

Food allergy testing in atopic dermatitis



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Food allergy and food-related worsening of dermatitis can occur in patients with atopic dermatitis (AD). We reviewed the relationship of AD with food allergen hypersensitivity and the risks and benefits of food allergen testing and avoidance in patients with AD. Skin prick testing and specific immunoglobulin E to aeroallergens may identify patients with immediate hypersensitivity. Atopy patch tests may detect non-immunoglobulin E-mediated reactions but are not standardized or routinely used. Younger children with more severe AD in whom the optimal management failed may have food-triggered AD. Egg, milk, and peanut account for most food allergens. Elimination of relevant food allergens should improve AD but must be guided by appropriate allergy testing and establishing clinical relevance. Serum immunoglobulin E panels for food allergens are discouraged in the primary care setting because of their difficulty of interpretation. Empiric avoidance of foods is entirely discouraged in AD because of their risk of causing nutritional issues, food allergy, and other problems. (JAAD Int 2022;9:50-6.)

Key words: adult; allergic; atopic dermatitis; child; eczema; food hypersensitivity; humans; immunoglobulin E; inflammation; patch test; prick test; rhinitis.

INTRODUCTION

The role of food sensitization in atopic dermatitis (AD) has been debated throughout the years.¹ Food allergy (FA) has been reported in up to one-third of patients with moderate-to-severe AD² and is associated with morbidity and even mortality. It is important to identify and eliminate exposure to clinically relevant food allergens. However, unnecessary allergen avoidance can have harmful consequences, including the loss of oral tolerance to foods, nutritional deficiencies, increased costs, and inconvenience. Clinicians who treat patients with AD should be aware of the evidence-based FA testing guidelines and best practices.

EPIDEMIOLOGY OF FA IN AD

AD is a risk factor for immediate, immunoglobulin E (IgE)-mediated FA.^{3,4} The Canadian Healthy Infant Longitudinal Development birth cohort study found that sensitization and AD at 1 year of age were

strong risk factors for FA at the age of 3 years.⁵ Neonatal skin barrier dysfunction, even when transient, was associated with FA at the age of 2 years.⁶ A recent systematic review supports that early-onset AD is particularly associated with the development of FA.⁴ A large, population-based study (HealthNuts) highlighted these findings, as 1 in 5 Australian infants with AD had FA compared with 1 in 20 without AD.⁷ Patients with AD were 6 and 11 times more likely to have egg and peanut allergies, respectively.⁷ Among children with moderate-to-severe AD, FA confirmed by double-blind, placebo-controlled, food challenges or open food challenges was identified in 33% to 81%.⁸⁻¹² Numerous population-based studies have found associations between AD and food allergen sensitization (ie, the presence of food-specific IgE). Food sensitization in infants with AD is up to 6 times higher than that in healthy controls at the age of 3 months.⁴ Moreover, up to 53% of children with AD have positive food-specific

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immunoglobulin E (sIgE) and/or skin prick tests (SPTs) with up to 15% demonstrating signs of FA on an oral food challenge,⁴ compared with 0.1% to 6% FA prevalence in the general population.¹³

The effect of AD on acquiring a natural tolerance (or outgrowing FA) is not clearly understood. In some studies, AD was associated with a persistent egg allergy.^{14,15} AD severity was associated with prolonged timing until the resolution of a diagnosed milk allergy.¹⁶ In contrast, another study found that AD did not affect the natural history of cow's milk allergy.¹⁷

A study of 400 children with AD from the Mechanisms of Progression from Atopic Dermatitis to Asthma in Children cohort found that the most common SPT⁺ allergens were egg white, followed by peanut, egg yolk, dog, trees, cat, ragweed, cockroach, mold, dust mite, grass, milk, weeds, soy, and wheat.¹⁸ Children with AD and sensitization to peanut, egg, cat, and dog had a greater baseline skin barrier dysfunction (increased transepidermal water loss and decreased skin FLG expression) in nonlesional skin and AD severity than those with allergy to other allergens or no allergen sensitization.¹⁸ Peanut and egg sensitization may occur through skin exposure in children.¹⁹⁻²³ Individuals with AD are more likely to develop peanut sensitizations through skin exposure.^{20,21} Moreover, children with severe AD show a dose-dependent relationship between household peanut allergen levels and peanut sensitization, even without enteral peanut exposure.^{22,24} Less is known about cutaneous sensitization to egg in childhood AD.

