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Atopic Dermatitis and Food Allergy: Best Practices and Knowledge Gaps—A Work Group Report from the AAAAI Allergic Skin Diseases Committee and Leadership Institute Project

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Allergists are often asked to evaluate children with atopic dermatitis (AD) for allergen triggers to disease. Testing, particularly for food triggers, often leads to elimination diets in an effort to improve AD control. However, the dual exposure hypothesis suggests that oral tolerance to food antigens is promoted through high-dose oral exposure, where sensitization occurs through lower dose cutaneous exposure. This suggests that strict elimination diets may pose some risks in children with AD. In addition, emerging evidence suggests an important role of skin inflammation in further allergic disease and the importance of dietary exposure to maintain oral tolerance. This work group report reviews current guidelines-based management for children with moderate-to-severe AD, the evidence for current recommendations for the evaluation and management of these children, provides a nuanced examination of these studies, and addresses current knowledge gaps in the care of these children. **(J Allergy Clin Immunol Pract 2022;10:697-706)**

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Abbreviations used
AAAAI- American Academy of Allergy, Asthma and Immunology
AAD- American Academy of Dermatology
ACAAI- American College of Allergy, Asthma and Immunology
AD- Atopic dermatitis
DBPCFC- Double-blind placebo-controlled food challenge
DC- Dendritic cell
EP- Expert panel
FA- Food allergy
ILC- Innate lymphoid cell
LEAP- Learning Early About Peanut Allergy Study
NIAID- National Institutes of Allergy and Infectious Diseases
NIH- National Institutes of Health
OFC- Oral food challenge
sIgE- Specific IgE
SPT- Skin prick test
Th2- T-helper type 2
TSLP- Thymic stromal lymphopoietin

Atopic dermatitis (AD) prevalence has increased from 7.4% in 1997-1999 to 12.5% in 2009-2011 on the National Health Interview survey.[1,2] There is also no doubt that the prevalence of food allergies has increased.[3,4] Rates of food allergy (FA) diagnosis, emergency room visits for FA, and hospital FA-related discharges have all increased.[2,5] Determining the true prevalence rate has been difficult due to the various symptoms and manifestations of FA, the intricacies of an FA diagnosis, survey selection, nonparticipation bias, and variations in methodologies and definitions in studies.[4,5] Despite these difficulties, it is clear that FA has increased. Using data from the US National Health Interview survey, the US Centers for Disease Control and Prevention reported that the prevalence of food allergies increased from 3.4% in 1997-1999 to 5.1% in 2009-2011.[2] More recently, in a survey of 38,408 US households using allergic reaction symptoms to establish a convincing pediatric FA diagnosis, the prevalence of FA in children was 7.6%.[6] Interestingly, prevalence rates were higher among children with other atopic comorbidities (asthma, allergic rhinitis, and AD) and among African American children.[6] In this population, the prevalence of physician-diagnosed AD in children with convincing FA was 16.2% in all ages and 22.7% of children aged 0 to 2 years.[7]

Using an oral food challenge (OFC) to 3 foods (peanut, egg, and sesame seed), an Australian population-based study (HealthNuts) found an 11% prevalence of FA at 1 year and a 3.8% prevalence at 4 years of age.[8] In addition, the children in HealthNuts were assessed by history and examination for eczema at age 1 year. Twenty percent of children with eczema were allergic to peanut, egg white, or sesame seed in comparison with 4% of children without eczema. One year olds with eczema were 6 times more likely to have an egg allergy and 11 times more likely to have a peanut allergy than those without eczema, highlighting that AD is a risk factor for FA.[9]

FOOD ALLERGY AND ATOPIC DERMATITIS COEXPRESSION, CAUSATION, AND MECHANISTIC LINKS

A landmark early study of 113 children with severe AD demonstrated 101 positive double-blind placebo-controlled food challenges (DBPCFCs). Eighty-four percent of challenges developed skin symptoms (often immediate symptoms, but also worsening AD), 52% of challenges included gastrointestinal symptoms, and 32% respiratory symptoms, illustrating clear coexpression of FA and AD.[10] More recently, a systematic review concluded that there is a strong association between AD, food sensitization, and FA, especially with increased severity and chronicity of AD.[11] The authors reviewed 18 population-controlled studies and found that the rate of food sensitization was up to 6 times higher in patients with AD versus healthy control subjects at 3 months of age. AD of earlier onset and/or increased persistence was particularly associated with FA. Importantly, the Danish Allergy Research Center cohort followed 562 babies from the Danish general population and found that AD preceded FA.[11]

Beyond coexpression, oral standardized provocation tests with foods have established that foods can be a potential cause for exacerbation of AD.[12] Older studies suggested a stronger link, whereas recent evidence suggests that this may be less common. A landmark study from 1988 evaluated OFCs in pediatric patients with AD recruited primarily from allergy clinics, revealing 33% with worsening eczema, most commonly to cow's milk, egg, and peanut.[13] An additional study also performed that year had shown that 37% of children with moderate-to-severe AD recruited primarily from dermatology clinics had FA, confirmed by food challenges.[14] The most common causes of FA were cow's milk, egg, peanut, wheat, soy, and fish.[15] The prevalence of AD has been shown to be highest in children with wheat, soy, and egg allergy.[7] It is important to note that these early studies considered all types of FA, including immediate reactions, mixed reactions, and worsening eczema. Therefore, it is not clear how common true food-triggered AD is as the only symptom of the FA, and subsequent studies have called this link into question.

