



Timing of food introduction and atopy prevention[☆]



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Abstract The apparent increase in atopic disease, particularly food allergy, over the past 2 decades has resulted in reconsideration of prevention strategies aimed at the infant's diet. Early advice to have atopy-prone infants delay ingestion of potential food allergens, such as egg, cow's milk, and peanut, was rescinded, as new evidence emerged that did not support these approaches. More recently, randomized controlled trials have provided data to support an opposite strategy, promoting early ingestion of allergens as a means of food allergy prevention. Specifically, new guidelines suggest early ingestion of peanut as a means to prevent peanut allergy. Additional dietary approaches regarding breastfeeding, early introduction of other types of food allergens, formula feeding, dietary nutrients, and probiotics are also under scrutiny as potential preventative strategies. This review focuses on the timing of food introduction as a preventative strategy for food allergy and also discusses other aspects of the infant diet that may provide opportunities for prevention of atopic disease.

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Introduction

The prevalence of atopic disease has been increasing and has been referred to as an “epidemic.”^{1–3} The prevalence of food allergy increased by 50% from 1999 to 2011, according to data from the US Centers for Disease Control and Prevention.⁴ During the same period, skin allergies (including atopic dermatitis) increased from 7.4% to 12.5%.⁴ The prevalence of respiratory allergy remains the highest at 17% in 2009–2011.⁴ Although there are exciting new treatments on the horizon for allergic diseases with the use of biologic drugs and immunotherapy, the overarching focus in the field has been rapidly shifting toward primary prevention of atopy⁵ and halting the

progression of the “atopic march,” the progression of atopic dermatitis and food allergy in infancy to the development of allergic rhinitis and asthma in childhood.⁶

Although atopic disease has a hereditary component, the rapid increase in prevalence must be attributed to environmental factors. The hygiene, or “old friends,” hypothesis^{7–9} is a leading theory that attributes the increase in atopic disease in Western society to the change in challenges against the immune system. Briefly, this theory suggests that industrialized society has reduced infectious burden through smaller families,⁷ sanitary living, lack of exposure to farming,^{10,11} and medical interventions to reduce infections.^{12,13} These changes may have resulted in immune dysregulation. Additional theories abound. The dual allergen exposure hypothesis^{14,15} addresses the observation that infants with atopic dermatitis are at risk for food allergy because they may become sensitized by environmental exposure to food allergens while they are not ingesting the same potential allergens, bypassing oral tolerance. Additional theories address nutrients in the diet, such

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as vitamin D^{16,17} and fatty acids,^{18,19} that may affect immune function. These theories suggest potential strategies for prevention of atopic disease.

This review addresses prevention of all atopic disease, including asthma, allergic rhinitis, atopic dermatitis, and food allergy, but focuses primarily on studies involving the prevention of food allergy by the timing of introduction of allergens in the infant diet. This area of prevention has undergone the greatest change in recent years due to the results of several randomized controlled trials.^{20–23} Also of note, the relationship of food allergy as a trigger for atopic dermatitis is a separate topic and is beyond the scope of this paper.

The food allergy “epidemic”: Were prior recommendations counterproductive?

In 2000 the American Academy of Pediatrics published recommendations²⁴ to delay the introduction of common allergens in the diets of infants at high risk for atopic diseases. High-risk infants were defined as infants with a history of atopy in two or more first-degree family members. The recommendations suggested delaying the introduction of solid foods in the diets of these infants until 6 months; dairy until 1 year; eggs until 2 years; and peanuts, tree nuts, and fish until 3 years. These guidelines were based on the hypothesis that exposures early in life result in sensitization to dietary allergens.^{25,26}

Shortly after the recommendations were published, various observational studies suggested that delayed ingestion might actually pose a risk of allergy. A 2004 publication²⁷ reported a birth cohort of 642 children in which delayed introduction of egg was associated with a higher risk of atopic dermatitis. Additional observational studies noted delayed allergen introduction was associated with more allergy, sensitization, or atopic dermatitis.^{28–33} Regarding peanut, a cross-sectional study reported a 10-fold higher rate of allergy in Jewish children living in the United Kingdom, compared with Jewish children living in Israel. The study noted that infants in Israel consumed peanut at a much younger age and in higher amounts than infants in the United Kingdom, raising the possibility that early introduction could be protective in the development of peanut allergy.³⁴ Additional observational studies suggested that a reason why allergy may be higher in those delaying introduction could be related to the dual allergen exposure hypothesis described earlier. Studies have found that topical peanut oil application (variant containing peanut protein)³⁵ or other environmental exposure^{36,37} to peanuts in infants with eczema is associated with higher risk of peanut allergy. By 2008 the American Academy of Pediatrics rescinded the prior recommendations to delay introduction of food allergens³⁸ for lack of evidence, but there were no specific recommendations to add allergens early.

