

Food allergy prevention, including early food introduction

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ABSTRACT

As the prevalence of immunoglobulin E (IgE)-mediated food allergy continues to increase without an imminent cure, prevention has become an urgent need. A breakthrough study that shows that early consumption of peanut can prevent the development of peanut allergy has led for a push in early interventions. Theories associated with the increasing prevalence of food allergy lend themselves to areas of potential intervention, e.g., age at time of food introduction, infant feeding practices, microbiome influences, diet composition, vitamin D deficiency, and increasing rates of eczema. This review focused on the available data from studies that investigated early interventions to decrease the risk of food allergy.

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Because the prevalence of immunoglobulin E (IgE)-mediated food allergy continues to increase without an imminent cure, prevention has become an urgent need. Theories associated with the increasing prevalence of food allergy lend themselves to areas of potential intervention, such as age at time of food introduction, infant feeding practices, the hygiene hypothesis, diet composition, vitamin D deficiency, and increasing rates of eczema. This review focused on prevention studies that used clinical food allergy, as opposed to only sensitization, as an outcome.

EARLY FOOD INTRODUCTION

More than a decade ago, in 2008, the American Academy of Pediatrics (AAP) rescinded recommendations to delay the introduction of common food allergens because the evidence did not support that this led to food allergy prevention.¹ Since then, several studies have associated the early introduction of common food allergens with a decreased risk of food allergy. This resulted in updated AAP recommendations in 2019, which incorporated evidence that the early introduction of peanut may prevent peanut allergy.² Knowing the optimal timing and method of introducing foods during infancy may be a tool to prevent food allergy.

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Peanut

Early peanut introduction seems to be protective. In the pivotal Learning Early about Peanut Allergy prospective trial, >600 infants at high risk (severe eczema, egg allergy, or both) were randomized to consume peanut until age 5 years versus peanut avoidance. Consumption of peanut was associated with a 86% relative reduction of peanut allergy (absolute risk difference 11.8% [95% confidence interval, 3.4–20.3]; $p < 0.001$) in those with baseline negative skin-prick testing (SPT), and 70% relative reduction of peanut allergy (absolute risk difference 24.7% [95% confidence interval, 4.9–43.3]; $p = 0.004$) of those with a baseline small positive SPT (wheal 1–4 mm).³ Subsequent 2017 National Institute of Allergy and Infectious Diseases Addendum Guidelines for the Prevention of Peanut Allergy⁴ in the United States recommend proactively evaluating infants at risk for peanut allergy and with severe eczema and/or egg allergy for possible introduction of peanut. The guidelines outline where and how peanut may be introduced based on initial testing, whether recommended supervised in the office as a feeding or graded challenge, or if it can be introduced at home (Table 1).⁴ Detailed instructions on how to incorporate peanut into infant diets can be found in the appendix of the guidelines.⁴

Although these peanut introduction guidelines are intended for infants at high risk, analysis of data from general population studies suggests that early introduction may also benefit infants at low risk. A recent prospective birth cohort study reported an increased risk of peanut sensitization (odds ratio [OR] 2.38) and probable allergy (OR 4.04) at age 3 years if peanut was introduced after 12 months of age, even after adjusting for moderate-severe eczema and egg sensitization.⁵

The Enquiring About Tolerance (EAT) trial⁶ investigated early introduction of multiple foods in >1300 exclusively breast-fed infants from the general population who were randomized to the introduction of six

Table 1 Recommendations for early peanut introduction in infants at high risk

Recommended Method of Introduction	Initial Peanut Testing
At home	sIgE level < 0.35 kU _A /L, SPT wheal 0–2 mm
Supervised feeding in the office	sIgE level < 0.35 kU _A /L, SPT wheal 0–2 mm (parent preference); SPT wheal 3–7 mm; and favorable sIgE level
Graded oral food challenge in the office	SPT wheal 3–7 mm, and favorable sIgE level
Avoidance	SPT wheal ≥8 mm, or highly predictive sIgE level