MECHANISMS OF AD ASSOCIATION WITH FA

Cutaneous exposure to food via a defective skin barrier is an important route of sensitization to food allergens.²⁵ The epidermis provides an essential barrier to the external environment, preventing water loss and intrusion of infectious agents and allergens.²⁶ A leaky skin barrier may promote allergic sensitization by facilitating allergen uptake. When allergens are captured and processed by epidermal Langerhans cells, they migrate to draining lymph nodes and can interact with naïve T cells to promote helper T cell type 2 (Th2) immunity leading to allergies.²⁷ Absorption of allergen through the disrupted skin barrier of AD is believed to lead to a Th2

response, IgE class switching, and clinical FA.^{28,29}

Food allergens penetrating the stratum corneum are taken up by local dendritic (Langerhans) cells, which migrate to local lymph nodes and induce Th2 immune response.¹⁹ Murine studies showed that innate immune cells (eosinophils and basophils) accumulate in the skin in response to exaggerated

thymic stromal lymphopoietin production after cutaneous application of food allergens.³⁰ Interleukin 4 produced by basophils and eosinophils promotes dendritic cell activation and presentation of food antigens to naïve T cells, leading to Th2 polarization³⁰ and intestinal IgE-mediated FA in mice.^{30,31} Further, mice sensitized epicutaneously to food allergens display intestinal mast

cell expansion and subsequent anaphylaxis upon exposure.³² In clinical studies, epicutaneous sensitization occurred after the application of peanut oil on eczematous skin³³ and peanut sensitization is associated with environmental exposure to peanuts.^{34,35} In addition, exposure to hydrolyzed wheat protein in facial soaps was suggested as a risk factor for a special phenotype of wheat allergy.³⁶ In contrast, oral ingestion of allergens generally promotes tolerance.²⁹

Genetic factors underlying skin barrier disruption are associated with FA.¹ Filaggrin loss-of-function mutation is associated with peanut sensitization in children with AD via environmental exposure to house dust peanut protein.³⁵ Skin microbiome dysbiosis may also contribute to food sensitization in patients with AD through skin barrier disruption.²⁹ Staphylococcal superantigens (eg, enterotoxin B) enhance epicutaneous sensitization to peanut in mice.³⁷ In addition, FA occurs more commonly in children with AD and colonization with *Staphylococcus aureus*.³⁸

FA and AD clinical overlap

Most foods reported to trigger AD are common food allergens, in general. In infants, eggs were most commonly reported, followed by cow's milk, peanuts, and soy. In children, eggs, cow's milk, and peanuts were again most common, followed by soy, wheat, tree nuts, fish, and shellfish. In older children and adults, peanuts were most common, followed by tree nuts, fish, and shellfish.³⁹ It is important to distinguish between immediate hypersensitivity reactions that may lead to anaphylaxis and be life

CAPSULE SUMMARY

- Elimination of food allergens to improve atopic dermatitis must be guided by appropriate allergy testing, after establishing clinical relevance.
- Empiric avoidance of foods in atopic dermatitis is discouraged because of the risk of losing oral tolerance to foods, and nutritional issues.

Abbreviations used:

AD:	atopic dermatitis
APT:	atopy patch testing
FA:	food allergy
IgE:	immunoglobulin E
sIgE:	food-specific immunoglobulin E
SPT:	skin prick test
Th2:	helper T cell type 2

threatening from delayed reactions that may exacerbate eczema. Additionally, reactions can be mixed, with some immediate symptoms and then eczema exacerbation.

Several studies linked FA and AD, especially in children with refractory, moderate-to-severe AD that has failed standard management.⁸ One study found that one-third of children with refractory, moderate-to-severe AD (judged by the Scoring of Atopic Dermatitis index) had sIgE antibodies and IgE-mediated clinical reactivity to milk, egg, wheat, soy, peanut, and/or fish proteins.⁸ Immediate reactions were not distinguished from isolated eczematous reactions in this study. This study and others led a task force on FA in children with AD commissioned by the European Academy of Allergy and Clinical Immunology to recommend that children aged ≤ 6 years with mild AD (respond easily to treatment, Scoring of Atopic Dermatitis index ≤ 25 , Eczema Area and Severity Index ≤ 7 , and Patient-Oriented Eczema Measure ≤ 8) with a history of immediate reactions to food or moderate-to-severe AD (more difficult to treat, Scoring of Atopic Dermatitis index > 25 , Eczema Area and Severity Index > 7 , and Patient-Oriented Eczema Measure > 8) with persistent AD or poor response to treatment be evaluated for FA.⁴⁰ Food allergens to be tested must be carefully selected according to the medical and dietary history of the child, including possible allergenic triggers and foods introduced into the diet.⁴⁰ Evaluation for sensitization to egg, wheat, milk, peanut, and soy in children aged < 5 years with moderate-to-severe AD should be considered in the following situations: (1) after ingestion of a specific food, there is a reliable history of an immediate reaction; and (2) there is persistent AD despite topical therapy and optimized management.⁴¹ Only relevant allergens should be tested because IgE testing has low specificity, especially for food.⁴² Clinicians should be aware of the iatrogenic harm of elimination diets based exclusively on blood or skin IgE testing due to the high false-positive rate for these tests.⁴² Testing should aim to confirm the clinical relevance of suspected allergens, especially with an equivocal history, and to facilitate safe

dietary expansion wherever possible. Tests include both SPT and sIgE, with or without component-resolved diagnostics.⁴⁰ Although oral food challenge is the gold standard for diagnosis, it is likely unattainable to most patients who have FA. If patients consume specific foods in their diet without adverse reactions, then allergy to that food is unlikely.⁴⁰ Referral to a specialist is recommended when considering testing for FA in AD.⁴³

