



The dual-barrier hypothesis theorizes that avoidance of a specific food (such as egg or peanut) can increase the risk of developing food allergy if the infant is still exposed to the food allergen in the environment and is percutaneously sensitized

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Introduction of Complementary Foods to Infants

by Christina E. West

Key insights

In the past, food allergy prevention strategies focused on the avoidance of allergenic foods in infancy. The current paradigm, however, is shifting from avoidance to controlled exposure. Recent evidence from randomized controlled trials suggests that the early introduction of allergenic foods such as peanuts may reduce the prevalence of food allergies in high-risk infants. In countries where peanut allergy is prevalent, healthcare professionals should recommend the introduction of peanut-containing products into the diets of “high-risk” infants early in life (between 4 and 11 months of age).

Current knowledge

Worldwide, the most common food allergies in children are allergies to cow’s milk, hen’s egg, soy, peanut, tree nuts, wheat, fish, and seafood. Although a large proportion of those with milk or egg allergies will develop tolerance as they age, certain subgroups remain allergic and are at risk of developing other disorders such as respiratory allergic disease. For instance, the presence of both egg allergy and eczema in infants is a predictor of later respiratory allergies. Those with high levels of IgE antibodies to cow’s milk, egg white, wheat, and soy are also more likely to have persistent food allergy.

Practical implications

Current international guidelines state that the introduction of allergenic foods (including egg and peanut) does not need to be postponed beyond 4–6 months of age, but they provide no

Introductory foods containing peanuts

- Smooth peanut butter mixed with milk or pureed fruit
- Peanut-containing snacks (for young infants, this may be softened with 20–30 mL water or milk and mixed with pureed fruit or vegetables)
- Peanut soup
- Finely ground peanuts mixed with other foods (i.e., yogurt)

Based on Fleischer DM, et al: Consensus communication on early peanut introduction and the prevention of peanut allergy in high-risk infants. *World Allergy Organ J* 2015;8:27.

Different types of peanut-containing products that may be introduced to the infant diet.

concrete guidance on whether these foods should be actively introduced within this time frame. The LEAP (Learning Early About Peanut Allergy) trial was the first prospective randomized study regarding early peanut introduction. Results from the LEAP study suggest that early introduction of peanut into the diets of high-risk infants may be beneficial. However, safety and practicality remain key issues when extrapolating the results of this study to the general population. Open questions remain on the optimal timing and doses that should be used, and whether such regimens should be stratified according to the infant’s allergy risk.

Recommended reading

*du Toit G, Tsakok T, Lack S, Lack G: Prevention of food allergy. *J Allergy Clin Immunol* 2016;137:998–1010.*

Introduction of Complementary Foods to Infants

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Key Messages

- There is level 1 evidence that early introduction of peanuts (from 4 to 11 months of age) reduces the prevalence of peanut allergy in infants at high risk of allergic disease (infants with severe eczema and/or egg allergy).
- The majority of current international guidelines recommend that complementary foods, including allergenic foods, can be introduced from 4 to 6 months of age irrespective of family history risk.
- As delayed peanut introduction may increase the risk of peanut allergy, interim guidelines state that healthcare providers should recommend introducing peanut-containing products into the diets of “high-risk” infants early on in life (between 4 and 11 months of age) in countries where peanut allergy is prevalent.

Keywords

Eczema · Egg · Food allergy · Infant · Peanut · Prevention · Solid foods

Abstract

While earlier food allergy prevention strategies implemented avoidance of allergenic foods in infancy, the current paradigm is shifting from avoidance to controlled exposure. This

review focuses on the outcome of recent randomized controlled trials, which have examined the early introduction of allergenic foods for allergy prevention, and discusses the implementation of results in clinical practice. In infants at high risk of allergic disease, there is now direct evidence that regular early peanut consumption will reduce the prevalence of peanut allergy, compared to avoidance. Many international infant feeding guidelines already recommend complementary foods, including allergenic foods, to be introduced from 4 to 6 months of age irrespective of family history risk. Interim guidelines from 10 International Pediatric Allergy Associations state that healthcare providers should recommend the introduction of peanut-containing products into the diets of infants at high risk of allergic disease in countries where peanut allergy is prevalent. Direct translation of the results obtained from a cohort of high-risk infants to the general population has proved difficult, and issues regarding feasibility, safety, and cost-effectiveness have been raised. Five randomized placebo-controlled trials have assessed the effects of early egg exposure in infancy with varying results. In a recent comprehensive meta-analysis, there was moderate-certainty evidence that early versus late introduction of egg was associated with a reduced egg allergy risk. Although promising, optimal timing, doses, and if the feeding regimen should be stratified according to infant allergy risk remain to be determined. The single study that assessed introduction of multiple foods from 3 months whilst breastfeeding compared with exclusive breastfeeding until 6 months of age showed no reduction in food allergy preva-

