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Continuing Education for Nutrition Professionals

Prevention of Peanut Allergy

Primum non nocere—first do no harm. And then feed peanut

Abstract

The *Addendum Guidelines for the Prevention of Peanut Allergy in the United States—Report of the NIAID-Sponsored Expert Panel* were developed to build on previous food allergy guidelines after several key studies demonstrated the benefit of early introduction of allergenic foods. These landmark studies including the Learning Early about Peanut (LEAP), LEAP-On and Enquiring about Tolerance trials created a paradigm shift in food allergy prevention. The "take home" messages of this guideline include that peanut should be introduced early in the first year of life, and for the majority of infants, peanut can be introduced at home. The only group of infants for which medical assessment is recommended is those with severe eczema, egg allergy or both. Here we summarize the Guideline recommendations, endorsed by the Canadian Society of Allergy and Clinical Immunology, and highlight important aspects relevant to Canadian practitioners.

Keywords: Peanut allergy, Prevention, High-risk, Infant

The *Addendum Guidelines for the Prevention of Peanut Allergy in the United States—Report of the NIAID-Sponsored Expert Panel* were developed to build on previous food allergy guidelines after several key studies demonstrated the benefit of early introduction of allergenic foods [1, 2]. These landmark studies including the Learning Early about Peanut (LEAP) [3], LEAP-On [4] and Enquiring about Tolerance [5] trials created a paradigm shift in food allergy prevention. We commend the authors of the Guidelines for recognizing the need for prompt dissemination of the findings. Here we summarize the Guideline recommendations, endorsed by the Canadian Society of Allergy and Clinical Immunology (CSACI), and highlight important aspects relevant to Canadian practitioners.

The Guidelines address the prevention of peanut allergy among three groups of infants. The "take home" messages include that peanut should be introduced early in the first year of life, and for the majority of infants, peanut can be introduced at home. The only group of infants for which medical assessment is recommended is those with severe eczema, egg allergy or both. In this group, the Guidelines suggest skin prick testing and/or peanut-specific IgE evaluation prior to peanut introduction around 4–6 months of age. Recognizing that timely access to subspecialist allergists can be limited, the Guidelines suggest that non-allergy physicians may consider performing a peanut-specific IgE level as an initial step for infants at high risk of peanut allergy. Testing for food allergy by non-allergy physicians, the authors wrote, has the potential to reduce the number of infants needing allergist screening by supporting home introduction. However, this recommendation warrants further discussion.

The definition of severe eczema is intended to classify patients who continue to experience frequent and extensive symptoms despite *optimal* management and adherence to treatment. However, it is our experience that many parents and healthcare providers use the term "severe" to refer to any patient presenting with bothersome symptoms, regardless of treatment. This discrepancy could lead to a significant increase in infants with mild or suboptimally managed eczema deemed inappropriately as

high risk for peanut allergy. Many infants could undergo unnecessary testing, thereby missing the window of opportunity of early peanut introduction. In the absence of specific IgE mediated symptoms, a positive skin/food-specific IgE test represents sensitization however does not prove clinical reactivity to the food. Individuals with atopic dermatitis, or other allergic conditions, are more likely to have elevated IgE levels, and are more likely to have false positive food-specific IgE tests [6].

Additionally, by recommending that non-allergy physicians perform peanut-specific IgE to help facilitate timely assessment of infants at high risk, our concern is that the opposite may result: referrals to subspecialty allergists may increase for assessment of false positive sIgE results among sensitized individuals. The increased wait time for allergy assessment may lead to further unnecessary delay in the introduction of peanut and possibly other foods. The Guideline authors emphasize that an undetectable peanut-specific IgE level has a "strong negative predictive value". However, many infants with a personal and/or family history of atopy will have clinically irrelevant sensitization identified by this test. The Guideline authors recommend that an infant with a detectable peanut-specific IgE level "be referred to a specialist for further consultation". It is our concern that many of these infants will instead continue to strictly avoid peanut and will not seek further assessment by a subspecialty allergist or be unable to see an allergist in a timely fashion.

Another concern is that healthcare providers less familiar with the pitfalls of ordering sIgE tests may order testing to foods other than peanut, even though the Guidelines specifically discourage this practice. A recent study determined that in an unselected population, food allergy panel testing had a positive predictive value of only 2.2% [7]. Similarly, many laboratories that process requisitions for peanut-sIgE automatically substitute a food 'mix' test. While a negative food 'mix' test would reasonably rule out clinically relevant peanut sensitization, a positive test does not identify which food from the mix to which an individual is sensitized and would result in testing for 5–6 additional foods. Each additional food yielding a positive result would necessitate further evaluation and potential delayed introduction.

Finally, care must be taken to ensure feeding infants first foods is not a medical act. An observational study found a low prevalence of peanut allergy in settings in which normal feeding practices included peanut among an infant's first solid foods [8]. As per the LEAP protocol, the Guidelines recommend that infants who tolerate peanut should continue to consume 6–7 grams over 3 servings each week. It is essential to make a distinction between what is feasible in a research setting and that which is practical and appropriate in the home setting.

How should one interpret the Guidelines and apply them to practice? Our recommendations include the following:

- The overwhelming majority of infants, including those with mild to moderate eczema, can introduce peanut early and at home without investigation.
- Early introduction of peanut is the primary goal as it is evident that there is an early window of opportunity for the development of tolerance.
- Peanut-specific IgE testing by non-allergist physicians should be considered for "at risk" infants only when a referral to an allergist is not available in a timely manner.
- Testing for foods beyond peanut, or the use of food panels, with specific IgE testing is strongly discouraged. Education of non-allergist physicians on the pitfalls of specific IgE testing is necessary in order to reduce harm.
- Subspecialty allergists have a duty to provide infants at high risk for peanut allergy timely access to consultation early in their first year of life, and to offer in clinic, observed first ingestion of peanut, when needed.

The increase in food allergy prevalence in recent decades is a public health problem and may in part be due to years of recommending delayed introduction of foods based on expert opinion only. We thank the authors of this Guideline for their collaboration in creating this timely document. Bearing in mind the issues discussed in this editorial, it is our hope that a strong message is heard that early introduction of peanut is the goal for most infants. First do no harm—and then feed peanut.

Addendum guidelines for the prevention of peanut allergy in the United States: report of the National Institute of Allergy and Infectious Diseases-sponsored expert panel

Abstract

Background: Food allergy is an important public health problem because it affects children and adults, can be severe and even life-threatening, and may be increasing in prevalence. Beginning in 2008, the National Institute of Allergy and Infectious Diseases, working with other organizations and advocacy groups, led the development of the first clinical guidelines for the diagnosis and management of food allergy. A recent landmark clinical trial and other emerging data suggest that peanut allergy can be prevented through introduction of peanut-containing foods beginning in infancy.

Objectives: Prompted by these findings, along with 25 professional organizations, federal agencies, and patient advocacy groups, the National Institute of Allergy and Infectious Diseases facilitated development of addendum guidelines to specifically address the prevention of peanut allergy.

Results: The addendum provides 3 separate guidelines for infants at various risk levels for the development of peanut allergy and is intended for use by a wide variety of health care providers. Topics addressed include the definition of risk categories, appropriate use of testing (specific IgE measurement, skin prick tests, and oral food challenges), and the timing and approaches for introduction of peanut-containing foods in the health care provider's office or at home. The addendum guidelines provide the background, rationale, and strength of evidence for each recommendation.

Conclusions: Guidelines have been developed for early introduction of peanut-containing foods into the diets of infants at various risk levels for peanut allergy.

Keywords: Food, Peanut, Allergy, Prevention, Guidelines

Background

Peanut allergy is a growing public health problem. In 1999, peanut allergy was estimated to affect 0.4% of children and 0.7% of adults in the United States [1], and by 2010, peanut allergy prevalence had increased to approximately 2% among children in a national survey [2], with similar results reported in a regional cohort [3]. Peanut allergy is the leading cause of death related to food-induced anaphylaxis in the United States [4, 5], and although overall mortality is low, the fear of life-threatening anaphylactic reactions contributes significantly to the medical and psychosocial burden of disease. In the majority of patients, peanut allergy begins early in life and persists as a lifelong problem. Therefore, cost-effective measures to prevent peanut allergy would have a high effect in terms of improving public health, reducing personal suffering, and decreasing health care use and costs.

The "Guidelines for the diagnosis and management of food allergy in the United States" [6] were published in December 2010 by an expert panel and a Coordinating Committee convened by the National Institute of Allergy and Infectious Diseases (NIAID). These guidelines did not offer strategies for the prevention of food allergy and particularly peanut allergy because of a lack of definitive studies at the time. The guidelines indicated that "insufficient evidence exists for delaying introduction of solid foods, including potentially allergenic foods, beyond 4–6 months of age, even in infants at risk of developing allergic disease." This statement differed from previous clinical practice guidelines in the United Kingdom [7] and United States, [8] which recommended the exclusion of allergenic foods from the diets of infants at high risk for allergy and is consistent with more recent recommendations regarding primary allergy prevention [9–12].

In February 2015, the New England Journal of Medicine published the results of the Learning Early about Peanut Allergy (LEAP) trial [13]. This trial was based on a prior observation [14] that the prevalence of peanut allergy was tenfold higher among Jewish children in the United Kingdom compared with Israeli children of similar ancestry. In Israel, peanut-containing foods are usually introduced in the diet when infants are approximately 7 months of age and consumed in substantial amounts, whereas in the United Kingdom children do not typically consume any peanut-containing foods during their first year of life. The LEAP trial randomized 640 children between 4 and 11 months of age with severe eczema, egg allergy, or both to consume or avoid peanut-containing foods until 60 months of age, at which time a peanut oral food challenge (OFC) was conducted to determine the prevalence of peanut allergy. LEAP trial participants were stratified at study entry into 2 separate study cohorts on the basis of pre-existing sensitization to peanut, as determined by means of skin prick testing: one cohort consisted of infants with no measureable skin test wheal to peanut (negative skin test response) and the other consisted of those with measurable wheal responses (1–4 mm in diameter). Infants with a 5 mm wheal diameter or greater were not randomized because the majority of infants at this level of sensitization were presumed to be allergic to peanut. Among the 530 participants in the intention-to-treat population with negative baseline skin test response to peanut, the prevalence of peanut allergy at 60 months of age was 13.7% in the peanut avoidance group and 1.9% in the peanut consumption group ($P < .001$; an 86.1% relative reduction in the prevalence of peanut allergy). Among the 98 participants with a measurable peanut skin test response at entry, the prevalence of peanut allergy was 35.3% in the avoidance group and 10.6% in the consumption group ($P = .004$; a 70% relative reduction in the prevalence of peanut allergy).