Age-related differences of FA in AD

Age is important in the association of AD with FA. Children diagnosed with AD at a younger age and requiring more medical therapy are more likely to have concomitant FA.⁷ Studies are much less convincing in older children and adults. A large-scale, Japanese birth cohort study showed that early-onset and persistent eczema negatively affected physical growth and increased the risk for low body weight, short stature, low body mass index, and increased FA.⁴⁴ AD onset before the age of 1 year and persistent AD had the strongest associations with the development of FA at the age of 2 years (odds ratio [95% CI] = 9.861 [9.115-10.668]) and 3 years (odds ratio [95% CI] = 11.794 [10.721-12.975]). In contrast, AD diagnosis at the age of 3 years had a weaker association with FA (odds ratio [95% CI] = 2.373 [2.02-2.789]).⁴⁴

ALLERGEN TESTING**Atopy patch testing in AD**

There are 2 broad categories of FA: IgE-mediated and non-IgE-mediated.⁴⁵ Although sIgE and SPT are useful to diagnose IgE-mediated reactions, these tests are inappropriate for non-IgE-mediated or mixed-type immune reactions, such as AD in some cases, food protein-induced allergic proctocolitis, enterocolitis syndrome, or enteropathy.⁴⁶ Atopy patch testing (APT) was used in the early 2000s to identify non-IgE and mixed-type FAs.⁴⁷ Previous studies have reported conflicting results about the diagnostic value of APT for FA overall and in patients with AD owing to its nonstandardized methods.⁴⁸

A Turkish study found increased sensitivity and accuracy but decreased specificity for APT in patients with AD compared with those with gastrointestinal symptoms; APT had a sensitivity of only 71.4% in patients with AD with cow's milk allergy.⁴⁹ A study evaluating non-IgE-mediated reactions in patients diagnosed with cow's milk allergy based on gastrointestinal manifestations (ie, perianal features, bleeding from the digestive tract, loss of appetite, gastroesophageal reflux, gastritis, ileitis, abdominal pain, vomiting, diarrhea, and constipation) showed 77% sensitivity and 73% specificity.⁵⁰ However, an

Italian study of the same patient group reported 53.8% sensitivity and 97.8% specificity.⁵¹ Another study in Thailand found lower sensitivity (42.9%) of APT to cow's milk allergy in patients with AD.⁵² In a meta-analysis, APT had a pooled 53.6% sensitivity and 88.6% specificity for diagnosing FA overall in children.⁴⁸ Conflicting results across studies may be due to differences in how FA was diagnosed (eg, oral food challenge vs SPT, blinding and placebo control for food challenge)⁵²⁻⁵⁴ and how APT were performed (eg, fresh foods vs lyophilized or powdered food, different concentrations).⁵⁴⁻⁵⁶ One study found 0% sensitivity of APT prepared with fresh whole cow's milk and powdered skimmed cow's milk in petrolatum but 33% sensitivity when prepared with powdered skimmed cow's milk in saline.⁵³ Thus, APT is generally not recommended to test for FA or food sensitivity.

Diagnosis of FA in AD

Diagnosis of FA is complicated in general and even more so in children with AD. The clinical course of AD fluctuates with many environmental triggers (allergens, irritants, infection), which can obscure whether a food worsens AD or the removal of the food improves AD. Moreover, children with AD often have high IgE levels to many allergens, which are not clinically relevant. A positive IgE test does not imply clinical relevance or an allergy per se. Diagnosis is made clinically and not based solely on laboratory testing.^{57,58}

Testing interpretation

SPT has an excellent negative predictive value (>95%) and a moderate positive predictive value (30%-50%).⁵⁹ sIgE has a lower sensitivity than SPT but can provide allergen-specific and age-specific predictive cutoffs that can help clinicians determine how likely the test is true or false positive.⁵⁹ "Class interpretation" (ie, class II allergy) is not helpful. Having multiple false positives may lead to unnecessary allergen avoidance, thereby increasing the risk of the development of an allergy with avoidance, increasing out-of-pocket costs for patients on expensive diets, and inducing anxiety over being allergic to multiple allergens. As such, broad sIgE panels for FA are strongly discouraged. Referral to a specialist is recommended for proper interpretation of these tests.^{57,58}