lence. Future research should aim at optimizing infant feeding regimens and support a tolerogenic gastrointestinal microenvironment during the period of food allergen introduction.

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Introduction

Over the past few decades, we have experienced a rising prevalence of Immunoglobulin E (IgE)-mediated food allergies in the pediatric setting, particularly in developed countries, although the prevalence also appears to be rising in developing countries [1]. Most reports are based on self-reported food allergy, however, and it has been repeatedly shown that self-reported data will overestimate the prevalence as compared with evaluation by an oral food challenge [2–4]. It is estimated that IgE-mediated food allergy affects approximately 6–8% of children in developed countries [1, 3, 4],

thereby posing a significant burden on the afflicted children, their families, and the healthcare system. Globally, the by far most common IgE-mediated food allergies in childhood are allergies to cow's milk, hen's egg, soy, peanut, tree nuts, wheat, fish, and seafood [3–5]. Tolerance development is prevalent in milk and egg allergy; and the majority of milk-allergic children [6, 7] and about a half to two-thirds of egg-allergic children [8, 9] will outgrow their food allergy before school age. The rate of peanut allergy resolution is worse; when assessed by oral food challenges both at diagnosis and at follow-up in the Australian HealthNuts cohort study, only 22% of the children outgrew their peanut allergy by 4 years of age [10]. Collectively, a significant proportion of children will remain food allergic and are at risk of developing other comorbidities such as respiratory allergic disease. For instance, infant egg allergy, particularly when coexisting with eczema, has been reported to be a predictor of later respiratory allergies [11], and high levels of IgE antibodies to cow's milk, egg white, wheat, and soy are predictors of persistent food allergy [12].

Avoidance remains the only available treatment in established food allergy. Oral immune therapy, which includes a stepwise dose increase of the food allergen followed by a maintenance phase, is an emerging treatment option. Oral immune therapy has been demonstrated to induce desensitization, i.e., an increase in the amount of

offending food that can be ingested as long as it is consumed regularly [13]. It is still undecided if permanent tolerance will develop, and oral immune therapy is not generally recommended unless within a clinical trials protocol. Adherence to an elimination diet is difficult, and there is still risk of accidental exposure and allergic reactions, including anaphylaxis [14]. Allergic children on elimination diets are also at risk of nutritional deficiencies [15, 16], impaired growth [16–18], and reduced quality of life [19]. Collectively, there is urgent need to develop effective strategies to promote tolerance development and prevent food allergy.

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The collective evidence from epidemiological studies reporting an association between delayed introduction of complementary foods and allergy risk, and animal models demonstrating that oral toler-

ance induction is driven by exposure to antigens and allergens [reviewed in 20, 21], led to the first randomized controlled trials (RCTs) to examine the role of early, regular exposure to “allergenic” foods for food allergy prevention. This review focuses on the outcome of these recently published RCTs and discusses the implementation of the results in clinical practice.

Risk Factors for Food Allergy

Both genetic and environmental factors will influence the risk of developing food allergy, and multifaceted changes in our modern environment are a likely driver. The hypotheses proposed to explain the epidemic rise in allergic disease include (a) the biodiversity hypothesis, which theorizes that reduced diversity and intensity of microbial exposures will impair normal development of immunoregulatory networks and increase allergy risk [22], (b) the vitamin D hypothesis that builds on epidemiological evidence that vitamin D deficiency is associated with an increased risk of allergic disease, and (c) the dual-barrier hypothesis [23, 24], which is discussed below. There are also data to suggest that food allergens, specific nutrients, lifestyle factors, and microbial exposures may influence the development of allergic disease through epigenetic mechanisms [25].

