Topic Overview

Concerns about food allergies are common in North America and other western countries. The prevalence of food allergy assessed by food challenge in children under the age of three years is between 2% to 10% (1,2). Self-reported estimates of food allergy are higher (3). It is only natural for new parents and caregivers to wonder how food allergy in infancy can be prevented. As a result, many dietitians receive questions from families, both those considered at low and high risk of food allergy development, about how and if food allergy can be avoided.

Understanding the possibility of reducing food allergy risk by altering the introduction of foods to infants has improved dramatically over the years. In the 1980s and 90s recommendations were made to delay exposing infants to common food allergens. However recent evidence suggests that delayed exposure to allergens increases food allergy prevalence and evidence suggests that earlier food introduction may be more effective.

Breastfeeding is the normal and unequalled method of infant feeding (4). The health, growth and developmental benefits of breastfeeding are widely supported. However, potential harms related to interrupting exclusive breastfeeding by introducing complementary foods before six months of age requires examination given recent evidence regarding food allergy prevention in infants.

This Evidence Clip will describe the current evidence for the early introduction of solid foods for infants to inform dietetic practice.

Current Guidelines

Current guidelines state withholding or delaying the introduction of allergenic foods past six months of age is not effective to prevent food allergies from developing in “at risk” infants (5-8).

Countries such as Canada, Australia and the United Kingdom follow the World Health Organization (WHO) recommendation (9) of exclusive breastfeeding for the first six months (10-13). A recent Cochrane review has investigated the optimal duration of exclusive breastfeeding and found only one infant related benefit from exclusive breastfeeding to six months compared to three to four months in studies from developed countries, which was a reduced rate of gastrointestinal infection (14). These results were from a cluster randomized trial study conducted in Belarus, commonly referred to as the PROBIT study (15). In this study, the rate of gastrointestinal infections was 9.1% among infants born in a Baby-Friendly Hospital Initiative (intervention) and 13.2% among infants born in control hospitals (15). These findings equate to an adjusted odds ratio of 0.60 (0.40-0.91), a relative risk reduction of 40% and an absolute risk reduction of 4.1%.

Looking at allergy related outcomes in previous literature, PROBIT (15) reported a 46% reduction in the odds of developing atopic eczema but no difference in the odds of developing two or more episodes of wheeze with the promotion of breastfeeding. When the 2012 Cochrane review (14) examined all the available evidence, they did not find differences for food allergy measured by food challenge at one year of age, or food allergy at ages five to seven years, comparing longer versus shorter
exclusive breastfeeding durations. Nor did the Cochrane review find any evidence of differences for eczema, hay fever, asthma, allergy to animal dander (positive skin prick tests), with duration of exclusive breastfeeding (14).

Evidence Analysis

New Evidence Regarding Allergy Prevention

The LEAP peanut trial of infants at high risk of food allergy – infancy study:

Two recently published randomized controlled trials examined the effectiveness of introducing allergenic foods before six months as a possible strategy to prevent the development of food allergies. The LEAP trial (Learning Early about Peanut) tested this hypothesis among “high risk” infants, defined as having an increased risk of developing a peanut allergy (16) (See Additional Content: Article Analysis: Peanut Consumption in Infants at Risk for Peanut Allergy). High risk of developing a peanut allergy was defined at baseline as the presence of eczema and/or an established sensitivity to egg protein but no peanut allergy. Prior to the start of the study, all the infants underwent a skin prick test to determine whether or not the infant was already sensitized to peanut protein, and then were placed in subgroups based on these test results. The infants were then randomized into two intervention groups, those who would be exposed to peanut during infancy and those who would have peanut withheld until five years of age. The parents of the peanut exposure group were asked to feed at least six grams of peanut each week beginning between four to eleven months of age until five years of age (16). The parents of the peanut withholding group were asked to avoid peanut until five years of age (16). The children were examined at five years for the presence of peanut allergy through an oral challenge to peanut (16). In brief, the results of LEAP showed amongst those not sensitized to peanut at baseline, those who were exposed weekly to peanut protein had an 86% reduced prevalence of developing a peanut allergy compared to infants who were not exposed to peanut until the age of 60 months (16). The overall rates of peanut allergy in the ‘intention to treat’ analysis (defined in Note 1), were 1.9% in the exposed group and 13.7% in the avoidance group (p<0.001). Among the subgroup that had positive skin-prick tests to peanut, the rates of peanut allergy were 10.6% in the exposed group and 35.5% in the avoidance group (p=0.004). Thus, this study revealed dramatic decreases in the prevalence of allergy among infants exposed to peanut beginning between four and eleven months of age up to five years compared to infants who were not exposed to peanut in their first years. It should be noted that exposure to peanut did not lead to zero peanut allergies, but reduced rates by 74%.

