

Early Introduction of Allergenic Foods is Safe and May Be Beneficial

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Practice Options from Beyond Our Pages focuses on identifying, critiquing, and placing into context research studies published in other journals that have the potential to change our clinical practices. It is written by Allergy-Immunology Fellows partnered with faculty members, and does not require an invitation for submission. This feature is coordinated by Editorial Board members Matthew Rank, MD and Julie Wang, MD.

REFERENCE

Perkin MR, Logan K, Tseng A, Raji B, Ayis S, Peacock J, et al., Randomized trial of introduction of allergenic foods in breast-fed infants. *N Engl J Med* 2016;374:1733-43.

BACKGROUND

Consensus guidelines in the United States in 2010 recommended not to delay the introduction of solid foods beyond age 4 to 6 months.¹ However, recommendations for the specific introduction of allergenic foods were less clear. The Learning Early About Peanut Allergy (LEAP) trial² and the Persistence of Oral Tolerance to Peanut (LEAP-On) trial³ showed that early consumption of peanut in high-risk infants reduced the development of peanut allergy.

The Enquiring about Tolerance (EAT) trial sought to answer 2 outstanding questions: (1) could these findings be applied to the general population?; and (2) can the early introduction of other common food allergens be similarly effective?

METHODS

The EAT trial was a randomized, controlled trial conducted at a single site in the United Kingdom. Participants were exclusively breast-fed, 3-month-old infants from the general population who were randomly assigned either to a standard-introduction group or to an early-introduction group.

Participants in the standard-introduction group were exclusively breast-fed up to age 6 months after which the consumption of allergenic foods was allowed according to parental discretion.

Participants in the early-introduction group were instructed to introduce 6 allergenic foods starting with milk, followed randomly by peanut, cooked egg, sesame, whitefish, and wheat. Skin prick testing (SPT) was performed before the introduction and those with

a wheal of any size underwent an oral food challenge (OFC). Only those who had a negative SPT result or a positive SPT result with negative OFC were continued in the study and asked to consume 2 g of the food allergen twice weekly.

Adequate adherence was defined by (1) consumption of at least 5 of the early-introduction foods, (2) consumption for at least 5 weeks between age 3 and 6 months, and (3) consumption of at least 3 g weekly. Compliance was measured by an online food consumption questionnaire and by the measurement of peanut-protein levels in dust taken from the participant's bedroom.

The primary outcome was challenge-proven food allergy to 1 or more of the 6 early-introduction foods between age 1 and 3 years. Secondary outcomes were allergy to individual foods and positive results on SPT for individual foods.

RESULTS

Adherence varied significantly with 92.9% in the standard-introduction group and 42.8% in the early-introduction group meeting per-protocol (PP) criteria. Within the early-introduction group, adherence to the different food allergens varied as well. The intention-to-treat (ITT) analysis included 87% of participants in the early-introduction group and 91.4% in the standard-introduction group. The PP analysis included 31.9% in the early-introduction group and 80.5% in the standard-introduction group.

In evaluating the primary outcome, the ITT analysis showed a nonsignificant 20% lower prevalence of food allergy in the early-introduction group (5.6% vs 7.1%). However, the difference in the PP analysis (2.4% vs 7.3%) did reach statistical significance driven mainly by a difference in the rate of peanut and egg allergy.

In evaluating the secondary outcomes, there was no significant difference in allergy to individual foods by the ITT analysis. In the PP analysis, there was a significant reduction in egg and peanut allergy whereas the reduction in milk and sesame allergy was nonsignificant. In a similar fashion, the ITT analysis failed to show a significant difference in SPT to all foods and to individual foods (except for wheat). However, the PP analysis showed a significantly lower rate of positive SPT to any food at 1 and 3 years.

With regard to safety, there were no deaths in the study and no episodes of anaphylaxis in the early-introduction group. Emergency department visits and hospitalizations were similar between the 2 groups.

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Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

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CRITICAL APPRAISAL**The early introduction of allergenic foods, in particular peanut and cooked eggs, may be effective**

In the ITT analysis, the study failed to meet its primary outcome. It would be tempting to stop any further consideration of this study on the basis of this fact. However, it is important to look at the participants who did not meet adherence benchmarks as they made up the difference between ITT and PP analyses. Reported reasons for nonadherence were nonwhite race, perceived symptoms, maternal quality of life, and eczema. However, it is possible that underlying these reported reasons was the influence of previous guidelines and/or cultural practices of food introduction. The ITT analysis was more true to the objective of learning whether the findings from LEAP and LEAP-On trials could be applied to the general population, but considering these subjects as treatment failures perhaps unfairly masked the actual treatment effect. In this scenario, it would seem reasonable that the PP analysis, which evaluated those who completed the intervention, could give a more accurate assessment of the intervention.

The dose and duration of the food introduction appears important

A dose-response analysis presented by the authors demonstrated that higher weekly allergen consumption between age 3 and 6 months correlated with a lower prevalence of food allergy at 12 months; however, the overall results did not meet significance in the ITT analysis. Adequate adherence up to age 24 months was considered sufficient in the highly successful LEAP study to be included in the PP analysis. It is possible that considering a short period of 5 weeks during a 3- to 6-month time period for adequate adherence may have resulted in a smaller difference in the development of food allergy in the intervention group when compared with controls and perhaps a

longer adherence period or a higher cumulative dose may be needed to develop the protective effect of early introduction.

The primary outcome is of several outcomes that are not necessarily related

The 6 allergenic foods in the study have no notable clinical cross reactivity and are known to have different clinical presentations (ie, develop at different ages and last or resolve at different times). Tying the primary outcome to the results of 6 potentially different disease processes may have made the outcome harder to achieve. Investigating the early introduction of individual foods would seem to provide a more specific assessment of the efficacy of early food introduction.

RECOMMENDATION

In the general population, introduction of peanut and cooked egg as early as age 3 months is safe and should be considered to help lower the rate of peanut and egg allergy. We would recommend a discussion with a pediatrician or allergist before commencing. Two grams should be consumed twice weekly between age 3 and 6 months although a longer duration would be ideal. An SPT should be performed before introduction only in high-risk infants. No definitive recommendations can be made regarding the introduction of milk, sesame, fish, or wheat on the basis of presented data.

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