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The challenges of preventing food allergy

Lessons learned from LEAP and EAT

Helen R. Fisher, PhD[*,†]; George Du Toit, MB, BCh[*,†,‡]; Henry T. Bahnson, MPH[§]; Gideon Lack, MB, BCh, FRCPCH[*,†,‡]

[*] *Paediatric Allergy Group, Department of Women and Children's Heath, School of Life Course Sciences, King's College London, London, United Kingdom*
[†] *Paediatric Allergy Group, Peter Gorer Department of Immunobiology, School of Immunology and Microbial Sciences, King's College London, London, United Kingdom*
[‡] *Children's Allergy Service, Guy's and St. Thomas' NHS Foundation Trust, London, United Kingdom*
[§] *Immune Tolerance Network, Benaroya Research Institute, Seattle, Washington*

Key Messages

- Allergy testing and/or supervised first introduction of the specific allergenic food is advisable for infants with eczema and/or preexisting food allergy before oral tolerance induction.
- A weekly dose of 2 g of peanut or egg protein appears to be protective against peanut or egg allergy.
- Oral tolerance induction is allergen specific and has only been proven to be successful in single introduction trials of peanut and egg; multiple allergen oral tolerance induction is a significant unmet need that requires investigation using novel approaches.
- The addition of peanut and other common food allergens (egg, fish, sesame, milk) to the infant diet has no adverse nutritional or growth effects and does not increase rates of food allergy. Breastfeeding rates are not adversely affected by these interventions in a clinical trial setting.
- In the Western world, nonwhite children have the highest risk of food allergy, but their families are the least likely to participate in oral tolerance induction programs; strategies to promote oral tolerance induction in nonwhite families are required.

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ABSTRACT

Objective: To highlight challenges associated with this novel preventive strategy.
Data Sources: The Learning Early About Peanuts (LEAP) and Enquiring About Tolerance (EAT) Studies, with reference to other oral tolerance induction studies.
Study Selections: Randomized clinial trials seeking to prevent food allergy through allergen introduction in infancy.
Results: Oral tolerance induction programs that use a regimen of consumption of 2 g/week of protein are effective in preventing peanut and egg allergy. LEAP findings suggest oral tolerance induction is allergen specific. Adding peanut and other common food allergens (egg, fish, sesame, milk) to the infant diet has no adverse nutritional or growth effects and does not increase rates of food allergy. Breastfeeding rates are not adversely affected by these interventions. In the Western world, nonwhite children have the highest risk of food allergy, but their families are the least likely to participate in oral tolerance induction programs.
Conclusion: Many challenges must be overcome to implement successful food allergy prevention strategies. Allergy testing of high-risk infants (those with moderate to severe eczema and/or egg allergy) before

Reprints: Gideon Lack, MB, BCh, FRCPCH, Paediatric Allergy Group King's College London, St Thomas' Hospital, Westminster Bridge Road, London SE1 7EH, United Kingdom; E-mail: gideon.lack@kcl.ac.uk.

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commencing oral tolerance induction is desirable, but access is not universal. Dietary interventions would ideally be implemented in infancy before allergic sensitization and allergy occur, using a program that provides protection against multiple common allergens. Further research and consensus with regard to food preparations, target populations, dosing regimens, and preparations and clearly defined adherence are now required.

Introduction

Driven by the continuing increase in food allergy prevalence[1,2] and the lack of an effective cure, the last decade has seen an increase in clinical trials investigating the prevention of food allergy. Earlier wisdom, predominantly derived from the findings of observational studies, considered that allergy prevention was best achieved through allergen avoidance.[3,4] After testing under randomised clinical trial (RCT) conditions, allergen avoidance has not been deemed a suitable means of preventing food allergy.[5,6]

As the allergy field has evolved, a view that opposes the allergen avoidance hypothesis has gained momentum: the dual allergen exposure hypothesis proposes that allergic sensitization may occur through the skin unless oral tolerance is first induced via the gastrointestinal tract.[7] The first aspect of this hypothesis, that allergic sensitization occurs through the skin, has been explored in epidemiologic studies. These studies found that atopic dermatitis precedes the development of food allergic sensitization (FS). There is also a strong association between atopic dermatitis severity and the risk of FS and food allergy.[8,9] RCTs examining the effect of optimal management of atopic dermatitis on FS are under way.