In a more recent study of 1186 DBPCFCs in 682 children in the Netherlands, DBPCFCs were performed for suspicion of FA due to AD or immediate allergic reactions, and clinical reactions to foods in patients with AD were characterized.[16] The authors found that children with AD were more frequently asymptomatically sensitized compared with children without AD. Immediate reactions, typically occuring within 2 hours of food ingestion, included most commonly included urticaria, angioedema, gastrointestinal and respiratory symptoms. Pruritus, usually occurring within 2 hours of food ingestion, can lead to exacerbation of AD.[15] However, although late reactions involving an AD exacerbation did sometimes occur between 6 and 48 hours after food ingestion, these reactions most commonly occurred after immediate reactions. Children with AD and a history of worsening AD as their only symptom reacted as often to placebo as to the food allergen. Therefore, the authors concluded that children with an exacerbation of AD in the absence of other allergic symptoms were unlikely to be food allergic.[16] A discussion of clinical practice guidelines based in part on these data is included below.

FA in adults with AD is less well studied. In a study of 179 adults with AD and reported wheat allergy, only 4% reacted during an oral wheat challenge.[17] In another study in adults with AD, only 1% had an allergy to milk.[18] Of note, other foods that have been implicated in exacerbating AD include birch pollen—related foods, including apple, carrot, hazelnut, and celery, particularly in Europe.[19] Although older recommendations have suggested consideration of testing for FA in patients with moderate-to-severe AD with persistent symptoms despite adequate skin care and currently consistently eating a potential suspect food,[20] these recommendations are no longer relevant.

TABLE I. Skin care recommendations in atopic dermatitis

Bathing and moisturizing
- Bath or shower for 5-10 minutes in lukewarm water, a comfortable temperature but not too hot
- Optimal bathing frequency is once daily*
- If topical medications are being used, they should be applied first to inflamed skin within minutes of patting dry
- A fragrance-free cream or ointment moisturizer should be applied to all other skin subsequently
- Bath additives should be minimized or discussed with the provider

Cleansing
- A gentle, fragrance-free cleanser should be used†
- Bubble baths should be avoided
- Dilute bleach baths may be recommended

Avoid irritants
- Minimize exposure to harsh fabrics (eg, wool)
- Children with environmental allergies may benefit from a quick shower/bath after outdoor play followed by appropriate care above
- After swimming pool exposure it is recommended that children rinse off at the pool and moisturize after rinse at the pool
- Dressing appropriately to avoid temperature extremes and occluded sweat when possible may be helpful for some

Application of appropriate topical anti-inflammatory medications
- Apply a thin layer of the appropriate strength anti-inflammatory medication to the affected area(s) until clear, and then 3-5 days after clearing, up to 14 consecutive days unless otherwise directed‡
- Typically topical corticosteroids will be used initially, but topical calcineurin inhibitors and crisaborole are other anti-inflammatory options that can be considered for maintenance therapy

*For those children who do not bathe every day, a moisturizer should still be applied twice daily.
†Infants may need little to no cleanser or shampoo; true soaps should be avoided in all patients.
‡For further reading: Boguniewicz M, Fonacier L, Guttman-Yassky E, Ong PY, Silverberg J, Farrar JR. Atopic dermatitis yardstick: practical recommendations for an evolving therapeutic landscape. Ann Allergy Asthma Immunol 2018;120:10-22.e2.

The immunologic mechanisms that link FA and AD are not well known. Initial sensitization to food allergens is thought to occur through the cutaneous route. In support of this idea, the amount of environmental peanut allergen exposure in living room dust increased the risk of peanut sensitization and peanut allergy in children with a history of AD.[21] In addition, filaggrin is an important protein in the epidermis, and *FLG* gene mutations have been associated with both AD and FA.[22-25] These data further support the role of the skin barrier in FA.

Further emphasizing the role of an impaired skin barrier, a recent retrospective study of infants less than 12 months of age suggested that starting aggressive use of topical steroids to clear eczema within 4 months of diagnosis resulted in fewer food allergies.[26] However, a prospective study designed to evaluate the role of early allergen introduction on FA found that more aggressive moisturization was associated with FA. But children receiving more moisturizer had higher SCORing Atopic Dermatitis (SCORAD) scores. In addition, olive oil was the most frequently used moisturizer, which has been shown to damage the skin barrier, illustrating that the type of moisturizer used may play an important role.[27] Furthermore, the study was not designed to assess the role of moisturization on FA.[28] More studies are needed to determine the optimal moisturizing regimen in patients with established AD and the relationship to FA. To further understand the mechanistic link of these diseases, Leung et al[29] used a minimally invasive skin tape strip sampling and a multiomics approach to evaluate uninvolved skin of children with AD with or without FA (AD FA+ or AD FA−) and nonatopic controls. Transepidermal water loss was increased in AD FA+. Reduced filaggrin breakdown products and other properties associated with an immature skin barrier as well as type 2 immune activation were found in nonlesional skin of children with AD FA+.

Shotgun metagenomic studies revealed that the nonlesional skin of AD FA+ had increased abundance of *Staphylococcus aureus* compared with nonatopic controls.[29] In addition, an analysis of *S. aureus* colonization in children with AD in the Learning Early About Peanut Allergy (LEAP) study showed that *S. aureus* colonization was significantly associated with eczema severity across the LEAP study, and children with *S. aureus* were more likely to have persistent egg allergy and peanut allergy at 60 and 72 months of age independent of eczema severity. Of note, 8 of 9 children who were consuming peanut and went on to develop peanut allergy were colonized with *S. aureus*. The authors speculate that *S. aureus* may potentiate peanut allergy or *S. aureus* may inhibit tolerance mechanisms during peanut consumption.[3] Future studies are needed to understand the interplay of AD, skin barrier abnormalities, type 2 immune activation, *S. aureus*, and FA.

