Food allergy: Update on prevention and tolerance

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Of the many possible hypotheses that explain the recent increase in childhood food allergy (FA), the dual-allergen exposure hypothesis has been the most extensively investigated. This chapter serves as a review and update on the prevention of FA and focuses on recently published randomized controlled trials exploring the efficacy of oral tolerance induction in infancy for the prevention of FA. As a result of these RCTs, National Institutes of Health recommendations now actively encourage the early introduction of peanut for the prevention of peanut allergy, and other countries/settings recommend the inclusion of potential common food allergens, including peanut and egg, in complementary feeding regimens commencing at approximately 6 months but not before 4 months of age. Further studies that explore the efficacy of oral tolerance induction to other common food allergens and that focus on optimal timing, duration, and adherence are required. (J Allergy Clin Immunol 2018;141:30-40.)

Key words: *Food allergy, peanut allergy, egg allergy, allergy prevention*

Abbreviations used

EAT:	Enquiring about Tolerance Study
FA:	Food allergy
ITT:	Intention to treat
LEAP:	Learning Early about Peanut Allergy
LEAP-On:	Twelve-month extension of the LEAP study: Persistence of Oral Tolerance to Peanut
PETIT:	Two-step egg introduction for prevention of egg allergy in high-risk infants with eczema
RCT:	Randomized controlled trial
RR:	Relative risk
SPT:	Skin prick test
STAR:	Solids Timing for Allergy Research
STEP:	Starting Time for Egg Protein
UK:	United Kingdom

"An ounce of prevention is worth a pound of cure" is an appropriate adage to describe much research into food allergy (FA) over the past decade. Given that there is currently no cure, research has focused increasingly on interventions aimed at FA prevention. These interventions are generally applied early in life and include primary prevention, which seeks to prevent the onset of IgE sensitization, and secondary prevention, which seeks to interrupt the development of FA in IgE-sensitized children.

This chapter will discuss possible reasons for the increase in FA, review current knowledge around methods for primary prevention from recently published research, describe statistical issues in FA prevention studies, and briefly outline potential directions for future research. The main focus will be on lessons learned from the recently published Learning Early about Peanut Allergy (LEAP), Persistence of Oral Tolerance to Peanut (LEAP-On), and Enquiring about Tolerance (EAT) randomized controlled trials (RCTs),[1-3] but other published FA prevention research is also included.

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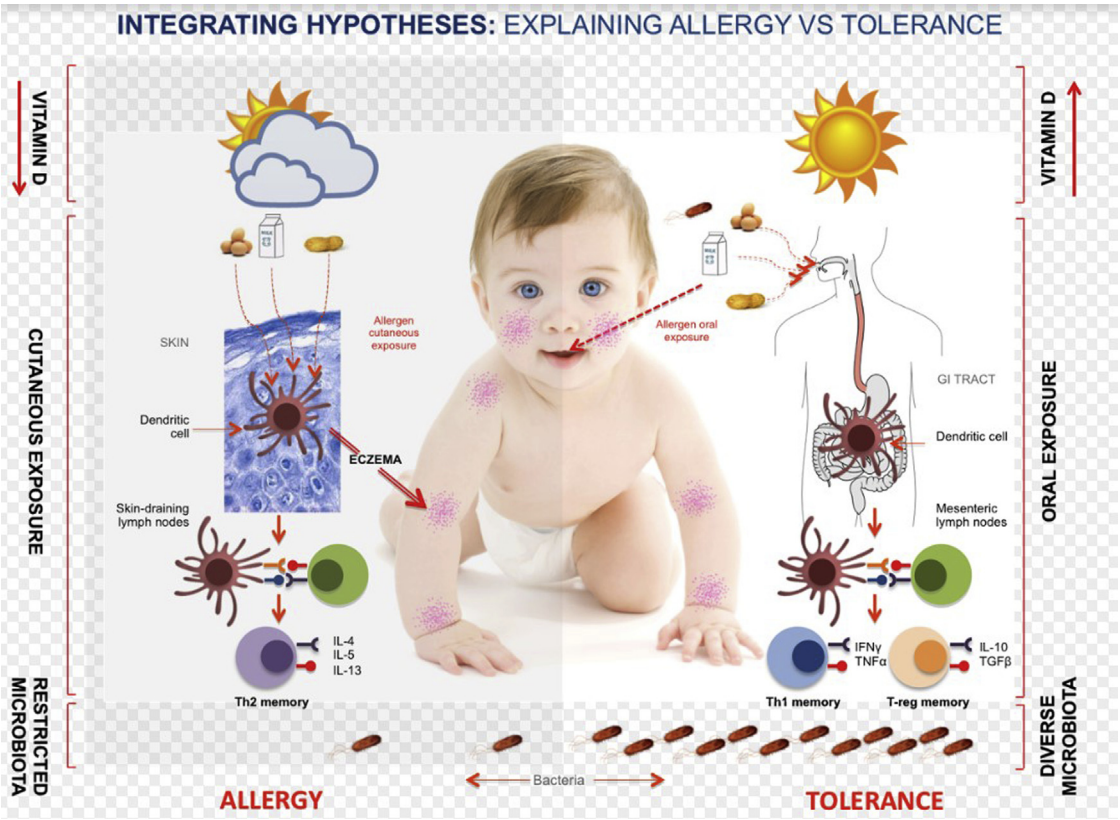