A commonly used definition of allergy risk is based on a history of allergic disease in a first-degree relative [26] and is frequently used in both epidemiological studies and clinical trials. In some of the recently conducted RCTs, however, only infants with an already established allergic phenotype (eczema and/or manifest egg allergy) were included as they are at an even heightened risk [27, 28] (Table 1). For instance, it has been demonstrated that infant eczema is associated with an increased risk of percutaneous sensitization to environmental food allergens, facilitated by an impaired skin barrier [29]. Normally, a food allergen is introduced to and handled by the immune system in the gut to induce a tolerogenic response to the food protein [20, 30]. Accordingly, the dual-barrier hypothesis theorizes that avoidance of a specific food (such as egg or peanut) can increase the risk of developing food allergy if the infant is still exposed to the food allergen in the environment and is percutaneously sensitized [24].

The “Optimal” Window of Introduction of Complementary Foods for Allergy Prevention

Almost 2 decades ago, the American Academy of Pediatrics Committee on Nutrition launched guidelines suggesting a delayed introduction of dairy products in the first year of life in infants with a family history of allergic disease: egg until 2 years, peanuts, nuts, and fish until 2–3 years of age [31]. This recommendation also became integrated in infant feeding guidelines in many other countries at the time. Following the publication of more recent epidemiological studies across the globe, the guidelines were revised to reflect the lack of solid scientific evidence that delayed introduction of complementary foods beyond 4–6 months of age, or avoidance of “allergenic” foods such as cow’s milk, egg, peanuts, tree nuts, fish, and seafood, reduce allergy risk [32–36]. Still, the “optimal” time for introduction of complementary food for allergy prevention is not known. There are data to suggest that starting complementary foods before 3–4 months of age may increase the risk of allergic disease [37, 38]. At that age, the gut is more permeable and gastrointestinal colonization is not yet well established, which might contribute to the observed risk increase [39, 40]. Consequently, many international infant feeding guidelines for allergy prevention recommend introduction of any solid food after 4 months of age [32–36].

RCTs for Food Allergy Prevention

Peanuts

In a cross-sectional study, du Toit et al. [41] found that the prevalence of peanut allergy was 10-fold higher in Jewish children in the UK compared with children in Israel. Interestingly, peanut consumption was initiated earlier and in larger quantities in Israel than in the UK. Based on these findings, the Learning Early About Peanut Allergy (LEAP) study was designed to examine if early, regular, controlled peanut consumption, compared with avoidance, could prevent peanut allergy in high-risk infants with severe eczema, egg allergy, or both [42] (Table 1). As part of the screening, a skin prick test (SPT) to peanut was performed, and infants with a wheal size ≥ 5 mm were excluded. The intervention was initiated between 4 and 11 months and continued until 5 years of age. The study results were pronounced; in the early-introduction group, peanut allergy was reduced with 86% in the group with a negative SPT to peanut at baseline, and with 70% in the group with SPT peanut 1–4 mm at baseline, compared with the avoidance group. Reassuringly, the investigators recently reported that 12-month peanut avoidance in the early-introduction group did not increase the prevalence of peanut allergy at the age of 6 years [43], suggesting that avoidance for a prolonged period will not break tolerance. Still, the long-term consequences of peanut avoidance beyond 12 months are unknown.

Egg

There is also epidemiological evidence to support that delayed introduction of egg to the infant diet increases allergy risk. In the HealthNuts cohort study, delayed introduction of egg at 10–12 months or after 12 months of age was associated with an increased risk of egg allergy compared with egg introduction at 4–6 months of age [44]. To date, 5 RCTs have examined if early versus late introduction of egg can reduce the risk of egg allergy [45–49] (Table 1). In the Solids Timing for Allergy Reduction (STAR) study, high-risk infants with moderate-to-severe eczema were randomized to intake of pasteurized raw whole egg powder or rice powder (placebo) from 4 to 8 months of age [45]. At 12 months of age, 33% in the active group versus 51% in the placebo group had developed egg allergy (relative risk 0.65, 95% CI 0.38–1.11, $p = 0.11$). In the Starting Time of Egg Protein (STEP) study, high-risk infants (based on maternal atopy but no allergic manifestation in the infant at baseline) were randomized to intake of pasteurized raw whole egg powder or rice powder (placebo) from 4 to 10 months of age [46]. At 12 months of age, 7% in the active group versus 10.3% in the placebo

Table 1. Overview of randomized clinical trials that have assessed early versus late introduction of complementary foods for allergy prevention

