

PEANUT INTRODUCTION AND THE PREVENTION OF PEANUT ALLERGY: EVIDENCE AND PRACTICAL IMPLICATIONS

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ABSTRACT

Peanut allergy, a major public-health concern, is persistent in the majority of cases, with no current long-term cure, therefore the prevention of peanut allergy presents an attractive option. The Learning Early about Peanut Allergy (LEAP) study, published in 2015, found significantly lower rates of peanut allergy in infants at high risk of peanut allergy if peanut was introduced early (between four and 11 months) and given regularly. These findings led to an international effort to develop practical clinical recommendations on peanut-allergy prevention. Such recommendations are discussed in this article, which aims to summarise the practical implications of recent research outcomes in peanut-allergy prevention.

INTRODUCTION

Peanut allergy (PA) is a major public-health concern estimated to affect between 0.5–2% of children.^{1–3} PA can be severe or life-threatening and is one of the most common causes of food-related anaphylaxis in the United States.⁴ Moreover, PA begins early in life for the majority of patients and is persistent in the vast majority of cases.⁵ Therefore, preventing PA would have a significant impact on the individual and potentially also at a public-health level.

EVIDENCE FOR EARLY PEANUT INTRODUCTION IN HIGH-RISK INFANTS: THE LEAP STUDY IN A NUTSHELL

The Learning Early about Peanut Allergy (LEAP) study was published in 2015, a landmark trial in the realm of PA prevention.⁶ This study enrolled 640 children at high risk of PA, which was defined for this study as infants between four and 11 months of age with severe eczema and/or egg allergy. At study entry, LEAP participants were stratified according to skin-prick test (SPT) results to peanut into those with a negative SPT response ($n = 530$) – a primary prevention group – and those with a measurable SPT response (1–4 mm, $n = 98$) – a secondary prevention group

– as the latter group were considered sensitised but not allergic to peanut at study entry. Participants with an SPT of greater than or equal to 5 mm were excluded because of their study-defined high risk of established PA, although these patients did not undergo oral food challenges (OFC) to determine whether they were truly peanut-allergic. Patients were randomised to consume at least 2 g of peanut protein thrice weekly or to avoid peanut-containing food until five years of age, at which stage a peanut OFC was performed. Infants randomised to consume peanut ingested a median of 7.7 g peanut protein per week during the first two years of the trial.

In the group with negative SPT at baseline, the prevalence of PA in the avoidance group was 13.7% at five years age versus 1.9% in the consumption group. This represented a 12.6% absolute risk reduction and an 86.1% relative reduction in PA ($p < 0.001$), with a number needed to treat (NNT) of 8.5 (number of infants needed to have early peanut introduction to prevent peanut allergy in one child). In the subgroup with a measurable SPT to peanut of 1–4 mm the prevalence of PA was 35.3% in the avoidance group and 10.6% in the consumption group. This represented a 24.7% absolute risk reduction and a 70% relative reduction

in PA ($p = 0.004$), and resulted in an NNT of 4. The results of the LEAP study are summarised in Figure 1.

Regarding trial safety, seven of the 319 children (2.2%) randomised to the consumption group reacted to peanut at the baseline OFC. This suggests that peanut OFCs are safe and feasible even in those children with minimally positive SPT. However, six children in the consumption group developed signs of PA during the study, therefore PA can still occur despite primary and secondary prevention strategies.

The LEAP-ON study⁷ demonstrated the long-term persistence of oral tolerance to peanut achieved in the LEAP trial when peanut consumers subsequently avoided peanut for one year from 60–72 months of age. A further analysis of nutrition in the LEAP cohort⁸ showed that the introduction of peanut did not affect the frequency or duration of breastfeeding and did not influence growth or nutrition.

