

Potential Pitfalls in Applying Screening Criteria in Infants at Risk of Peanut Allergy

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Case Description

An 8-month-old male infant was seen prior to peanut ingestion in the allergy clinic because of a history of potential food allergy in his older sibling. His 3-year-old sister had severe eczema and had never ingested peanut, egg, or finned fish, but skin prick testing had been positive in the past and as a result she had avoided them. The patient was scheduled to be seen at 6 months of age but the family missed the appointment.

In light of his sister's presumed peanut allergy, the family had not yet fed him peanut and was reluctant to do so at home. The patient had tolerated some cow's milk in the form of infant formula, and egg yolk a few times. He had not yet eaten other allergenic foods including tree nuts.

The patient had a history of eczema since the first month of life, and had been followed by a pediatric dermatologist since 2 months of age. Skin was moisturized daily with an emollient, but low potency topical corticosteroid was used only infrequently. A moderate potency topical corticosteroid was recommended by the dermatologist but met with strong parental reluctance. His past medical history was otherwise unremarkable. There was no history of chronic cough or wheeze. Immunizations were up to date.

Only pertinent on physical examination was the presence of fairly widespread, erythematous, scaly, papules and patches to the torso with the presence of some excoriation but no evidence of lichenification or skin superinfection. He was scratching throughout the examination. He also had some mild rhinorrhea because of a concurrent mild viral infection. The remainder of the head and neck, cardiac, and respiratory examinations were unremarkable.

After a discussion with the family, the mother opted to do an oral challenge (observed feed) with peanut in the allergy office without pre-emptive skin or specific IgE blood testing, to avoid any further delays in peanut introduction. After the third incremental dose of peanut butter, the infant started crying inconsolably and scratching at his skin. There was no urticaria, angioedema, vomiting, diarrhea, or respiratory symptoms. The oral challenge was terminated and a skin prick test to peanut completed, which was positive at 6 mm mean wheal diameter. The infant was observed for over an hour and discharged home looking well. About 2 hours later, the family called the allergy clinic as the infant had developed facial angioedema and urticaria with associated irritability. He took a nap, and symptoms resolved with no therapy.

LEAP Learning Early About Peanut
NIAID National Institute of Allergy and Infectious Diseases

An epinephrine autoinjector was prescribed, and the family will return to the allergy clinic for consultation about next steps. In the interim, introduction of other allergenic foods besides peanut at home without delay was strongly recommended.

Did This Infant Require Pre-Emptive Testing Prior to Peanut Introduction?

The National Institute of Allergy and Infectious Diseases (NIAID) has recently released an addendum guideline about peanut introduction,¹ largely motivated by the compelling results of the Learning Early About Peanut (LEAP) study.² In this randomized controlled trial of 640 infants at high risk of peanut allergy (because of severe eczema, egg allergy, or both), early introduction of peanut at 4-11 months significantly reduced the rate of peanut allergy compared with avoidance until 5 years of age (3.2% vs 17.2%; $P < .001$).² As a result, the NIAID-sponsored expert panel addendum guidelines recommend that in high-risk infants (with severe eczema and/or egg allergy), peanut should be introduced as early as 4-6 months of age with strong consideration (but not mandatory) for in-office evaluation (ie, pre-emptive skin or specific IgE blood testing) prior to introduction.¹ For infants with mild to moderate eczema, peanut should be introduced around 6 months of age at home without pre-emptive evaluation. For infants without eczema, peanut should be introduced in accordance with parental preference and cultural norms. Therefore, based on the NIAID guideline, this infant would have required pre-emptive testing only if he had severe eczema or egg allergy.

Did This Infant Meet the NIAID Definition of Severe Eczema?

The LEAP study and NIAID guideline differ slightly in the definition of severe eczema (Table). Although the LEAP study used more specific criteria, such as a modified Scoring Atopic Dermatitis score, the NIAID guideline is broader in its definition and relies on healthcare provider assessment of severe eczema.

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Table. Definition of severe eczema

Studies/guidelines	Definition of severe eczema
LEAP ²	A rash that required the application of a topical creams and ointments containing corticosteroids or calcineurin inhibitors and if the participant is: • <6 months of age, lasted for at least 12 out of 30 days on two occasions, or; • >6 months of age, lasted for at least 12 out of 30 days on two occasions in the last 6 months, or; • Has been described by the participant's parent or guardian in a pre-enrollment questionnaire as "a very bad rash in joints and creases" or "a very bad itchy, dry, oozing, or crusted rash", or; • Is currently or was previously graded ≥ 40 using the modified SCORAD evaluation.
NIAID ¹	"Persistent or frequently recurring eczema with typical morphology and distribution assessed as severe by a healthcare provider and requiring frequent need for prescription-strength topical corticosteroids, calcineurin inhibitors, or other anti-inflammatory agents despite appropriate use of emollients."