Dietary elimination in AD

A retrospective study of children with concern for food-triggered AD found that 41% were diagnosed with food allergen-triggered AD or developed an immediate reaction to food allergens. Almost half of

these patients had no previous immediate-type reactions, suggesting a change in immune responses from type IV delayed to type I immediate hypersensitivity.⁶⁰ Risk factors for an immediate reaction at baseline included older age, personal history of AD, and avoidance of food causing reaction.⁶⁰ Increased immediate hypersensitivity reactions secondary to dietary elimination are important because anaphylaxis may develop in patients upon allergen exposure (up to 36%). Other risks related to food avoidance include nutritional deficiencies, reduced growth velocity, poor growth, and feeding difficulties.⁶⁰ As such, dietary elimination of potential allergens should be discouraged unless there is clear evidence of allergy to these allergens.

Patients presenting with concern for food-worsened AD should be referred for a proper diagnosis of FA. Counseling is required about the potential risks of strictly avoiding foods, including worsening FA and anaphylaxis, nutritional deficiencies, cost of and difficulty implementing the diet, anxiety, etc. A comprehensive review of this topic was recently published.⁴³

Prevention of peanut allergy in AD

In infants with AD who currently have no FA, age-appropriate food introduction should be encouraged. In the Learning Early About Peanut study,⁶¹ avoiding peanuts led to an increased risk of the development of FA. Early introduction of peanuts resulted in 81% and >90% reduction in peanut allergy in intent-to-treat and per-protocol analyses, respectively.⁶¹ These results led to a consensus that in infants with AD and no evidence of peanut allergy, early introduction of peanuts should be encouraged. Those with moderate-to-severe AD or an egg allergy by the age of 4 to 6 months may benefit from an evaluation by an allergist and an early introduction to peanuts. Additionally, regular feeding of peanuts before 11 months of age leads to a decreased risk of the development of peanut allergy.

Patients who should be referred to an allergist include infants with a history of immediate hypersensitivity reactions to foods and reproducible history of AD worsening with foods and children with persistent AD requiring >2 months of topical corticosteroids. Referral can also be considered for those patients with a family history of FA and families with strong parental concern for FA.

COMPONENT-RESOLVED DIAGNOSTICS

Detection of IgE antibodies against allergenic molecules is feasible using singleplex (1 assay per sample) or multiplex (multiple assays per sample) measurement platforms.⁶² The most commonly used platform

for IgE antibody measurement is the ImmunoCAP ISAC Test (Thermo Fischer Scientific, Inc).

The ISAC test combines biochip technology and purified natural and recombinant allergen components in a miniaturized assay and yields semiquantitative results (ISAC standardized units/ISU) of sensitization to 103 allergen components.⁶² The latest generation ISAC microarray contains 112 specific and cross-reactive allergen components, including risk markers for FA and specific markers for pollen, mite, animal, mold, crustacean, insect venoms, and markers of sensitization to cross-reactive carbohydrate determinants.⁶² Multiplex assays are emerging in allergy diagnostics owing to improved risk assessment, identification of allergens for immunotherapy, and unknown sensitizations.⁶² Multiplex assays require only 30 μ L of serum/plasma that can be obtained from a capillary blood sample in children and enable the investigation in allergic patients with complex symptomatology (eg, severe eczema, unstable asthma, and chronic urticaria) in a more cost-efficient manner than singleplex tests.⁶²

CONCLUSION

Some younger children with moderate-to-severe AD who failed standard therapy may have FA coexpression or food-triggered AD. Egg, milk, and peanut account for >80% of FA in AD. The elimination of relevant food allergens should improve AD but must be guided by appropriate allergy testing and establishing clinical relevance. sIgE panels for food allergens are discouraged in the primary care setting owing to their difficulty in interpretation. Empiric avoidance of foods is discouraged in AD because of the risk of increasing FA and nutritional issues.

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Conflicts of interest

Dr Singh has received consultation fees from AbbVie and serves on a data safety monitoring board for Siolta Therapeutics. Dr Ong has received consultation fees from Incyte, AbbVie, Regeneron, Sanofi, and Janssen. Dr Silverberg reports personal fees from AbbVie, Afyx, Arena, Asana, BioMX, Bluefin, Bodewell, Boehringer-Ingelheim, Celgene, Dermavant, Dermira, Eli Lilly, Galderma, GlaxoSmithKline, Incyte, Kiniksa, Leo, Luna, Menlo, Novartis, Pfizer, RAPT, Regeneron, and Sanofi-Genzyme, and their institution received grants from Galderma. Dr Ramírez-Marín has no conflicts of interest to declare.

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