IMPLICATIONS OF THE LEAP STUDY

The significant reduction in PA in the early consumption group led to an international effort to develop practical clinical recommendations on PA prevention. Although many existing infant-feeding guidelines prior to 2015 had already suggested the introduction of allergenic foods from 4–6 months onwards, these did not specifically emphasise that avoidance may be harmful. However, a population programme aiming to identify and screen all infants at risk of PA would pose major logistic and economic challenges,

TABLE I: RECOMMENDATIONS FOR PEANUT INTRODUCTION IN INFANTS ACCORDING TO RISK STRATIFICATION

INFANT CRITERIA	RECOMMENDATIONS	EARLIEST AGE OF PEANUT INTRODUCTION
No eczema and no other food allergies	Introduce peanut-containing foods	In accordance with family preferences and cultural practices, but no need to delay beyond six months
Mild to moderate eczema	Introduce peanut-containing foods	Around six months
Severe eczema,* egg allergy or both	Evaluation by sIgE measurement and/or SPT and, if necessary, an OFC. Based on test results, introduce peanut-containing foods (see Figure 2 and Table II)	Around 4–6 months

* Severe eczema defined as persistent or frequently recurring eczema with typical morphology and distribution assessed by a healthcare provider, requiring frequent need for prescription-strength topical corticosteroids or calcineurin inhibitors despite appropriate use of emollients.

hence a more pragmatic approach needs to be taken for patients.⁹ A consensus statement about the implementation of the LEAP findings was published after the LEAP findings in 2015 on behalf of nine international professional societies.¹⁰ In addition, the National Institute of Allergy and Infectious Diseases (NIAID) published addendum guidelines for the prevention of PA in the United States in 2017.¹¹ This is an addendum to the 2010 'Guidelines for the diagnosis and management of food allergy in the United States'.