Although evidence was accumulating to suggest earlier allergen ingestion might be protective of allergy, there was no

convincing evidence due to a lack of randomized controlled trials. More recently the Learning Early About Peanut Allergy (LEAP) study (described in the next section)²⁰ proved peanut allergy could be prevented by early introduction to high-risk infants, and the Enquiring About Tolerance (EAT) study (described in the next section),²³ although hindered by poor adherence, provided some additional evidence supporting this approach. Given these newer observations, the focus has now shifted toward prevention of allergy by earlier introduction of peanut in the infant's diet.

Timing of introduction of allergens in the infant's diet

Peanut

Peanut allergy affects 1–3% of children in many Western countries, with a tripling of prevalence noted in the past 10 to 15 years.^{39–43}

The landmark LEAP study²⁰ provided clear evidence that early introduction of peanut to a high-risk population was indeed protective against the development of peanut allergy. The LEAP study enrolled infants from 4 to 11 months of age at high risk of developing peanut allergy (defined by having moderate or severe eczema and/or egg allergy) and divided them into separate cohorts based on the size of their peanut skin tests. Infants with a peanut skin prick test > 5 mm were considered already allergic and were excluded from the study; the remaining infants were considered sensitized (skin test 1–4 mm) or not (negative skin test). The infants were randomly assigned to receive either peanut or placebo starting at 4 months of age. By age 5 years, the prevalence of peanut allergy was significantly lower in the peanut ingestion group at 1.9% ($P < .001$) compared with 13.7% in the control group among children who had initially had no sensitization to peanut. In the cohort with initial skin tests 1 to 4 mm, the prevalence was 10.6% in the peanut ingestion group and 35.3% in the avoidance group, also significantly less ($P = .004$). The results of this trial led to a consensus statement advocating the early introduction of peanut in infants at high risk.³⁹

In the EAT study,^{23,44} multiple allergens were introduced to breastfed infants starting around 3 months of age. This group of infants was not selected for the presence of atopy, although there was self-selection for increased atopic disease risk. The infants were randomly assigned to either early introduction of six allergenic foods from 3 months of age (early intervention group) or introduction of allergens per standard guidelines (standard introduction group). The allergens introduced were cow's milk followed by, in random order, peanut, cooked hen's egg, sesame, and white fish, followed by wheat. The results in the intention-to-treat analysis indicated no benefit. This could be attributed to the low rate of adherence (42.8% in the early intervention group compared with 92.9% in the standard introduction group); however, statistical

significance was achieved for overall allergy reduction (2.4% versus 7.3%, $P = .01$), reduction of peanut allergy (0% versus 2.5%, $P = .003$), and reduction of egg allergy (1.4% versus 5.5%, $P = .009$) in the per-protocol analysis.

Based on the results of the LEAP trial and the EAT trial, a recently published meta-analysis⁵ reported a reduction in the absolute risk of peanut allergy (2.5% incidence) if peanut was introduced between the ages of 4 and 11 months.

An expert panel convened by the National Institute of Allergy and Infectious Diseases has now introduced an addendum⁴⁵ to their food allergy guidelines published in 2010.⁴⁶ These guidelines advocate early introduction of peanut between the ages of 4 to 6 months to infants who are considered at high risk of developing a peanut allergy. High-risk children are described as those with severe eczema or those with an egg allergy as described in the LEAP study. The guidelines define severe eczema as “persistent or frequently recurring eczema with typical morphology and distribution, assessed as severe by a health care provider and requiring frequent need for prescription-strength topical corticosteroids, calcineurin inhibitors or other anti-inflammatory agents despite appropriate use of emollients.”

Before the introduction of peanut, these high-risk infants should be screened for peanut sensitization by skin test or serum test. Although an earlier consensus statement³⁹ recommended screening only with skin prick testing, the guidelines allow serum tests to alleviate some of the practical difficulties with getting all such infants to an allergist’s office for skin testing in a timely manner, as the allergen-specific immunoglobulin E test can be sent from a pediatrician’s or dermatologist’s office. It is noted, however, that the serum tests may be more often positive without clinical disease in this setting. The guidelines recommend against testing additional food allergens due to the risk of false positive results and “over diagnosis of food allergy.”