The LEAP-ON peanut trial of infants at high risk of food allergy – five year olds study:

The LEAP-ON trial was an extension of the LEAP trial. This two-group comparison design investigated whether or not children who had consumed peanut in the LEAP trial remained protected against peanut allergy if they stopped consuming peanuts for 12 months. All the participants in the primary trial were eligible for inclusion in this follow-up study. Results indicated peanut allergy remained more prevalent in the children who avoided peanut during infancy. While a small number of new cases of peanut allergy developed in both groups, there was a further statistically significant increased proportion of infants with peanut allergy in the original LEAP peanut avoidance group. The incidence of peanut allergy increased in the peanut exposed group from 1.9% to 4.5%, and the incidence in the peanut avoidance group increased from 13.7% to 18.6%, P<0.001 (18). Therefore, although
peanut allergy development was not completely eliminated, there was a protective effect of exposing high risk of allergy infants to peanut beginning in the first year of life that persisted even when peanuts are avoided for 12 months and measured at 72 months of age (18).

What Do We Know About Prevention of High Risk Infants?

Because the LEAP trial intervention focused on high risk infants, it was still unknown whether early food allergen introduction would be protective for infants at lower risk for allergy (19). Nonetheless, some health care professionals have suggested that parents be advised to introduce allergenic foods, including peanut protein, at four to six months of age to prevent allergy (20). These authors suggested that the age of four to six months is a “window of opportunity” for early food introduction and that this window should not be missed (20).

The National Institute of Allergy and Infectious Diseases in the United States, in a new addendum to their 2016 draft guidelines, provide advice for infants considered high risk based on the severity of eczema (8). They recommend that infants with severe eczema, egg allergy or both be introduced to age-appropriate peanut containing foods between four and six months. The draft guideline recommends peanut should not be the first food introduced. It also recommends parents of children at high risk of allergy consult an allergist to conduct a skin prick test to determine sensitization to peanut before peanut is introduced into the infant’s diet. The recommendation for parents of infants between four and six months of age with mild to moderate eczema but without egg allergy is to introduce age appropriate peanut at home or in the presence of a physician. These new draft guidelines did not specify an ideal age of introducing solid foods to low risk infants (i.e. those without a family history or without eczema). Instead, the draft guidelines suggest these infants at low risk of developing food allergy consume age-appropriate peanut-containing foods that are freely offered (8).

The EAT Trial of Infants at Low Risk of Food Allergy

To help answer the question of whether the early introduction of commonly allergenic foods (peanut, egg, cow’s milk, sesame, fish and wheat) to infants in the general population would be effective at reducing allergies, the Enquiring about Tolerance (EAT) study (21) was conducted. This study was a population-based randomized controlled trial, designed to test whether early introduction of common food allergens at three to four months of age to breastfed infants of various risk of allergy would decrease allergy risks compared to those infants who were exclusively breast-fed for approximately six months prior to food exposure.

Exclusively breastfed infants between 13 and 17 weeks of age (three to four months old) were recruited for the EAT trial regardless of their atopic status or family history of food allergy. Infants were randomly assigned using an independent online service to the early solid intervention or the standard introduction (control group).

Parents in the EAT intervention group were asked to sequentially introduce six of the foods thought to be the most allergic foods to cause IgE-mediated food reactions in children; cow’s milk, peanut, egg, sesame, fish (cod), and wheat, after allergy testing (22). Specifically, infants were started on infant rice cereal, pureed fruits or vegetables or both during the first week until solid food introduction was established between three to four months of age. Infants continued on these first foods and then were introduced to cow’s milk yogurt in the second week. During weeks three and four, the six allergic foods were introduced sequentially in any order, with two new foods introduced per week. After four
months of age and by week six of the intervention, infants were ideally consuming the required amount of all six allergenic foods each week. Four grams of each allergen was recommended to be consumed by six months of age.

The introduction of non-allergenic foods was not restricted during the intervention period. The weekly amount of the allergenic foods were as follows:

- 2 small (40 - 60 g) portions of cow’s milk yogurt
- 3 rounded tsp of peanut butter
- 1 small hard-boiled egg
- 3 rounded tsp of sesame paste
- 25 g white fish
- 2 wheat based cereal biscuits (23).

To be considered compliant to the protocol, families in the early introduction group were asked to report whether their infants consumed five or more of the allergenic foods in at least 75% of the recommended amounts (3 g of allergenic protein per week) for at least five weeks between three and six months of age. These foods were to be introduced alongside continued breastfeeding.