The second aspect of the dual allergen hypothesis, whether oral tolerance may be induced via the gastrointestinal tract, has been explored in recent RCTs. Most trials have focused on the introduction of one food only, with egg and peanut being the most commonly investigated.[2,10-14] Only one trial, the Enquiring About Tolerance (EAT) study, has investigated oral tolerance induction to multiple foods. This trial compared the effect of early introduction (from 3 months of age) of the 6 most common childhood food allergens (cow's milk, hen's egg, peanut, sesame, cod fish, and wheat) with exclusive breastfeeding until approximately 6 months of age for the prevention of childhood food allergy.[15]

The results of these early introduction trials are variable.[1,5] The most notable results are those from the Learning Early About Peanuts (LEAP) study. This RCT randomized the introduction or avoidance of peanut in infants aged 4 to younger than 11 months who were at high risk of developing peanut allergy (with moderate-severe eczema and/or egg allergy), and demonstrated an 81% relative reduction in peanut allergy at 5 years of age compared with children who avoided peanut-containing products for the same period.[2] Other studies have either failed to meet their primary outcomes or not found such a strong effect, and a meta-analysis investigating the timing of allergenic food introduction to the infant diet found moderate evidence that egg introduction at 4 to 6 months was associated with reduced egg allergy and that peanut introduction at 4 to 11 months was associated with reduced peanut allergy.[5] There is currently no evidence that early introduction of cow's milk, fish, sesame, and wheat protects against the development of food allergy, but, to date, few studies have investigated oral tolerance induction to these foods.[5] The dearth of clinical trials exploring multiple oral tolerance induction and the limited number of foods that have been explored in single allergen oral tolerance induction mean that the scope of oral tolerance induction in preventing food allergy is unclear. However, in the absence of further data, introducing allergenic foods into an infants' diet appears to be the most effective means of preventing food allergy at the current disposal of the allergist. Drawing predominantly on the lessons learned from LEAP and EAT but with reference to other oral tolerance induction studies (Table 1), we discuss some of these challenges associated with oral tolerance induction.

The Window of Opportunity

Choosing when to introduce a food to the infant diet presents a significant challenge. Oral tolerance induction must begin when the child is developmentally able to consume foods other than breast or formula milk but before a child has become allergic. For some infants, this window of opportunity can be narrow.

When Does Allergic Sensitization or Allergy Occur?

Allergic sensitization and, in some cases, food allergy begin early. Data from older infants in the HealthNuts study reveal high rates of food allergy at 12 months of age, with 3.1% (95% confidence interval [CI], 2.6%-3.6%) of infants demonstrating oral food challenge (OFC)–proven allergy to peanut, 10.1% to egg (95% CI, 9.2%-11.0%), and 0.7% to sesame (95% CI, 0.5%-0.9%).[16] Because the prevalence of food allergy at 10 to 14 years of age may be as high as 4.5%[17] it is evident that, for many children, early allergy is not transient, and thus effective allergy prevention is essential.

Although it is clear that FS begins in infancy, to date no studies have used sequential testing to discover the natural history of the onset of FS in very early childhood. Oral tolerance induction studies, including LEAP and EAT, shed some light on this biological process. Children were enrolled into the LEAP study between the ages of 4 and younger than 11 months, with a mean age of 7.8 months. All children underwent skin prick testing (SPT) to peanut at their screening visit and 76 of 834 (9.1%) were excluded from LEAP because they were assumed to already be allergic, with a SPT result (wheal) greater than 4 mm.[18] Of those who were eligible for LEAP participation 98 of 640 (15.3%) were sensitized (1-4 mm) to peanut, and 6 of 47 (12.8%) in the sensitized group who were randomized to the intervention were found to be allergic during their baseline OFC.[2] Similar findings were evident in the Beating Egg Allergy Trial (BEAT) of egg oral tolerance induction in infants at high risk of allergic disease[11]; 13 of 332 (3.9%) of infants had an SPT result (wheal) of greater than 2 mm by 4 months of age, and 14 of 165 infants (10.0%) were deemed to be egg allergic during the study entry OFC despite having an SPT result (wheal) less than 2 mm.