SCORAD, Scoring Atopic Dermatitis.

Severe eczema in childhood is relatively rare, and the underlying goal of the NIAID guideline was that only a small number of children would be screened prior to peanut introduction. A recent analysis of the US Survey of Children's Health noted that in a national sample of 91 642 children, the prevalence of childhood eczema was 12.97% (95% CI 12.42-13.53) of which only 7.0% (95% CI 5.8-8.3) had severe disease.³ Based on this study, only approximately 0.9% of infants in the US would meet the criteria of severe eczema and require pre-emptive evaluation. Data from a prospective Irish birth cohort study of 68 684 births in the year 2013 found that 18.7% of Irish children had eczema at 6 months of age, of whom only 13.5% (2.4% of the overall population) had severe eczema.⁴

However, Turner et al described the concern of a "screening creep," in which infants who do not have severe eczema are screened prior to peanut introduction partially because of overdiagnosis of eczema severity.⁵ The authors make a compelling case that with the large prevalence of eczema, even a small shift in the definition could result in a large number of infants being overscreened. As an example, an Australian population-based repository of 5276 infants recently determined that if moderate/severe eczema was defined more broadly, screening all infants with either moderate/severe eczema and/or egg allergy would require testing 16% of the population.⁶

In addition, questions have been raised about the NIAID definition relying on "frequent need" for prescription-strength topical medications. Low adherence rates with topical therapies for treatment of pediatric eczema have been well documented. A study of 37 children with eczema prescribed a topical corticosteroid that contained an electronic monitor noted mean adherence rates of 32%.⁷ A recent review of adherence to topical therapies in eczema noted that among 7 studies in the pediatric population, rates of adherence varied from 32% to 93%, with good compliance rates only noted with very short treatment periods, for example, the adherence rate of 93% had a 3-day treatment period.⁸ As a result, how can the criterion of "frequent need" for prescription-strength medications be relied

upon? In addition, it is not defined how parental refusal to use topical therapies, such as in the case of the infant above, impact this definition. If the above infant had been treated with the moderate potency topical corticosteroid recommended by the pediatric dermatologist, one could theorize that the infant would not have had moderate to severe eczema.

There are several consequences to potential overscreening prior to peanut introduction. Although the NIAID guideline is clear that testing is not required prior to introduction of foods other than peanut, if pre-emptive testing is initiated, "parental pressures and perhaps physician over cautiousness" may result in testing for foods other than peanut.⁶ It has been demonstrated that <40% of patients with positive peanut screening are clinically allergic.⁹ Testing could inadvertently result in overdiagnosis of peanut allergy because of high false positive rates, combined with poor availability of infant oral food challenge procedures. With the necessary screening steps (specialist referral, allergy testing, potentially an observed oral challenge) pre-emptive evaluation could inadvertently delay peanut introduction. There may be issues both with logistics and resource availability for screening on a large scale.⁵ This lack of access may result in peanut being avoided for an extended period of time unnecessarily, therefore, actually increasing the risk of peanut allergy.

Great care must be taken to ensure that only those infants with severe cutaneous disease, which is refractory to regular emollient use, should have pre-emptive testing prior to peanut introduction. In our opinion, based on this definition, the infant in this case would not have met the definition of severe eczema and did not require pre-emptive peanut screening.

Was Sibling Peanut Allergy an Indication for Pre-Emptive Screening in This Infant?

There are several studies that support an increased rate of sensitization (ie, positive skin prick testing or positive serum specific IgE to peanut) in siblings of children with peanut allergy. The large cohort Study of Asthma, Genes and the Environment found that in 514 families, rate of peanut allergy was significantly higher in siblings of children with peanut allergy (OR 6.72, 95% CI 2.04-22.12).¹⁰ In addition, a nationwide survey of 622 adults and children with peanut allergy and their families found a prevalence of peanut allergy in siblings to be 7%, which was significantly higher than the rate among their parents, aunts and uncles ($P < .001$) and significantly higher than the rate of nut allergy reported in the general population.¹¹ As a result, previous guidelines have noted that a sibling with peanut allergy, while not a direct indication for pre-emptive peanut screening, "may complicate decision making."¹²

