Editorial

Implications of the "Consensus Communication on Early Peanut Introduction in the Prevention of Peanut Allergy in High-Risk Infants" for Allergists, Primary Care Physicians, Patients, and Society

Scott H. Sicherer, MD[a], S. Allan Bock, MD[b,c], and Robert S. Zeiger, MD, PhD[d] *New York, NY; Boulder, Aurora, Colo; and San Diego, Calif*

In a landmark collaborative action, 10 international medical professional organizations, 2 among them not being allergist-immunologist based (the American Academy of Pediatrics and the Society for Pediatric Dermatology), created a "Consensus communication" suggesting that the approaches taken in the Learning Early About Peanut (LEAP) trial[1] should be actualized for clinical care "in more diverse settings throughout the world."[2-4] The Consensus communication is receiving widespread publication and media coverage. The purpose of this editorial is to bring attention to this Clinical communication for the readership, and to underscore a number of implications that were not discussed in the guidance.

Briefly, the LEAP trial enrolled 640 infants between 4 and up to 11 months of age (average age almost 8 months) having severe eczema, egg allergy, or both.[1] The study enrollment procedures included skin testing to peanut. Infants with skin tests greater than 4 mm were excluded with the assumption that they were likely already allergic. Infants enrolled and randomized to ingest peanut did so initially under physician supervision, with a graded feeding for those with positive tests (overall, 7 of 319 reacted at the baseline feeding). The results after supervised feeding at 5 years of age showed that the rate of peanut allergy was 17% in those who were avoiding peanut compared with 3% in those who ate peanut early. Approximately 7 children would need to be treated for one to obtain this benefit. Compared with avoidance, randomization to eat peanut early was associated with an 86% relative risk reduction in peanut allergy among infants entering the study with negative peanut allergy tests and a 70% risk reduction among those with small positive peanut allergy tests.

The Consensus communication[2-4] provides "interim guidance" focused on "high risk" infants. It suggests that infants in the first 4 to 6 months of life with early onset atopic disease, such as severe eczema or egg allergy, might benefit from evaluation by an allergist or physician trained in the management of allergic disease, to diagnose any food allergy and assist in implementing the introduction of peanut early. Although not specifically stated in the Consensus communication, the above statement would presumably apply to high-risk infants from 4 to up to 11 months of age, the ages studied in LEAP. The evaluation could consist of performing peanut allergy skin tests and in-office observed peanut ingestion, or both, as appropriate. The guidance suggests that the clinician can perform an observed peanut food challenge for infants with a positive peanut skin test before home introduction. Also noted is that serum testing for peanut-specific IgE antibody, if performed instead of skin testing, could result in considerably higher rates of identified sensitization, which could result in performing numerous unnecessary oral food challenges (OFCs). The Consensus communication presents the LEAP enrollment criteria, describes aspects of skin testing, and gives examples of foods used that avoid choking hazards related to peanuts and peanut butter.

The Consensus communication acknowledges a number of limitations and constraints. It points out that there are no data about alternative dosing regimens, minimal length of time needed for "treatment," or risks of discontinued or sporadic feeding. Additionally, the guidance clearly notes that it has focused on "high risk" infants and peanut allergy and has not attempted to generalize the results to other foods or lower risk populations. Importantly, the document reminds the reader that prior guidelines have *not* recommended delaying allergen introduction in the general to low-risk population, and underscores the point that feeding peanut early to high-risk infants will require engagement of the medical community to change the culture of early feeding practices. The document also introduces the fact that a National Institute of Allergy and Infectious Diseases Working Group and European Academy of Allergy, Asthma and Clinical Immunology Guidelines Group are addressing a best-practices approach with more extensive guidelines.

[a]Division of Pediatric Allergy and Immunology, Department of Pediatrics, Jaffe Food Allergy Institute, Icahn School of Medicine at Mount Sinai, New York, NY
[b]Boulder Valley Asthma and Allergy Clinics, Boulder, Colo
[c]Department of Pediatrics, National Jewish Health, Denver, Colo and University of Colorado School of Medicine, Aurora, Colo
[d]Department of Allergy, Kaiser Permanente Southern California Region, San Diego, Calif

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Corresponding author: Scott H. Sicherer, MD, Division of Allergy/Immunology, Mount Sinai Hospital, Box 1198, One Gustave L. Levy Place, New York, NY 10029-6574. E-mail: scott.sicherer@mssm.edu.

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The interim guidance, essentially suggesting recapitulation of the LEAP study, raises a number of practical and theoretical issues that impact primary care providers, allergists, patients, and society/the health care system. Although the communication provides some details about the LEAP study procedures, including enrollment criteria, general description of skin tests, examples of foods used, and so on, it does not provide a specific protocol and remains open-ended about details that could arise in decision making.

For the pediatrician, the guidance essentially suggests referral of "high risk" patients. If the pediatrician is tempted to perform serum IgE testing to peanut, the guidance points out that, based on the LEAP study, such testing is associated with a substantially higher rate of sensitization, and would result in many more "unnecessary" OFCs. The communication defines early-onset atopic disease with the terms "such as severe eczema, or egg allergy." Although the document does not specifically advise using the LEAP enrollment criteria, the enrollment criteria are provided and include complex descriptions where egg skin testing can be used in isolation to identify egg allergy, and severe eczema is defined with complex criteria including standardized scoring systems or defined periods of rash and medication use. Clearly, the pediatrician will need to apply some judgment in deciding on which infants fulfill the high-risk criteria. One may argue that more liberal inclusion is completely acceptable, but this would result in many more infants being referred for allergy evaluations. More user-friendly descriptions of "high risk" are needed if these guidelines continue to be focused only on this LEAP-like, high-risk infant group. There is, of course, the potential unintended consequence that drawing attention to requiring an evaluation before allowing peanut consumption may result in more delays in introduction or avoidance of peanut, and full guidance will need to consider this issue, for example assessing risks for home introduction and making comments about management of lower risk infants.