LEAP and BEAT both enrolled infants who already had, or were at risk of, atopic disease and were thus at high risk of having FS or allergy; however, the EAT study enrolled infants from the general population. Despite being a lower-risk population, infants who took part in EAT also had FS or allergy from an early age[15]; 33 of 652 3-month-old infants (5.1%) had a positive SPT result to at least one of the study foods (SPT wheal range, 1-16 mm). Of these, 19 of 652 (2.9%) had an SPT result (wheal) of 5 mm or larger. Any infant with a positive SPT underwent an OFC, and 7 of 652 (1.0%) were deemed allergic to at least one of the six study foods at 3 months of age.

These data highlight that the window of opportunity to prevent allergy may be narrow, and, unless oral tolerance induction begins in infancy, the window may be closed for those infants at most risk of food allergy. In addition, the practicalities of intervening in early infancy also presents challenges.

Access to Services

Recent updates to the allergy prevention guidance issued by the United States (National Institute of Allergy and Infectious Diseases [NIAID]) and Australia (Australasian Society of Clinical Immunology and Allergy [ASCIA]) encourage the early introduction of peanut

Table 1
Summary of Oral Tolerance Induction Studies

Study	Study type	Population	Screen failures attributable to allergy or likely allergy	Intervention group (protein per week)	Control Group	Age at study entry, mo	Age at outcome assessment, mo	Per-protocol adherence rates in intervention/ control groups	Primary outcome	Outcome in ITT group (*P* value)
Learning Early About Peanut (LEAP), United Kingdom	RCT, open label (n = 640)	High risk (infants with moderate-severe eczema and/or egg allergy)	76/834 SPT result ≥5 mm	Peanut snack or peanut butter (6 g)	Peanut avoidance until 60 mo	4-11	60	Negative SPT result group: intervention, 96%; control, 93% Positive SPT result group: intervention, 95%; control, 98%	Peanut allergy (OFC)	ARR, 11.8%; 95% CI, 3.4-20.3 ($P < .001$)
Enquiring About Tolerance (EAT), United Kingdom	RCT, open label (n = 1303)	General population	No exclusions required per protocol	Cooked whole HE, peanut butter, cow's milk (yogurt), fish (white, cooked), sesame (tahini), wheat (wheat based breakfast cereal) (4 g of each allergen)	Exclusive breast-feeding and avoidance of all 6 study foods until 6 mo of age	3	12-36	Intervention, 31.9%; control, 92.9%	HE allergy (OFC)	RR, 0.69; 95% CI, 0.40-1.18 ($P = .17$)
Hens' Egg Allergy Prevention (HEAP), Germany	RCT, blinded (n = 298)	General population	23/406 egg white IgE ≥0.35 kUA/L	Pasteurized raw HE white powder (7.5 g), HE-free diet	Placebo powder (rice), HE-free diet	4-12	12	Intervention, 86.7%; control, 93.5%	HE sensitization (sIgE)	RR, 2.20; 95% CI, 0.68-7.14 ($P = .24$)
Solids Timing for Allergy Research (STAR), Australia	RCT, blinded (n = 86)	High risk (infants with moderate-severe eczema)	Not required per protocol	Pasteurized raw whole HE powder (6.3 g)	Placebo powder (rice)	0-8	12	Intervention, 94%; control, 97%	Raw HE allergy (OFC) and sensitization (SPT)	RR, 0.65; 95% CI, 0.38-1.11 ($P = .11$)
Starting Time for Egg Protein (STEP), Australia	RCT, blinded (n = 820)	Moderate risk (atopic mothers)	Not required per protocol	Pasteurized raw whole HE powder (2.8 g)	Placebo powder (rice)	4-10	12	Intervention, 84%; control, 85%	Raw HE allergy (OFC) and sensitization (sIgE)	Adjusted RR, 0.75; 95% CI, 0.48-1.17 ($P = .20$)
Beating Egg Allergy (BEAT), Australia	RCT, blinded (n = 254)	Moderate risk (first-degree relative with allergy)	13/332 SPT result ≥2 mm	Pasteurized raw whole HE powder (2.45 g), HE-free diet	Placebo powder (rice) HE-free diet	4-8	12	Intervention, 81%; control, 89%	HE sensitization (SPT)	OR, 0.46; 95% CI, 0.22-0.95 ($P = .03$)
Two-step egg introduction for prevention of egg allergy in high-risk infants with eczema (PETIT), Japan	RCT, blinded (n = 121)	Moderate risk (with atopic dermatitis)	Not required per protocol	Heated HE powder (0.175 g for 3 mo then 0.875 g for 3 mo)	Placebo powder (squash)	4-12	12	Intervention, 92%; control, 93%	HE allergy (OFC)	RR, 0.222; 95% CI, 0.08-0.61 ($P = .0012$)

