort levels.

Peanut Consumption

Another question that frequently arises is how often does an infant need to consume peanut after being determined to be peanut tolerant. In the LEAP trial, infants were consuming 2 g of peanut 3 times a week. It is unclear if this amount or this frequency is necessary to maintain tolerance. For many families, this can be challenging, especially if there are other children with peanut allergy in the house or if the infant does not like peanut products.

Because it is unknown if the recommendation of consuming peanut 3 times a week is necessary to maintaining peanut tolerance, it is very important for families of high-risk infants to find a way to maintain peanut in their diet regularly to help ensure they remain tolerant to peanut. In clinical practice, often infants are seen who either passed an OFC to peanut, had negative skin testing to peanut, or safely consumed peanut product at home later develop a peanut allergy. This often occurs after a period of a few weeks without consuming peanut. It is not known if these infants would have developed a peanut allergy had they been regularly consuming peanut. It also is not known the exact frequency with which this happens. However, other studies have documented that people can redevelop a peanut allergy after passing an OFC to peanut when peanut is not regularly ingested.³⁴

Timing of Peanut Introduction to Allergy Testing

Another scenario that is frequently encountered is when infants who had negative allergy testing were told to introduce peanut into their diet. Often, when they return for follow-up, they have not yet introduced peanut for a variety of reasons. In these situations, retesting with peanut is recommended because of the risk of resensitization. Although it is unknown how often this occurs in the infant population, other studies have clearly documented resensitization to peanut can occur.³⁴ In general, the author recommends relying on the peanut SPT for up to 4 weeks. If peanut is not introduced in this window, retesting is recommended.

FUTURE CONSIDERATIONS/SUMMARY

Although unanswered questions, challenges with increasing education, and skepticism about the feasibility of large-scale implementation remain, much is to be gained from adopting new practices that center on early peanut introduction. Recently, much interest has been given to treatment of food allergy. However, prevention can be much more powerful than treatment. When adopted properly, this relatively simple intervention, exposing high-risk infants to peanut early in life, can dramatically decrease the burden of peanut allergy. Caregivers, allergists, and community physicians must work together to develop a system that ensures all infants are being exposed to peanut early in life and high-risk infants are being evaluated by an allergist when needed.

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