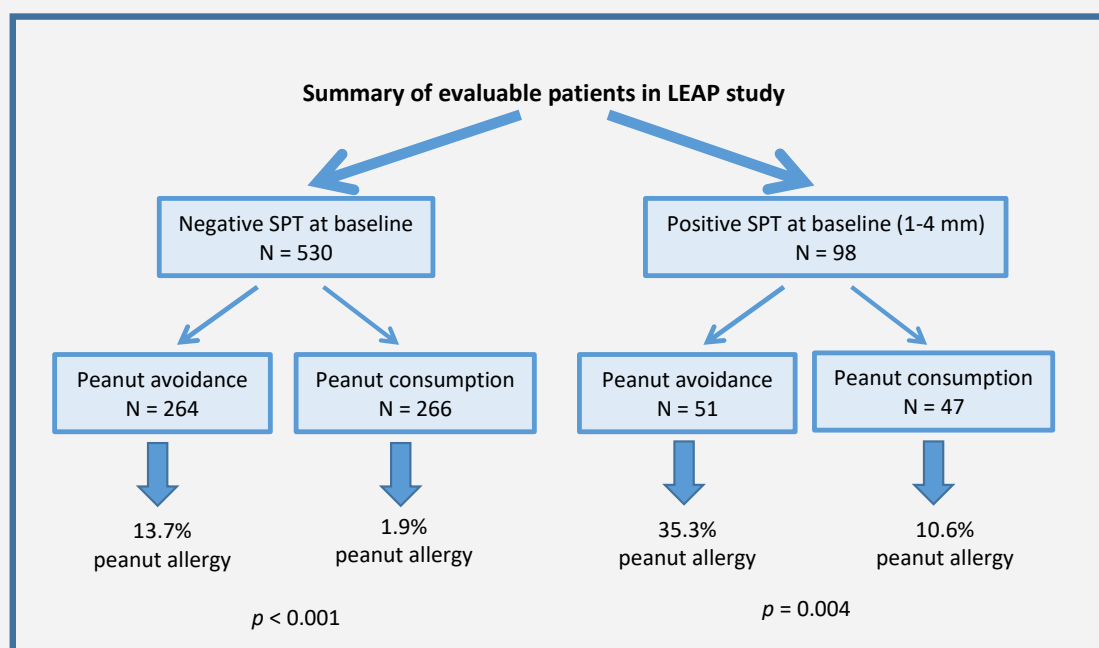


Figure 1: Summary of LEAP Study Outcome

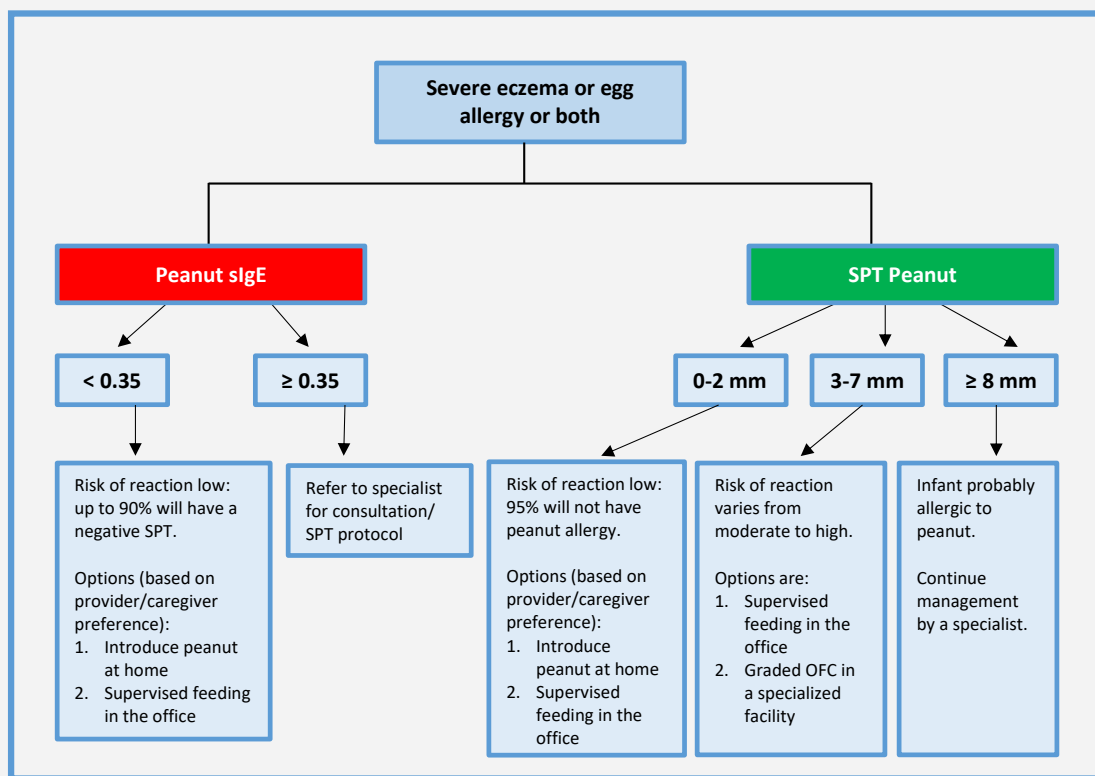


Figure 2: Peanut protein introduction in infants at high risk of PA (adapted from reference 11)

The latter two sources of recommendations for the introduction of peanut were used as a basis for this summary below.

RECOMMENDATIONS FOR PEANUT INTRODUCTION IN INFANTS

Table 1 summarises the general recommendations for peanut introduction in infants according to risk level for PA.¹¹

INFANTS AT LOW RISK OF PA

- There is no evidence for restricting allergenic foods in infants without known risk for food allergy.
- There is no evidence to suggest that mechanisms of oral tolerance induction differ in infants at low risk of PA from mechanisms that are protective in infants at higher risk of PA.
- Therefore, infants without eczema or any food allergy should have age-appropriate peanut-containing foods introduced freely into the diet after the initial introduction of other age-appropriate solid foods.
- Introduction should be in accordance with cultural practices and family preference.
- This low-risk category was not studied in the LEAP study. However, in the EAT study (Enquiring about Tolerance), in which infants from the general

population were introduced to six allergenic foods from the time of enrolment at three months, the per protocol group who had early peanut introduction showed a significant reduction in peanut sensitisation and allergy at three years.¹²

INFANTS AT 'MEDIUM' RISK OF PA

The NIAID addendum guidelines suggest that infants with mild to moderate eczema should be introduced to age-appropriate peanut-containing foods around six months of age to reduce the risk of PA.¹¹

- The exact timing and method of peanut introduction should be in accordance with family preference and cultural practice.
- Other solid foods should be introduced before peanut-containing foods to show that the infant is developmentally ready.
- Infants in this category may have peanut introduced at home without further evaluation.
- However, some caregivers or healthcare providers may prefer in-office evaluation, supervised feeding or both.
- This risk category was not targeted by the LEAP study, therefore data to support recommendations have been extrapolated from the LEAP and EAT studies.^{6,12}