The LEAP trial was the first randomized trial to study early allergen introduction as a preventive strategy. Because of the size of the observed effect and the large number of study participants, its outcome received wide publicity in both the medical community and the press. This raised the need to operationalize the LEAP findings by developing clinical recommendations focusing on peanut allergy prevention. To achieve this goal and its wide implementation, the NIAID invited the members of the 2010 Guidelines Coordinating Committee and other stakeholder organizations to develop this addendum on peanut allergy prevention to the 2010 "Guidelines for the diagnosis and management of food allergy in the United States." Twenty-six stakeholder organizations participated in this 2015–2016 Coordinating Committee. Of note, unrelated to this effort, a consensus statement on behalf of 9 international professional societies regarding the implications and implementation of the LEAP trial findings was published as well [15].

Additional evidence on early introduction of allergenic foods comes from the LEAP-On study [16], which demonstrated the durability of oral tolerance to peanut achieved in the LEAP trial and the enquiring about tolerance study [17], which assessed the potential benefits of early introduction of 6 allergenic foods in a non–high-risk cohort.

Development of the 2017 addendum to the 2010 "Guidelines for the diagnosis and management of food allergy"

The process to develop the 2017 addendum closely followed that used in the 2010 guidelines [6].

Coordinating committee

The NIAID established a Coordinating Committee (CC), the members of which are listed in Appendix A, to oversee the development of the addendum; review drafts of the addendum for accuracy, practicality, clarity, and broad utility of the recommendations in clinical practice; review and approve the final addendum; and disseminate the addendum. The CC members represented 26 professional organizations, advocacy groups, and federal agencies.

Expert panel

The CC convened an expert panel (EP) in June 2015 that was chaired by Joshua Boyce, MD. The 26 panel members, listed in Appendix B, were specialists from a variety of relevant clinical, scientific, and public health areas. Panel members were nominated by the CC organizations, and the composition of the panel received unanimous approval by the CC member organizations.

The charge to the EP was to use the literature review prepared by the NIAID (see the next section) in conjunction with consensus expert opinion and EP-identified supplementary documents to (1) develop evidence-based recommendations for the early introduction of dietary peanut to prevent peanut allergy; (2) agree on principles for grading the evidence; (3) achieve consensus while allowing ample opportunity for consideration of divergent opinions; (4) determine whether the recommendations could extend beyond peanut to other food allergens; and (5) keep patient and societal interests at the forefront. The new recommendations are intended to supplement and modify guidelines 37 to 40 in Section 5.3.4 of the 2010 guidelines: "Prevention of food allergy."

Literature review

NIAID staff conducted a literature search of PubMed limited to the years 2010 (January) to 2016 (June). Using the following specific search terms ([food allergy or milk allergy or egg allergy or peanut allergy] OR [eczema or atopic dermatitis] AND prevention), PubMed returned more than 1500 articles. NIAID staff reviewed 1506 abstracts and assessed each for relevance to the topic of food allergy prevention with an emphasis on peanut allergy. Sixty-four publications (original research articles, editorials/letters, and systematic reviews) were deemed relevant and placed into 2 tiers: tier 1 contained 18 items considered highly relevant to the early introduction of peanut or other allergenic foods (see Appendix C), and tier 2 contained 46 items on related topics, such as food allergy or eczema prevention.

Assessing the quality of the body of evidence

For each of the 18 tier 1 references, the EP assessed quality by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [18]. GRADE provides a comprehensive and transparent methodology to develop recommendations for the diagnosis, treatment, and management of patients. In assessing the body of evidence of a group of relevant articles or of a single article, GRADE considers study design and other factors, such as the precision, consistency, and directness of the data. By using this approach, GRADE then provides a categorical assessment of the contribution of individual publications and the overall quality and strength of the body of evidence.

Each publication was assigned a grade according to the following criteria [19, 20]:

- High: further research is very unlikely to have an effect on the quality of the body of evidence, and therefore the confidence in the recommendation is high and unlikely to change.
- Moderate: further research is likely to have an effect on the quality of the body of evidence and may change the recommendation.
- Low: further research is very likely to have an important effect on the body of evidence and is likely to change the recommendation.

A GRADE designation of "low" for the quality of evidence does not imply that an article is not factually correct or lacks scientific merit. For example, a well-designed and executed single-site study of a treatment in a small cohort of highly selected subjects may still yield an overall GRADE rating of "low." This is because such a study is characterized as providing "sparse" data, and the patient population may not be representative of the at-risk population. Each of these factors reduces the level of evidence from "high," which is the initial designation for evidence from randomized controlled trials. It is worth emphasizing that these 2 limitations are not of the study per se but of the body of evidence.

Preparation of the draft addendum

The draft version of the addendum, prepared by the NIAID, contained 3 new guidelines and was reviewed, modified, and endorsed by the EP members. The EP-approved document was forwarded to the CC members for review.

Public comment period, addendum revision, and final approval

Concurrent with CC member review, the draft addendum was posted to the NIAID Web site in March 2016 for a period of 45 days to allow for public review and comment. One hundred four comments were received. All comments were reviewed by the EP and the CC, and

some contributed to the final revision of the addendum. The final addendum was reviewed and approved by the EP and the CC.

Dissemination of the addendum guidelines

The final addendum is published herein and available through the Internet.

Defining the strength of each clinical guideline

The EP has used the verb "recommends" or "suggests" for each clinical recommendation.

These words convey the strength of the recommendation, defined as follows:

- *Recommend* is used when the EP strongly recommended for or against a particular course of action.
- *Suggest* is used when the EP weakly recommended for or against a particular course of action.

Addendum guidelines

Table 1 provides a summary of the 3 addendum guidelines to be used as a quick reference.

The EP came to consensus on the following 3 definitions used throughout the addendum guidelines.

- *Severe eczema* is defined 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.
- *Egg allergy* is defined as a history of an allergic reaction to egg and a skin prick test (SPT) wheal diameter of 3 mm or greater with egg white extract, or a positive oral egg food challenge result.
- A *specialist* is defined as a health care provider with the training and experience to (1) perform and interpret SPTs and OFCs and (2) know and manage their risks. Such persons must have appropriate medications and equipment on site.

Addendum guideline 1

The EP recommends that infants with severe eczema, egg allergy, or both have introduction of age-appropriate peanut-containing food as early as 4–6 months of age to reduce the risk of peanut allergy. Other solid foods should be introduced before peanut-containing foods to show that the infant is developmentally ready. The EP recommends that evaluation with peanut-specific IgE (peanut sIgE) measurement, SPTs, or both be strongly considered before introduction of peanut to determine if peanut should be introduced and, if so, the preferred method of introduction. To minimize a delay in peanut introduction for children who may test negative, testing for peanut sIgE may be the preferred initial approach in certain health care settings, such as family medicine, paediatrics, or dermatology practices, in which skin prick testing is not routine. Alternatively, referral for assessment by a specialist may be an option if desired by the health care provider and when available in a timely manner.

Figure 1 provides recommended approaches for evaluation of children with severe eczema, egg allergy, or both before peanut introduction.

A peanut sIgE level of less than 0.35 kUA/L has strong negative predictive value for the diagnosis of peanut allergy [21]. Therefore, peanut sIgE testing may help in certain health care settings (eg, family medicine, paediatric, or dermatology practices, where skin prick testing is not routine) to reduce unnecessary referrals of children with severe eczema, egg allergy, or both and to minimize a delay in peanut introduction for children who may have negative test results. However, the EP emphasizes that a peanut sIgE level of 0.35 kUA/L or greater lacks adequate positive predictive value for the diagnosis of peanut allergy, and an infant with a value of 0.35 kUA/L or greater should be referred to a specialist.

Thus, peanut sIgE testing can place an infant into one of 2 categories (Fig. 1):

- sIgE Category A: If the peanut sIgE level is less than 0.35 kUA/L (ImmunoCAP), the EP recommends that peanut should be introduced in the diet soon thereafter, with a cumulative first dose of approximately 2 g

Table 1 Summary of addendum guidelines 1, 2, and 3

Addendum guideline	Infant criteria	Recommendations	Earliest age of peanut introduction
1	Severe eczema, egg allergy, or both	Strongly consider evaluation by sIgE measurement and/or SPT and, if necessary, an OFC. Based on test results, introduce peanut-containing foods	4–6 months
2	Mild-to-moderate eczema	Introduce peanut-containing foods	Around 6 months
3	No eczema or any food allergy	Introduce peanut-containing foods	Age appropriate and in accordance with family preferences and cultural practices

of peanut protein given in this feeding. This can be given as a feeding at home (Appendix D), considering the low likelihood of a severe allergic reaction. If the caregiver or health care provider has concerns, a supervised feeding can be offered at the health care provider's office (Appendix E).

- sIgE Category B: If the peanut sIgE level is 0.35 kUA/L or greater (ImmunoCAP), the EP recommends that the child be referred to a specialist for further consultation and possible skin prick testing.

The EP does not recommend food allergen panel testing or the addition of sIgE testing for foods other than peanut because of their poor positive predictive value, which could lead to misinterpretation, overdiagnosis of food allergy, and unnecessary dietary restrictions [6].

