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Changing guidelines: Recommendation of early peanut introduction for prevention of peanut allergy in infants with severe eczema

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ABSTRACT A clinical decision report appraising Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *New Eng J Med*. 2015;372(9):803-813. https://doi.org/10.1056/nejmoa1414850.

Keywords: *allergy, peanut allergy, peanut introduction, peanut, allergy prevention, anaphylaxis, eczema, atopy*

Clinical Context

Daniel Yousif (pseudonym), a 6-month-old Chaldean male, presents to the clinic with his mother for observed exposure to peanuts and tree nuts. He has a 5-year-old brother with severe eczema and multiple food allergies, including peanuts and tree nuts, who is treated at the clinic. His oldest brother has no eczema, asthma, or allergies. His mother was anxious about introducing peanuts at home due to traumatic anaphylactic reactions in her middle son. She was advised to bring Daniel into clinic due to her concerns. His history is completely benign with exception of his family atopic history. He was breastfed for two months and has since transitioned to formula. He consumes pureed fresh fruits and vegetables. On physical exam, Daniel is a happy, chubby baby. He is dermatographic and has eczema covering about 80% of his body surface area (BSA) with redness, diffuse dryness, and midline sparing. Some increased redness is noticed in the folds of his fat rolls. His pediatrician had diagnosed this as dry skin, but in clinic was classified as severe eczema, due to a SCORAD>40. Mrs. Yousif and the team discussed how this discovery changed their planned peanut introduction process. They discussed options for peanut introduction, including at-home exposure vs. observed ingestion in the office. Mrs. Yousif had reservations about exposure in the office due to the length of time required and concerns for allergic reaction. The primary physician assured Mrs. Yousif that she would never do anything to hurt Daniel and emphasized the importance of introducing peanuts at this age.

Clinical Question

What is the best protocol to follow in peanut introduction for an infant with severe eczema and family history of atopy?

Research Article

Du Toit GD, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *New Eng J Med*. 2015;372(9):803-813. https://doi.org/10.1056/nejmoa1414850.

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Related Literature

A search of PubMed was performed using the terms “peanut allergy” AND “introduction” in the title or abstract, yielding 120 results. After careful consideration, it was determined there were 8 results of primary research and 3 systematic reviews. Read but not considered for review were 109 papers categorized as secondary analyses, editorial responses, reviews, or consensus statements. Of the 11 articles examined in-depth, there were three randomized controlled trials, four cohort studies, one cross-sectional study, two meta-analyses,[1,2] and one systematic review.[3] An additional cohort study[4] and a cross-sectional study[5] were found in the review of the meta-analyses and systematic reviews. Due to the presence of multiple primary research sources, the meta-analyses and systematic review were excluded from ultimate consideration. As our patient was breastfed only briefly, two studies limited to exclusively breastfed infants were excluded as well.[6,7]

The Joseph study4 was a birth cohort study of 594 infants recruited from obstetrics clinics in Detroit, MI and Augusta, GA. Participants were followed from age 1 months to 3 years. Parents of participants were interviewed about their children’s eating habits at 6 months, 12 months, 2 years, and 3 years. Total and specific IgE concentrations were significantly elevated in those with food avoidance at age 1 compared to those who had consumed the allergen, both those with and without parental atopic history. This study was not chosen as it did not have a true control group and did not perform an oral food challenge (OFC), the gold standard of allergy testing, as a measured outcome.

The Barajas study5 was a comparative cross-sectional study of 304 children with asthma or allergic rhinitis. All children were less than 16 years old, with a median age of 7.3 years. Exclusion criteria for this study were evidence of dermatographism or immunodeficiency. Parents of participants were interviewed regarding their children’s peanut consumption and all eligible participants were evaluated for peanut allergy via open OFC. Participants who had peanut allergy had a later median age of first exposure than participants who did not have a peanut allergy. As our patient had significant dermatographism, he met exclusion criteria for the study, and this study was not chosen.

The HealthNuts study[8] was a general population-based cohort study of 5300 infants who were assessed for peanut allergy via OFC. Their ages ranged from 11 to 15 months with a mean age of 12.6 months. Participants were characterized based on sex, eczema status, age of egg introduction, egg allergy, and prior peanut introduction. Other outcomes included skin-prick test (SPT) wheel size and peanut IgE level. Based on prior findings in the LEAP study, analyzed later, infants were risk-stratified based on eczema status and egg allergy. There was no true control group, as this study was simply a survey of prior parentally-led peanut introductions. Despite having pertinent conclusions to our clinical question, this was not chosen due to establishing a weaker level of evidence.

The Bégin study[9] was a prospective cohort study of 154 peanut-naive younger siblings of peanut-allergic children instructed to have supervised peanut introduction and weekly consumption thereafter. Participants were at least 6 months of age with a median age of 23 months. Measured outcomes were parental anxiety and preference and anaphylaxis occurrence. The results were consistent with concerns expressed by our patient’s mother. However, stronger and more pertinent evidence was presented in the research source ultimately chosen.