TABLE II: TYPICAL PEANUT-CONTAINING FOODS AND PORTION SIZES¹¹

FOOD	TYPICAL SERVING CONTAINING 2 G OF PEANUT PROTEIN	FEEDING TIPS
PEANUT BUTTER	8–10 g (2 teaspoons) 	Mix with warm water, breast milk or formula milk for a smoother texture. In older children, mix with pureed fruit or vegetables.
PEANUTS	8 g peanuts = approximately ten whole peanuts or 2½ teaspoons of ground peanuts (whole peanuts are a choking hazard in young children under the age of three years) 	Add ground peanuts to a portion of yoghurt or pureed fruit.
PEANUT FLOUR (50% PEANUT PROTEIN)	4 g Approximately two teaspoons 	Mix with yoghurt, apple sauce or apple juice.
BAMBA SNACK	17 g (2/3 of a 28 g packet or 21 sticks) 	For a smooth texture, mix with warm water/ infant milk and mash well.



INFANTS AT HIGH RISK OF PA

In infants with severe eczema, egg allergy or both, early introduction of peanut-containing foods (ideally 4–6 months but up to 11 months may be beneficial) has been shown to reduce the risk of PA.

- Other solid foods should be introduced before peanut to show that the infant is developmentally ready.
- Evaluation of SPT to peanut, peanut-specific IgE or both should be strongly considered before the introduction of peanut.
- If SPTs are not immediately available, testing for specific IgE may be the preferred approach to minimise delay in peanut introduction.

- The results of the specific IgE or SPT will determine the feasibility of peanut introduction and the details around it, as outlined in Figure 2.

HOW MUCH PEANUT PROTEIN SHOULD BE GIVEN?

The first dose of peanut protein should be a cumulative dose of around 2 g of peanut protein (see Table II). After that, the total minimum amount of peanut protein should be 6–7 g per week, consumed over three or more feedings per week.^{6,11} However, this is a suggested amount based on the LEAP study, which was the only amount and frequency studied. Therefore, it is not known if other amounts and frequencies of ingesting peanut would have the same results.

ILLUSTRATIVE CASES: PATIENTS AT HIGH RISK OF PA

CASE 1

Background: Patient MB, seven months old, severe relapsing eczema and rash around the mouth after egg introduction, breastfed with selected solids, mainly fruits and vegetables. Never eaten peanut before, no cow's milk products, soya, wheat, fish in diet yet.

SPT: Egg white 4 mm, fresh raw egg white 7 mm, peanut 2 mm. Cow's milk, soya, hake fish, wheat: 0 mm.

Risk assessment: Confirmed egg allergy. Risk of PA relatively low, based on SPT result of 2 mm.