Trial name Country	Study population	Intervention	Primary outcome	Ref.
LEAP (Learning About Peanut Allergy) UK	Infants with severe eczema and/or egg allergy ($n = 640$ randomized, 319 to peanut, 321 to avoidance)	Peanut (snack or peanut butter) from 4 to 11 months to 5 years <i>or</i> Peanut avoidance until 5 years	Peanut allergy ¹ at 5 years; in the group with negative SPT to peanut ($n = 530$): 1.9% in the active vs. 13.7% in the avoidance group ($p < 0.001$); in the group with SPT to peanut 1–4 mm: 10.6% in the active vs. 35.3% in the avoidance group ($p = 0.004$)	42
STAR (Solids Timing for Allergy Reduction) Australia	Infants with moderate to severe eczema ($n = 86$ randomized, 49 to egg, 37 to placebo)	Pasteurized raw whole egg powder <i>or</i> Rice powder (placebo) from 4 to 8 months	Egg allergy ¹ at 12 months; 33% in the active vs. 51% in the placebo group (relative risk 0.65, 95% CI 0.38–1.11, $p = 0.11$)	45
STEP (Starting Time of Egg Protein) Australia	Infants of allergic mothers ($n = 820$ randomized, 407 to egg, 413 to placebo)	Pasteurized raw whole egg powder <i>or</i> Rice powder (placebo) from 4 to 6 months until 10 months	Egg allergy ¹ at 12 months; 7% in the active vs. 10.3% in the placebo group (adjusted relative risk 0.75, 95% CI 0.48–1.17, $p = 0.20$)	46
BEAT (Beating Egg Allergy Trial) Australia	Infants with 1 (or both) parents with a history of allergic disease ($n = 319$ randomized, 165 to egg, 154 to placebo)	Pasteurized raw whole egg powder <i>or</i> Rice powder (placebo) from 4 to 8 months	Egg sensitization ² at 12 months; 11% in the active vs. 20% in the placebo group (odds ratio 0.46, 95% CI 0.22–0.95, $p = 0.03$)	47
PETIT (Prevention of Egg Allergy with Tiny Amount Intake) Japan	Infants with eczema ($n = 147$ randomized, 73 to egg, 74 to placebo)	Heated egg powder (50 mg) <i>or</i> Squash powder (placebo) from 6 to 9 months, with a dose increase of egg protein from 9 to 12 months	Egg allergy ¹ at 12 months; 9% in the active vs. 38% in the placebo group (risk ratio 0.221, 95% CI 0.09–0.543, $p = 0.0001$)	48
HEAP (Hen's Egg Allergy Prevention Trial) Germany	Infants from the general population ($n = 406$ screened for egg sensitization, 383 nonsensitized randomized, 184 to egg, 199 to placebo)	Pasteurized egg white powder <i>or</i> Rice powder (placebo) from 4 to 6 months until 12 months	Egg sensitization ³ at 12 months; 5.6% in the active vs. 2.6% in the placebo group (relative risk 2.20, 95% CI 0.68–7.14, $p = 0.24$)	49
EAT (Enquiring About Tolerance) UK	Exclusively breastfed infants for at least 3 months from the general population ($n = 1,303$ randomized, 652 to early introduction of 6 foods while breastfeeding, 651 to exclusive breastfeeding and no allergenic foods before 6 months)	Continued breastfeeding with introduction of cow's milk, peanut, hard-boiled egg, sesame, cod, and wheat in a sequential order from 3 months (early introduction) <i>or</i> Exclusive breastfeeding for 6 months (standard introduction)	Allergy to any of the 6 foods at 3 years: 5.6% in the early-introduction vs. 7.1% in the standard-introduction group (relative risk 0.80, 95% CI 0.51–1.25, $p = 0.32$)	50

SPT, skin prick test. ¹ Confirmed by an oral food challenge. ² Egg white skin prick test ≥ 3 mm. ³ Specific IgE to egg ≥ 0.35 kU/L.

group had egg allergy (adjusted relative risk 0.75, 95% CI 0.48–1.17, $p = 0.20$). The Beating Egg Allergy Trial (BEAT) also included high-risk infants (based on allergic disease in any or both parents) [47]. Infants were randomized to pasteurized raw whole egg or rice powder (placebo) from 4 to 8 months of age. The primary outcome was egg sensitization at 12 months of age, and 11% in the active group versus 20% in the placebo group were sensitized (odds ratio 0.46, 95% CI 0.22–0.95, $p = 0.03$). Twenty-one infants were classified as having probable egg allergy. Of these, 6.2% were in the active group and 10.5% were in the placebo group ($p = 0.20$).