The GUSTO study[10] was a population-based birth cohort study of 1152 infants in Singapore assessed for allergy to egg yolk, egg white, milk, peanut, and shellfish via clinical history and SPT. They were followed from birth until the age of 48 months. This specifically targeted patients of Chinese, Malay, and Indian ethnicity due to lack of research in a population with generalized low allergy rates. Participants were characterized based on sex, ethnicity, mode of delivery, maternal education, household income, household smoking, breastfeeding, atopic family history, sibling, childcare, pets, eczema presence, and introduction of allergens into the diet. There was no significant association with the introduction of peanut and the development of peanut allergy in this study. As the patient is Chaldean, this was an exclusion criterion for the study and it was not considered.

The EarlyNuts study[11] was a population-based cross-sectional observational study of 860 infants recruited at immunization appointments assessed for allergen introduction practices. Patients were 11 to 15 months old surveyed from November 2016 and October 2018. Number of participants first introduced to peanut and egg by 12 months significantly increased in low and high risk infants in 2018 compared to a similar study in 2011. This study did not evaluate associated rates of peanut or egg allergy and was thus not chosen as the primary research article.

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The study chosen for clinical appraisal was the LEAP study by Du Toit et al.[12] (2015), cited as the preeminent study with regards to peanut allergy in virtually all sources. The study was a randomized open-label controlled trial of 640 infants with egg allergy, severe eczema, or both assigned to either avoid or consume peanuts until 60 months of age. Participants were 4 to 11 months old at randomization with median age of 7.8 months and divided into separate cohorts based on SPT size of no wheel vs 1-4 mm wheel. Randomization occurred within those cohorts. Within both cohorts, patients who were assigned to peanut consumption had a significantly decreased rate of peanut allergy at 60 months of age when compared with patients assigned to peanut avoidance. The patients in this study were followed further in the LEAP-On study[13] (2016) in which rates of peanut allergy in both cohorts were demonstrated to be maintained despite peanut avoidance for a year after 60 months. Given the above sources of related literature, the body of evidence would be considered a Grade-A Strength of Recommendation based on the SORT criteria.

Critical Appraisal

This publication was a randomized open-label controlled trial with CEBM evidence level of 1b and SORT evidence level of 1. The primary outcome was the prevalence of peanut allergy at age 60 months, as measured by OFC. Inclusion criteria were (1) children from 4-11 months of age with successful introduction of solid foods and (2) egg allergy, severe eczema, or both. Severe eczema was defined as "(1) frequent need for treatment with topical corticosteroids or calcineurin inhibitors, (2) parental description of 'a very bad rash in joints or creases' or 'a very bad itchy, dry, oozing, or crusted rash,' or (3) a severe SCORAD grade (>/= 40) by a clinician before or at the time of screening."[14]

834 participants were screened for the study, with 194 excluded due to either SPT>4 mm or absence of severe eczema. The remaining 640 participants were placed into cohorts based on SPT size. 542 were SPT-negative and 98 were SPT-positive. 270 of the SPT-negative cohort and 51 of the SPT-positive cohort were assigned to peanut avoidance. 272 of the SPT-negative cohort and 47 of the SPT-positive cohort were assigned to peanut consumption. Those assigned to peanut consumption had a baseline OFC, with one in the SPT-negative cohort and 6 in the SPT-positive cohort having a reaction and instructed to avoid peanuts. Peanut consumption was defined as at least 6g of peanut protein weekly, distributed in at least 3 meals. Adherence to the protocol was verified in some, but not all, patients by the measurement of peanut levels in dust collected from the patient's bed. Participants were assessed at baseline, 12 months, 30 months, and 60 months with additional telephone consultations between in-office assessments. At 60 months, participants were evaluated for peanut allergy via a double-blinded, placebo-controlled OFC. Of the SPT-negative cohort, 7 (2.5%) in the avoidance group and 5 (1.8%) in the consumption group were lost to follow-up. Minimal difference between the groups and an overall <5% attrition rate poses a low risk for attrition bias, with any bias accounted for via worst-case imputation analysis. No attrition was found in the SPT-positive cohort.[12]

Intention-to-treat analysis of risk reduction was done using the formulas: Absolute risk reduction (ARR) = (peanut allergy prevalence in avoidance group - peanut allergy prevalence in consumption group). ARR in SPT-negative and SPT-positive cohorts were 11.8% and 24.7%, respectively. Further analysis was performed as per-protocol and worst-case imputation, with consistent results. The analysis found strongly significant primary prevention ($p<0.001$ in SPT-negative cohort) and secondary prevention ($p=0.004$ in SPT-positive cohort) of peanut allergy development with the intervention of peanut consumption up to the age of 60 months.[12]

Patients were recruited via child health professionals, a flyer posted to parents of young infants, and word of mouth. Interested families had to pass a pre-screening questionnaire.[14] There is likely participation bias of participants with personal atopy or family atopic history. That was used to the study's advantage as personal atopy was an inclusion criterion. However, the participants may be enriched for family atopic history, as in our patient, which was not addressed in the study. As our patient had severe eczema, he would meet the inclusion criteria for this study.