The guidelines suggest that if the allergen-specific immunoglobulin E level is < 0.35 kUA/L, peanut can be introduced at home or under medical supervision depending on provider and family assessment. If the level is > 0.35 kUA/L, a referral to an allergist is recommended for further evaluation with a skin prick test. The guidelines also provide guidance on the amount of peanut to be used for initial introduction (2 g of peanut protein) and recommend a minimum amount of 6 g of peanut protein to be regularly consumed per week, as was done in the LEAP study. Because peanuts and peanut butter are choking hazards for infants and young children, the guidelines provide options for safe forms of peanuts that can be used for introduction. These include softened Bamba, thinned smooth peanut butter, smooth peanut butter puree, and peanut flour and peanut butter powder.⁴⁵ A follow-up to the LEAP study, the LEAP-On study,²¹ has provided evidence that the tolerance achieved by these children was sustained even after peanut consumption was halted for a period of 1 year after the 5 years of frequent consumption.

The guidelines⁴⁵ also recommend the introduction of peanut-containing foods to patients with mild to moderate eczema around 6 months of age and to patients with no eczema or food

allergy “freely into the diet...in accordance with family preferences and cultural practices.” For these groups, the guidelines do not recommend any testing, although this may be an option for consideration in those with eczema. This guideline for early introduction to infants without severe eczema is supported by the results of the EAT study,⁴⁴ where early introduction of six allergenic foods was done with an unselected population.

Egg

There are currently no guidelines suggesting early introduction of egg for infants at risk. The data (summarized in Table 1)^{22,23,47–50} have been mixed. As noted in Table 1, the target populations among the randomized controlled trials were different, as was the treatment and endpoints. An overarching observation was that many infants were already egg allergic at enrollment from 4 to 6 months of age. The form of egg used in the studies was particularly important for safety reasons. More reactions were noted in studies that used raw egg powder^{22,47,48} for introduction versus heated egg^{44,49}; however, a recently published meta-analysis⁵ concluded, based on the results of five trials^{22,23,47,48,50} (summarized in Table 1), that there was reduced egg allergy from early introduction of egg at 4 to 6 months. Of note, the conclusions were heavily based on one study⁵⁰ that was not published in a peer-reviewed form. The current US guidelines do not suggest delaying introduction of egg, but remain silent on attempting purposeful early introduction. (See Table 2).

Milk

A prospective Finnish study of more than 6000 infants suggested that the introduction of cow’s milk protein within the first few days of life at maternal hospitals increased the risk of subsequent cow’s milk allergy.⁵¹ In contrast, an Israeli observational study reported that early exposure to cow’s milk within the first 14 days of life was protective against the development of cow’s milk allergy, with a high incidence of cow’s milk allergy if milk was introduced between 4 and 6 months of age.³² The EAT study,²³ which analyzed the role of early introduction of six major antigens (including milk), did not find a reduction in milk allergy in the early intervention group.

In a cohort of more than 3000 children, introduction of milk before 4 months was associated with the development of atopic dermatitis but decreased the risk of allergic rhinitis.⁵² There is currently no specific guideline regarding the timing of introduction of cow’s milk protein (other than that it can be included along with other foods), although whole cow’s milk is not given to infants in the first year of life for nutritional reasons.

Cereals

An observational birth cohort of 1612 children followed prospectively⁵³ found that exposure to wheat before 6 months of age was protective against the development of wheat

Table 1 Characteristics of randomized controlled trials investigating early introduction of egg