Abbreviations: ARR, absolute risk reduction; CI, confidence interval; HE, hen's egg; OFC, oral food challenge; OR, odds ratio; RCT, randomized clinical trial; RR, relative risk; sIgE, specific IgE; SPT, skin prick test.

protein into infant diets. The specifics of this guidance vary, with ASCIA recommending this approach for all infants, regardless of atopic risk,[19] and the NIAID emphasizing this approach for high-risk children who have eczema or egg allergy.[20]

Which infants should undergo allergy testing before commencing oral tolerance induction is still under debate. Infants who took part in LEAP underwent SPTs, specific IgE tests, and OFCs before the introduction of the study foods. Unexpectedly, in LEAP, 17% children who had no SPT sensitization at enrollment had peanut specific IgE sensitization of 0.35 kU/L or greater. Moreover, 56% of children with SPT sensitization of 1 to 4 mm and 91% with SPT results of 5 mm or larger (not eligible for LEAP participation) had peanut specific IgE sensitization of 0.35 kU/L or higher.[18] Of children who already demonstrated SPT sensitivity (1-4 mm) at LEAP enrollment, 6 of 47 (12.8%) of those randomized to the intervention were allergic during their baseline OFC.[2]

In the HealthNuts study, SPTs of eczematous infants (16% of the population) were able to identify 77% of all children who subsequently developed peanut allergy.[21] This finding highlights the potential effectiveness of screening before commencing oral tolerance induction. Although the issues of national screening programs to prevent food allergy are controversial,[21-23] testing is likely to be beneficial in high-risk groups, namely, children with severe eczema or egg allergy in the first 11 months of life, as in the LEAP study. The approach proposed by NIAID seems to balance logistical and safety concerns by adopting a 3-tiered approach: (1) children with severe eczema, egg allergy, or both should aim to introduce peanut at approximately 4 to 6 months after undergoing SPTs and/or IgE testing and, depending on the results, an OFC; (2) children with mild to moderate eczema should introduce peanut at approximately 4 to 6 months; and (3) children with no eczema should introduce peanut-containing foods according to family preferences.[20]

If testing and/or OFC are to be used before commencing oral tolerance induction then, to maximize effectiveness, high-risk infants should attend specialist allergy services in early infancy or when risk factors for food allergy are first demonstrated. However, in many countries, where access to specialist services are limited, this will be difficult to achieve. Improving access to specialist services by increasing the number of training places for physicians, specialist nurses, and dietitians is essential to facilitate early intervention. Developing rapid access oral tolerance induction, clinics would also ensure the infants who are at the highest risk of developing allergy are able to safely introduce allergenic foods into their diets. Such clinics will allow identification and introduction of the highest-priority allergens with respect to allergens that are most likely to persist in later childhood, allergens to which the child is already sensitized, and allergens that form a regular part of the familial diet.

WHO Advice Regarding Exclusive Breastfeeding vs Oral Tolerance Induction

The World Health Organization (WHO) advocates exclusive breastfeeding for the first 6 months of life[24]; this advice is also promoted by the health departments of many countries, including the United Kingdom's Department of Health. At least in developed countries, few mothers adhere to this advice, with 44.3% of UK mothers breastfeeding when their infant is 6 to 8 weeks old,[25] and only 3.6% of mothers exclusively breastfeeding until 6 months of age.[26] Rates of exclusive breastfeeding to 6 months are higher in the United States, approximating 25%,[27] but still fall short of the expectations of the WHO. Introduction of solid food before 6 months of age is also common, with 30% of UK infants having solid foods introduced by 4 months of age and 75% by 5 months of age.[26]

The WHO guidelines for infant feeding are appropriate for many children but do not appear to be suitable for infants with risk factors for the development of food allergy. Such infants may benefit from introduction of specific allergenic foods, alongside breastfeeding, before this time.[28] International guidelines for allergy prevention now encourage active introduction of peanut protein into the diet of high-risk infants at 4 to 6 months of age (NIAID[20]) and all allergenic foods to all infants from 4 months of age (ASCIA[19]).