The LEAP study was a randomized, open-label, controlled study. Randomization was performed using a stratified randomization method, in which participants were first separated into SPT-positive and SPT-negative cohorts before randomization. The process of randomization was not described in the publication, however, more details are available in their official protocol.[12] Randomization occurred centrally for each individual, with personnel calling the PPDI Interactive Voice Response System (IVRS) which assigned each participant a randomization number based on the randomization schedule. This allowed allocation to remain concealed with randomization well-established. The authors note that "an open-label design was chosen because participants and their parents were necessarily aware of their assigned group."[12] However, one could envision a scenario where blinding could be possible,

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perhaps involving pre-packaged meals containing the absence or presence of the desired amount of peanut protein. This does raise the risk of participant attrition due to personal eating preferences and difficulty of integration into daily life for 4 years. This study could have been additionally strengthened by mandatory bedroom dust analysis at regular intervals to ensure optimal participant compliance.

LEAP was funded by the National Institute of Allergy and Infectious Diseases (NIAID), Food Allergy Research and Education (FARE), the Medical Research Council and Asthma UK, the United Kingdom Department of Health, a National Institute for Health Research comprehensive Biomedical Research Center award, St. Thomas's NHS Foundation Trust, King's College London, King's College Hospital NHS Foundation Trust, the National Peanut Board, and the United Kingdom Food Standards Agency. Bamba peanut snacks were used in the study, purchased at a discounted rate. There could be speculation for possible funding bias by the National Peanut Board and the manufacturer of Bamba snacks. However, the study states that "no manufacturer of peanut products contributed to the design of the study, the accrual or analysis of the data, or the preparation of the manuscript."[12]

Clinical Application

Mrs. Yousif brought her 6-month old son, Daniel, into clinic to discuss introducing peanuts at home due to the presence of multiple food allergies in her middle child. We noted that Daniel had severe eczema with a SCORAD > 40. On skin prick testing, he had a 3 mm x 3 mm result. Our patient met the LEAP inclusion criteria for the SPT-positive group and would have an expected peanut allergy RRR of 70.0% by having regular consumption of 6g of peanut protein weekly in at least 3 separate exposures.[12] LEAP did not address Mrs. Yousif's initial concerns of Daniel being at increased risk due to family atopic history.

Conclusions from the LEAP study were ground-breaking, as prior guidelines for allergen introduction had encouraged peanut avoidance until age 3.[3] The strong significance of the LEAP results has made future randomized controlled trials ethically limited to less extreme deviations. NIAID guidelines15 have been modified, most recently in 2017, based upon the results of the LEAP study. They outline a protocol for the determination of peanut allergen introduction and are widely used by practicing allergists in the US. Based on these guidelines, Daniel was given a 5-step graded exposure. This was furthermore reassuring to Mrs. Yousif, as she realized a reaction would be caught at the earliest possible moment. She was instructed to give peanuts three times weekly and to incorporate other allergenic foods into Daniel's diet on a similar weekly schedule.

The LEAP study demonstrates the enormous potential benefit of early peanut introduction. However, the obvious risk of allergic reaction, specifically anaphylaxis, can be disconcerting for parents, especially those with an older child with food allergy. The initial in-office OFC provides some comfort but does not preclude the later development of a peanut allergy. Parents should be advised to introduce potentially allergenic foods individually and monitor for signs of allergic reaction, including tongue or lip swelling, urticaria, chest tightness, difficulty breathing, wheezing, or vomiting.

New Knowledge Related to Clinical Decision Science

Although initially hesitant, Mrs. Yousif decided to introduce peanuts to Daniel in the office. The decision to introduce peanuts in a young child is one that might be difficult for many parents, especially those with a family member with severe allergies. Prior to LEAP, many parents were advised to avoid peanuts and peanut-containing products in order to avoid development of peanut allergy. Despite the high quality of evidence, this is new advice that can seem counter-intuitive and frightening to concerned parents and other caregivers. This highlights the importance of providing families with reassurance and education when making this decision.

The Clinical Decision Science framework is useful to address the topic of newer clinical research and the changing nature of clinical guidelines. The advice given to Mrs. Yousif changed since she had to make decisions regarding the five year old sibling. Doctors need the skills to discuss changing recommendations, as patients may lose confidence in “science” if given contradictory advice during the course of an illness or in this case a family illness.

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NIAID guidelines[15] recommend introducing peanuts around 6 months of age and after introduction of solid foods. However, current American Academy of Pediatrics (AAP) guidelines[16] encourage exclusive breastfeeding until 6 months of age as well. These conflicting recommendations may confuse some parents. The LEAP study[13] enrolled patients from age 6-11 months of age. As a result, the benefits of early peanut introduction can still be found with introduction past 6 months. NIAID guidelines emphasize that peanut introduction should follow family preferences and cultural practices in moderate and low-risk infants and thus could be compatible with exclusive breastfeeding until 6 months. In high-risk patients, the potential benefits of exclusive breastfeeding must be balanced against the risk of future peanut allergy. This requires open dialogue between the patient's family, primary care physician, and allergist.

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