CURRENT CLINICAL GUIDELINES FOR MODERATE-SEVERE ATOPIC DERMATITIS AND FOOD ALLERGY TESTING

In 2010, a multidisciplinary expert panel (EP) convened by the National Institutes of Allergy and Infectious Diseases (NIAID) published consensus FA guidelines that addressed the role of food as a trigger for AD. For children less than 5 years of age with moderate-to-severe eczema, the EP recommended that clinicians consider evaluation for milk, egg, peanut, wheat, and soy sensitization, if at least one of the following conditions were present: (1) the child has persistent AD in spite of optimized management and topical therapy or (2) the child has a reliable history of an immediate reaction after ingestion of a specific food. No specific recommendation was made for older children or adults.[30] It is known that when testing for food allergies with skin prick tests (SPT) or specific IgE (sIgE) levels, the potential for false-positive results is high, particularly in patients with AD, and these older guidelines may be less relevant based on current evidence. In 2017, the EP reconvened to incorporate evolving recommendations relating to primary peanut allergy prevention based on the LEAP study.[31] For infants with severe eczema, egg allergy, or both, exposure to age-appropriate peanut-containing foods was recommended as early as 4 to 6 months of age (after appropriate evaluation).[1] The American Academy of Dermatology (AAD) adopted the 2010 National Institutes of Health (NIH) recommendations in their 2014 AD consensus management guidelines, though these predated the LEAP study and therefore contain no peanut-specific discussion.[32]

A joint task force of the American Academy of Allergy Asthma and Immunology (AAAAI) and American College of Allergy, Asthma and Immunology (ACAAI) published an AD practice update that adopted similar language to the NIH guidelines for children with moderate-to-severe AD under the age of 5 years, but cautioned that the clinician should only test for relevant allergens because IgE testing, especially for foods, has low

specificity. This task force further recommended against elimination diets based exclusively on skin or blood IgE testing due to the high false-positive rate and risk of iatrogenic harm.[33] In fact, recent articles illustrate that food removal in AD may promote immediate FA symptoms, in as many as 13% to 20% of participants with AD.[31,34,35] Consistent with this observation, Chang et al[34] report that 19% of children diagnosed with food-triggered AD converted from no history of immediate reaction to immediate reactions after eliminating a food. Importantly, approximately 30% of these children developed anaphylaxis on re-exposure, illustrating potential harm from food elimination. Other children who had a history of immediate reactions developed immediate reactions to new foods after elimination.[34] The American Academy of Pediatrics likewise cites the 2010 NIH guidelines in their recommendations for AD care.[36] The AAD and AAAAI/ACAAI guidelines emphasize the importance of good skin care including use of frequent emollients, appropriate use of topical medications, irritant avoidance, and wet wraps. General skin care recommendations are described in Table I. The guidelines also note the key role of education to promote adherence. Recently published guidelines from the European Academy of Dermatology and Venereology still advise patients with moderate-to-severe AD to observe a therapeutic diet eliminating those foods that elicited clinical early or late reactions on controlled oral provocation tests.[37] Thus, guidelines from different bodies are contradictory, and updated guidelines in light of recent evidence are urgently needed. It is likely that more recent work will inform future guidelines due to the close association between eczema, food sensitization, and FA. The link to developing food allergies is stronger with eczema that starts earlier, is more severe, and persists for longer.[11,38-40]

BENEFITS OF TESTING AND FOOD ELIMINATION

Clinical benefits

As foods have been shown to trigger AD exacerbations as described, food testing can be helpful to determine potential food triggers in some patients. Foods that may be considered for testing should include foods implicated by medical history (and not indiscriminately). One recent study found that 91% of children with moderate-to-severe AD were sensitized to at least 1 common food allergen, with over half of those reporting acute clinical reactivity to a food.[4]

Another study evaluated whether sIgE levels to foods could predict immediate hypersensitivity food reactions in children with moderate-to-severe AD.[39] Patients who had clinical symptoms to either egg, milk, wheat, peanut, or soy were included in the study, and food sIgE levels were assessed. Food sIgE levels, particularly to milk, egg, and peanut, were significantly higher in the patients with AD who demonstrated immediate clinical reactivity to these foods compared with children with AD without clinical reactivity. They were also higher than the commonly used values felt to be strongly predictive of FA reactions (32 kUA/L for milk, 7 kUA/L for egg, and 15 kUA/L for peanut). For example, the authors estimated that AD subjects with sIgE values of milk IgE of 43 kUA/L, egg IgE of 28 kUA/L, and peanut IgE of 36 kUA/L had at least a 50% chance of not being allergic to the food.[39] More work is required to validate these findings. Of note, negative skin test and/or negative sIgE testing is usually sufficient to exclude FA. IgG testing has not shown any scientific validity and should not be performed.[41]

Elimination diets to a suspected food with a positive allergy test can be a practical diagnostic tool; however, subsequently improved AD may be due to a placebo effect or other factors.[41] Therefore, current guidelines recommend OFC after dietary elimination to confirm the diagnosis. The standardized OFC, either open or DBPCFCs, can be used with AD. Before a food challenge, patients should have relatively stable AD symptoms as well as be avoiding systemic anti-inflammatory medications, including antihistamines.[41]