SPTs with peanut extract can place an infant in one of 3 categories (Fig. 1):

- SPT Category A: If an SPT to peanut extract produces a wheal diameter of 2 mm or less above saline control, the EP recommends that peanut be introduced in the diet soon after testing, with a cumulative first dose of approximately 2 g of peanut protein given in this feeding. This can be given at home (Appendix D), considering the low likelihood of a severe allergic reaction. If the caregiver or health care provider has concerns, a supervised feeding can be offered at the health care provider's office (Appendix E).
- SPT Category B: If an SPT to peanut extract produces a wheal diameter of 3 to 7 mm greater than

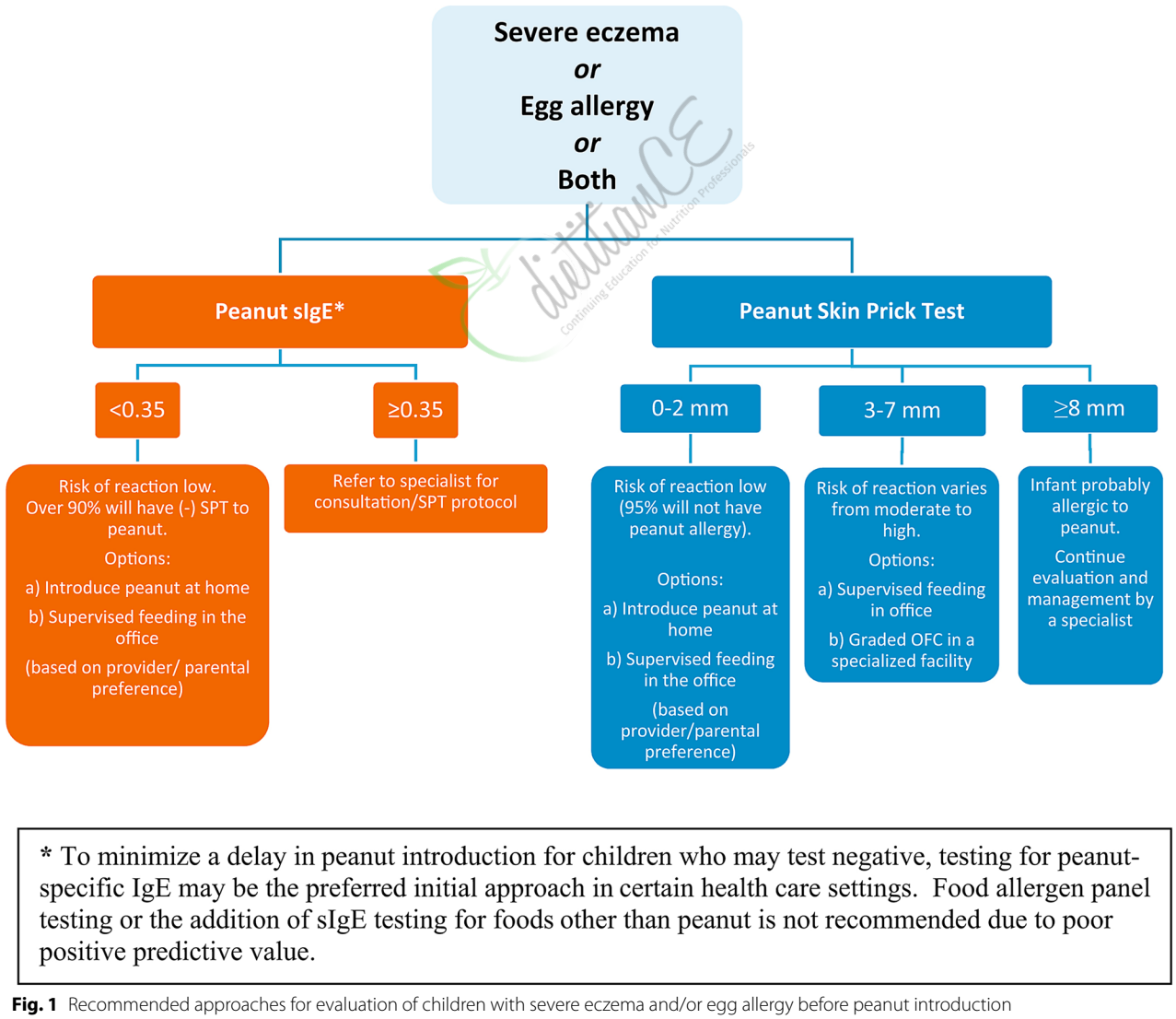

Fig. 1 Recommended approaches for evaluation of children with severe eczema and/or egg allergy before peanut introduction

that elicited by the saline control, the EP suggests that a supervised peanut feeding or a graded OFC be undertaken at a specialist's office or a specialized facility (see Appendices E and G, respectively). Infants in this category can be sensitized without being allergic to peanut and might benefit from early peanut consumption. If the supervised peanut feeding or graded OFC yields no reaction, the EP recommends that peanut should be added to the child's diet. If the supervised peanut feeding or the graded OFC results in an allergic reaction, the EP recommends that the child should strictly avoid dietary peanut and the family should be counselled regarding food allergy management.

- SPT Category C: If an SPT produces a wheal diameter 8 mm or greater than that elicited by the saline control, the likelihood of peanut allergy is high. Children in this category should continue to be evaluated and managed by a specialist [21–23].

Box 1 Important considerations for skin prick testing

SPT reagents, testing devices, and methodology can differ significantly among health care providers in the United States or elsewhere.22 The EP recommends that specialists adjust their SPT categorization criteria according to their own training and experience.

Health care providers conducting OFCs in infants with 3 mm or greater SPT responses should be aware that the probability of a positive challenge response increases with wheal size. These data come from the HealthNuts Study in children 12 to 18 months of age; of note, the severity of these reactions was relatively mild [21, 23].

How much dietary peanut protein to introduce

If the decision is made to introduce dietary peanut based on the recommendations of addendum guideline 1, the total amount of peanut protein to be regularly consumed per week should be approximately 6 to 7 g over 3 or more feedings (see Appendix F). In the LEAP trial, at evaluations conducted at 12 and 30 months of age, 75% of children in the peanut consumption group reported eating at least this amount of peanut, based on analysis of a 3-day food diary recorded just before the evaluation.

Rationale

Infants with severe eczema, egg allergy, or both are at high risk for the development of peanut allergy. Significant evidence on this group is available from the infants who participated in the LEAP trial or were screened for the LEAP trial but were not enrolled because of a large SPT response (>4 mm). At 60 months of age, approximately 23% of peanut avoiders and those infants not enrolled had food allergy [24].

Balance of benefits and harms

In the LEAP trial, among the 530 participants in the intention-to-treat population with negative baseline SPT responses to peanut, 13.7% of the avoidance group and 1.9% of the consumption group had peanut allergy at 60 months of age ($P < .001$; a 12.6% absolute risk reduction and an 86.1% relative risk reduction in the prevalence of peanut allergy, resulting in a number needed to treat of 8.5 [number of infants needed to have early introduction of peanut to prevent peanut allergy in one child]). Among the 98 participants with positive peanut SPT responses at entry, 35.3% of the avoidance group and 10.6% of the consumption group had peanut allergy at 60 months of age ($P = .004$; a 24.7% absolute risk reduction and a 70% relative risk reduction in the prevalence of peanut allergy, resulting in a number needed to treat of 4).

The LEAP-on study [24] demonstrated that the benefits achieved in the LEAP trial persisted when LEAP trial peanut consumers subsequently avoided peanut for 1 year from 60 to 72 months of age. This indicates that the oral tolerance achieved in the LEAP trial was durable.

The LEAP trial did not include infants with SPT wheals greater than 4 mm, and therefore no data are available on the potential effectiveness of peanut consumption in preventing peanut allergy in this group. However, EP members believe it is possible that some of these infants may benefit from early introduction of peanut provided that they tolerate oral peanut.

As shown in Fig. 1, the EP recommends that infants with severe eczema, egg allergy, or both, with peanut sIgE levels of less than 0.35 kUA/L or with a peanut SPT wheal of 2 mm or less have dietary peanut introduced as early as 4–6 months of age without a need for further evaluation. This recommendation is supported by expert opinion and analysis of the LEAP population findings. In the LEAP trial, infants consuming peanut in this post hoc defined category had a relative risk reduction of 79% of having peanut allergy at 60 months of age compared with infants who avoided peanut.

In the LEAP trial, at study entry, all infants randomly assigned to the consuming group had a baseline peanut OFC. Of the 272 infants with no wheal induced by peanut SPT and who received a baseline oral peanut challenge, only 1 had a reaction presenting as an erythematous urticarial rash that was graded as a "moderate" adverse event and was treated successfully with chlorpheniramine. Among the 29 infants with a wheal diameter of 1–2 mm who received a baseline oral peanut challenge, 2 had reactions, which also presented with mild symptoms not requiring treatment with epinephrine. Therefore, for the SPT Category A children, the risk of a severe reaction to peanut at first introduction is low, and introduction of peanut at home is an option. However, it is understandable that some caregivers of infants with severe eczema, egg allergy, or both may be uncomfortable introducing

dietary peanut at home. In such cases the health care provider should offer the option of a supervised feeding of a peanut-containing food in the office.

The rate of positive peanut OFC results at baseline for infants with a 3–4 mm wheal diameter (4/17 infants) was higher than in infants with 0 to 2 mm wheal diameters (3/301 infants), but the elicited symptoms were mild. Infants with larger wheal diameters (>4 mm) were not included in the LEAP trial, and therefore no safety data are available from this group. However, based on the Australian HealthNuts study, which conducted peanut OFCs in a large number of older (12–18 months old) children from the general Australian population, the rate of reactions to peanut is expected to be substantially higher with increasing SPT wheal diameter [21, 23]. In the HealthNuts study [23] an SPT wheal diameter of 8 mm or greater had a 95% positive predictive value for peanut allergy (positive oral peanut challenge result). Therefore, the EP recommends that for SPT Category B infants (3–7 mm SPT wheal diameter), a supervised feeding or a graded peanut OFC should be conducted in a specialist's office or a specialized facility (Appendix G). SPT Category C infants are considered high risk for established allergy to peanut and should not receive peanut-containing foods in their diet, unless such foods are recommended by a specialist after further evaluation.

Quality of evidence: moderate

The designation of the quality of evidence as "moderate" (as opposed to "high") is based on the fact that this recommendation derives primarily from a single randomized, open-label study: the LEAP trial. However, it should be noted that the assessment of the LEAP trial's primary outcome was based on a double-blind, placebo-controlled OFC. Furthermore, confidence in this recommendation is bolstered by the large effect size demonstrated in the LEAP trial and prior epidemiologic data that peanut allergy is relatively infrequent in Israel, where early childhood consumption of peanut is common.

Contribution of expert opinion

Significant.