In the Prevention of Egg Allergy with Tiny Amount Intake (PETIT) study, high-risk infants with established eczema were randomized to intake of either heated egg powder or squash powder (placebo) from 6 to 12 months of age, with an increased dose of egg protein from 9 months [48]. There was a marked effect of the intervention with egg allergy diagnosed at 12 months in 9% in the active group versus 38% in the placebo group (risk ratio 0.221, 95% CI 0.09–0.543, $p = 0.0001$). In fact, the striking effect of the intervention in the preplanned interim analyses led the investigators to terminate the trial prematurely. As discussed by the investigators [48] the difference might be biased, leading to a bigger difference between the active and placebo groups than if the study had not been closed.

In contrast to the above-mentioned studies that included high-risk infants, the Hen’s Egg Allergy Prevention (HEAP) study, randomized infants with normal risk (from the general population) to intake of pasteurized egg white powder or rice powder from 4 to 6 months until 12 months of age [49]. Infants were screened for egg sensitization, and all included infants had specific IgE to egg < 0.35 kU/L at baseline. As in the BEAT study [47], the primary outcome was egg sensitization at 12 months. 5.6% in the active group were sensitized to egg versus 2.6% in the placebo group (relative risk 2.20, 95% CI 0.68–7.14, $p = 0.24$). At that age, 2.1% in the active group had egg allergy versus 0.6% in the placebo group (relative risk 3.30, 95% CI 0.35–31.32, $p = 0.35$).

Collectively, 4 out of 5 conducted RCTs designed for egg allergy prevention were negative (Table 1), although 3 of these studies [45–47] had nonsignificant results that might suggest a benefit of early egg introduction.

Multiple Foods Approach

Observational studies have also reported an association between low food diversity in early life and both sensitization [50] and allergic manifestations [51]. In the

Table 2. Practical implications for clinical practice based on interim guidelines from 10 International Pediatric Allergy Associations [54]

“Health care providers should recommend introducing peanut-containing products into the diets of ‘high-risk’ infants¹ early on in life (between 4 and 11 months of age) in countries where peanut allergy is prevalent, because delaying the introduction of peanut can be associated with an increased risk of peanut allergy”

A clinical assessment by a pediatric allergist or a physician trained in pediatric allergy may be considered in infants that have already developed allergic disease (severe eczema and/or egg allergy) in the first 4–6 months of age; this could be helpful in the diagnosis of any food allergy and in the evaluation of appropriateness of peanut introduction

The clinical evaluation may include peanut skin testing, ingestion of peanut in the clinic, or both, for infants with already established allergic disease (severe eczema and/or egg allergy)

If the skin test to peanut is positive, an observed peanut challenge to examine if the infant is clinically reactive before introducing peanuts at home can be considered

¹ High-risk criteria used in the LEAP trial were egg allergy and severe eczema [42].

Enquiring About Tolerance (EAT) study [52] (Table 1), 3-month-old breastfed infants from the general population were randomized to continued breastfeeding with introduction of cow’s milk, peanut, hard-boiled egg, sesame, white fish, and wheat in a sequential order from 3 months of age or to continued exclusive breastfeeding for the first 6 months of life [52]. In the intention-to-treat analysis, 5.6% of the children in the early-introduction group had developed food allergy at 3 years of age compared to 7.1% in the group that introduced solid foods from the age of 6 months (relative risk 0.80, 95% CI 0.51–1.25, $p = 0.32$). Of note, only 42% in the early-introduction group were able to adhere to the food introduction regimen, demonstrating that it can be difficult to introduce multiple foods as compared to a single food item. In the per protocol analysis, however, the prevalence of “any” food allergy was 2.4% in the early-introduction group compared with 7.3% in the standard-introduction group ($p = 0.01$). The prevalence of peanut and egg allergy was also reduced in the early-introduction group (0 vs. 2.5%, $p = 0.003$, and 1.4 vs. 5.5%, $p = 0.009$, respectively). There was no difference between the 2 groups in the prevalence of allergy to milk, sesame, fish, or wheat.