Potential Immunologic changes after food removal: what we can learn from *in vitro* and animal models

When a food is removed in an attempt to improve AD, immunologic changes are observed, but the degree to which these changes impact AD clinically is unclear. Subjects with AD and lesional skin have been shown to overexpress thymic stromal lymphopoietin (TSLP).[42,43] TSLP can activate various cell types by binding to its receptor on target cells. Dendritic cells (DCs) are one of the primary targets for TSLP, and on receptor activation, TSLP can upregulate the expression of CD80, CD86, and OX40L on DCs, thereby promoting T-helper type 2 (Th2) polarization and the production of the Th2 cytokines IL-4, IL-5, and IL-13 in both human *in vitro* and animal models.[44-47] The presence of Th2 cytokines can also increase the high-affinity IgE receptors on antigen-presenting cells, and further promote the synthesis of IgE antibodies.[48] In addition, TSLP has been shown to stimulate Th2 cytokine responses by targeting innate lymphoid cells (ILCs), epithelial cells, macrophages, mast cells, and basophils in animal models.[49-51] Thus, control of AD may decrease TSLP expression and thereby Th2 inflammation.

Another known epithelial-derived cytokine involved in the epithelial inflammatory response is IL-33. The expression of IL-33 is also increased in AD, in both humans and mice.[52-54] The IL-33 receptor, or ST2, can be expressed on Th2 cells, ILC2s, DCs, basophils, macrophages, mast cells, and regulatory T cells.[55-57] Mouse studies have shown that overexpression of epithelial derived IL-33 can promote dermatitis and ILC2 infiltration.[58] In addition, antibodies targeted against ST2 on mouse DCs led to reduced priming of T cells *in vitro*, compared with isotype control-treated mice in a peanut-allergy mouse model.[59] In addition to TSLP and IL-33, epithelial and endothelial cells can also express IL-25.[60,61] IL-25 expression is increased in AD and inhibits filaggrin expression.[62,63] Thus, disruption of the epithelial barrier promotes the release of IL-25, IL-33, and TSLP from damaged keratinocytes and can stimulate the migration of DCs to lymph nodes, thereby activating a Th2 response via antigen presentation to naïve T cells. By extension, improved AD control with elimination diets in patients with food triggers may potentially decrease overall Th2 inflammation.

Supporting this, data from animal studies of atopy have demonstrated the role of TSLP, IL-33, and IL-25 in the development of allergic inflammation and possibly the atopic march. Mouse models of skin sensitization have shown that TSLP is induced after tape stripping or topical application of MC903 (a low calcemic analog of vitamin D3), which can drive local skin inflammation resembling AD. Epicutaneous sensitization to ovalbumin (OVA) via tape stripping can also lead to the development of dermatitis in mice. Importantly, the same mice had increased numbers of eosinophils in the bronchoalveolar lavage fluid and increased airway responsiveness after challenge with aerosolized OVA.[64]

In summary, studies have demonstrated the role of the skin barrier in the development of type 2 inflammation. Defects in the integrity and health of the skin barrier provide a route for antigen exposure and sensitization. In addition, the role of microbial diversity, genetic defects of barrier dysfunction, and alterations of epidermal immunity are all important in the development of type 2 inflammation, and additional studies are needed to further understand the interplay between how these components work individually and in concert with each other to promote allergic inflammation.

RISKS OF TESTING AND FOOD ELIMINATION

Risks of food testing

In all patients, diagnosis of FA requires clinical judgment, as available testing is sensitive, but with low specificity. SPT to foods have a high negative predictive value, and negative testing is often considered sufficient to rule out FA. However, most of these studies have evaluated immediate reactions. In the setting of AD, a study of over 1000 children aged 3 to 18 months with mild-severe AD by Spergel et al[65] demonstrated that IgE testing may not identify trigger foods. In this study, approximately 16% of infants developed FA, and screening sIgE did not predict the probability of FA for most foods, although increased severity of AD was associated with FA.[65] Further demonstrating the difficultly in predicting which patients with AD truly have an FA, Keck et al[66] demonstrated that 9 of 88 children with mild-severe AD had clinical reactions to egg, peanut, and milk. No child reacted to other foods, including wheat or soy during 3 years of follow-up.[66] Interestingly, although only approximately 10% reacted to a food, 30% had elevated sIgE to the respective food, illustrating that most patients with elevated sIgE did not react. Similarly, Fleischer et al[67] also found a high false-positive rate among children with AD. In this study, negative food challenges occurred in 89% of 364 challenges.[67] Finally, a cohort of highly selected patients with a history suggestive of cow's milk allergy were evaluated for delayed eczematous reactions up to several days after a challenge with cow's milk. However, delayed eczematous reactions were found in only 28 of 135 children, or approximately 20% of this preselected group.[68] Critically, all of the patients with eczematous exacerbations except 1 showed associated gastrointestinal and/or respiratory manifestations, suggesting that eczema flare alone is a rare occurrence. As discussed, eczema flare alone as a symptom was also rare in the Roerdink study from the Netherlands.[16]

In addition, practices vary widely with what food allergens should be tested in the setting of AD. Overall, egg, milk, and peanut are the most consistently implicated food allergen triggers in AD. Egg was implicated in AD exacerbations, whereas peanut reactions were more likely immediate.[69] Testing for other allergens, such as tree nuts, fish, and shellfish, is often considered by clinicians, given the high allergenic potential of these foods.