FIG 1. Integration of the vitamin D deficiency, hygiene, and dual-allergen exposure hypotheses. Sufficient levels of vitamin D, a diverse microbiota, and oral allergen exposure support the development of tolerance. Conversely, allergic sensitization is promoted through cutaneous exposure, reduced diversity of the microbiota, and vitamin D deficiency. Diminished microbial diversity and vitamin D deficiency are thought to interrupt the regulatory mechanisms of oral tolerance, with the latter also contributing to decreased epidermal barrier function. *GI*, Gastrointestinal; *T-reg*, regulatory T cells. Graphic modified from Lack.[4]

HYPOTHESIZING THE INCREASE IN FA

Various hypotheses have been put forward to explain the increase in FA. Integration of the vitamin D deficiency, hygiene, and dual-allergen exposure hypotheses (which is the focus of this chapter) are shown in Fig 1.[4] This article focuses on the dual-allergen exposure hypothesis, which suggests that allergic sensitization to food occurs through low-dose cutaneous sensitization, whereas early consumption of food protein induces oral tolerance.[4] This hypothesis was developed after publication of studies demonstrating a strong association between dietary exposure, eczema, and the development of FA.

Studies demonstrating the role of cutaneous sensitization in patients with FA

Animal and human observational and *in vitro* studies demonstrate transcutaneous sensitization to food allergens through inflamed eczematous skin. In human subjects the topical application of *Arachis* species (peanut) oil onto eczematous skin during infancy was significantly associated with peanut allergy in eczematous children.[5] Environmental exposure to peanut during infancy (assessed by household peanut consumption) increased the risk of peanut allergy; however, if infants consumed peanut in the first year of life, they were protected against peanut allergy.[6]

More recent studies found that eczema severity amplifies the risk of peanut sensitization and likely allergy resulting from exposure to peanut antigen in household dust.[7] A similar increase in peanut sensitization and allergy risk was seen in children with filaggrin loss-of-function mutations exposed to high levels of peanut allergens in household dust.[8] This provides a good example of gene-environment interactions leading to the development of peanut allergy in young infants.

A cross-sectional study assessed the route of peanut exposure in the development of allergy and captured maternal peanut consumption during pregnancy, breast-feeding, and the first year of life through a questionnaire. Household peanut consumption was also quantified. Median weekly household peanut consumption in the patients with peanut allergy was significantly increased (18.8 g) compared with that in control subjects without allergy (6.9 g) and high-risk control subjects (1.9 g).[6] These findings suggest that high levels of environmental exposure to peanut during infancy can promote sensitization and support the hypothesis that peanut sensitization occurs as a result of environmental exposure.

Studies demonstrating the role of tolerance induction in early childhood

An ecological study exploring the prevalence of peanut allergy in infants in Israel compared with infants in the United Kingdom