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

common food allergens (peanut, cooked egg, cow’s milk [CM], sesame, whitefish, and wheat) at age 3 months versus the standard introduction at age 6 months. This intention-to-treat analysis did not show a significant difference in food allergy prevalence between early versus standard introduction at ages 1–3 years; however, per-protocol analysis showed a significant reduction in the prevalence of total food allergy (2.4 versus 7.3%; $p=0.01$), peanut allergy (0 versus 2.5%; $p=0.003$), and egg allergy (1.4 versus 5.5%; $p=0.009$).⁶ The amount of allergen that led to significantly lower prevalence was 2 g of egg white or peanut protein per week.⁶ Adherence was low (42.8%) to all allergens in the intervention group, which reflected the challenges of infant feeding; specifically, there was 43% adherence to egg and 62% adherence to peanut.⁶

Egg

Early egg introduction seems to be trending towards being protective against development of egg allergy. Comparing trials that investigated early egg introduction is complicated by heterogeneity in variable risk populations, and the form and dose of egg used. A meta-analysis of five trials, including the EAT trial⁶ and four randomized,⁷ placebo controlled trials, reported that egg introduction by age 4–6 months was associated with a relative risk (RR) 0.56 of reduction of egg allergy compared with later egg introduction ($p=0.009$).⁷ One randomized controlled trial (RCT) reported that, of 17 subjects with detectable egg white specific IgE (sIgE) who underwent a double-blind, placebo controlled food challenge at baseline, 16 reacted, and 11 experienced anaphylaxis.⁸ A second RCT

reported that 10 of 49 subjects (31%) reacted to the egg intervention, 10 on first ingestion, and one with anaphylaxis.⁹ These data are a reminder that infants as young as 4–6 months may already be clinically reactive and that reactions can be systemic.

CM

It is not currently clear if early CM introduction is protective. Although results of an older prospective unselected cohort study suggested that exposure to CM at birth in the hospital was associated with an increased risk of CM allergy, a subsequent prospective population-based cohort study of >13,000 infants demonstrated that 0.05% of the infants who consumed CM formula within 14 days of life versus 1.75% who did not consume CM until age 3.5–6.5 months developed CM allergy within the first year of life ($p<0.001$).^{10,11} This correlates with a retrospective case-control study that reported that no or delayed CM formula introduction after the first month of life was associated with an increased risk of CM allergy by an average age of 5 years (adjusted OR [aOR] 23.74).¹² Analysis of these data suggests that very early CM introduction within the first month of life may be protective.

In the EAT trial, CM introduction at age 3 months did not decrease the risk for CM allergy, despite 85% protocol adherence. A meta-analysis of two trials, including the EAT trial and a single-blind (subject) RCT, concluded that early CM introduction before 6 months of age did not affect the risk of CM allergy in the first few years of life.⁷ A second meta-analysis, of five cohort studies, also concluded that there was no association between the introduction of CM before 1 month or 4 months of age and the risk for CM allergy, although this report had some inconsistencies.¹³

Wheat

Not enough data exist to assess protection of early wheat introduction. The EAT study⁶ did not find an association between the early introduction of wheat and the risk of wheat allergy with 40% protocol adherence. There was only one documented case of wheat allergy from the intervention group and this subject was nonadherent.⁶ The study did report decreased rates of positive wheat SPT at 12 and 36 months ($p=0.03$ and $p=0.04$, respectively) in the intervention group.⁶ One prospective birth cohort study selected for nonatopic risk factors and followed up for a mean 4.7 years found that the introduction of wheat after age 6 months increased the risk of IgE-mediated wheat allergy.¹⁴

MATERNAL DIET

Currently, there are no recommendations to restrict or to include allergens in the maternal diet during pregnancy or lactation due to the lack of support for

the role of maternal diet in the development of food allergy.^{2,15} Although one cohort study in young children at high risk correlated frequent maternal ingestion of peanut during pregnancy with a predictive peanut sIgE value of ≥ 5 kU/L (OR 4.99), a systemic review of two case-control studies and a cross-sectional study found no association of maternal ingestion of peanut during pregnancy or lactation with peanut sensitization or allergy.^{16,17} In one cohort study that investigated possible *in utero* sensitization, a peanut sIgE level could not be detected in the cord blood from 23 patients with peanut allergy, even though total IgE levels were measured.¹⁸ In addition, a Cochrane Database review¹⁹ and a more recent systemic review²⁰ did not support a protective effect of maternal allergen avoidance on the incidence of atopy in childhood.