However, a recent large cohort study calls into question these previous findings. This study of 2834 children in Chicago assessed the prevalence of food sensitization and clinical allergy among siblings of food allergic children.¹³ They found that 33.4% of siblings had neither sensitization nor clinical food allergy, 53.0% had sensitization but no clinical food allergy, and only 13.6% of siblings had both food sensitization and

clinical food allergy. In addition, among the siblings that were food allergic, it was not necessarily to the same food as the index sibling. For example, among siblings of children with peanut allergy, although 4.9% were allergic to peanut, the same number were allergic to egg and 4.0% were allergic to cow's milk. The conclusion of this study was that pre-emptive testing in siblings was "unjustified" and may lead to negative consequences such as food avoidance because of false positive sensitization.

In addition, it has been hypothesized that previously reported increased rates of peanut allergy in siblings may be due to delayed peanut introduction, or inaccurate diagnosis, instead of genetic susceptibility. This is supported by a large study of 932 Registry families within the Canadian Peanut Allergy Registry that found that although about 9% of siblings in a questionnaire were reported as peanut allergic, almost one-half had no history of an allergic reaction to peanut.¹⁴ If the siblings were born after a child with peanut allergy they were more likely to have never been exposed to peanut (OR 6.2; 95% CI 4.1-9.4) and/or to be labeled as peanut allergic without confirmatory testing or supportive clinical history (OR 12.7; 95% CI 1.3-120.7). In addition, a recent study of 154 siblings of children with peanut allergy, who had never eaten peanut themselves, found a much higher rate of reactions upon peanut exposure if they were older, further supporting the notion that siblings may be at risk due to delayed introduction.¹⁵

The current American Academy of Allergy, Asthma, and Immunology position statement on prevention of allergic disease has concluded that although there may be reluctance to introduce peanut in siblings of children with peanut allergy, initial introduction of peanut at home (ie, without pre-emptive testing) is "encouraged."¹⁶ The NIAID guideline does not list sibling of children with peanut allergy as an indication for pre-emptive peanut screening, although it does acknowledge the role of discussion with a caregiver prior to introduction.

Parents can be counseled that introducing peanut in a sibling of a children with peanut allergy at the young age recommended by the NIAID guideline (around 6 months of age) carries low risk, may benefit their child, and that fatal reactions to first exposure to peanut have not been reported.¹⁶ In light of the potential harms of screening prior to introduction in siblings of children with peanut allergy related to overdiagnosis, no screening in siblings of children with peanut allergy is required. In this case, having a sibling with a potential peanut allergy would not have been an indication for pre-emptive testing.

How Do You Define Egg Allergy as a Criterion for Pre-Emptive Peanut Screening?

The LEAP study's definition of high risk was validated in a prior proof of concept study that found both IgE-mediated egg allergy and severe eczema to be strong risk factors for peanut sensitization in 834 infants (OR 2.31 [95% CI 1.39-3.86] and OR 2.47 [95% CI 1.14-5.34], respectively).¹⁷ As a result, egg allergy

was included as an indication for pre-emptive screening prior to peanut introduction in the NIAID guideline. However, this indication applies only to infants with a history of a clinical reaction to egg and a positive skin prick test to egg, or a positive oral challenge to egg. It also only applies to IgE-mediated egg allergy, and not other types of egg allergy such as food protein-induced enterocolitis syndrome.

The overall prevalence of egg allergy is about 1.0% in older children¹⁸ and at 4-6 months of age it is likely that many infants will not have ingested egg when peanut introduction is recommended. Parents or practitioners may erroneously believe that egg should be introduced prior to peanut because of the presence of this criterion, and it must be reiterated that the NIAID guideline does not require, nor recommend, egg introduction prior to peanut introduction.

Was This Infant's Reaction Convincing for Peanut Allergy?

Guidelines on oral food challenges in children recommend control of eczema prior to an observed ingestion.¹⁹ Poorly controlled eczema makes interpretation of an oral challenge very difficult. For example, in this case, the infant's pruritus and irritability may have been due to underlying eczema. Urticaria (and related angioedema) may have been due to underlying dermatographism, or irritation of the skin because of scratching. However, irritability, urticarial, and angioedema are all symptoms of IgE-mediated food allergy²⁰ and, indeed, this reaction may likely have been indicative of clinical allergy.