When testing is undertaken, results can be difficult to interpret in the setting of AD. Although predictive values for sIgE levels have been studied in immediate reactions, specific cutoffs for patients with food-triggered AD are not known. In addition, related to their AD status, these patients often have high levels of total and sIgE. Perhaps because of these high levels of sensitization, it is well established that the specificity of SPT and serologic testing is low. As described above, food sIgE in patients with AD who reacted to foods were higher than the commonly used values felt to be strongly predictive of FA reactions.[39] Thus, the clinical relevance of SPT and sIgE can be difficult to predict and may require an OFC to confirm a diagnosis of FA in AD.

Risks of food elimination

With the increasing prevalence of FA, recent studies of oral tolerance and FA have provided insight on factors that help maintain oral tolerance. Although avoidance diet may lead to improvement of eczema control and severity, it is not without risk. The dual exposure hypothesis suggests that oral tolerance to food antigens is promoted through high-dose oral exposure, where food sensitization and FA are promoted through lower dose cutaneous exposure, particularly with inflamed skin.[70] Support for this hypothesis was proven in the LEAP study, where strict elimination of peanut promoted peanut allergy in high-risk children.[31] In this study, early, consistent peanut ingestion decreased peanut allergy by over 80%. Similar findings have been suggested for egg in some studies, although results are mixed.[71,72] In addition, ingestion of extensively heated egg and milk is felt to accelerate the development of natural tolerance in children with egg and milk allergy.[73] Importantly, in a retrospective study of food-triggered AD, 40% of children with food-triggered AD who removed a food developed an immediate reaction to a new food, and 19% developed an immediate reaction who had never had an immediate reaction previously.[34] Another study of OFC failures described a failure rate of 13% in patients with AD who remove a previously ingested food that did not provoke immediate clinical reactions from the diet.[35] Together, these studies suggest that oral exposure promotes oral tolerance, whereas removal of tolerated foods, particularly in high-risk patients, may increase the risk for immediate IgE-mediated FA symptoms.

In addition, food elimination has serious potential for nutritional deficiencies. Elimination of food allergens can lead to essential macro- and micronutrient deficiencies and feeding difficulties, in addition to poor growth.[74-76] Infants and children with milk allergy and multiple food allergies have been observed to have the highest risk for growth failure and nutritional deficiencies.[77-84] In addition to concerns for calcium and vitamin D intake, which are important for bone growth and mineralization, studies looking at infants and children on elimination diets have also shown that they are also at risk of lower intake of key nutrients such as folic acid, zinc, iron, vitamin A, and B vitamins.[80] Several studies in patients with AD who were on avoidance diets have demonstrated reduced growth velocity and poor weight gain, especially as the number of sensitized food allergen avoidances was increased.[82-85]

Therefore, patients undergoing elimination diets require close observation, and the support of a registered dietician is important to prevent any unnecessary growth impairments. The dietician can provide individualized nutritional counseling and growth monitoring for children on elimination diets, and can also provide tailored advice to expand the infant or child's diet, in order to ensure dietary adequacy and avoid growth interruption or nutritional deficiencies.

MEDICAL DECISION-MAKING: WHOM AND WHEN TO TEST FOR FOODS

As discussed, treatment of AD begins with education and addressing the skin barrier with optimal skin care, including use of topical steroids when needed and addressing potential barriers

such as steroid phobia. A recent retrospective study in infants less than 12 months of age found that early aggressive use of moderate potency topical steroids followed by maintenance proactive therapy was associated with decreased FA diagnosis.[26] Clinical decisions regarding testing should be considered once these efforts fail. The high levels of sensitization, together with lower specificity of SPT and serologic testing, have real potential to misguide patients and physicians, arguing against indiscriminate testing. Moreover, there is growing concern that acting on a false-positive result by avoiding a food could actually lead to developing a true allergy and/or nutritional deficiencies. There have been multiple reports of children with AD on elimination diets where the reactions to the eliminated foods become more severe over time, including anaphylaxis.[34,86,87] Dietary restrictions can also be difficult for patients, potentially adding stress that is a known triggering factor for AD,[88] all while potentially distracting from basic therapy, which could delay treatment for someone suffering with itch, poor sleep, and perhaps infection.

These findings nicely demonstrate some of the complexities involved: the significant risk of actual FA in the more severe patients, the very high sensitization rate in these patients, and the lower specificity of testing. This train of evidence led to guidelines suggesting that children less than 5 years old with moderate-severe AD unresponsive to topical therapy undergo testing for FA, including OFC or trial of elimination diet.[30] Of note, clinical care should always start with optimization of skin care and topical therapies; when these efforts are unsuccessful, testing can be considered. The risks and benefits of testing and food elimination should be discussed with the family before recommending testing or dietary elimination, and age and AD severity should be taken into account. The benefit may include an improvement in AD, but food removal will not cure AD. The risks include potential development of anaphylaxis and effects on nutrition and quality of life.