Breast-Feeding

Data of the investigation of the effect of exclusive breast-feeding or the duration of breast-feeding on the development of food allergy are insufficient at this time. One meta-analysis of six cohort and six cross-sectional studies with high heterogeneity found that breast-feeding was not associated with food allergy.²¹ The updated 2019 AAP report² has not changed the statement from the 2008 AAP report¹ that there seems to be no benefit of exclusive breast-feeding beyond 3–4 months on the prevention of atopic disease. Changing breast-feeding recommendations and trends as well as confounding factors, such as families at high risk and who may lean toward breast-feeding longer, may be masking a discernable effect of breast-feeding on food allergy.²² For more on the association between breast-feeding and food allergy see the article by Pier and Jarvinen²³ in this Food Allergy Primer.

NONCONVENTIONAL FORMULAS

A 2006 Cochrane Database review²⁴ suggested that hydrolyzed CM formulas may reduce CM allergy in infants at high risk and who are not able to exclusively breast-feed. Newer data, however, has not supported this. One RCT found no difference in risk CM, egg, or peanut allergy in infants at high risk and on conventional CM, partially hydrolyzed whey, or soy formulas in the first 2 years of life.²⁵ In addition, a meta-analysis of 13 prospective intervention trials found no significant difference in a risk of food allergy between partially or extensively hydrolyzed and standard formulas, between partially and extensively hydrolyzed formulas, or between extensively hydrolyzed casein and whey formulas.²⁶ The 2019 AAP report² concludes that there is a lack of evidence that extensively or partially hydrolyzed formula prevents atopic disease even in infants at high risk.

Probiotics and Prebiotics

Factors that influence the gut microbiota and its possible effects on allergic disease is an area of active interest. Some of these factors tie into the hygiene hypothesis, including type of delivery, maternal microbiota, type of feeding, diversity of microbial exposure, use of antibiotics, animal exposure, and probiotic and/or prebiotic supplementation. Several RCTs that examined the effect of maternal and infant probiotic supplementation during pregnancy, lactation, and early childhood on atopic disease found some evidence of a protective effect, particularly against eczema; however, to date, none of these investigated the association between probiotics and food allergy directly.²⁷ Although generally considered safe, one randomized, placebo controlled trial did report that infant consumption of *Lactobacillus acidophilus* was associated with an increase of allergic sensitization at age 12 months ($p=0.03$).²⁸ Although American and European allergy societies have not recommended the use of probiotics in primary prevention of allergy,²⁹ recommended considering probiotics in infants at high risk due to the reported benefit seen in primary prevention of eczema. Adding prebiotics to formula has been considered in an attempt to mimic beneficial aspects of breast milk. Two RCTs that investigated the effect of prebiotics in CM formula or partially hydrolyzed whey formula reported conflicting results on prevention of eczema and did not examine food allergy prevalence.^{30,31}

DIET COMPOSITION

Although several studies have examined the effect of a Mediterranean diet and omega-3 polyunsaturated fatty acids (PUFA) as well as individual nutrients, such as vitamin D, on atopic disease, few have investigated an association of these diet components with the risk of food allergy directly.²⁷ Three cohort studies found that fish (high in PUFAs) introduction before ages 6–9 months was associated with a reduction of sensitization to any food allergen.⁷ One RCT reported that maternal PUFA supplementation was associated with decreased risk of food allergy in infancy (RR 0.13).³² Additional studies are required before recommendations can be established. In a population-based cohort study, vitamin D insufficiency in infants was associated with peanut allergy (aOR 11.52; $p=0.006$), egg allergy (aOR 3.79; $p=0.025$), and multiple food allergies (aOR 10.48).³³ Another cohort study reported an association between higher levels of maternal and cord blood vitamin D levels and food allergy in the first 2 years.³⁴ Larger RCTs are needed to clarify these conflicting data.