Eczema also makes results of allergy skin testing difficult to interpret. Although skin prick test to peanut was positive in this infant, the rate of false positive skin prick testing is higher in children with eczema with reported false positive rates of up to 40%.⁹

This case illustrates the difficulty in introducing peanut and performing oral challenges in infants with uncontrolled eczema. If a family is reluctant to treat eczema despite seeing a pediatric dermatologist and other measures, feasibility of oral challenge is compromised. Booking the infant for challenge on another date after increasing topical eczema care may reduce uncertainty about the challenge results. However, it also causes further delay and increases the risk of future peanut allergy, and may not be fruitful if the family continues to refuse to use topical medications long term. If an oral challenge is performed despite uncontrolled eczema, the results of the challenge may be difficult to interpret. As severe eczema is a criterion for pre-emptive screening in the NIAID guideline, this will become an ever-emerging challenge in the months and years ahead.

If the Infant Had Not Missed His 6-Month Appointment Would the Outcome Have Been Different?

Primary analysis of the LEAP cohort data suggests that earlier introduction within the 4- to 11-month window may be

beneficial. The percentage of subjects in the LEAP study with positive skin tests to peanut at enrollment increased progressively as the age in months of enrollment increased between 4 and 11 months.² In addition, 76 children were excluded at baseline due to skin test sizes highly suggestive of peanut allergy and all were over 5 months of age. This suggests that, within the 4- to 11-month window, earlier peanut introduction may confer an added benefit. However, a secondary analysis of LEAP data through multiple logistic regression suggested that in the early introduction group, the probability of peanut tolerance was significantly higher with peanut introduction at 6-11 months of age compared with 4-6 months of age.²¹

A recent meta-analysis and systematic review of timing of introduction of allergenic foods and risk of allergic disease has found moderate certainty evidence (2 trials; 1550 patients) that peanut introduction between 4 and 11 months of age reduces the risk of peanut allergy (relative risk 0.29; $P = .009$).²² Within this window, however, it is unclear if earlier evaluation would have been beneficial, based on a paucity of conclusive data. Practical issues, such as potential long waitlist times for the necessary screening steps may also influence expediency of evaluation. At present, the question of whether the outcome would have been different at 6 months of age for this infant cannot be answered, but it would seem prudent to avoid unintended delays beyond a few months.

Does This Infant Need to Avoid Tree Nuts Pending Further Evaluation?

Tree nuts (almond, hazelnut, pistachio, cashew, walnut, pecan, brazil nut) are commonly avoided in children with peanut allergy. Tree nut allergy has been reported in between 23% and 50% of patients with peanut allergy who are otherwise atopic, although the rate of co-allergy is significantly lower (2.5%) in nonatopic populations.²³ A study of 324 children and adults referred for peanut/tree nut allergy to a tertiary care center noted that 86% of those with peanut allergy were sensitized to tree nuts, and 34% had a documented clinical allergy to tree nuts.²⁴

However, a recent study questions the notion of peanut and tree nut co-allergy. Couch et al performed a retrospective review of open oral food challenges to tree nuts in a tertiary care allergy referral center.²⁵ Of 109 children (mean age 11.2 years), the vast majority with tree nut sensitization tolerated tree nuts on oral challenge (overall pass rate of 86%). In 68 oral challenges to tree nuts in 46 children with peanut allergy and tree nut co-sensitization, 96% tolerated the tree nut on oral challenge. The conclusion of this study was that because almost all children with peanut allergy tolerated tree nuts despite positive sensitization, the concept of co-allergy should be questioned.

Studies on this are ongoing, such as the ProNut study, a multicenter study of children aged 12 months to 16 years with a convincing clinical history of a nut or seed allergy whose primary aim is to determine clinical cross-reactivity to other nuts based on oral food challenges ([ClinicalTrials.gov: NCT01744990](https://clinicaltrials.gov/ct2/show/study/NCT01744990)).

As noted in a review by Sicherer et al, “the clinician must consider the age of the patient, history, and perhaps sensitization in considering categorical elimination.”²³ For example, there may be a role for pre-emptive testing to tree nuts in older children with peanut allergy, largely because of prolonged avoidance of tree nuts. In addition, the pros and cons of categorical nut elimination must be considered with the family. The benefits include decreased risk of accidental reactions because of cross-contamination and potential ease and the risks include potential decreased quality of life and possible increased risk of becoming allergic to tree nuts that would have otherwise been tolerated.²⁶ In our opinion, this infant could have nonchoking tree nuts introduced in an age appropriate manner without pre-emptive testing because of low likelihood of co-allergy at such a young age and potential increased future risk of tree nut allergy from delayed introduction.