Early peanut introduction: a special consideration

The LEAP study was seminal and prompted an addendum to the NIAID guidelines for peanut allergy testing. The first recommendation focused on infants with severe AD, egg allergy, or both, who were found to be at the highest *a priori* risk for developing peanut allergy in the LEAP study. For this subgroup, measurement of the peanut sIgE level, SPT, or both is strongly recommended before introducing peanut protein into the diet. The second addendum recommends that peanut-containing foods should be introduced into the diets of infants with mild or moderate AD at approximately 6 months of age without the need for prior screening via peanut sIgE or SPT, whereas the third and final addendum recommends freely introducing peanut-containing foods together with other solid foods in infants without AD as the family wishes.[1]

One of the issues with these guidelines is that defining "severe" AD may be more complicated than it seems, particularly when definitions of severe AD are not well established in clinical practice and may vary between physicians given that they are somewhat subjective. As fleshed out in a follow-up document, the criteria used for defining "severe" AD in the LEAP study were AD that meets 1 or both of these:

- Requires the application of topical creams and/or ointments containing corticosteroids or calcineurin inhibitors, and if the participant is <6 months of age, lasted for at least 12 of 30 days on 2 occasions, or if >6 months of age, lasted for at least 12 of 30 days on 2 occasions in the last 6 months.
- AD that is currently or was previously graded ≥40 using the modified SCORAD evaluation.[89]

The former is difficult as it is nonstandardized and may be onerous for a clinician to elicit this history appropriately, whereas the latter requires training to properly perform a SCORAD, which is not typically performed in a clinical setting.

In the addendum guidelines, "severe" AD was 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."[1] Although simpler and more clinical, it again defaults to the somewhat subjective designation of "severe" by different clinicians across specialties. In addition, testing can be costly and can possibly inadvertently delay introduction if access to testing and OFCs are limited.

Finally, *S. aureus* colonization has increasingly been implicated in the pathogenesis of AD and, remarkably, may also impact food sensitization.[3] Distilling these disparate studies and observations, it seems that there may be different criteria depending on the FA sought and the age group, but, in general, in children under 12 months of age with severe AD, any documented food reaction, especially to egg, should have allergy testing at least to peanut before introducing it into the diet. Further work needs to be done on defining eczema severity and finding more reliable markers beyond these for when to test.

Best practices in the approach to food allergy evaluation in atopic dermatitis are summarized in Table II.

KNOWLEDGE GAPS

- It is not known how often eczema is a symptom of an FA, particularly eczema only, as opposed to a consequence of itching or scratching from immediate symptoms.
- There are no clear clinical scenarios or biomarkers for removal of a tolerated food to improve eczema alone. Removing a tolerated food to improve AD has the potential to cause FA and may not improve disease.
- A more rigorous definition of severe AD, particularly in those who have attempted skin care, will help determine whom and when to test for potential food triggers.
- The optimal management and skin care before embarking on FA testing is not known.
- As easy measure of skin barrier dysfunction and emollients proven to improve skin barrier dysfunction are needed.
- Diagnostic tests to differentiate food sensitization from true FA, particularly in patients with severe AD, are needed.
- The effects of skin and gut microbiome on AD and FA are unknown. More work is required to better understand these relationships.
- The role of proactive use of topical steroids in AD to reduce FA is not known.
- The role for early emollient barrier therapy, and if therapy should be considered for primary prevention of FA, is not known.

- NIAID addendum guidelines suggest that testing and peanut introduction in patients with severe AD decrease peanut allergy (including OFC for positive SPT up to 7 mm). It is not clear how "severe AD" should be defined. In addition, it is not clear if testing is really necessary or how to best get peanut in the diets of children with mild-moderate AD within the first year of life.

CASE DISCUSSIONS

Case 1: infant

A 6-month-old White girl presented with severe AD. Her AD had started at the age of 3 months, complicated by 1 *S. aureus* skin infection (methicillin sensitive *S. aureus*). The infant's diet included cow's milk—based infant formula, rice cereal, fruits, and vegetables. Given the difficult-to-control AD, laboratory testing performed by her primary care physician demonstrated an increased total IgE (286 kUA/L) and detectable sIgE (kUA/L) to cow's milk (0.7), egg white (5.73), peanut (2.44), wheat (11.3), and oat (3.22). She was then referred to an allergist.

Skin care was optimized, including daily bathing, wet wraps as needed, and use of low potency topical steroids. She originally improved in the first 5 days, but AD continued to be moderate. Skin tests (expressed as average wheal diameter in mm) were positive to egg white (9 mm), borderline to peanut (3 mm), but negative to cow's milk, wheat, and oat. With positive SPT, positive sIgE testing, and moderate AD, egg avoidance was recommended. Given the lack of any reaction history and negative skin testing, introduction of cow's milk, oat, and wheat was recommended at home. With a borderline peanut SPT, family was instructed to return for an OFC to peanut. The infant passed a food challenge to peanut (cumulative dose of 4.3 g of peanut protein), and regular consumption according to the LEAP study guidelines (2 g of peanut protein per serving = 2 teaspoons of peanut butter 3 times a week) was recommended. In addition, she was able to successfully introduce cow's milk, wheat, and oat. She also passed an extensively heated (baked) egg OFC and was consuming extensively heated egg approximately once per week. Her AD also improved, and by the age of 1 year, she was maintained on daily baths with moisturization and egg avoidance with minimal dermatitis.

At the age of 2, she developed perioral hives and a burning feeling on her tongue after eating 1 bite of a peanut butter and jelly sandwich. She had been eating 1 teaspoon of peanut butter approximately 1 to 2 times a month. Repeat testing at this time demonstrated that her sensitization to peanut had increased: SPT to peanut was now positive (7 mm) and sIgE was 3.33 kUA/L (total IgE: 420 kUA/L). The parents declined a repeat peanut challenge. They avoided tree nuts during this time. Given new peanut allergy and parental concern, after discussing the risks and benefits, testing was performed to tree nuts (almond, hazelnut, walnut, pecan, cashew, and pistachio). At this time, she developed significant sensitization to cashew (skin test 11 mm, sIgE 19; other tests were negative). When she was evaluated at the age of 2, she had no active AD while receiving daily baths followed by moisturization.