BARRIER CREAMS

There is research that supports that initial exposure to allergens through the skin often leads to sensitization, whereas oral exposure typically results in

Table 2 Summary of proposed food allergy prevention strategies

Intervention	Efficacy
Studies that support prevention	
Early peanut introduction	Strong evidence for infants at high risk from a prospective randomized trial ³ : 85% relative reduction of peanut allergy in subjects with initial negative SPT and 70% reduction with small positive SPT; some evidence for infants at normal risk
Early egg introduction	Moderate evidence for infants at high risk and those at normal risk from meta-analysis ⁷ of five RCTs: an RR 0.56 reduction of egg allergy when introduced by age 4–6 months
Studies that do not currently support prevention	
Maternal diet alteration during pregnancy with or without lactation	A Cochrane Database review ¹⁹ and a systemic review ²⁰ did not support a protective effect of maternal allergen avoidance.
Exclusive breast-feeding beyond 3–4 months of age	A meta-analysis ²¹ of six cohort and six cross-sectional studies did not find a protective effect of breast-feeding
Hydrolyzed or soy formula	A meta-analysis ²⁶ of 13 prospective intervention trials did not find a protective effect of cow's milk formula with intact protein. One RCT reported no protective effect of soy formula ²⁵
Emollients to repair skin barrier impairment	Two multicenter RCT studies ^{40,41} did not find a decreased the risk of eczema in the first 2 years of life and, therefore, unlikely to prevent food allergen sensitization or allergy
Not enough evidence to determine	
Early cow's milk introduction	Some evidence of very early introduction within the first month of life from a population-based cohort study ¹¹ reduced the risk of cow's milk allergy; other studies did not see protection when introduced before 6 months of age; the timing was unclear
Probiotics and/or prebiotics	Several RCTs ²⁷ found some evidence of a protective effect against eczema; unknown for food allergy; caution, because one randomized, placebo controlled trial ²⁸ reported that one particular strain increased allergic sensitization
Mediterranean diet and/or omega-3 PUFA	Some evidence of protection in childhood against atopic disease but not specific to food allergy
Vitamin D supplementation	Two studies ^{33,34} found conflicting evidence for protection against food allergy; evidence for protective effect against atopic disease were inconclusive

SPT = Skin-prick test; RCT = randomized controlled trial; RR = relative risk; PUFA = polyunsaturated fatty acids.

immune tolerance.³⁵ A defective skin barrier and inflammatory state can promote a T-helper type 2 allergenic response to allergens, *e.g.*, in eczema. This is likely why up to 80% of children with eczema exhibit allergen sensitization and approximately one-third demonstrate clinical food allergy.³⁶ For more on the association between food allergy and atopic dermatitis see Banzon *et al.*³⁷ in this Food Allergy Primer.

One case-control study that used questionnaires that were completed before the child's known peanut allergy status correlated high environmental peanut exposure from peanut consumption by all household members with an increased risk of peanut allergy in infants at high risk.³⁸ Notably, maternal

consumption during pregnancy and lactation were significant in this study but became insignificant when adjusting for household peanut levels. Thus, besides early oral introduction ideally before environmental exposure, repairing the skin barrier and perhaps preventing eczema may be a dual method in preventing food allergy. Results of one RCT study suggested that a daily emollient during the newborn period reduced the RR of atopic dermatitis by 50% at age 6 months.³⁹ However, two more recent multicenter RCT studies with 3791 infants combined did not find that daily to at least 4 days a week of emollients decreased the risk of eczema in the first 2 years of life.^{40,41}

CONCLUSION

A breakthrough study that showed that early consumption of peanut can prevent the development of peanut allergy has led to a push in food allergy prevention. See Table 2 for a summary of potential interventions. The concept of oral exposure, inducing tolerance before cutaneous exposure, is intriguing. Unfortunately, increased use of skin emollients has not proven to be protective. There is little evidence that maternal avoidance diets or hypoallergenic formulas prevent food allergy and are not recommended at this time. Studies are not conclusive on the potential for breastfeeding to prevent atopic disease. Further studies are required to understand the association between probiotics and prebiotics, omega-3 PUFA, or vitamin D supplementation, and food allergy.

CLINICAL PEARLS

- There is strong evidence that early introduction of peanut can prevent peanut allergy in infants at high risk. Analysis of data on early introduction of egg is also promising, whereas early cow's milk introduction is still inconclusive.
- Recent large studies on increased use of skin emollients has not proven to be protective against eczema, and therefore this intervention is unlikely to prevent food allergy.
- There is little evidence that maternal avoidance diets during pregnancy and lactation or hypoallergenic formulas prevent food allergy, and these are not recommended at this time.
- Currently, there is no evidence that exclusive breastfeeding beyond 3–4 months of age is protective against atopic disease.
- Further studies are required to understand the association between probiotics and prebiotics, omega-3 PUFA, or vitamin D supplementation, and prevention of food allergy.

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