Additional comments

1. Breast-feeding recommendations: the EP recognizes that early introduction of peanut may seem to depart from recommendations for exclusive breast-feeding through 6 months of age [25, 26]. However, it should be noted that data from the nutrition analysis of the LEAP cohort [27] indicate that introduction of peanut did not affect the duration or frequency of breast-feeding and did not influence growth or nutrition.
2. Age of peanut introduction: for children with severe eczema, egg allergy, or both, the EP recommends that introduction of solid foods begins at 4–6 months of age, starting with solid food other than peanut, so that the child can demonstrate the ability to consume solid food without evidence of nonspecific signs and symptoms that could be confused with IgE-mediated food allergy. However, it is important to note that infants in the LEAP trial were enrolled between 4 and 11 months of age and benefitted from peanut consumption regardless of age at entry. Therefore, if the 4- to 6-month time window is missed for any reason, including developmental delay, infants may still benefit from early peanut introduction. On the other hand, older age at screening is associated with larger wheal diameters induced by peanut SPT and hence a higher likelihood of established peanut allergy [28].
   A practical consideration for applying this guideline at 4–6 months of age is that infants visit their health care provider for well-child evaluations and infant immunizations at this time. This provides a fortuitous opportunity for eczema evaluation, caregiver reporting of egg allergy, and, if needed, referral to a specialist for peanut allergy evaluation before dietary introduction of peanut.
3. Considerations for family members with established peanut allergy: the EP recognizes that many infants eligible for early peanut introduction under this guideline will have older siblings or caregivers with established peanut allergy. The EP recommends that in this situation caregivers discuss with their health care providers the overall benefit (reduced risk of peanut allergy in the infant) versus risk (potential for further sensitization and accidental exposure of the family member to peanut) of adding peanut to the infant's diet.
4. Children identified as allergic to peanut: for children who have been identified as allergic to peanut, the EP recommends strict peanut avoidance. This may include those children in SPT Category B who fail the supervised peanut feeding or the OFC, or those children in SPT Category C who, on further evaluation by a specialist, are confirmed as being allergic to peanut. These children should be under long-term management by a specialist.

Addendum guideline 2

The EP suggests that infants with mild-to-moderate eczema should have introduction of age-appropriate peanut-containing food around 6 months of age, in accordance with family preferences and cultural practices, to reduce the risk of peanut allergy. Other

solid foods should be introduced before peanut-containing foods to show that the infant is developmentally ready. The EP recommends that infants in this category may have dietary peanut introduced at home without an in-office evaluation. However, the EP recognizes that some caregivers and health care providers may desire an in-office supervised feeding, evaluation, or both.

Rationale

The LEAP trial did not target infants with mild or moderate eczema. The EP considered the potential risk/benefit ratio of early dietary peanut introduction in infants with mild-to-moderate eczema and concluded that the individual and societal benefits of introducing peanut in this population would be significant. The EP has no reason to believe that the mechanisms of protection of early dietary peanut differ in infants with mild-to-moderate eczema from those that lead to protection in infants at higher risk of peanut allergy.

Balance of benefits and harms

The LEAP trial included only infants with severe eczema or egg allergy based on careful medical history. Therefore, some infants who participated in the LEAP trial based on the presence of egg allergy had atopic dermatitis severity scores (SCORAD scores [29]) at screening that would have placed them in the moderate or mild eczema category. The EP considered the outcomes of these children and concluded that infants with mild-to-moderate eczema would likely benefit from early peanut introduction.

Quality of evidence

Low.

The quality of evidence is low because this recommendation is based on extrapolation of data from a single study.

Contribution of expert opinion

Significant.

Additional comment

Additional support for early introduction of peanut in infants who do not have severe eczema comes from the Enquiring About Tolerance study [17], which enrolled infants from the general population at 3 months of age and sequentially introduced 6 allergenic foods beginning at the time of enrolment. These children were not intentionally selected based on increased risk of food allergy or atopy. Although the intention-to-treat group did not show benefit, most likely because of relatively poor compliance with feeding recommendations, the children in the per-protocol group who had peanut introduced early in infancy showed a significant reduction in peanut sensitization and peanut allergy at age 3 years. This study also provides support for guideline 3 below.

Addendum guideline 3

The EP suggests that infants without eczema or any food allergy have age-appropriate peanut-containing foods freely introduced in the diet together with other solid foods and in accordance with family preferences and cultural practices.

Rationale

No evidence exists for restricting allergenic foods in infants without known risks for food allergy. The probability for development of peanut allergy in such children is very low. However, approximately 14% of all children with peanut allergy at age 12–18 months in the Health-Nuts Study lacked known risk factors for food allergy [16]. Consequently, because such children constitute a significant majority of any birth cohort, they contribute substantially to the overall societal burden of peanut allergy. The EP finds no evidence to suggest that mechanisms of oral tolerance induction would differ in these infants from the immunologic mechanisms that are protective in infants at higher risk of peanut allergy. Thus, the early introduction of dietary peanut in children without risk factors for peanut allergy is generally anticipated to be safe and to contribute modestly to an overall reduction in the prevalence of peanut allergy. Furthermore, in countries such as Israel, where peanut products are a popular component of the diet and where they are introduced early in life, the prevalence of peanut allergy is low [14].

Balance of benefits and harms

The EP acknowledges that any analysis of benefit and harm in this population relies primarily on expert opinion and is subject to current differences in regional/societal rates of peanut consumption and peanut sensitization. In countries where peanut products are not widely consumed by adults, early dietary introduction of peanut could lead to an increase in sensitization and allergic manifestations. Hence the EP cautions that this guideline be implemented in the context of societal routines/norms.

Quality of evidence

Low.

Contribution of expert opinion

Significant.

Box 2 Clinical implications

These guidelines will help health care providers with early introduction of peanut-containing foods in infants at various risk levels for peanut allergy. Early introduction of peanut will result in the prevention of peanut allergy in a large number of infants.

Abbreviations

CC: Coordinating Committee; EP: expert panel; GRADE: Grading of Recommendations Assessment, Development and Evaluation; LEAP: Learning Early about Peanut Allergy; NIAID: National Institute of Allergy and Infectious Diseases; OFC: oral food challenge; sIgE: specific IgE; SPT: skin prick test.

Appendix D. Instructions for home feeding of peanut protein for infants at low risk of an allergic reaction to peanut

These instructions for home feeding of peanut protein are provided by your doctor. You should discuss any questions that you have with your doctor before starting. These instructions are meant for feeding infants who have severe eczema or egg allergy and were allergy tested (blood test, skin test, or both) with results that your doctor considers safe for you to introduce peanut protein at home (low risk of allergy).

General instructions

1. Feed your infant only when he or she is healthy; do not do the feeding if he or she has a cold, vomiting, diarrhea, or other illness.
2. Give the first peanut feeding at home and not at a day care facility or restaurant.
3. Make sure at least 1 adult will be able to focus all of his or her attention on the infant, without distractions from other children or household activities.
4. Make sure that you will be able to spend at least 2 h with your infant after the feeding to watch for any signs of an allergic reaction.

Feeding your infant

1. Prepare a full portion of one of the peanut-containing foods from the recipe options below.
2. Offer your infant a small part of the peanut serving on the tip of a spoon.
3. Wait 10 min.
4. If there is no allergic reaction after this small taste, then slowly give the remainder of the peanut-containing food at the infant's usual eating speed.

What are symptoms of an allergic reaction? What should I look for?

- Mild symptoms can include:
  - a new rash
    or
  - a few hives around the mouth or face
- More severe symptoms can include any of the following alone or in combination:
  - lip swelling
  - vomiting
  - widespread hives (welts) over the body
  - face or tongue swelling
  - any difficulty breathing
  - wheeze
  - repetitive coughing
  - change in skin color (pale, blue)
  - sudden tiredness/lethargy/seeming limp

If you have any concerns about your infant's response to peanut, seek immediate medical attention/call 911.

Four recipe options, each containing approximately 2 g of peanut protein

Note: Teaspoons and tablespoons are US measures (5 and 15 mL for a level teaspoon or tablespoon, respectively).

Option 1: Bamba (Osem, Israel), 21 pieces (approximately 2 g of peanut protein)

Note: Bamba is named because it was the product used in the LEAP trial and therefore has proven efficacy and safety. Other peanut puff products with similar peanut protein content can be substituted.

a. For infants less than 7 months of age, soften the Bamba with 4 to 6 teaspoons of water.
b. For older infants who can manage dissolvable textures, unmodified Bamba can be fed. If dissolvable textures are not yet part of the infant's diet, softened Bamba should be provided.

Option 2: Thinned smooth peanut butter, 2 teaspoons (9–10 g of peanut butter; approximately 2 g of peanut protein)

a. Measure 2 teaspoons of peanut butter and slowly add 2 to 3 teaspoons of hot water.
b. Stir until peanut butter is dissolved, thinned, and well blended.
c. Let cool.
d. Increase water amount if necessary (or add previously tolerated infant cereal) to achieve consistency comfortable for the infant.

Option 3: Smooth peanut butter puree, 2 teaspoons (9–10 g of peanut butter; approximately 2 g of peanut protein)

a. Measure 2 teaspoons of peanut butter.
b. Add 2 to 3 tablespoons of previously tolerated pureed fruit or vegetables to peanut butter. You can increase or reduce volume of puree to achieve desired consistency.

Option 4: Peanut flour and peanut butter powder, 2 teaspoons (4 g of peanut flour or 4 g of peanut butter powder; approximately 2 g of peanut protein)

Note: Peanut flour and peanut butter powder are 2 distinct products that can be interchanged because they have, on average, a similar peanut protein content.

a. Measure 2 teaspoons of peanut flour or peanut butter powder.
b. Add approximately 2 tablespoons (6–7 teaspoons) of pureed tolerated fruit or vegetables to flour or powder. You can increase or reduce the volume of puree to achieve desired consistency.

Appendix E. For health care providers: In-office supervised feeding protocol using 2 g of peanut protein

General instructions

1. These recommendations are reserved for an infant defined in guideline 1 as one with severe eczema, egg allergy, or both and with negative or minimally reactive (1 to 2 mm) SPT responses and/or peanut sIgE levels of less than 0.35 kU_A/L. They also may apply to the infant with a 3 to 7 mm SPT response if the specialist health care provider decides to conduct a supervised feeding in the office (as opposed to a graded OFC in a specialized facility [see Fig. 1]).
   These recommendations can also be followed for infants with mild-to-moderate eczema, as defined in guideline 2, when caregivers and health care providers may desire an in-office supervised feeding.
2. Proceed only if the infant shows no evidence of any concomitant illness, such as an upper respiratory tract infection.

a. Start with a small portion of the initial peanut serving, such as the tip of a teaspoon of peanut butter puree/softened Bamba.
b. Wait 10 minutes; if there is no sign of reaction after this small portion is given, continue gradually feeding the remaining serving of peanut-containing food (see options below) at the infant's typical feeding pace.
c. Observe the infant for 30 minutes after 2 g of peanut protein ingestion for signs/symptoms of an allergic reaction.