For the allergist, these interim guidelines clearly raise the idiom, "the devil is in the details." Although the guidance discusses the exclusion of infants in LEAP with a larger than 4-mm wheal size to peanut on skin testing, advice about a specific cutoff is not provided in the Consensus communication. In an editorial by Gruchalla and Sampson,[5] it is pointed out that some infants with larger skin tests excluded in the LEAP study may have actually tolerated peanut and may have benefited from the intervention, although they espouse using the 4-mm cutoff. The Consensus communication includes a brief but incomplete description of skin testing procedures used in the LEAP study, including that duplicate skin tests should be performed, and using an average of the maximum wheal diameters. What is not discussed in detail is that the LEAP study used lancets, which in prior studies result in smaller responses than some other devices,[6] and they used the forearm unless there was too much rash in which case they use the back (in general, skin tests on the arm are smaller than on the back[7]). They measured tests at 15 minutes and used a third skin test if there was discordance over 2 mm and then averaged the closest 2 readings. Knowing these details may play a part in decision making for individual patients with larger positive skin tests who, in the allergist's clinical judgment and family comfort, may warrant an OFC despite the possible higher risk.

The Consensus communication is also open-ended about the initial introduction of peanut, not specifically commenting on whether those with negative skin tests can be advised on home introduction compared with an observed feeding (not graded food challenge), the latter being done in the LEAP study (1 of 272 in that study with negative skin tests reacted). A "baseline" graded challenge was performed in the study when skin tests were positive to a total cumulative dose higher than the amount given to infants in the observed feeding (6 of 47 reacted). Clearly, several decision points guided by clinical judgment are needed in this arena as well. The protocol regarding OFC is available online. It is likely that many allergists have limited experience with OFCs in the infant age group, which also needs to be addressed in actualizing these approaches. Although there is some comfort in the observation that the baseline food challenges resulted in only mild symptoms, severe reactions are clearly possible in infants.[8] Thankfully, the Adverse Reactions to Foods Committee of the American Academy of Allergy, Asthma and Immunology is working on a report with advice on performing OFCs to peanut in this age group.

From a parent's perspective, applying the LEAP study approach to their child can be promising, but also may engender queries about practical and safety issues. The participants in the LEAP study appeared to be highly motivated toward incorporating peanut into the child's diet. The study advised a rather large dose of peanut on a weekly basis, equivalent to about 3 rounded teaspoons per week. Whether this amount is "necessary" is unknown, but clearly families will need to know about safe products to choose because of choking risks, what to do about pickiness in eating, and about theoretical eventualities if peanut is discontinued or fed sporadically. The LEAP study developed from an observation that Israeli Jewish children had a 10-fold lower rate of peanut allergy than Jewish children in the UK, with relative avoidance of peanut in the first year in this latter group.[9] The Israeli children, primarily because of popularity of a particular snack food, Bamba, reported a consumption rate of 7.1 g peanut protein monthly (actually lower than that prescribed in the study, 6 g weekly). Given that peanut is not currently ubiquitous in infant foods in many countries, parents are faced with more effort to ensure incorporation of peanut into the diet, which may reduce "adherence," particularly in nonstudy conditions. The implications of less adherence remain unknown.

Follow-up on LEAP participants who have entered a follow-on study where peanut was avoided will help inform whether the intervention results in tolerance or a state of desensitization dependent on frequent ingestion. Also to be discussed with parents is the possibility of development of peanut allergy despite dietary incorporation. In LEAP, 8 participants discontinued peanut in the diet because of allergic reactions after tolerating the baseline feeding (7 had converted to having a positive skin test on re-evaluation and 1 participant who experienced enterocolitis had negative tests; 5 of these 8 participants had peanut allergy at age 5 years). A discussion is also needed for a family that has an older sibling with peanut allergy, when the family may have decided to avoid peanut in the household because care is needed to avoid exposing the allergic older sibling.

From a community or societal perspective, various issues arise. Can the medical system handle performing skin tests and feeding tests on a potentially large number of high-risk children? Could attempts at applying detailed protocol-like feeding instructions to routine care result in unintended consequences, such as increased reactions if peanut is discontinued for various lengths of time? Would this approach potentially increase risks in situations when peanut is not a typical component of the diet? Given the major

public health consequences from adoption of the Consensus communication, prototype programs need to be developed to determine how best to implement them and also measure their benefits, costs, and possible unintended consequences. Public funding will be needed to assure that such outcome programs are supported and encouraged. Maintaining outcome registries could help inform practice.

Despite the aforementioned unknowns, and current lack of guidance about approaches to other foods or lower risk groups, application of the LEAP study to high-risk children presents an unprecedented opportunity to potentially prevent a serious allergy, and it behooves allergists to ensure that application of the guidance is undertaken. Studies suggest that peanut allergy has increased, having tripled in US children.[10] The LEAP trial provides clear evidence that peanut avoidance is associated with allergy in high-risk children. Such children are precisely those for whom allergist-immunologists have previously suggested prolonged avoidance, which, based on the LEAP study, appears to be counterproductive. This guidance, therefore, emphasizes an opportunity to intervene and significantly reduce risks. Although the Consensus communication did not attempt to generalize the findings, it also reminds the reader that multiple guidelines have not recommended delaying allergen introduction in the general to low-risk population.[11-13] The need for a change in culture of early feeding practices with regard to allergy is clearly at hand.

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