Prior to the start of the allergen introduction, infants in the intervention group underwent duplicate skin prick testing. If these were positive, an open food challenge to the six food allergens was conducted. Parents completed an online questionnaire, which included a food frequency questionnaire of their child’s food intake, completed monthly until infants were 12 months of age and then every three months between 12 and 36 months.

The control or standard introduction group was simply asked to comply with the current United Kingdom government infant feeding guidelines of exclusive breastfeeding until around six months of age. Parents in the control group were asked not to feed their infants any of the six allergenic foods before six months of age but could introduce them as they wished after six months of age.

The primary outcome for the EAT trial was the prevalence of IgE-mediated food allergy confirmed by double-blind, placebo-controlled food challenge to any of the six allergenic foods measured between one and three years of age. Secondary outcomes were reported based on results of skin prick testing to the six allergenic foods.

The EAT trial recruited 1303 three-month-old infants, who were geographically and demographically representative of the population of England and Wales. Parental history of atopy (any eczema, asthma, or hay fever in either parent) affected 81.9% of the cohort. Ninety-seven percent of the intervention (Early Intervention Group) group and 98% of the control (Standard Introduction Group) group were still being breastfed at six months of age (22). This randomized trial provides evidence that the introduction of solids before six months of age does not interfere with breastfeeding duration.

A feasibility sub-study for the EAT trial (22) reported that consumption was low for all allergenic foods in the intervention group except for milk at four months of age. Four of the six foods (peanut, egg, sesame, and whitefish) at five months and two (egg and whitefish) at six months of age were being consumed by only 25% of the intervention group only once a week. Overall, 42.2% of the parents in the intervention group compared to 92.2% of parents in the control group complied with the study protocol for their group.

At the end of the study, there was a non-significantly lower rate of IgE-mediated food allergy to one or more of the six allergenic foods of 5.6%; (32 of 567 participants) in the group randomized to the early introduction of the allergens and 7.1% (42 of 595) in the control group. These rates equate to a relative risk of 0.80 (95% CI, 0.51 to 1.25, p=0.32).
When those who did not comply with the protocol were removed from the analysis, in a ‘per-protocol analysis’ (defined in Note 2), the rate of any food allergy was statistically significantly lower in the early introduction group 2.4% (5 of 208 participants) compared to the standard introduction group of 7.3% (38 of 524), \( p=0.01 \). The relative risk in the per-protocol analysis was 0.33 (95% CI, 0.13 to 0.83; \( p=0.01 \)), representing a prevalence that was 67% lower than that in the standard-introduction group (21).

In other words, families in the intervention group, who complied with the study protocol, had a statistically significant reduction in allergy for peanut and egg. Additionally, a dose response was noted in the per-protocol analysis as there was a lower probability of developing a food allergy with higher amounts of egg and peanut consumed. There were no cases of anaphylaxis reported during the initial introduction regimen (21).

**The Big Picture**

There are two potential main concerns about introducing solid foods before six months of age; the possible occurrence of adverse health outcomes associated with the cessation of exclusive breastfeeding and the cessation of any breastfeeding.

Other than the modest effect on GI infection rates, there is little evidence regarding infant health benefits for exclusive breastfeeding six to seven months compared to three to four months in the developed world. There is also no rigorous evidence suggesting the introduction of solid foods before six months of age negatively impacts breastfeeding. It is noteworthy that the EAT randomized controlled trial found no impact on breastfeeding duration when solids were recommended to be introduced at three to four compared to six months (22).

Potential benefits of introducing solids before six months is the possible improvement in iron status (24,25) food texture acceptance and less picky eating (26,27).

An internationally recognized pediatric allergist, Dr. Chan, has commented “perhaps the prevention of chronic and potentially life-threatening food allergies are more of a concern for parents compared to the possible risk associated with gastrointestinal infections” (28). He supports continued breastfeeding after solids have been introduced, but agrees with advice to exclusively breastfeed for “about” six months rather than a rigid six months so that solids can be started a bit earlier if the infant is developmentally ready. In Canada for example, viral gastroenteritis in infancy is manageable and of short duration, whereas food allergy such as peanut allergy is often life-long and severe. He questions the applicability of the association of breastfeeding with reduced gastrointestinal infections, as this is based on only a single study (demonstrating a reduction from 13.2% to 9.1%) conducted in 2000 in the eastern European country of Belarus (15), findings which may not be relevant in developed nations in 2016 (28).

Additionally, the gastrointestinal infections in the PROBIT study were not confirmed by lab tests such as detection of viral antigens in stool samples. Instead, they were defined by subjective criteria such as two days of increased stool frequency, loose stools, or vomiting.