Four recipe options, each containing approximately 2 g of peanut protein

Note: Teaspoons and tablespoons are US measures (5 and 15 mL for a level teaspoon or tablespoon, respectively).

Option 1: Bamba (Osem, Israel), 21 pieces (approximately 2 g of peanut protein)

Note: Bamba is named because it was the product used in the LEAP trial and therefore has known peanut protein content and proven efficacy and safety. Other peanut puffs products with similar peanut protein content can be substituted for Bamba.

a. For infants less than 7 months of age, soften the Bamba with 4 to 6 teaspoons of water.
b. For older infants who can manage dissolvable textures, unmodified Bamba can be fed. If dissolvable textures are not yet part of the infant's diet, softened Bamba should be provided.

Option 2: Thinned smooth peanut butter, 2 teaspoons (9–10 g of peanut butter; approximately 2 g of peanut protein)

a. Measure 2 teaspoons of peanut butter and slowly add 2 to 3 teaspoons hot water.
b. Stir until peanut butter is dissolved and thinned and well blended.
c. Let cool.

d. Increase water amount if necessary (or add previously tolerated infant cereal) to achieve consistency comfortable for the infant.

Option 3: Smooth peanut butter puree, 2 teaspoons (9–10 g of peanut butter; approximately 2 g of peanut protein)

a. Measure 2 teaspoons of peanut butter.
b. Add 2 to 3 tablespoons of previously tolerated pureed fruit or vegetables to peanut butter. You can increase or reduce volume of puree to achieve desired consistency.

Option 4: Peanut flour and peanut butter powder, 2 teaspoons (4 g of peanut flour or 4 g of peanut butter powder; approximately 2 g of peanut protein)

Note: Peanut flour and peanut butter powder are 2 distinct products that can be interchanged because they have, on average, a similar peanut protein content.

a. Measure 2 teaspoons of peanut flour or peanut butter powder.
b. Add approximately 2 tablespoons (6–7 teaspoons) of pureed tolerated fruit or vegetables to flour or powder. You can increase or reduce the volume of puree to achieve desired consistency.

Appendix F. Peanut protein in peanut-containing foods

If the decision is made to introduce dietary peanut to the infant's diet, the total amount of peanut protein to be regularly consumed per week should be approximately 6 to 7 g over 3 or more feedings. In the LEAP trial, at evaluations conducted at 12 and 24 months of age, 75% of children in the peanut consumption group reported eating at least this amount of peanut.

Be aware of choking risks

- Whole nuts should not be given to children less than 5 years of age.
- Peanut butter directly from a spoon or in lumps/dollops should not be given to children less than 4 years of age.

If, after a week or more eating peanut, your infant or child displays mild allergic symptoms within 2 h of eating peanut, you should contact your health care provider.

Typical peanut-containing foods, their peanut protein content, and feeding tips for infants are provided in Table 2, and their nutritional content is found in Table 3.

Appendix G. Graded OFC protocol

From "Conducting an oral food challenge to peanut in an infant: a work group report" [30].

General instructions

1. A graded OFC should be performed only by a specialist with the training and experience to (1) perform and interpret skin prick testing and OFCs and (2) know and manage their risks. Such persons must have appropriate medications and equipment on site.
2. Four peanut preparations are provided:

   a. *Option 1*: Smooth peanut butter mixed with either a previously tolerated pureed fruit or vegetable.
   b. *Option 2*: Smooth peanut butter dissolved carefully with hot water and cooled.
   c. *Option 3*: Peanut flour mixed with either a previously tolerated pureed fruit or vegetable. Peanut butter powder can be used instead of the peanut flour.
   d. *Option 4*: Bamba peanut snack dissolved in hot water and cooled or even as a solid (ie, as a stick).
   Note: Bamba (Osem, Israel) is named because it was the product used in the LEAP trial and therefore has known peanut protein content and proven efficacy and safety. Other peanut puff products with similar peanut protein content can be substituted for Bamba.
3. The peanut protein content of the graded OFC protocol is identical for all peanut preparations provided below, except that the volume of food ingested per dose is different. The protocol consists of 5 incremental doses, given 15 to 20 min apart, with a cumulative peanut protein total of approximately 4 g per the 3.9 g total in the LEAP trial.
4. Refer to Table 4 and direct parents to discontinue specific medications for the prescribed amount of time before the graded OFC. Note that certain medications are allowed.

Be prepared in case of a severe reaction (see Table 5)

Note: Teaspoons and tablespoons are US measures (5 and 15 mL for a level teaspoon or tablespoon, respectively).

Protocol instructions for options 1, 2, and 3 (see Tables 6, 7, and 8)

1. Measure peanut butter, peanut flour, or peanut butter powder for dose 1.
2. Prepare the first dose:

Table 2 Typical peanut-containing foods, their peanut protein content, and feeding tips for infants

	Bamba	Peanut butter	Peanuts	Peanut flour or peanut butter powder
Amount containing approximately 2 g of peanut protein	17 g *or* % of a 28-g (1-oz) bag *or* 21 sticks	9–10 g *or* 2 teaspoons	8 g *or* ~10 whole peanuts (2½ teaspoons of grounded peanuts)	4 g *or* 2 teaspoons
Typical serving size	1 bag (28 g)	Spread on a slice of bread or toast (16 g)	2½ teaspoons of ground peanuts (8 g)	No typical serving size
Peanut protein per typical serving	3.2 g	3.4 g	2.1 g	No typical serving size
Feeding tips	For a smooth texture, mix with warm water (then let cool) or breast milk or infant formula and mash well Pureed or mashed fruit or vegetables can be added Older children can be offered sticks of Bamba	For a smooth texture, mix with warm water (then let cool) or breast milk or infant formula For older children, mix with pureed or mashed fruit or vegetables or any suitable family foods, such as yogurt or mashed potatoes	Use blender to create a powder or paste 2-2½ teaspoons of ground peanuts can be added to a portion of yogurt or pureed fruit or savory meal	Mix with yogurt or apple sauce

Bamba (Osem, Israel) is named because it was the product used in the LEAP trial and therefore has known peanut protein content and proven efficacy and safety. Other peanut puff products with similar peanut protein content can be substituted for Bamba

Teaspoons and tablespoons are US measures (5 and 15 mL for a level teaspoon or tablespoon, respectively)

Table 3 Nutritional content of peanut-containing foods

Per approximately 2 g of peanut protein	Bamba[a] (17 g)	Peanut butter (10 g)	Peanuts (8 g)	Peanut butter powder (4 g)	Peanut flour (4 g)
kcal	93	59	45	15	13
Sugar (g)	0.4	0.65	0.38	0.4	0.33
Salt (mg)	68	48	1	31	7
Fat (g)	6.1	4.95	3.94	0.49	0.02

[a] The nutritional content of peanut puff products (other than Bamba) can be obtained from their manufacturers

Table 4 Medication discontinuation considerations before OFC

Medications to be discontinued	Last dose before OFC
Cetirizine	5 days
Cyproheptadine	10 days
Diphenhydramine	3 days
Fexofenadine	3 days
Loratadine	7 days
Short-acting bronchodilator (eg, albuterol)	8 h
Medications that can be continued	
Antihistamine eye drops	
Inhaled/intranasal corticosteroids	
Topical (cutaneous) steroids	
Topical (cutaneous) pimecrolimus, tacrolimus	

a. If using option 1, add previously tolerated pureed fruit or vegetable to measured dose 1 peanut butter and stir until well blended. You can increase or reduce volume of puree to achieve desired consistency. *Note*: Increasing the volume may increase the difficulty of getting through the entire protocol with a young baby.
b. If using option 2, slowly add hot water to measured dose 1 peanut butter and stir until peanut butter is dissolved, thinned, and well blended. Let the mixture cool. You can increase water volume (or add previously tolerated infant cereal) to achieve desired consistency.
c. If using option 3, add previously tolerated pureed fruit or vegetable to measured dose 1 peanut flour or peanut butter powder and stir until well blended. You can increase or reduce volume of puree to achieve desired consistency. *Note*: Increasing the volume may increase the difficulty of getting through entire protocol with a young baby.

3. Label dose 1.
4. Repeat steps 1 to 3 for the remaining doses 2 through 5, labeling each dose appropriately and before proceeding to the preparation of the next dose.

Table 5 Emergency medications for a severe reaction during an office-based infant OFC

	Medication	Dose
First-line treatment	Epinephrine (1:1000 concentration)	0.01 mg/kg IM in the mid-outer thigh in health care settings *or* 0.15 mg of autoinjector IM in the mid-outer thigh in community settings Epinephrine doses may need to be repeated every 5-15 min
Adjunctive treatment	Albuterol nebulization	0.15 mg/kg every 20 min × 3 doses (minimum of 2.5 mg per dose) over 5-15 min
	Albuterol MDI inhalation	2 puffs, 90 µg per puff, with face mask
	Oxygen	8-10 L/min through a face mask
	Diphenhydramine	1.25 mg/kg administered orally
	Cetirizine	2.5 mg administered orally
	Normal saline (0.9% isotonic solution) or lactated ringers	20 ml/kg per dose administered over 5 min intravenously
	Steroids	Prednisolone 1 mg/kg administered orally *or* Solu-Medrol 1 mg/kg administered intravenously

Table 6 Option 1: Measures for smooth peanut butter puree

Dose	Peanut butter volume[a]	Equivalent weight of peanut butter (g [peanut protein content in grams])[b]	Pureed fruit or vegetable volume	Total volume
1	1/8 teaspoon	0.67 (0.15)	1/2 teaspoon	5/8 teaspoon
2	1/4 teaspoon	1.33 (0.29)	3/4 teaspoon	1 teaspoons
3	1/2 teaspoon	2.67 (0.59)	1 teaspoons	1 1/2 teaspoons
4	1 teaspoon	5.33 (1.17)	2 teaspoons	3 teaspoons[c]
5	1 1/2 teaspoons	8 (1.6)	4 teaspoons	5 1/2 teaspoons
		Total protein: 3.96 g		

[a] Amounts (volume) of peanut butter measured as teaspoons are approximate measures to keep the dosing as practical as possible

[b] Peanut protein content is calculated on the average amount of protein for a range of butters using "Report: 16167, USDA Commodity, Peanut Butter, smooth," from the USDA Nutrition Database (http://ndb.nal.usda.gov/ndb/foods)