This typical case highlights several important points as well as questions. Even before consultation with an allergist, the infant had positive sIgE testing for several allergens. Importantly, the infant was seen by an allergist in a timely manner, and several of the foods to which she tested positive were successfully introduced. This highlights the importance of clinical history, the potential for false-positive tests when interpreting testing, and the importance of food introduction in maintaining oral tolerance. In addition, despite the positive sIgE testing, she passed an infant OFC to peanut and was able to introduce peanut in her diet successfully. Unfortunately, the family did not continue the recommended peanut protein of 2 g 3 times weekly.

Clinical conundrum: Had the family more strictly followed the dietary recommendations of 2 g of peanut protein 3 times per week? Would oral tolerance to peanut have been maintained? Are there strategies, handouts, or messaging that can promote early ingestion adherence? Or was she "predestined" to have an FA due to her skin barrier and/or *S. aureus* skin infection? In addition, how should the family proceed with regard to tree nuts and could cashew sensitization (with >95th percentile positive predictive value) have been prevented with regular and early cashew introduction?

Case 2: toddler

A 2-year-old African American boy presented with severe AD (SCORAD 100, decreased to 29 after 12 days of intense skin therapy at an outpatient day program). His AD had started at the age of 2 weeks, complicated by *S. aureus* (methicillin resistent *S. aureus*) skin colonization. Without dietary avoidance, but a change in climate while vacationing at the beach, his AD had cleared in the past. He tolerated extensively heated milk protein and less heated milk protein in yogurt; baked egg protein including waffles; wheat; soy; and smaller amounts of peanut, tree nuts, and sesame seeds. Family had removed milk (but not all milk products as described) in an effort to help with AD, but otherwise he was eating an unrestricted diet. His parents had perceived no association between ingestion of specific foods and the severity of his AD. Given his difficult-to-control severe AD, sIgE testing and SPT were performed.

Skin tests were positive to milk (6 mm), egg white (8 mm), wheat (4 mm), and peanut (8 mm), but negative to soy and all tree nuts. His total IgE was 2366 kU/L with sIgE (kUA/L) to milk (64.3), casein (32.5), egg white (90.2), ovomucoid (>100), wheat (5.39), and peanut (>100). In an effort to improve his AD, avoidance of milk, egg, and peanut was originally recommended. The patient passed a food challenge to wheat that included baked milk protein (cumulative dose of 1.3 g of milk protein). Continued ingestion of baked milk and wheat was allowed. Continued ingestion of baked egg protein was also recommended based on reported previous tolerance. A food challenge to milk or yogurt was planned.

Given the positive testing to milk, egg, and peanut, the potential for milk, egg, and peanut triggering AD was discussed. Given his high sIgE to peanut and egg, he is likely allergic. Before dietary removal, it is critical to discuss risks and benefits of dietary removal with the family. This is particularly important as there is literature to suggest that dietary avoidance of foods such as milk, egg, and peanut based on sensitization by skin test and sIgE in an attempt to improve AD may lead to the loss of oral tolerance in such a child and requires self-injectable epinephrine prescription. Thus, he is now at risk for anaphylaxis with reexposure. Risks and benefits of dietary elimination need to be discussed in detail with shared decision-making. In addition, this patient requires close follow-up of both his AD and FA status.

Clinical conundrum: Can patients with high sIgE to a food allergen such as egg or peanut safely continue ingesting the food? If he had no reactions to the food, would he have been better off without having any testing and avoidance? Would newer tests or biomarkers (such as basophil activation testing), or more aggressive OFC testing have been helpful?

TABLE II. Best practices in the approach to food allergy evaluation in atopic dermatitis

First steps
- AD and immediate food allergy are often co-expressed. A detailed history for *immediate hypersensitivity reactions* to foods should be obtained, and appropriate testing and management of *immediate hypersensitivity reactions* should be completed.
- Use shared decision-making for peanut introduction or peanut testing in accordance to guidelines derived from the LEAP study. To avoid confusion, education of the parent of the "special circumstances" with regard to peanut compared with other foods is helpful.
- Before any additional testing, optimal skin care (Table I) should be implemented, including use of topical anti-inflammatory medications.
- If the child has failed optimal skin care/medical management, discuss and address any barriers to adherence.

Risk assessment and testing
- If the child has failed optimal skin care/medical management, and barriers to adherence have been addressed, perform a risk assessment for food allergy.
- Factors to consider include:
  - age of the child (children less than 1 year are more at risk)
  - severity of the AD (the more severe the AD, the higher the risk)
  - increased chronicity/persistence of AD
  - history of superinfections (suggesting *S. aureus* colonization)
  - dietary ingestion history (the child must be consuming a food to be reacting to it)
- Discuss risks, benefits, and limitations of food testing and potential food elimination before testing
- Use shared decision-making when pursuing testing (and elimination)

If a shared decision results in testing
- Detailed discussion of testing interpretation, including NPV, PPV, lack of clear cutoffs, particularly in patients with AD
- Discuss potential need for food challenges
- Discuss risks and benefits of dietary elimination including immediate hypersensitivity reactions such as anaphylaxis
- Employ shared decision-making regarding potential elimination diets