TABLE III: PRACTICAL TIPS FOR WEANING

GENERAL WEANING	PEANUT INTRODUCTION	OTHER ALLERGENS
The weaning period is the ideal time to set the foundations for healthy eating habits. Tastes and flavours that infants are exposed to affect their food preferences for life. The more an infant is exposed to certain flavours, the more likely they are to eat those; this highlights the importance of regular vegetable and fruit intake. ¹³	Whole peanuts can cause choking in children under five years of age. Whole, shelled peanuts and lumps of peanut butter should not be given to children under five years of age due to the risk of choking. The NIAID guidelines recommend that you give your baby peanut puffs (e.g. Bamba), smooth peanut butter mixed with hot water and then cooled down, peanut flour or peanut powder. ¹¹	There are currently no guidelines about the introduction of other allergens – suggestions for the introduction of other allergens are adapted from the EAT study and listed below. ¹² Also take into consideration infant readiness and the recommendation of your physician.
Textures are important. Start with purees or soft finger foods but step up timely to mashed, dissolvable and finger foods – the aim should be for infants to eat family-type meals by 12 months. Infants who have not eaten lumpy foods by ten months of age are more likely to develop picky eating behaviour. ¹⁴	Infants often refused to eat or may eat less than usual. The median intake of peanut protein in the LEAP study was above the recommended guidance for the study – this was despite the fact that some of the infants did refuse peanut from time to time. ⁶ Just keep feeding when the infant is ready and well.	Milk – infant formula, if not totally breastfeeding. If breastfeeding: milk in baked foods or yoghurt (cheese can be given from around 6–7 months due to high salt content).
Importance of variety. The more varied the foods introduced during the first few months, the more likely children will have a varied diet later. A diet that includes a large variety of foods, with regular intake of these, may prevent the development of allergic diseases. ^{15–17}	Some infants have really good appetites and love peanut. There is no need to adhere strictly to just 2 g of peanut protein; allow the infant to eat more if they prefer – toddlers in particular may want to eat the whole bag of Bamba as opposed to just 2/3 of the bag.	Egg – give baked cooked/fully cooked egg to start with (such as low sugar cookies, muffins or pancakes) rather than soft-boiled egg/poached egg/raw egg powder/pasteurised egg. Raw/undercooked egg is also not recommended for children under one year of age in most countries.
Food preparation. Commercial foods contain less natural bacteria than homemade foods; the anti-oxidant content and variety may be less as well. ¹⁸ There is no need to avoid commercial food, but do cook as often as possible.	Some infants are picky eaters and will not eat any of the options suggested in the NIAID guidelines. Any peanut-containing foods providing about 2 g of peanut protein is acceptable – a dietitian may be very helpful in finding local and culturally acceptable options that the infant will eat. Any dietitian (irrespective of their knowledge of food allergy) can advise parents about the peanut content of food by calculating it from the label (if peanut is the only ingredient) or from information obtained from the manufacturer.	Soy – soy milk, soy yogurt or tofu (there is not much protein left in soy sauce and the salt content is very high – best to avoid these).
	Do not medicalise the weaning process. Infants are ready for solid foods at different ages; look out for developmental cues – there is no need to start weaning at an exact age – all infants are different.	Sesame – hummus and tahini.
	Is it safe to eat peanut around an older peanut-allergic sibling? This should be dealt with individually within each family.	Fish – the fish species that the family eats; continue with regular intake (check the local guidance on fatty fish intake in toddlers).
		Wheat – softly cooked pasta, bread fingers (check ingredients for other allergens that have not been tried).



Action: Office-based short peanut challenge in two stages: 0.5 g peanut and 2 g peanut with observation for one hour.

Outcome: Peanut challenge passed. Patient advised to include peanut in diet, around 2 g three times a week. Eczema management discussed. Egg avoidance discussed. Counselling to include other allergenic foods in diet. Reassessed for eczema two weeks later and again six months later: peanut being consumed with no reactions.

Learning point: In patients at high risk of PA, after initial assessment, PA can be successfully introduced into the diet in many cases and a potential PA avoided.

CASE 2

Background: Patient KD, five months old, severe relapsing, difficult-to-control eczema from three months of age,

exclusively breastfed and not yet on any solids.

SPT: Egg 3 mm, fresh raw egg white 10 mm, cow's milk 3 mm, fresh cow's milk 7 mm. Peanut, soya, hake fish, wheat 0 mm.

Risk assessment: Highly probable egg and cow's milk allergy. Risk of PA low (<5%), based on negative SPT result.

Action: Eczema management discussed. Egg and cow's milk avoidance discussed. Simple solid purees including fruits and vegetables introduced. Two weeks later, office-based short peanut challenge in two stages: 0.5 g peanut and 2 g peanut with observation for one hour.

Outcome: Peanut challenge passed. Patient advised to include peanut in diet, around 2 g three times a week. Reassessed for eczema one month later: peanut being consumed with no reactions.

Further course: At six months, patient unexpectedly reacted to cashew nut. Thereafter, refused regular peanut butter and did not consume peanut products for two months. At eight months, peanut reintroduced and led to urticarial rash around mouth and vomiting. SPT peanut repeated two weeks later: 5 mm.

Learning point: The LEAP study protocol involved the consumption of peanut at a minimum of 6–7 g per week for the first five years of life. While it is not known whether shorter periods or different amounts of ingestion would prevent allergy, the cessation of consumption of peanut after initiation may result in the development of PA in some patients. Therefore, in patients at high risk of PA, if peanut consumption has been initiated, it should be encouraged regularly.