**Key Practice Points**

**Advice for the General Population**

Regarding the general population, the available evidence currently does not justify the introduction of allergenic foods between three and four months of age since there was no important or statistically significant reduction of allergy in the EAT study’s intention-to-treat
analysis. This intention-to-treat analysis is the strongest evidence from this well-designed RCT, by definition. In the EAT trial, the large proportion of parents in the early intervention group did not comply with the intervention protocol which appears to have led to a dilution of the effects and the non-significant findings, but we do not know for sure if this is the reason. Using a per-protocol analysis, introducing allergens between three and four months of age appeared to be effective at reducing food allergy amongst those families who followed the intervention protocol. However, this per-protocol analysis is not based on the randomized allocation but based on compliance, so is considered to be lower level evidence. Thus at this point in time, we lack strong evidence that the early introduction of food allergens intervention among non-high risk infants is feasible at reducing allergies when introduced according to the methodology of the EAT study.

Nonetheless, the positive findings of the per-protocol analysis are compelling and could be informing us that the introduction of allergenic foods before six months may indeed support food allergy prevention. Currently, infant feeding advice states the introduction of solids could take place a few weeks before or just after six months (10). This practice guidance also notes that commonly allergenic foods can be first foods, as several are sources of dietary iron. These foods should be introduced regularly and should not be restricted (29).

**Summary of Key Practice Points for the General Population:**

- Introduce complementary foods at about six months. Waiting longer than six month may increase iron deficiency and food allergy.
- First foods should be those high in iron. Some iron rich foods are also allergenic foods. Introduce the most common allergens one at a time, in any order. They should be consumed regularly and without restrictions.

- Further information on the introduction to complementary foods, including country specific guidelines; see [Infant Nutrition - Complementary Feeding Knowledge Pathway in PEN](#).

**Advice for Families At High Risk of Allergy**

The LEAP trial findings found important preventive effects for the early introduction of peanut between four and eleven months in infants. Parents of infants at high risk of developing food allergy, who have severe eczema, should consult with a physician or allergist to determine the appropriateness and safety of introducing peanut containing foods between four and six months of age.

Given the compelling results of the LEAP and EAT trials collectively, softening of the “exclusive breastfeeding for six months” population level recommendation to “about six months” is justified.

Parents should be aware that foods such as peanut butter, when served on its own, is an established choking hazards in infancy (29,30). However, peanut butter can be diluted or mixed into other foods so that it does not present a choking hazard (8).

It is very important not to delay solid food introduction to later than six months of age for several reasons including allergen exposure (5-8), the need for iron containing foods (10), and for food texture acceptance (26,27).

**Summary of Key Practice Points for Families at High Risk of Allergy:**

- Consult with physician or allergist to determine if infant is a candidate for introducing peanut containing foods between four and six months of age.
  - Peanuts and peanut butter are a choking hazard in children under the age of four years of age. Mix peanut
butter into other foods, or dilute with water, before serving.

- Once introduced, provide regular consumption of peanut butter to maintain tolerance.

- Introduce complementary foods no later than six months of age.

- Further information on the introduction to complementary foods, including country specific guidelines, see: Infant Nutrition - Complementary Feeding Knowledge Pathway.

The Bottom Line

Current food allergy prevention advice encourages that the population of “standard risk” infants or infants with a family history of a first degree relative with atopy continue to breastfeed while they are introduced to complementary foods, including commonly allergenic foods, at about six months of age. It is important to introduce foods to infants in their sixth month for allergen exposure, the need for iron containing foods, to support food texture acceptance and less picky eating. Parents and caregivers of infants at highest risk (infants with severe eczema or egg allergy) are encouraged to consult a physician or allergist for advice about introducing solid foods before six months to decrease the risk of developing food allergy. Once introduced, regular, frequent ingestion may help to maintain tolerance.


Note 1: Intention-to-treat (ITT) is the recommended analysis for randomized trials. This analysis method analyzes the trial results using the groups the participants were assigned to, whether or not the participants received, accepted or completed the intervention. "Failure to follow this approach defeats the main purpose and advantage of random allocation and can cause serious confounding bias” (17). An ITT analysis is recommended since it keeps the randomization scheme, which is important for randomized trials since it is designed to give comparable groups in terms of their known and unknown risk factors.

Note 2: Per-protocol analysis - limits the analysis to those who followed the protocol. Although this analysis seems to make sense, it is not analyzed by the randomization scheme, and so confounding may have been introduced, since those who comply with the randomization versus those who do not may be different in important unknown ways that influences their risk of the outcome (17).

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References


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