Consensus Communication on Early Peanut Introduction and the Prevention of Peanut Allergy in High-Risk Infants

On behalf of American Academy of Asthma, Allergy, and Immunology, American Academy of Pediatrics, American College of Allergy, Asthma, and Immunology, Australasian Society of Clinical Immunology and Allergy, Canadian Society of Allergy and Clinical Immunology, European Academy of Allergy and Clinical Immunology, Israel Association of Allergy and Clinical Immunology, Japanese Society for Allergology, Society for Pediatric Dermatology, and World Allergy Organization

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Abbreviations: LEAP: Learning Early About Peanut; NIAID: National Institute of Allergy and Infectious Diseases; EAACI: European Academy of Allergy and Clinical Immunology; SPT: skin prick test; ITT: intention-to-treat; NNT: number needed to treat

Introduction and Rationale

Peanut allergy is an increasingly troubling global health problem, which affects between 1-3% of children in many westernized countries. Although multiple methods of measurement have been used and specific estimates differ, there appears to be a sudden increase in the number of cases in the past 10 – 15 year period, suggesting that the prevalence may have tripled in some countries, such as the USA. Extrapolating the currently estimated prevalence, this translates to nearly 100,000 new cases annually (in the USA and UK), affecting some 1 in 50 primary school-aged children in the USA, Canada, UK, and Australia. A similar rise in incidence is now being noted in developing countries such as Ghana.[1-6]

The **purpose of this brief communication** is to highlight emerging evidence to existing allergy prevention guidelines regarding potential benefits of supporting early, rather than delayed, peanut introduction during the period of complementary food introduction in infants. The recent study, entitled "*Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy (Learning Early About Peanut - LEAP Trial),*" demonstrated a successful 11% - 25% absolute reduction in the risk of developing peanut allergy in high-risk infants (and a relative risk reduction of up to 80%) if peanut was introduced between 4 and 11 months of age.[7] In light of the significance of these findings, this document serves to better inform the decision-making process for healthcare providers regarding such potential benefits of early peanut introduction. More formal guidelines regarding early-life, complementary feeding practices and the risk of allergy development will follow in the next year from the National Institute of Allergy and Infectious Diseases (NIAID)-sponsored Working Group and the European Academy of Allergy and Clinical Immunology (EAACI), and thus this document should be considered as interim guidance.

Summary of New Evidence

In the LEAP trial, 640 high-risk UK infants (See Textbox 1) between the ages of 4 to 11 months were randomized to consume peanut products at least three times a week (6 g of peanut protein; equivalent to 24 peanuts or 6 teaspoons of peanut butter per week) or to completely avoid peanut products for the first five years of life. This included 542 infants found to have negative skin prick tests (SPT) to peanut at study entry, and 98 infants with SPT wheal diameters to peanut between 1 to 4 mm (minimally SPT positive) at study entry. An additional 76 children were excluded from study entry prior to randomization based on SPT $\geq$ 5mm, which was assumed to have a very high likelihood of reacting to a peanut challenge. In an Intention-To-Treat (ITT) analysis, 17.2% in the peanut avoidance group compared to 3.2% in the peanut consumption group developed food challenge-proven peanut allergy by age 5 years, corresponding to a 14% absolute risk reduction, a number needed to treat (NNT, e.g. number of persons needed to be treated for one to receive benefit) of 7.1, and a relative risk reduction of 80%.[7]

When examined in further detail, the isolated beneficial effects for both the primary and secondary prevention of peanut allergy translated to a NNT = 8.5 within the SPT negative and NNT = 4 within the minimally SPT positive infants. Secondary analyses also showed similar levels of prevention in White, Black and Asian (Indian and Pakistani) children. Overall, the risk of early introduction in this group was low – 7 of the 319 children randomized to the consumption group reacted to peanut at the baseline food challenge suggesting that peanut food challenges and introduction, even in minimally SPT positive infants, is safe and feasible. Six children in the consumption group developed peanut allergy during the study indicating that peanut allergy can still develop despite attempts at primary and secondary prevention. Finally, the LEAP trial only included high-risk infants with a minimal or negative SPT to peanut, and therefore does not address a strategy for those without these risk factors for developing peanut allergy.[7]

How Does The LEAP Trial Affect Present Guidance for Early Complementary Feeding Practices?

Existing guidelines pertaining to the early introduction of complementary foods have indicated that the introduction of highly allergenic foods, such as peanut, need not be delayed past 4 or 6 months of life. However, they do not actively recommend introduction of peanut between 4 – 6 months of age in high-risk infants, and some of these guidelines specify that certain infants considered at high risk for the development of allergic disease are recommended to first consult an expert.[8-14]

The LEAP data provide *Level 1* evidence that the practice of early peanut introduction is safe and effective in selected high-risk infants. This study is the first prospective, randomized trial of early peanut intervention, and informs provider decision-making regarding high-risk infants, including those already with a positive peanut SPT but not yet clinically reactive, to receive the benefits noted in the LEAP study, which may reduce the risk of developing peanut allergy up to 80%.