Further studies that consider the effect of early introduction of allergenic foods on breastfeeding rates and explore the long-term effects of both on child health are required. Until such data are published, reassurance is provided from the EAT findings in which introduction of solid food from 3 months of age had no effect on (already established) breastfeeding rates- (>97% of infants were still being breastfed at 6 months of age).[15] Furthermore, between-group comparisons in LEAP and EAT show early introduction of one or more allergenic (and thus energy-dense) food had no deleterious nutritional or growth outcomes at 72 and 36 months, respectively).[15,29]

Developmental Ability of the Child

Beginning to wean an infant to food substances alongside breast or formula milk feeding requires that an infant expresses interest, can hold their head up, can sit with support, and has lost the tongue thrust reflex that prevents food from passing to the back of the mouth. These developmental milestones tend to occur between 4 and 6 months, but atopic children may already be sensitized or allergic by this age.

In addition, introduction of allergenic foods before 6 months of age in specific quantities is discordant with baby-led weaning and responsive feeding, weaning principles that are gaining in popularity. Studies exploring how to apply oral tolerance induction to very young infants and alongside responsive weaning methods are required. The challenges of intervening to prevent allergy during the window of opportunity are compounded by a lack of evidence regarding the most appropriate oral tolerance induction regimen. In the following section, we discuss some of these challenges.

Dose and Adherence in Early Introduction Regimens

Choosing the quantity, frequency, and type of the early introduction regimen poses additional challenges, not only in ensuring the regimen is effective but also in balancing an effective regimen with one that is not so onerous as to be unachievable.

Varying Types of Allergenic Food Introduction

Studies examining oral tolerance induction to egg have differed in the type of egg protein used. Three studies (Hens' Egg Allergy Prevention,[12] Starting Time for Egg Protein,[14] and Solids Timing for Allergy Research[13]) used raw egg protein, whereas two (EAT,[15] Two-Step Egg Introduction for Prevention of Egg Allergy in

High-Risk Infants With Eczema [PETIT][10]) used cooked egg. None of the studies using raw egg protein found a difference in effect (Table 1). In all 3 studies using raw egg protein, a high proportion of infants experienced allergic reactions during the entry OFC or home consumption. Two studies were discontinued early: in the Hens' Egg Allergy Prevention study, 10 of 16 children (62.5%) with egg allergy experienced anaphylaxis during OFC,[12] whilst in the Solids Timing for Allergy Research study, recruitment was paused to allow the independent data safety monitoring committee to examine the rates of allergic reaction and anaphylaxis to study powder. The committee found that the study could continue but was subsequently discontinued for logistical reasons.[13]

The safety profile of oral tolerance induction using raw egg powder contrasts with the EAT and PETIT studies, which used cooked egg protein. PETIT found oral tolerance induction to be effective, and EAT found an effect to egg in the per-protocol group. Both studies demonstrated the safety of cooked egg oral tolerance induction, with no cases of anaphylaxis at home or during OFC.

Dose

The dose of protein consumed by children in the oral tolerance induction studies published to date has been somewhat varied. In one study (PETIT), substantially smaller doses of protein were found to be effective in preventing hen's egg allergy; however, there are several differences between PETIT and LEAP and between EAT and BEAT (Table 1). Children in PETIT were already sensitized to egg white at enrolment, with a mean sIgE level of 0.73 kUA/L (range, 0.17-5.55 kUA/L). Subgroup analysis of the 36 children with an egg sIgE level of less than 0.35 kUA/L found no risk difference between the groups (2/24 active vs 3/12 placebo; risk difference, 16.7%; 95% CI, −10.2 to 43.5; $P = .31$).[10] This finding suggests that PETIT is predominantly a secondary prevention rather than a primary prevention study. Similarly, for a subgroup of participants, the LEAP intervention acted as a secondary prevention strategy. Although most infants (n = 542) in the LEAP study had a negative peanut SPT result at enrollment, and thus for them the intervention was preventive, 98 children were sensitized (SPT result, 1-4mm) at enrollment.[2] However, unlike PETIT, the LEAP the intervention was effective in both groups. The difference in findings between the nonsensitized infants who were enrolled in LEAP and PETIT suggest that small quantities of protein may not be sufficient for primary oral tolerance induction.