Meta-Analysis of Egg and Peanut Prevention Trials

In a recent comprehensive systematic review and meta-analysis, Ierodiakonou et al. [53] included the trials discussed above that had assessed early versus late egg introduction for egg allergy prevention (5 trials, 1,915 participants) [45–49] (Table 1). They found with moderate certainty evidence that early versus late introduction of egg was associated with a reduced egg allergy risk (risk ratio 0.56, 95% CI 0.36–0.87, $p = 0.009$). They also identified the LEAP [43] and EAT [52] studies (Table 1) (2 trials, 1,550 participants) to be included in a meta-analysis of early versus late introduction of peanuts and reported that early introduction was associated with a reduced peanut allergy risk (risk ratio 0.29, 95% CI 0.11–0.74, $p = 0.009$). The authors underscored that the studies were few and that the certainty of the evidence was reduced due to imprecision, indirectness, and heterogeneity in interventions and study populations [53]. An interesting finding, however, was that there was no distinct difference among infants at “normal” versus high risk of allergy in their analyses.

Allergic Reactions and Safety Issues

A shared feature of the studies that included high-risk infants and used pasteurized raw egg powder is that a varying proportion (4.7–31%) of the participants in the early egg intake groups discontinued egg ingestion due to allergic reactions to the egg powder [45–47]. This has raised the question if screening for sensitization would be necessary before introducing egg to the infant diet. Reassuringly, in the STEP trial that included infants with familial predisposition but no eczema, there were no anaphylactic reactions to the egg powder [46]. The authors underscored that assessment of egg sensitization before the introduction of egg and egg-containing products to the infant diet is not necessary in the community setting [46]. In the PETIT trial [48], which included high-risk infants with eczema, a few participants reported mild to moderate allergic manifestations following ingestion of the study powder, but at a similar frequency in the active and placebo groups. No participant discontinued the intervention because of allergic reactions to the egg powder, and it has been argued that this could be a matter of reduced allergenicity of heated versus pasteurized (raw) egg powder [48]. The risk of adverse reactions to peanut was low in the LEAP study; 5% of infants randomized to early peanut intake reacted at the baseline peanut challenge. However, infants at a presumably higher risk (peanut wheal size ≥ 5 mm) were excluded.

Current Recommendations

Current international guidelines already state that introduction of allergenic foods, including egg and peanut, does not need to be postponed beyond 4–6 months of age [32–36]. With a few exceptions, these guidelines do not, however, advocate that allergenic foods should be *actively* introduced to the infant diet between 4–6 months of age. Based on level 1 evidence from the LEAP study [42], interim guidelines on peanut introduction for allergy prevention in high-risk infants were launched in 2015 (Table 2) [54]. In an opinion paper, Allen and Koplin [55] identified and discussed the challenges in translating the findings from the LEAP study to the general population level. Safety remains one issue, particularly in very high-risk infants, as the LEAP study excluded infants with an SPT to peanut ≥ 5 mm, cost-effectiveness another [55]. Very recently, addendum guidelines for peanut allergy prevention in the United States were launched [56]. In brief, the guideline panel suggests introducing peanuts at home to the majority of infants in the first year of life. Infants with severe eczema, egg allergy, or both should undergo medical assessment including assessment of sensitization to peanut before peanut introduction at 4–6 months of age [56]. If other allergenic foods, such as egg, should also be actively introduced to the infant diet from 4 to 6 months of age remains undetermined. Recent allergy prevention guidelines in Australia now suggest introducing cooked (but not raw) egg from 4 to 6 months of age irrespective of allergic heredity [36]. As underlined by Ierodiakonou et al. [53], the findings from their systematic review on early versus late introduction of complementary foods for allergy prevention cannot be directly translated to new guidelines. Collectively, the optimal timing, doses and form of egg, and if these regimens should be stratified according to the infant’s allergy risk remain to be determined.

Conclusion

The level 1 evidence from the LEAP study [43] has resulted in interim guidelines recommending early introduction of peanut into the diets of “high-risk” infants [54]. Further studies should aim at optimizing infant feeding regimens. Supporting the most favorable “tolerogenic” microenvironment in the gut during the period of food allergen introduction is also likely to involve “optimal” colonization of the gastrointestinal tract, breastfeeding, and other dietary factors with immunomodulatory capacity [39, 40].

Disclosure Statement

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