[c] Three teaspoons = 1 tablespoon

Table 7 Option 2: Measures for smooth thinned peanut butter

Dose	Peanut butter volume[a]	Equivalent weight peanut butter (g [peanut protein content in grams])[b]	Volume of hot water	Total volume
1	1/8 teaspoon	0.67 (0.15)	1/8 teaspoon	1/4 teaspoon
2	1/4 teaspoon	1.33 (0.29)	1/4 teaspoon	1/2 teaspoon
3	1/2 teaspoon	2.67 (0.59)	1/2 teaspoon	1 teaspoon
4	1 teaspoon	5.33 (1.17)	1 teaspoon	2 teaspoons
5	1 1/2 teaspoons	8 (1.76)	1 1/2 teaspoons	3 teaspoons[c]
		Total protein: 3.96 g		

[a] Amounts (volume) of peanut butter measured as teaspoons are approximate measures to keep the dosing as practical as possible

[b] Peanut protein content is calculated on the average amount of protein for a range of butters using "Report: 16167, USDA Commodity, Peanut Butter, smooth," from the USDA Nutrition Database (http://ndb.nal.usda.gov/ndb/foods)

[c] Three teaspoons = 1 tablespoon

Table 8 Option 3: Measures for peanut flour or peanut butter powder

Dose	Peanut flour or peanut butter powder volume[a]	Equivalent weight peanut flour or peanut butter powder[b] (g [peanut protein content in grams])	Pureed fruit or vegetable volume	Total volume
1	1/8 teaspoon	0.25 (0.13)	1/2 teaspoon	3/4 teaspoon
2	1/4 teaspoon	0.5 (0.25)	1 teaspoon	1 1/4 teaspoons
3	1/2 teaspoon	1.0 (0.5)	2 teaspoons	2 1/2 teaspoons
4	1 teaspoon	2.0 (1.0)	3 teaspoons[c]	4 teaspoons
5	2 teaspoons	4.0 (2.0)	6 teaspoons[d]	8 teaspoons
		Total protein: 3.88 g		

[a] Amounts (volume) of peanut flour or peanut butter powder measured as teaspoons are approximate measures to keep the dosing as practical as possible

[b] Information regarding peanut powder and flour reflects averages obtained from the producers. Most brands of peanut flour/peanut butter powder are approximately 50% peanut protein by weight. However, weight can vary based on the fat content and also the brand chosen. Therefore a weight measurement can be more accurate than household measurements

[c] Three teaspoons = 1 tablespoon

[d] Six teaspoons = 2 tablespoons

Table 9 Option 4: Bamba peanut snack (Osem, Israel)

Dose	Bamba, no. of sticks	Equivalent weight (peanut protein content [g])[a]	Volume of hot water (approximate, will need to be adjusted for each child)	Approximate final volume
1	1 stick	0.81 (0.1)	½ teaspoon	¾ teaspoons
2	3 sticks	2.43 (0.3)	1 teaspoon	1½ teaspoons
3	5 sticks	4.05 (0.5)	1½ teaspoons	2¼ teaspoons
4	10 sticks	8.1 (1.0)	3 teaspoons	4 teaspoons
5	21 sticks	17.01 (2.0)	6 teaspoons	7½ teaspoons
		Total protein: 3.9 g		

Other peanut puffs products with equivalent peanut protein content can be substituted for Bamba

[a] The amount of Bamba sticks is an approximate measure looking at a range of Bamba products. Bamba snacks from different parts of the world have a varied peanut protein content [30]. The peanut protein content of Bamba was calculated according to the publication by Du Toit et al. [13]

5. Feed dose 1 to infant and observe for symptoms of reactivity for 15 to 20 min.
6. If no symptoms appear, repeat with dose 2 and observe for 15 to 20 min.
7. Continue in this manner with doses 3, 4, and 5.

Protocol instructions for option 4 (see Table 9)

1. Count Bamba sticks for dose 1.
2. Prepare the first dose by slowly adding hot water to measured Bamba and stirring until Bamba is dissolved, thinned, well blended, and cooled. You can increase water volume to achieve desired consistency. *Note*: Increasing the volume may increase the difficulty of getting through the entire protocol with a young baby.
3. Label dose 1.
4. Repeat steps 1 to 3 for the remaining doses 2 through 5, labeling each dose appropriately and before proceeding to the preparation of the next dose.
5. Feed dose 1 to the infant and observe for symptoms of reactivity for 15 to 20 min.
6. If no symptoms appear, repeat with dose 2 and observe for 15 to 20 min.
7. Continue in this manner with doses 3, 4, and 5.

Consensus communication on early peanut introduction and the prevention of peanut allergy in high-risk infants

Abstract

The purpose of this brief communication is to highlight emerging evidence to existing guidelines regarding potential benefits of supporting early, rather than delayed, peanut introduction during the period of complementary food ntroduction in infants. This document should be considered as interim guidance based on consensus among the following organizations: American Academy of Allergy, Asthma & Immunology; American Academy of Pediatrics; American College of Allergy, Asthma & 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. 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 – sponsored Working Group and the European Academy of Allergy and Clinical Immunology.

Keywords: Allergy prevention, Complementary feeding, Peanut allergy

Introduction and rationale

Peanut allergy is an increasingly troubling global health problem affecting between 1 % and 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- to 15-year period, suggesting that the prevalence might have tripled in some countries, such as the United States. Extrapolating the currently estimated prevalence, this translates to nearly 100,000 new cases annually (in the United States and United Kingdom), affecting some 1 in 50 primary school-aged children in the United States, Canada, the United Kingdom, 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 for existing allergy prevention guidelines regarding potential benefits of supporting early rather than delayed peanut introduction during the period of complementary food introduction in infants. A recent study, entitled "Randomized trial of peanut consumption in infants at risk for peanut allergy" demonstrated a successful 11 % to 25 % absolute reduction in the risk of 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 Learning Early About Peanut Allergy (LEAP) trial, 640 high-risk United Kingdom infants (See Box 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 g peanuts or 3 teaspoons of peanut butter per week) or to completely avoid peanut products for the first 5 years of life. This included 542 infants found to have negative skin prick test (SPT) responses to peanut at study entry, and 98 infants with SPT wheal diameters to peanut of between 1 and 4 mm (minimally positive SPT response) at study entry. An additional 76 children were excluded from study entry before randomization based on an SPT response of greater than 5 mm, which was assumed to result in a very high likelihood of reacting to a peanut challenge. In an intention-to-treat analysis, 17.2 % in the peanut avoidance group compared to 3.2 % in the peanut consumption group had food challenge-proved peanut allergy by age 5 years, corresponding to a 14 % absolute risk reduction, a number needed to treat (NNT, eg, number of persons needed to be treated for one to receive benefit) of 7.1, and a relative risk reduction of 81 % [7].

When examined in further detail, the isolated beneficial effects for both the primary and secondary prevention of peanut allergy translated to an NNT of 8.5 among the infants with negative SPT responses and an NNT of 4 among the infants with minimally positive SPT responses. 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 infants with minimally positive SPT responses, are safe and feasible. Six children in the consumption group had 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 response to peanut and therefore does not address a strategy for those without these risk factors for 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 and 6 months of age in high-risk infants, and some of these guidelines specify that certain infants considered at high risk for 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 having a positive peanut SPT response but not yet clinically reactive, to receive the benefits noted in the LEAP trial, which might reduce the risk of peanut allergy up to 80 %.

Of note, since children with lesser risk factors for peanut allergy were excluded from enrollment in the LEAP trial, 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 applying the findings of 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 health care 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 diets of "high-risk" infants early on in life (between 4 and 11 months of age) in countries where peanut allergy is prevalent because delaying the introduction of peanut can be associated with an increased risk of peanut allergy.
- Infants with early-onset atopic disease, such as severe eczema, or egg allergy in the first 4 to 6 months of life (see Box 1 for example LEAP criteria), might 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 might consist of performing peanut skin testing, in-office observed peanut ingestion, or both, as deemed appropriate after discussion with the family. The clinician can perform an observed peanut challenge for those with evidence of a positive

peanut skin test response to determine whether they are clinically reactive before initiating at-home peanut introduction. Both such strategies were used in the LEAP trial 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) per week during the first 2 years of the trial compared with a median of 0 g in the avoidance group (see Box 2 for examples of peanut-containing foods used in the LEAP trial). Although 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.

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 application of topical creams, ointments, or both, containing corticosteroids or calcineurin inhibitors, and that, if the participant is <6 months of age, lasted for at least 12 of 30 days on 2 occasions, or, if the participant is >6 months of age, lasted for at least 12 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

- SPTs to peanut should be performed in the presence of a negative control and a positive histamine control.
- SPTs should be performed in duplicate, and the maximum wheal diameter of the two SPTs should be calculated and rounded up to the greatest whole millimeter

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

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

- Smooth peanut butter (1 teaspoon) mixed with milk or with mashed or pureed fruit
- *Bamba® snack (Osem; approximately two thirds of a 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.

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

The LEAP trial 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 health care 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.

Peanut sensitization pattern in Norwegian children and adults with specific IgE to peanut show age related differences

Abstract

Background: Peanuts contain potent food allergens and the prevalence of allergy is reported to increase, especially in children. Since peanut sensitization may differ between different geographical regions, we wanted to investigate the sensitization pattern to the individual peanut allergens in a Norwegian population.

Methods: Cases reported to the Norwegian Food Allergy Register with sera positive to peanut extract were analyzed for specific IgE (sIgE) to the recombinant peanut allergens Ara h 1, Ara h 2, Ara h 3, Ara h 8 and Ara h 9 and to birch pollen extract. Serum samples negative to the above allergens were analyzed for sIgE to Ara h 6, and sIgE to Pru p 3 in peach were analyzed in sera positive to the cross-reactive allergen Ara h 9.

Results: Highest frequency of sIgE to Ara h 2, often co-sensitized to Ara h 1 and 3, were found in the small children up to 6 years of age. From the age of 6 years, sensitization to Ara h 8 was predominant. The sIgE levels to the storage proteins Ara h 1, 2 and 3 were strongly correlated, as was the sIgE levels to Ara h 8 and birch pollen extract. A low sensitization rate of sIgE to Ara h 9 in young adults was observed, which sIgE levels were very strongly correlated to Pru p 3.