Author	Country of origin	Eligibility criterion	Intervention	Outcome measure	Conclusion
Palmer et al. ²²	Australia	Moderate to severe eczema	Raw egg powder (0.9 g protein daily) vs rice powder daily from 4-8 months of age	At 12 months, all infants were analyzed with an OFC with raw egg and SPT	Trend toward decreased egg allergy incidence in the egg group, but also high (31%) risk of reaction with initial egg introduction
Perkin et al. ²³	United Kingdom	Unselected population of breastfed infants	Early introduction of six allergenic foods (boiled egg, 4 g protein per week used for introduction of egg protein) at age 3 months vs standard introduction of foods	Allergy to any of the six early introduced foods proven by OFCs between 1-3 years of age	Statistically significant reduction in egg allergy in the EIG compared with the SIG in the per-protocol analysis but no difference in the intention-to-treat analysis
Bellach et al. ⁴⁷	Germany	Unselected infants with no evidence of egg sensitization (egg sIgE < 0.35 kU/L)	Received egg white powder (2.5 g egg protein) vs rice powder at 4-6 months of age	Diagnosis of egg allergy by OFC or egg sIgE $\geq$ 0.35 kU/L at age 1 year	No evidence of protection offered by early introduction of egg in the prevention of egg allergy in infants who have no evidence of sensitization
Natsume et al. ⁵⁰	Japan	Infants with eczema	Heated egg powder from 6-12 months of age (50 mg from 6-9 months and 250 mg from 9-12 months) vs placebo from 6-12 months	Egg allergy diagnosed by OFC at age 12 months	Early introduction of egg resulted in significant reduction in incidence of egg allergy in infants with atopic dermatitis; adverse events were reduced in the early introduction group by use of a smaller dose in the first few months after introduction
Tan et al. ⁴⁸	Australia	Infants with primary relative with history of egg allergy and egg SPT < 2 mm	Whole egg powder (350 mg egg protein daily) vs rice powder at age 4 months	Egg allergy diagnosed by OFC with lightly cooked egg	Significant reduction in egg sensitization in the early introduction group but no statistically significant reduction in egg allergy
Palmer et al. ⁴⁹	Australia	Infants with maternal atopy but with no personal allergic disease history and no prior egg ingestion	Received 0.9 g pasteurized whole egg raw powder per day from 4-6.5 months until 10 months of age vs rice powder Cooked egg and egg products introduced at 10 months to both groups	Egg allergy diagnosed by OFC with pasteurized raw egg and SPT at age 12 months	No difference in the prevalence of egg allergy between the two groups

EIG, early introduction group; OFC, oral food challenge; SIG, standard introduction group; sIgE, specific immunoglobulin E; SPT, skin prick test.

Table 2 Factors influencing infant diet in the development of atopy *

Risk factors	Protective factors	Benefit questioned
Severe atopic dermatitis	Early introduction of specific foods	Hydrolyzed formula
Family history of atopy	Omega-3 long chain polyunsaturated fatty acids	Vitamin D supplementation
Delayed introduction of peanut, egg	Breastfeeding	Prebiotics/probiotics

* Based on review of literature, the evidence seems to point to the following strategies being either risk factors, protective factors, or controversial in the prevention of atopic disease.

allergy; however, the EAT study did not find any effect on the incidence of wheat allergy by early introduction of wheat in an unselected population.²³ Another group⁵² also found in their Finnish cohort of 3000 children a decrease in the development of atopic disease (risk of asthma, allergic rhinitis) with introduction of wheat, rye, oat, and barley by 5 months of age. They found conflicting results with some other cereals, including maize, rice, millet, and buckwheat. The introduction of these cereals before 4 months was associated with the development of eczema. Another prospective study analyzed a birth cohort of 1293 children and found a protective effect of early oral oat introduction on the development of persistent asthma.⁵⁴ The recent meta-analysis published in *JAMA* was not able to establish a protective effect of early introduction of cereals in the prevention of allergy.⁵

Fish

Fish, with its high omega-3 fatty acid content, has been of interest for its potential role in reducing inflammation and thus preventing atopy.^{18,19} Although some studies^{19,55,56} have found evidence of a protective effect of early fish introduction (before 12 months) on the development of allergic rhinitis^{19,52,54,55,57} and on asthma,^{19,55,56,58} others report no association.⁵⁹ One study⁶⁰ reported a tendency toward the development of less asthma and eczema with early fish introduction but did not find an effect on sensitization. Early introduction of fish has also been associated with decreased risk of eczema.⁶¹ Another group⁵² found in their Finnish cohort of more than 3000 children a decrease in the development of atopic disease (risk of asthma, allergic rhinitis) with introduction of fish by 6 to 9 months. The recently published *JAMA* meta-analysis⁵ concluded that there may be “low certainty to very low certainty evidence” that the early introduction of fish into the diets of infants before the age of 9 months may have been associated with reduced risk of sensitization to *any* allergen, including food allergens, as well as reduced risk of rhinitis. This property of reduction in sensitization to any allergen seems indeed to be unique to fish.

Other strategies for modifying infant diets

Maternal diet

In 1996, peanut allergy was found to be presenting earlier in life and it was concluded that this might be due to the increased consumption of peanut by pregnant and nursing mothers.⁶² In

2000, the American Academy of Pediatrics suggested dietary avoidance of peanuts²⁴ for pregnant women with a family history of atopy; however, later studies found no evidence of prenatal sensitization to peanut from the maternal diet.³⁵ The results of a prospective randomized controlled trial^{63,64} consisting of 212 women did not find any protective benefit in the development of atopy in the babies of mothers who avoided cow's milk and egg in their diet from mid-pregnancy onward compared with infants of mothers who did not avoid these foods. A Cochrane Database review⁶⁵ published in 2012 did not suggest any evidence of protection from the development of eczema in infants of mothers who avoided the ingestion of antigens during pregnancy.