Of note, since children with lesser risk factors for peanut allergy were excluded from enrollment in LEAP, there are no prospective, randomized data investigating the benefit or risk of early peanut introduction in the general to low-risk populations. Consequently, this communication's guidance is limited to integrating the findings learned in the LEAP trial to other similar high-risk children in more diverse settings around the world. However, multiple guidelines have not recommended delaying allergen introduction in the general to low-risk populations.

Interim Guidance Regarding Early Peanut Introduction

Based on data generated in the LEAP trial and existing guidelines, the following interim guidance is suggested to assist the clinical decision-making of healthcare providers:

- There is now scientific evidence (*Level 1* evidence from a randomized controlled trial) that healthcare providers should recommend introducing peanut-containing products into the diet of "high-risk" infants early on in life (between 4 – 11 months of age) in countries where peanut allergy is prevalent, since delaying the introduction of peanut may be associated with an increased risk of developing peanut allergy.

- Infants with early-onset atopic disease, such as severe eczema, or egg allergy in the first 4-6 months of life (see Text Box 1 for example LEAP criteria), may benefit from evaluation by an allergist or physician trained in management of allergic diseases in this age group to diagnose any food allergy and assist in implementing these suggestions regarding the appropriateness of early peanut introduction. Evaluation of such patients may consist of performing peanut skin testing and/or in-office observed peanut ingestion, as deemed appropriate following discussion with the family. The clinician may perform an observed peanut challenge for those with evidence of a positive peanut skin test to determine if they are clinically reactive, before initiating at-home peanut introduction. Both such strategies were used in the LEAP study protocol.

- Adherence in the LEAP trial was excellent (92%) with infants randomized to consume peanut ingesting a median of 7.7 g peanut protein (interquartile range: 6.7 – 8.8 g)/week during the first 2 years of the trial compared to a median of 0 g in the avoidance group (see Text Box 2 for examples of peanut-containing foods utilized in the LEAP trial). While the outcome of the LEAP regimen was excellent, the study does not address use of alternative doses of peanut protein, minimal length of treatment necessary to induce the tolerogenic effect, or potential risks of premature discontinuation or sporadic feeding of peanut.

Rationale for evaluating and applying this policy to a high-risk population

The LEAP study demonstrates that early peanut introduction can be successfully carried-out in a high-risk population (such as the population defined in the LEAP trial). However, without intervention by healthcare providers, there is the potential that such high-risk infants will remain at risk for delayed introduction of solids and allergenic foods into their diet, because of the widespread belief that such foods may exacerbate eczema.

There will be more extensive guidelines in the near future from the NIAID Working Group and EAACI Guidelines Group with their multidisciplinary stakeholders. These groups will consider all the available data and determine whether there is sufficient evidence to apply prevention strategies to the general population. However, engagement of the primary care, allergy and dermatology communities to rapidly implement these findings and change the culture of early feeding practices is essential, and the forthcoming NIAID Working Group's and EAACI Guidelines Group's documents will better clarify a best-practices approach.

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Text Box 1: Enrollment Criteria Used in the LEAP Study

Infants considered at "high risk" as defined by the LEAP study criteria:

Egg allergy: Children with either –

1) A SPT wheal diameter ≥6 mm from exposure to raw hen's egg white and no history of previous egg tolerance,

or

2) A SPT wheal diameter ≥3 mm from exposure to pasteurized hen's egg white and allergic symptoms related to exposure to hen's egg.

Severe eczema: An eczematous rash that –

1) Requires the application of topical creams and/or ointments containing corticosteroids or calcineurin inhibitors, and if the participant is <6 months of age, lasted for at least 12 out of 30 days on two occasions, or if >6 months of age, lasted for at least 12 out of 30 days on two occasions in the last 6 months,

Or

2) Is currently or was previously graded ≥ 40 using the modified SCORAD evaluation

Example of method of skin prick testing: used in the LEAP study

- Skin prick test to peanut extract done in the presence of a negative control and a positive histamine control.
- Skin prick testing should be performed in duplicate and the maximum wheal diameter of the two skin prick tests should be calculated and rounded up to the greatest whole millimeter

Of note, in the LEAP trial, the use of IgE measurement to peanut resulted in considerably higher rates of sensitization compared to skin testing, which could lead to numerous unnecessary oral peanut challenges.

Text Box 2: Examples of Peanut-containing Foods Utilized in the LEAP Trial

- Smooth peanut butter (2 teaspoons) mixed with milk or with mashed or pureed fruit
- *Bamba® snack (Osem; ~2/3's of 1 oz. (25 g) bag; 21 sticks of Bamba®)
  - for young infants (<7 months), softened with 20 – 30 ml water or milk and mixed with milk or with mashed or pureed fruit or vegetables
- Peanut soup
- Finely ground peanuts mixed into other foods such as yoghurt
- **(*Other foods more customary to particular nations/cultures may be substituted)**

Whole peanut is not recommended for introduction as this is a choking hazard in children under the age of 4.

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