Conclusion: The sensitization to peanut allergens in a Norwegian population shows a clear age dependent pattern. The results add to the previously published research on the sensitization patterns of peanut sensitized patients in different geographical areas.

Keywords: Peanut sensitization pattern, sIgE, Age related differences, Peanut allergens, Ara h 2, Ara h 8

Background

Peanut allergy represents a worldwide problem, it is often severe, potentially fatal and often persistent throughout life [1, 2]. The estimated prevalence of peanut allergy is between 0.5 and 2.0 % and appears to be increasing especially in children [3–5]. An accurate diagnosis of peanut allergy is essential since it may represent a significant burden on both quality of life and socio-economy [6]. Medically supervised oral food challenges (double-blind placebo-controlled food challenge, DBPCFC) are considered the gold standard for diagnosis but are resource-intensive and may be associated with risk of severe allergic reaction or anaphylaxis. In the last decades, however, several of the peanut allergens have been characterized, and analysis of specific IgE (sIgE) on a molecular basis has been evaluated as a diagnostic tool for peanut allergy [7–10].

The major peanut allergens Ara h 1, 2 and 3 belong to the seed storage proteins of the vicilin, conglutin and glycinin families, respectively, and are considered to be responsible for the original sensitization to peanut in susceptible individuals. The seed storage proteins are stable and associated with increased risk of severe reactions or anaphylaxis. The storage protein Ara h 6, a conglutin, has sequence identities to Ara h 2 and is also reported to be associated with clinical reactivity to peanut. [11]. The relationship between allergy to pollen and vegetables, nuts, peanuts and fruits is caused

by cross-reacting epitopes due to homology between proteins and often give rise to milder symptoms such as the oral allergy syndrome. The peanut protein Ara h 8 is homologous to the birch pollen protein Bet v 1, and contributes to a substantial cross-reactivity between peanut and birch pollen [12]. Cross-reactivity between profilin in grass pollen and peanut may also occur [13]. The peanut allergen Ara h 9 is an enzyme-stable non-specific lipid transfer protein (LTP) with cross-reactive epitopes to other LTPs such as Pru p 3 in peach and Cor a 8 in hazelnut [14]. The protein Ara h 9 is reported to be an allergen of importance in the Mediterranean area that may cause systemic reactions in addition to oral allergy syndrome [15].

Recent studies have shown that peanut allergy in USA, Australia and different parts of Europe have different clinical and immunological patterns, due to differences in pollen exposures and differences in dietary traditions [13, 14, 16]. Since Norway is a birch endemic country and birch pollen gives rise to cross-reactions to peanut, we wanted to investigate the sensitization pattern to the individual peanut allergens in cases reported to the Norwegian National Reporting System and Register of Severe Allergic Reactions to Food (the Norwegian Food Allergy Register). The cases are submitted with serum samples routinely analyzed for a standard panel of allergen extracts [17]. All patients sensitized to peanut extract were analyzed for sIgE to the recombinant peanut allergens, in relation to age, gender, onset of reaction, symptoms and number of co-sensitizations to other foods and to birch pollen.

Methods

Patients

The Norwegian Food Allergy Register was established at the Norwegian Institute of Public Health in 2000 in collaboration with the Norwegian Food Safety Authority and the National Veterinary Institute [17]. Cases are reported on a voluntary basis by first-line doctors and submitted together with a serum sample. The reports contain patients' information such as a short case history including gender, age, the suspected or incriminating food, and onset of reaction, known allergies, symptoms and the medication given. A written consent form is signed by all patients. A total of 1250 sera submitted to the Food Allery Register, routinely analyzed for sIgE to a panel of food allergens including peanut, birch- and timothy pollen were screened for sIgE to peanut extract. Two hundred and fourteen sera had sIgE antibodies to peanut extract above the cut off value 0.35 kU/l and were included in the study. The 214 patients were equally distributed between genders, 101 females and 113 males, and comprised ages from <1 to 80 years.

Serological analysis

The patient sera were analyzed for sIgE using ImmunoCap® (Phadia AB, Uppsala, Sweden). Due to limited volume of serum available for some of the patients, specific IgE antibodies to the three storage proteins Ara h 1, Ara h 2 and Ara h 3 were analyzed in 192 patient sera. IgE reactivity to Ara h 8, Ara h 9 and to birch pollen extract were analyzed in all 214 sera. Sera with sIgE to Ara h 9 were analyzed for sIgE to the peach allergen Pru p 3 known to result in cross-reactions to the lipid transfer protein. Sera with sIgE antibody levels >0.35 kU/l were considered positive. Since ImmunoCap with Ara h 6 is not commercially available, sera negative to all the above peanut allergens were analyzed for sIgE to Ara h 6 by ImmunoSorbent Allergen bioChip assay, ISAC (Thermo Fisher Scientific, Oslo, Norway), reported in standard units (ISU). ISU >0.3 were considered positive.

Statistics

Pearson correlation was used to establish the strength of the relationship between sIgE antibody levels. Syntax of recoded combinations of sera with sIgE to the major allergens Ara 1, 2 and 3 made it possible to obtain the frequency of all combinations. Frequency analysis and plots of the collected data were made using the statistical programs IBM SPSS Statistics 22 and SigmaPlot 12.3.

Results

Gender, onset of reaction, symptoms and treatment in relation to age groups

Frequency analysis of the ages of the 214 patients sensitized to peanut showed four age groups (Fig. 1). As seen from the figure, the frequency of sensitization peaked

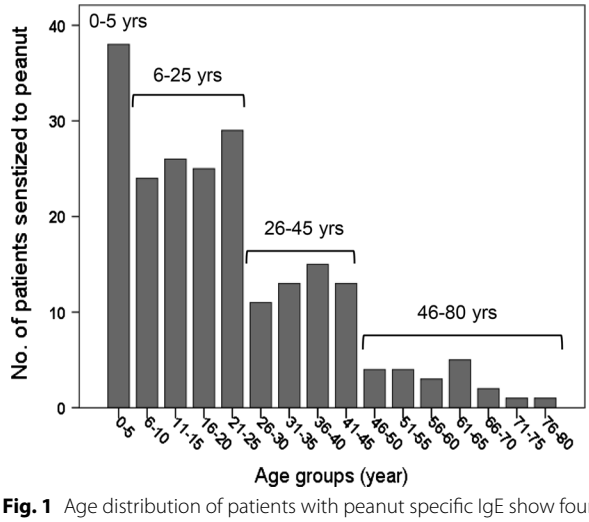

Fig. 1 Age distribution of patients with peanut specific IgE show four age groups; 0–5 years, 6–25 years, 26–45 years and 46–80 years of age

at ages 0–5 years, the second group comprised the ages from 6 to 25 years, the third group from 26 to 45 years and the lowest frequency of sensitization was seen for the ages 46 to 80 years. The gender distribution shifted from 76:24 % males:females in the small children's group to 23:77 % males:females in the oldest group (Table 1). The onset of reaction reported to occur within 1 h after intake of the suspected food was highest in the youngest group, 97 %, and decreased by age to 69 % in the oldest group (Table 1). The organ systems reported to be most often affected were symptoms in the skin (urticaria, and angioedema, sudden itching of eyes and nose), most often in combination with gastrointestinal tract (oral pruritus, lip swelling, abdominal pain, diarrhea, and vomiting) and/or respiratory symptoms (rhinorrhea, wheezing, chest tightness, cough, stridor, dyspnoe, and respiratory arrest). Patients reported to have symptoms affecting more than one organ system, which is related to high risk of severe reactions, were highest in the youngest age group, 76.7 %, declining with age to 54.5 % in the oldest age group (Table 1). The four age groups also differed in that severe skin symptoms were more often reported and loss of consciousness less reported in the youngest children. Cardiac arrest was not reported for the youngest and the oldest age groups. The therapeutic treatment employed was reported to be antihistamines alone (23.5 %), in combination with steroids (24.1 %) or most commonly in a combination of both epinephrine and steroids (32.1 %). Epinephrine alone and steroids alone was used in 14.2 and 6.2 % of the reported cases, respectively.

Specific IgE levels to the peanut allergens

Seventy-four (38.5 %) of the 192 patient sera analyzed had sIgE to the three seed storage proteins Ara h 1, 2, and 3 in different combinations and sIgE co-sensitized to all three proteins was seen in 36 (48.7 %) patient sera. The proteins Ara h 1 and Ara h 2 were co-sensitized in 51 (68.9 %) of the patients, Ara h 2 and Ara h 3 in 39 (52.7 %) patients and Ara h 1 and Ara h 3 were co-sensitized in 38 (51.4 %) patients. Seventeen patients were mono-sensitized to Ara h2, Ara h1 and Ara h3 in frequencies of 9 (12.2 %), 6 (8.1 %) and 2 (2.7 %), respectively. The IgE levels to all three recombinant allergens were strongly correlated ($r = 0.65–0.71$, $p < 0.01$).

One hundred and eight (50.5 %) of the 214 patients sensitized to peanut extract had sIgE to the birch pollen homologue Ara h 8 and were co-sensitized to the birch pollen extract in all but two patients. Their sIgE levels were strongly correlated ($r = 0.61$, $p < 0.01$). Thirty-seven (34 %) of the patients with sIgE to Ara h 8 were co-sensitized to the three peanut storage proteins in different combinations and showed no correlation with respect to sIgE levels.

Twenty-four (11 %) of the 214 patients, showed to be sensitized to the lipid transfer protein Ara h 9 with co-sensitization to Pru p 3 with similar sIgE levels. The sIgE levels to the two allergens were very strongly correlated ($r = 0.99$, $p < 0.01$). Thirteen (54.2 %) of these patients showed co-sensitization in different combinations to Ara h 1, 2, 3 and 8.

Thirty-five (16.3 %) patient sera had no sIgE to any of the above peanut allergens and were analyzed for sIgE to the Ara h 2 homologue Ara h 6. Four (11.4 %) patients had sIgE to Ara h 6 with ISU values characterized as low (0.3 ISU), moderate to high (4.0 ISU and 7.9 ISU) and very high (20.0 ISU).

Thirty-one patient sera were negative to all six peanut allergens and had low levels of sIgE to peanut extract. These sera were all from patients between the ages 0–10 years and showed to have sIgE to birch- and/or timothy pollen and/or to seeds and nuts indicating cross-reaction to peanut due to primary sensitization to pollen or to seeds or nuts. Sensitization to peanut due to cross-reactivity between 2S albumins in nuts like walnut, and sesame seeds has been reported [18].