LEAP, EAT, and BEAT all used larger quantities of protein than PETIT. LEAP study children consumed 6 g of peanut protein per week, divided into 3 doses of 2 g, and EAT study children consumed 4 g of each of the 6 study foods per week divided into 2 doses of 2 g. The LEAP regimen was successful, achieving an 86.1% reduction in peanut allergy in the SPT-negative stratum.[2] The EAT intention-to-treat analyses showed no effect, but, although the absolute numbers were small, per-protocol analyses reveal a 75% reduction in egg allergy and a 100% reduction in peanut allergy.[15] These quantities concur with the upper quartiles of peanut consumption in Israeli infants who appeared to be protected against peanut allergy in an ecologic study on the prevention of peanut allergy.[30]

A dose somewhere between the PETIT and LEAP/EAT doses is also effective. Weekly consumption of 2g of protein promoted oral tolerance induction in the BEAT study, which achieved a 47.8% relative reduction in the frequency of IgE sensitization to egg white using a weekly quantity of 2.45 g of protein, which was consumed in 0.35-g daily aliquots, although no effect was noted on rates of clinical allergy to egg.[11] Dose response analyses of EAT study data reveal similar findings to the BEAT study; a mean weekly dose of 2 g of peanut or egg protein was protective against peanut or egg allergy.[15] Furthermore, an ecologic study of Israeli children who consumed peanut in early life found that consumption of 1.7 g of peanut protein per week was protective against peanut allergy.[30] It is notable that comparable doses of protein were required for prevention of egg and peanut allergy, and the evidence therefore suggests that a weekly dose of approximately 2 g of egg or peanut protein is likely to be sufficient to prevent egg or peanut allergy in most children. This dose, which represents 1 tsp of peanut butter or 1 hardboiled egg per week, is also likely to be achievable for most infants. This is particularly important given the challenges associated with adherence to oral tolerance regimens.

Adherence

The EAT study demonstrates that adherence to the treatment regimen is necessary for oral tolerance to be effective. Specifically, a per-protocol analysis found a 67.1% ($P = .01$) relative reduction in allergy compared with a 21.1% ($P = .32$) relative reduction in the intention-to-treat analysis.[15] Moreover, it is reassuring that early introduction group infants who were nonadherent to the intervention had similar rates of allergy compared with the control group. This finding implies, although it does not prove, that the presence of allergy was not responsible for nonadherence in the intervention group.[15] Potential bias in the per-protocol analysis resulting from poor adherence was examined in the EAT study using an instrument variable analysis. Specifically, the complier average causal effect (CACE) method projects the rate of allergy observed in the nonadherent intervention group onto the control arm. Using the assumption that randomization balances all factors, the CACE method estimates the effect of confounding potentially caused by nonadherence and removes it from the per-protocol intervention effect. In the EAT study, the unbiased CACE estimate was almost identical to that of the per-protocol analysis (risk difference, 2.47% vs 2.51%). This finding indicates that nonadherence was likely not attributable to reverse causality (ie, that children did not adhere because they were allergic and thus unable to consume the foods).[31]

Rates of adherence in oral tolerance studies are variable (Table 1); however, consumption of 2 g of peanut protein 3 times a week did not pose significant problems in LEAP, with 92% of participating families adhering to the intervention.[2] In EAT, for which 6 study foods were investigated, adherence (defined as consumption of ≥2 g per week of allergenic protein for ≥4 weeks) was much lower at 31.9%. Adherence in BEAT and PETIT, for which lower overall quantities of egg protein were consumed, was also good, with BEAT achieving 85% adherence[11] and PETIT achieving 79%.[10]