Could Regular Emollient Use Have Been Recommended as a Strategy to Prevent Food Allergy in This Infant?

There is emerging evidence that eczema is due to skin barrier dysfunction and that food sensitization can occur through the skin.²⁷ Decreased ceramide levels and claudin-1 levels contribute to defective epidermal barrier and increased transepidermal water loss in children with eczema.²⁷ In addition, mutations in the filaggrin (FLG) gene (involved in skin hydration and water retention) have been strongly linked with eczema.²⁸ A meta-analysis of 24 studies has noted increased risk of eczema (OR 4.78; 95% CI 3.31-6.92) in patients with FLG mutations, with potentially stronger associations noted for moderate-to-severe eczema.²⁹ A longitudinal birth cohort of approximately 7000 children found FLG null alleles to be associated with early, persistent disease (hazard ratio for eczema resolution 0.67; 95% CI 0.58-0.77) as well as increased asthma risk (OR 1.80; 95% CI 1.34-2.41) and aeroallergen sensitization (OR 2.12; 95% CI 1.03-4.37).³⁰ There has been increasing awareness that FLG loss of function mutations are also associated with food allergy.³¹ It is hypothesized that this association may explain the concept of transcutaneous sensitization to foods. For example, the Avon Longitudinal Study of Parents and Children cohort of 13 971 children found that children who had oral challenge-confirmed peanut allergy by age 5 years were more likely to have severe eczema in infancy, and to have used skin preparations containing peanut oil (OR 6.8; 95% CI 1.4-32.9), suggesting transcutaneous sensitization to peanut.³²

Three small studies have suggested that regular use of emollients from birth can reduce the risk of eczema. A recent randomized controlled trial of twice daily ceramide dominant emollient application for the first 6 months of life found a trend toward reduced eczema and food sensitization at both 6 and 12 years of life.³³ A randomized controlled trial of 124 neonates at high risk of eczema (parental or sibling atopy) found that full-body emollient therapy at least once a day in the first 3 weeks of life significantly reduced the incidence of eczema

at 6 months of age compared with no emollient use (relative risk, 0.50; 95% CI 0.28-0.9; $P = .17$).³⁴ A randomized controlled trial of 118 infants at high risk of eczema (parental or sibling atopy) also found that regular emollient use from the first week of life for 32 weeks significantly reduced the cumulative incidence of eczema (32% reduction, $P = .012$).³⁵ This study did not find a statistically significant difference in rate of egg sensitization, but that was a secondary outcome only, which going forward requires more investigation with carefully designed trials.

Based on these small studies, regular emollient use starting in early infancy may have been a means of eczema prevention, although further studies are required to determine the implications for food allergy prevention. This approach provides a potential noninvasive and safe intervention that may reduce rate of eczema, and thereby potentially food sensitization and food allergy.

Conclusions

In the past few years, there have been several studies supporting early food introduction as a means of allergy prevention. The NIAID guideline provides comprehensive instruction on the introduction of peanut into the diet of infants, stratified based on infant risk. However, implementing this guideline has presented some challenges as outlined in this article. The goal of the NIAID guideline was that the vast majority of infants would have peanut introduced in an age appropriate way at about 6 months of age at home, without pre-emptive testing. There are concerns that misinterpretation of this message may inadvertently delay peanut introduction in infancy. In addition, clinicians should be aware of the various potential pitfalls that could occur when applying screening criteria in the real world.

Care must be taken to ensure that only infants with severe eczema and/or egg allergy are screened prior to peanut introduction. Family history of peanut allergy is not an indication for pre-emptive testing. Egg introduction is not required prior to peanut introduction. Ideally eczema would be well controlled prior to allergy assessment as poorly controlled eczema presents major challenges for food allergy evaluation.

Our best evidence to date suggests that for infants at high risk who require an oral challenge, it should be done as soon as possible, but results must be interpreted carefully to avoid overdiagnosis. If symptoms are not consistent with peanut allergy, early introduction on its own is not enough. Regular ongoing peanut ingestion for several years appears to be equally important for long-term prevention and maintenance of tolerance.

To avoid overdiagnosis, clinicians assessing infants for food introduction should always be mindful of the potential pitfalls of screening infants for peanut allergy. The gold standard procedure of infant oral challenges should be used as often as possible in a timely fashion for high-risk infants or infants whose families are reluctant to introduce nonchoking peanut at home, to circumvent screening pitfalls. ■

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