Table 1 Gender ratio, onset of reaction within 1 h and symptoms affected in more than one organ system reported in the 214 patients in relation to the four age groups

Age group	Reported date			ImmunoCap® analysis		
Years	Gender ratio %	Onset of reaction %	Symptoms %	Ara h 2 %	Ara h 8 %	Birch pollen %
	Male:female	<1 h	>1 organ affected	sIgE >2.0 kU/l[b]	sIgE kU/l	sIgE kU/l
0–5 (N[a] = 43)	76: 24	97	76.7	51.2	23.3	41.9
6–25 (N = 96)	49: 47	80	72.0	31.3	56.3	83.3
26–45 (N = 53)	26.5: 73.5	90	58.5	15.0	54.7	79.2
46–80 (N = 22)	23: 77	69	54.5	0.0	68.2	86.4

The patients sera analyzed for sIgE to Ara h 2 with levels >2.0 kU/l, sIgE to the birch pollen homologue Ara h 8 and birch pollen extract is also shown

[a] Number of patient sera

[b] Sera with sIgE to Ara h 2/6 >2.0 kU/l (marker for clinical allergy)

Age related IgE profiles to peanut allergens

Specific IgE sensitization to the individual peanut allergens differed between the four age groups. Sensitization to the major storage proteins was highest in the youngest age groups and lowest in the oldest age group. The decrease according to age was especially marked with respect to Ara h 2 (Fig. 2). The youngest children (0–5 years) were most frequently sensitized to the seed storage protein Ara h 2 (58.0 %), but were frequently co-sensitized to Ara h 1 (44 %) and Ara h 3 (27 %) in different combinations. The four sera with sIgE to Ara h 6 were all from patients in the small children's group. Sensitization to the lipid transfer protein Ara h 9 was seen in all age groups (only one positive in the children's group) but most frequently among the young adults (26–45 years) (Fig. 2). The birch pollen homologue Ara h 8 increased markedly in frequency from 23.3 % in the youngest children to 56.3 % at the age of 6 years and was found to be 68.2 % in oldest age group. Similarly, sensitization to birch pollen showed a marked increase in frequency of sensitization from 41.9 % in the youngest children to 83.3 % at the age of 6 and showed similar high frequencies in the two older age groups (86.4 %) (Fig. 2). A level of sIgE to Ara h 2 > 2.0 kU/l, considered to be diagnostic for clinical peanut allergy [19], was found in 51.2 % of the sera from patients in the youngest age group. Sera with levels above this value decreased with age to 31.3 % in the second age group, 15 % in the third age group to none in the oldest age group (Table 1).

Co-sensitizations, to 1, 2 or 3 other food allergens or to more than 3 food allergens were equally common in all age groups. The most common sensitizations to allergens other than peanut were to other legumes, celery, wheat, seeds and tree nuts.

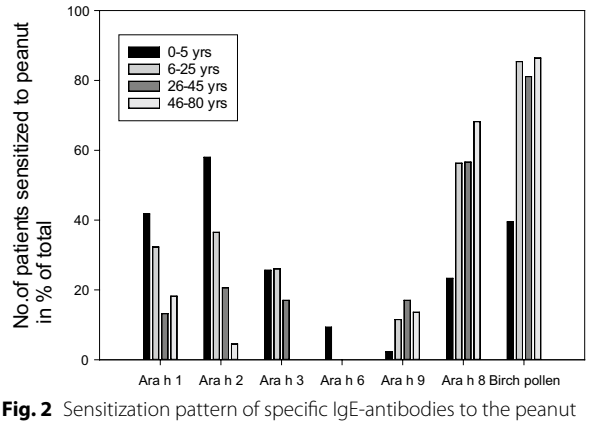

Fig. 2 Sensitization pattern of specific IgE-antibodies to the peanut allergens and birch pollen extract in the four age groups showing highest frequency of sensitization to Ara h 2 in the youngest age groups, and highest frequency of sensitization to Ara h8 from the age of 6 years and in the older age groups

Discussion

The pattern of sensitization to the six individual peanut allergens Ara h 1, 2, 3, 6, 8 and 9 was evaluated in patients reported to the Norwegian Food Allergy Register. Frequency analysis of the ages of the 214 patients sensitized to peanut showed four age groups; 0–5, 6–25, 26–45 and 46–80 years (Fig. 1). The sensitization pattern showed highest frequency of sIgE to the major peanut allergens Ara h 2/6, 1, and 3 in the youngest age group (58.5 %) and lowest frequency in the oldest age group (4.5 %), as opposed to the birch pollen homologue Ara h 8 which showed the highest frequency of sensitization in the oldest age group (68.2 %) and lowest frequency of sensitization in the youngest age group (23.3 %) (Fig. 2; Table 1).

Similar changes in gender distribution by age, as presently observed, from 76:24 % male:female in the youngest age group to the opposite ratio in the oldest group, has been reported for both asthma and allergy and is explained by hormonal changes, genetic susceptibility and differences in environmental exposure. The early onset of sensitization to the major peanut allergens and the early onset from intake of food to elicitation of symptoms in the children's group, together with high incident of more than one organ system affected, indicate that the reactions were severe in these patients. Although the medical treatment of allergic reactions will vary between the individual doctors, all patients were treated with antihistamines, epinephrine and steroids or a combination of the three, indicating that the reactions were considered to be severe. Severity, however, based on the reports of symptoms, and the medication given is difficult to measure since it will depend on at which time course of reaction the patients were treated. An early onset of effective treatment will always be aimed at to avoid the most severe reactions which may explain why loss of consciousness and cardiac arrest was seldom reported.

The results showed the highest frequency of sensitization to Ara h 2, less to Ara h 1 and to a much less extent to Ara h 3 in the youngest children. Ara h 2 and Ara h 6 have been found to account for the majority of the effector activity in crude peanut extract [20], with equal diagnostic value [21] and hence, to be more potent than Ara h 1 and Ara h 3 [22]. However, co-sensitization to all 3 allergens has been shown to be correlated to severity of symptoms [23]. In the present study, sIgE to Ara h 6 was detected in four sera from the youngest children. Sensitization to Ara h 6 without concomitant sensitization to Ara h 2 was also reported in a Swedish study to be responsible for severe reactions [24]. In two of the present cases, sIgE levels to Ara h 6 were high (20.0 and 7.9 ISU) and the patients were reported to react with acute anaphylactic reaction after intake of one peanut. In the other two cases, however, with low sIgE levels to Ara h 6 (ISU 0.3 and 4.0),

high levels of sIgE to cashew nut was detected. This may indicate primary sensitization to cashew nut with cross-reactivity to Ara h 6 due to sequence identity between storage proteins. The early onset of severe peanut allergy in children found in the present study is in line with findings in other population studies in children [7, 25, 26]. Further, in the studies comparing immunological differences among patients of different ages and in different geographical regions, early onset of sIgE to the three allergens Ara h 1, 2 and 3 were also reported, often presented with severe symptoms [13, 14, 16]. One may speculate if the high sensitization rate to the major peanut allergens in the youngest children is due to dietary changes with an increase in the overall use of peanuts in foods and as snacks over the last decades and/or as Ballmer-Weber et al. [16] speculates, an increase due to an intestinal permeability in genetically predisposed children. A recent study [27], however, showed that delayed oral exposure to peanut was associated with a greater frequency of clinical peanut allergy and hence may be responsible for the increased prevalence in this age group.

A study from Italy [28] reported no differences in sensitization among ages up to 16 years for the major peanut allergens, but reported increased levels of sIgE to Ara h 8 according to age, as found in the present study. The high correlation of sIgE levels to birch pollen extract and Ara h 8 may suggest primary pollen sensitization with following cross-reaction to Ara h 8, and possibly to other labile PR-10 proteins homologous to Bet v 1. The increase, however, in sensitization to birch pollen and Ara h 8 observed at the early age of 6 years, may, in part, be due to a milder climate and thereby longer pollen season [29]. Even if cross-reactions in general are considered to give milder reactions than sensitization to the major, stable allergens, the symptoms may have been experienced as severe and treated and reported as such. Thirty-seven (34 %) of the patients, however, with sIgE to Ara h 8 were co-sensitized to the three peanut storage proteins in different combinations, and may in these cases have been responsible for the severe reactions reported. Reactions caused by cross-sensitizations or co-sensitization to other food allergens than peanut cannot be ruled out.

All sera with sIgE to the lipid transfer protein Ara h 9, also had sIgE to Pru p 3 with similar sIgE levels and half of these patients were co-sensitized in different combinations to Ara h 1, 2, 3 and 8. All sera were in addition co-sensitized to other foods and often to hazelnut. The severe symptoms reported may, therefore, have been caused by sensitization to the major peanut allergens or by cross-reactions to LTP in hazelnut rather than to Ara h 9. The diagnostic value of Ara h 9 is said to be poor [19] and the clinical relevance of sensitization to Ara h 9 is difficult to interpret.

Various thresholds for sIgE to Ara h 2 have been suggested to predict clinically relevant peanut allergy but regional differences in addition to large individual variations make extrapolations between studies difficult [16]. The use of recombinant allergens, therefore, may be useful to distinguish patients with high risk of severe symptoms from those with less severe symptoms but cannot still replace oral challenges in determining thresholds and severity. Although the cases reported in the present study were submitted by first-line doctors who considered the reactions as being severe, the weaknesses of the study are that the results are based on cases with reported symptoms and serological analysis not verified by oral challenges. Hence, the overall information given including the severity of symptoms may have been biased by the reporting habits of the doctors. Further, the volume of the serum sample submitted, were in some cases small which limited the number of analysis. Still, the results from the submitted reports and the present analyses of peanut allergens in sensitized subjects, contribute to the information on peanut sensitization patterns in different populations.

Conclusion

Component based analysis of peanut in patient sera from cases reported to the Norwegian Food Allergy Register sensitized to peanut, demonstrate a clear age dependent pattern. The early onset of sensitization to the main allergens Ara 1, 2 and 3 found in the children below the age of 6 years, showed highest frequency of sIgE to Ara h 2, indicating the importance of using Ara h 2 in diagnosing small children sensitized to peanut. The early debut of pollen sensitization, may be caused by warmer climate and longer pollen season and suggest a majority of primary sensitization to birch pollen from the age of 6 years, with following cross-sensitization to the birch pollen homologue Ara h 8 in peanut.

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