To date, single oral tolerance induction trials have had a high level of adherence, whereas the EAT study had low adherence to the intervention (adherence in the control arm was 92.9%[2]). It is easy to assume that the clear difference in rates of adherence in the single oral tolerance induction studies and (to date) the only published multiple oral tolerance induction study is the result of the number of foods being introduced; however, other factors are also likely to be relevant. For example, palatability, texture, overall portion size, and ease of preparation by parents of young infants are likely to be relevant to adherence. This is evidenced by data from the EAT study showing that specific foods were associated with lower adherence. Adherence to wheat was low, but this was, at least in part, attributable to the study design; wheat was the last of the foods to be introduced, making it more difficult to meet the protocol definition of adherence. With respect to the other study foods, those that were easy to prepare and palatable to an infant (eg, cow's milk and peanut) achieved the highest levels of adherence; those that required more preparation and/or had a taste or texture that was unfamiliar or unpleasant to an infant (eg, egg, sesame, and fish) had the lowest adherence.

The factors that influenced adherence in LEAP and PETIT could not be investigated because adherence was high. However, adherence was lower in the EAT study, affording the opportunity for investigation. A dominance analysis of nonadherence in the EAT study found that 78% of the variance could be accounted for by 4 main factors: nonwhite race (odds ratio [OR], 2.21; 95% CI, 1.18-4.14), parent perception that the child experienced symptoms to one of the study foods (OR, 1.70; 95% CI, 1.02-2.86), reduced maternal quality of life (psychological domain) (OR, 0.69; 95% CI, 0.47-1.00), and the child having eczema at enrollment into EAT (OR, 1.38; 95% CI, 0.87-2.19).

Health inequalities influence access to health services, engagement with health services, and adherence to treatment.[32-34] Maternal ethnic group, educational level, and social class are also relevant to infant feeding and influence breastfeeding[35] and infant weaning practices.[36] Nonwhite race was the strongest predictor of nonadherence in the EAT study. The BEAT study similarly found that children who were lost to follow up, were withdrawn, or had no primary outcome data were more likely to have a parent born outside Australasia ($P < .001$ for father and $P < .02$ for mother) than those who had complete data. Nonwhite children had a greater risk of food allergy in both LEAP and EAT. Notably, children with the greatest risk of food allergy are most likely to come from families who are least likely to

take up the intervention. Prevention studies and strategies must focus on such communities; patient and public involvement in these studies and strategies will be essential if oral tolerance induction is to be effective.

Allergen Specificity

Single allergen oral tolerance induction studies have shown promising results; however, atopy and food allergy are rarely isolated conditions; for example, between a third and half of children with peanut allergy are allergic to at least one tree nut.[37,38] Early introduction of peanut did not hasten the resolution of egg or milk allergy or atopic dermatitis and did not prevent the development of asthma or allergic rhinitis. Despite potential cross-reactivity to T-cell or B-cell epitopes, early introduction of peanut did not protect against new-onset tree nut or sesame allergy.[39] Conversely, long-term follow-up of the LEAP cohort revealed a small and inconsistent but statistically significant increase in tree nut sensitization and parent-reported allergy in children in the early introduction arm.[39] This finding is being further investigated in the LEAP ad-lib study. Given the specificity of oral tolerance induction, multiple oral tolerance induction strategies are necessary to facilitate adherence and successful oral tolerance induction.

Conclusion

Allergy prevention is beset by difficulties. Use of SPTs and/or IgE testing in children at high risk of allergy (those with moderate-severe eczema and/or egg allergy) before commencing oral tolerance induction is desirable but may be difficult to implement. Intervening while the window of opportunity is open (before allergy occurs), using a program that provides protection against multiple allergens, presents significant challenges and may not be easily achievable at such a young age. The findings of recent trials provide evidence that allergy prevention through oral tolerance induction programs that use a regimen of protein consumption of 2 g/week is effective in preventing peanut and egg allergy. However, there is currently no evidence with respect to other common food allergens, and it is not clear whether this lack of evidence is simply the result of a lack of high-quality studies or reflects true differences in the underlying mechanisms of allergic sensitization and tolerance. For example, it may be that the dual allergen exposure hypothesis only applies to specific foods. Moreover, not all allergy is IgE mediated, and there is no evidence that oral tolerance induction is appropriate for non–IgE-mediated allergy. Further research and consensus with regard to food preparations, target populations, dosing regimens, and preparations and clearly defined adherence are now required.[1,40,41]

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