VIEWPOINT

Implementing Primary Prevention for Peanut Allergy at a Population Level

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Peanut allergy is increasingly common, with an estimated prevalence in children of 2% to 3% in the United States,[1] the United Kingdom,[2] and Australia.[3] Decades of well-intentioned advice from specialist organizations to avoid introducing peanuts (and other nuts) into the diet of infants and young children may have contributed but is unlikely to have been the only reason for this increase. Evidence from a randomized clinical trial (RCT), the Learning Early About Peanut Allergy (LEAP) study, suggested that the introduction of peanut into the diets of infants at high risk of peanut allergy between 4 and 11 months decreases the risk of a clinical peanut allergy at the age of 5 years,[4] with persistence of the protective effect at 6 years demonstrated by the follow-up study.[5] The Enquiring About Tolerance (EAT) study examined early introduction of multiple foods, including peanut, from 4 months of age in a population not selected for atopic risk.[2] This study failed to show a protective effect for peanut introduction by intention-to-treat analysis, although a per-protocol analysis suggested a potential benefit.

In January 2017, the National Institute of Allergy and Infectious Diseases (NIAID) released a guideline for the prevention of peanut allergy in the United States,[6] a document designed to apply primary prevention at a population level. The guideline is complex: infants are stratified, on the basis of pre-exposure risk of peanut allergy, into 3 groups: (1) those who closely resemble the infants from the LEAP study, with severe eczema, egg allergy, or both (high-risk guideline); (2) those with mild-moderate eczema as their predisposing risk factor (medium-risk guideline); and (3) those with no eczema or any known food allergy (low-risk guideline). Family history of atopy is not included as a risk factor, and it is unclear how infants who are allergic to a food other than egg and without eczema are to be categorized.

> Do not delay introduction of peanut; introduce into the diet within the first year of life when both the family and the infant are ready.

Guideline 1 recommends screening high-risk infants with serum peanut IgE levels or peanut skin prick tests and an oral food challenge if necessary, with peanut introduction at 4 to 6 months of age based on test results. Guidelines 2 and 3 recommend introduction of peanut-containing foods without diagnostic testing at "around 6 months" for medium-risk infants and "age appropriate and in accordance with family preferences and cultural practices" for low-risk infants.[6]

The recommendation for early introduction of peanut into the diets of high-risk infants between 4 and 6 months is based on the LEAP study. However, in that trial, the mean age of the infants at the time of peanut introduction was 8 months; only 18% of the cohort (116 infants) were younger than 6 months at the time of first peanut introduction.[4] Although a post hoc analysis suggested that the benefit was greater in younger infants (based largely on increasing skin prick test sizes with age), a subsequent analysis raised questions about this finding.[7]

In addition, there is no convincing evidence from RCTs to support the recommendations for lower-risk groups. While infants with mild-moderate eczema are at higher risk of developing a food allergy, there is no evidence from RCTs to separate or make different timing recommendations for medium-risk and low-risk groups. The authors of the guidelines justify guidelines 2 and 3 on the basis of expert opinion, a per-protocol analysis of a single RCT, and the "likely to do no harm" principle. This appears logical; however, population recommendations preferably should be made on the basis of high-level evidence and more than one RCT in a single region, to ensure the "do no harm" principle.

In simple terms, guideline 1 (high-risk infants) attempts to identify infants who have peanut allergy prior to peanut exposure. However, the available diagnostic tests are imperfect with low specificity, which the authors of the guidelines acknowledge. For example, many infants generate peanut-specific IgE but may be clinically tolerant to peanut. However, no better simple, easily administered tests are available that reliably identify clinical peanut allergy. Nevertheless, high sensitivity and specificity are considered crucial elements of test suitability for population-based screening programs.

The distinction between screening to make a diagnosis of peanut allergy and for the purpose of identifying an at-risk population for implementation of a primary prevention strategy is subtle but important. Screening prior to introduction in this high-risk group is based on the concern that infants will have an allergic reaction on peanut exposure. Although this is a genuine concern, is it a valid reason to screen? Is the aim to avoid any clinical reaction or avoid death from severe anaphylaxis? The latter is likely the key driver in the guideline, but what is the evidence? Most infants and children present to health care professionals having had an allergic reaction to a food without prior

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screening. Fatality as a result of first exposure to foods within the first 12 months of life is extremely rare: to date, no deaths have been reported related to peanut exposure within the first year of life.[8]

In Israel, where it was first noted that a significantly lower prevalence of peanut allergy was associated with earlier introduction of peanut into the infant diet, no recommendations exist for screening of high-risk infants, and peanut (in the form of Bamba) is a common weaning food, typically introduced around 6 months of age. This long-standing convention has not been associated with fatal events, although cow's milk allergy has. Even though cow's milk has caused infant fatalities from anaphylaxis in the United States and United Kingdom, there are no recommendations for screening prior to introducing other common allergenic foods.

The risk of death due to anaphylaxis after exposure to peanut introduced in infancy should be weighed against possible adverse consequences of the guidelines. What is the likelihood that many parents will be deterred by a 2-step screening and introduction process, due to a lack of access or absence of medical insurance or financial means to undertake peanut exposure under supervision? Might the tight and proscriptive 4- to 6-month age window ultimately be counterproductive, with a parent having missed the window deciding not to introduce peanut at all?

Another potential unintended consequence of the guideline to consider is "screening creep," in which infants who are not in a high-risk category may undergo screening due to parental anxiety, physician overcautiousness, or overdiagnosis of mild or moderate eczema (the definition of severe eczema used in the guideline is unclear and potentially open to overdiagnosis). Given that up to 20% of children have eczema in infancy, even a relatively small shift in risk stratification would lead to a large increase in the numbers of infants being screened, needing specialist referrals, and having food challenges, and therefore the possibility of delayed introduction. Also, even though the NIAID guidelines specifically discourage testing for other foods at the time of screening for peanut allergy, parental pressure and perhaps physician overcautiousness may result in testing for multiple foods. Of greatest concern is the risk that foods that are already tolerated in the diet will be removed on the basis of a "positive" allergy test. This is already a significant issue with "panel testing" performed on many children with eczema, under the (mostly) false assumption that it will identify foods that contribute to delayed eczema flares. The removal of a clinically tolerated food in the presence of a positive allergy test may lead to loss of tolerance and development of food allergy instead.

The NIAID guidelines may have resource and equity-of-access implications as well. Modeling the screening recommendations in the Australian[9] and Irish[10] populations has generated serious concerns about logistics and resources, and it is reasonable to consider whether there is sufficient evidence for population-based screening outside the resources of a clinical trial. Although the guideline has been specifically written for the US population, it has global implications and will likely influence screening practices worldwide. Implementation within low-resource communities (within and outside the United States) will be difficult.

Overall, the evidence for introduction of peanut into an infant's diet within the first year of life is compelling for those with severe eczema and egg allergy. The guideline is a valiant attempt to reduce the burden of peanut allergy in these high-risk infants. However, the focus on 4 to 6 months as a key window and the complex and resource-intensive screening process is debatable, for both may detract from the overall implementation, uptake, and success of the guidelines. Population-based health interventions need to be simple. Instead, perhaps the message should be: do not delay introduction of peanut; introduce into the diet within the first year of life when both the family and the infant are ready. Whether a complex risk stratification and screening process will assist or hinder widespread uptake of this primary prevention strategy at a population level remains to be seen.

ARTICLE INFORMATION

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