If elimination diets are implemented, the child is considered food allergic
- Food allergy education and management, including prescribing injectable epinephrine, emergency action plans, and nutritional guidance
- Close follow-up within 2-4 weeks to assess response to food elimination
  - If no improvement, reintroduce the food. Be mindful of length of elimination, as longer elimination times increase risk for development of new food allergy. Consider reintroduction in a supervised setting.
  - If improvement, consider OFC to confirm the diagnosis of food-triggered eczema. If no immediate type reaction, discuss the benefits and risks of reintroduction of the food to maintain oral tolerance while achieving eczema control with other therapies.
- Regular follow-up as with other food allergy patients
  - Education, anticipatory guidance on living with food allergy
  - Nutritional screening and follow-up
  - Monitoring for natural tolerance

AD, Atopic dermatitis; *LEAP*, Learning Early About Peanut Allergy Study; *NPV*, negative predictive value; *OFC*, oral food challenge; *PPV*, positive predictive value.

Cases 3 and 4: school-age children

Seven- and eight-year-old White sisters have a history of severe AD and multiple food allergies. The 7-year-old sister presented with a SCORAD of 47 (decreased to 5.5 after 12 days of intense skin therapy). Her AD had started at the age of 2 months, complicated by recurrent *S. aureus* (MSSA) and Herpes Simplex Virus-skin infections. Until the age of 2, she had been consuming regularly and with good tolerance milk, egg, soy, and smaller amounts of peanut and tree nuts. Given her AD, skin testing and sIgE testing were performed. Based on positive skin testing and sIgE to these foods, avoidance of milk, egg, soy, peanut, and tree nuts was initially recommended. This was unsuccessful in improving her AD, and at the age of 3.5, the patient reintroduced milk, egg, and soy into her diet without worsening of her AD. She continued avoidance of peanuts and tree nuts.

When she was seen to establish care with a new allergist at the age of 7, she had a positive peanut SPT of 13 mm, peanut sIgE of 38.5 (kUA/L), and total IgE of 4233 kU/L. She failed a peanut challenge (cumulative dose of 2.1 g of peanut protein) when she developed hives, abdominal pain, and vomited. She had developed significant sensitizations to cashew (SPT: 15 mm, sIgE: 15.5) and pistachio (SPT: 20 mm, sIgE: 21.1), and continued avoidance was recommended. She was able to reintroduce all other tree nuts.

The 8-year-old sister presented with a SCORAD of 33 (also decreased to 5.5 after 12 days of intense skin therapy). Similar to her sister, her AD had started at the age of 2 months, complicated by 2 *S. aureus* (MSSA) skin infections. Until the age of 3.5, the patient had been consuming regularly and with good tolerance milk, egg, soy, peanut, and tree nuts. Avoidance of these foods was recommended based on positive skin tests, but her AD, at that time severe, did not improve. At the age of 4.5, she reintroduced milk, egg, and soy into her diet, and continued avoidance of peanut and tree nuts. At the age of 8, her peanut skin test was positive (10 mm), peanut sIgE was 30.4 kUA/L, and total IgE was 5181 kU/L. She passed a peanut challenge (cumulative dose of 12 g of peanut protein). She had developed sensitizations that were considered significant to almond (SPT: 13 mm, sIgE: 9.7), cashew (SPT: 9 mm, sIgE: 4.44), and pistachio (SPT: 13 mm, sIgE: 31.5), and was recommended continued avoidance unless tolerance could be demonstrated by OFCs. She was able to introduce other tree nuts.

Thus, both sisters had ingested peanut early on in life, which was removed from the diet at the age of 2 in case of the 7-year-old sister and at the age of 3.5 in case of the 8-year-old sister based on sensitization per skin test and/or sIgE in hopes of improving their AD. The older sister had consumed peanut for 1 year longer than her younger sister at the time when avoidance was recommended.

This case nicely illustrates the pervasive positive testing in children with severe AD that may not be clinically relevant. Despite positive testing, both siblings were able to successfully reintroduce milk, egg, and soy without any adverse effects. However, the question remains with regard to how the children may have done had they continued peanut or tree nuts, and how much ingested protein is needed to maintain oral tolerance.

Clinical conundrum: As the older sister was able to tolerate peanut while the younger sister could not, did longer peanut ingestion for 3.5 years early in life in case of the older sister contribute to more sustained oral tolerance compared with peanut ingestion for only 2 years in case of the younger sister? If the children had maintained higher doses of nut ingestion, would this have altered their clinical course?

CONCLUSION

AD has many triggers and comorbidities, and FA is only one of the potential triggers and comorbid conditions. With regard to AD management, education and skin care are most important.

Optimal skin care includes appropriate bathing recommendations, use of emollients, topical medications, wet wraps, and where indicated, systemic medications such as dupilumab. Behavioral interventions for itch and sleep should also be part of the plan, diagnosis and treatment of mental health comorbidities must be addressed, and potential evaluation for contact dermatitis should also be considered. With regard to FA, patients with immediate allergic reactions to foods should be evaluated for FA and appropriate avoidance diets recommended. In the absence of immediate reactions, appropriate management is more nuanced. Recent research points away from random testing and food elimination for the majority of patients with AD. For infants who do not respond to aggressive skin care, limited food allergens may be tested. If testing and potential elimination diets are proposed, a frank discussion regarding the risks of false-positive testing and dietary elimination is required. AD significantly affects families, and these patients require a comprehensive approach to management focused on education, barrier restoration, and limitation of inflammation. Potential triggers and food elimination should be handled thoughtfully and with care.

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