Breastfeeding

Numerous components of breast milk, including secretory immunoglobulin A and lactoferrin, are thought to play immunomodulatory and antiinflammatory roles in the infant⁶⁶ and possibly influence the development of atopic disease. In 2000, the American Academy of Pediatrics recommended breastfeeding for the first year of life for high-risk infants, with supplementation (if required) with a hypoallergenic formula. It was recommended that breastfeeding mothers eliminate peanuts, tree nuts, and also “consider eliminating eggs, cow's milk, fish, and perhaps other foods from their diets while nursing.”²⁴ Although some earlier studies support that exclusive breastfeeding for the first 4 months of life leads to reduction in atopic dermatitis in high-risk infants,^{67–69} more recent data have questioned if the protection is offered by exclusivity. In 2013, data from 3000 children did not reveal any protective benefit of exclusive breastfeeding in the development of subsequent atopy⁵²; however, the researchers found that a longer duration of breastfeeding was protective and concluded that duration rather than exclusivity was protective.

In terms of asthma, there is a reported decreased incidence of wheezing in infants who are breastfed, but the protection does not persist beyond infancy.^{66,70,71}

Current data do not provide conclusive evidence in support of or against the role of breastfeeding in protection against the development of food allergy,^{72–76} but breastfeeding is recommended exclusively to around 6 months of age for other reasons.

Hydrolyzed formula

In 2008, American Academy of Pediatrics guidelines advocated the use of hydrolyzed formula for supplementation in

high-risk infants for at least the first 4 months based on evidence that it is protective against the development of atopic disease, especially atopic dermatitis^{77,78}; however, the current recommendation has recently been challenged by the results of a systematic review and meta-analysis of 37 interventional trials. The authors did not find evidence that the use of hydrolyzed formula reduced the risk of eczema or of cow's milk allergy.⁷⁹

Prebiotics/probiotics

There is general interest in the role of the gut microbiota in the development of atopic disease. The uses of antibiotics and low-fiber diets (which lead to a lower consumption of prebiotics) have affected the gut microbiota, resulting in increased allergic disease.^{80–83} A recent World Allergy Organization guideline panel suggests “using probiotics in pregnant women at high risk for having an allergic child; using probiotics in women who breastfeed infants at high risk of developing allergy; and using probiotics in infants at high risk of developing allergy.”⁸⁴ The panel acknowledged that these recommendations are based on low-quality evidence.

Vitamin D

The role of vitamin D and its association with atopic disease has also been a topic of investigation. Although the HealthNuts study⁸⁵ concluded that sufficient vitamin D levels might be protective against food allergy in infancy, there are other studies that have implicated vitamin D supplementation as the cause of increasing allergic disease,⁸⁶ and still others that have noted no effect.⁸⁷ More conclusive studies are needed before a definitive association can be identified.

Omega-3 long chain polyunsaturated fatty acids (LCPUFAs)

Diets rich in omega-6 LCPUFAs generate potent inflammatory mediators, whereas diets rich in omega-3 LCPUFAs produce lower-potency inflammatory mediators and have anti-inflammatory effects.⁸⁸ The increase in omega-6/omega-3 ratios in Western diets has coincided with the increase in food allergy incidence⁸⁸ and has remained an area of active interest. A recently published Cochrane review analyzed eight randomized controlled trials of omega-3 LCPUFAs during pregnancy or lactation or both and found “limited evidence” to support supplementation with omega-3 LCPUFAs in pregnancy and lactation to reduce the incidence of allergy in children.⁸⁹

Conclusions

There have been significant pendulum swings in food allergy recommendations as new investigations reveal new

findings: from suggesting delaying the introduction of allergenic foods in 2000²⁴ to not delaying introduction^{38,78} and most recently to consideration of early introduction.^{20,21,23,34} Although convincing evidence for early introduction of peanut is now available,^{5,20,23} there are not convincing data for most other foods. The National Institute of Allergy and Infectious Disease guidelines have recently been revised to provide guidance on early introduction of peanuts.⁴⁵ Attention is now focused on other allergens, with some discordant but overall encouraging results.^{5,22,23,47,48} There are ongoing studies looking at the early diet and skin care for prevention of atopic disease, such as Preventing Atopic Dermatitis and Allergies in Children, which may be able to provide more evidence. We also await more studies on dietary interventions such as vitamin D, infant formula, and prebiotics and probiotics, among other potential strategies. Numerous ongoing studies are sure to inform this rapidly evolving area of public health policy and scientific investigation.

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