CASE 3

Background: Patient AM, six months old, moderate to severe relapsing eczema from three months of age, breastfed and on some pureed vegetables. Mother worried that the baby has macular rashes when the mother herself consumes egg and dairy.

SPT: Egg 3 mm, fresh raw egg white 5.5 mm, cow's milk 5 mm, fresh cow's milk 8 mm. Peanut 3.5 mm. Soya, hake fish, wheat 0 mm.

Risk assessment: Highly probable egg and cow's milk allergy. Risk of PA moderate to high based on 3.5 mm positive SPT result.

Action: Eczema management discussed. Egg and cow's milk avoidance discussed. Formal peanut challenge performed with incremental doses, cumulative dose 3.5 g peanut protein. Observed for two hours after last dose.

Outcome: Peanut challenge passed. Patient advised to include peanut in diet, around 2 g three times a week.

Further course: Three days later, when mother gave the first home instalment of peanut butter, patient reacted within 15 minutes with urticaria around the mouth, followed one hour later by profuse vomiting and a loose stool. Settled with oral fluids and quick-acting antihistamines.

Learning point: Even in the LEAP study, some patients in the consumption group became allergic during the course of the study. Unfortunately, after the promising initial peanut challenge (which may possibly have represented a rapid desensitisation in this case), the patient presented with symptoms of a true PA, and avoidance with regular follow-up was advised.

PRACTICAL POINTERS FOR WEANING AND INTRODUCTION OF PEANUT AND OTHER ALLERGENS

Table III contains practical advice for weaning, including the introduction of peanut and other allergens.

CONCLUSION

The LEAP study provides level 1 evidence that healthcare providers should recommend introducing peanut-containing products into the diet of 'high-risk' infants (those with severe eczema and/or egg allergy) early on in life, between four and 11 months of age.

Infants at risk of food allergy with early-onset eczema, difficult to control moderate–severe eczema, or an existing IgE-mediated food allergy may benefit from evaluation by an allergist to evaluate the appropriateness of early peanut introduction and help implement it practically. Those with a positive peanut SPT (3–7 mm) may benefit from an observed incremental peanut challenge.

A practical consideration for applying this guideline at 4–6 months of age is that infants visit their healthcare provider for routine healthcare visits during this time. This provides a fortuitous opportunity for the evaluation of risk factors such as eczema and/or reported milk or egg allergy, and a prompt referral to a specialist for PA evaluation and introduction advice.

The LEAP study included a high-risk population and cannot make recommendations on the benefit of early peanut introduction in the general or low-risk populations. In general, the guidelines do not recommend delaying any major allergen's introduction into the diet, even in the low-risk population. In addition, areas of uncertainty include the value of lower doses of peanut protein than those used in the LEAP study, minimal length of treatment to induce tolerogenic effect, effect of sporadic feeding of peanut, and potential disadvantages of premature discontinuation of regular peanut feeding.

What is certain is that healthcare providers will need to be a major source of education and support for patients in order to implement the early introduction of allergenic foods such as peanut. This strategy goes against a parent's intuition that peanut is a risky food and may cause or exacerbate eczema. Furthermore, the longstanding notion that the delayed introduction of certain foods may help reduce allergies will have to be 'undone' as we learn now that avoidance may in fact be harmful. Allergists and healthcare providers taking care of young infants and children need to take this evidence-based approach and 'leap' into action.

DECLARATION OF CONFLICT OF INTEREST

C Gray and S Emanuel have no conflicts of interest to declare. C Venter has received honoraria for

consultation work/lectures for Danone, Mead Johnson, Nestlé, ThermoFisher. D Fleischer is a member of the scientific advisory council for the National Peanut Board, represented the American Academy of Allergy, Asthma and Immunology in the formation of the Consensus Communication on Early Peanut Introduction and the Prevention of Peanut Allergy in High-Risk Infants; was a Coordinating Committee and Expert Panel member of the NIAID-sponsored Guidelines for Peanut Allergy Prevention; is a member of physician/medical advisory boards for Aimmune Therapeutics, DBV Technologies, INSYS Therapeutics, Intromune Therapeutics, Kaleo Pharmaceutical, and Nestlé; receives royalties from UpToDate; and received grant support from DBV Technologies and Aimmune Therapeutics.

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