# Food allergy and atopic dermatitis

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**ABSTRACT**

*Atopic dermatitis (AD), characterized by intense pruritus, eczematous lesions, and a relapsing disease course, is a chronic inflammatory skin disease that affects both children and adults. AD often begins in infancy and is associated with atopic diseases in the personal or family history.[1] Environmental factors may trigger AD by affecting the skin barrier and by triggering inflammation. The elicitation of T-helper type 2 cytokines further impairs the epidermal barrier and leads to the penetration of irritants and allergens into the epidermis and thereby perpetuating inflammation. The presence of AD and its severity has been shown to positively correlate with risk of developing food allergy (FA). Children with AD are estimated to be six times more likely to develop FA compared with their healthy peers. It has been reported that nearly 40% of children with moderate-to-severe AD have immunoglobulin E (IgE) mediated FA compared with only 6% in the general population. Although analysis of experimental data has linked skin inflammation in AD to FA, with food challenges reproducing symptoms and avoidance diets improving AD, elimination diets are not known to cure AD and may have unfavorable consequences, such as loss of tolerance, which leads to immediate-type allergy, including anaphylaxis, nutritional deficiencies, growth failure, and reduction of quality of life for the patient and family. Exacerbation of AD can be inaccurately attributed to foods. Individuals with AD are often sensitized to foods with positive testing results, however, able to tolerate the food. In light of widespread ordering and commercial availability of serum specific IgE for FA, testing for FA is recommended only if, from a detailed clinical history, immediate-type allergic symptoms occur with ingestion of food, or in infants with AD who do not improve with optimal skin care.*

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Atopic dermatitis (AD), characterized by intense pruritus, eczematous lesions, and a relapsing disease course, is a chronic inflammatory skin disease, which affects both children and adults. AD often begins in infancy and is associated with atopic diseases in the personal or family history.[1] Eczematous changes in AD are often found in flexural areas in any age group, the face, neck, and extensors in infants and children, and usually spare the groin, axillary region, and tip of the nose. AD, determined by a genetic predisposition, is characterized by an impaired skin barrier and T-helper type 2 (Th2) predominant inflammation. AD affects ~20% of all children at age 6 and 5% of adults in Western industrialized countries.[1] Environmental factors may trigger AD by further affecting the skin barrier and inflammation, where Th2 cytokines promote impairment of the epidermal barrier. Consequently, irritants and allergens penetrate into the epidermis and perpetuate inflammation. In >80% of patients with AD, the skin has been found to be colonized by *Staphylococcus aureus*, which can further impair the skin barrier, stimulate type 2 immune responses, and perpetuate inflammation.[2]

The atopic march, which refers to the natural history of allergic diseases as they develop, classically begins with AD and is often followed by progression to immunoglobulin E (IgE) mediated food allergy (FA), asthma, and allergic rhinitis.[3] The presence of AD and its severity, most proximal on the atopic march, has been shown to positively correlate with a risk of developing FA. The U.S. Centers for Disease Control and Prevention reported an 18% increase in the prevalence of FA in 2007, and children with AD are estimated to be six times more likely to develop FA compared with their healthy peers.[2] It has been described that nearly 40% of children with moderate-to-severe AD have IgE-mediated FA compared with only 6% in the general population.[3]

In the first months of life, food specific IgE responses can be detected. This peaks at ~10% prevalence at 1 year of age.[4] Sensitization to foods is thought to occur *via* exposure through the inflamed and compromised

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skin barrier of patients with AD as opposed to the gastrointestinal tract, which induces tolerance after exposure to foods. Furthermore, peanut exposure in house dust has been shown to positively correlate with the likelihood of developing peanut allergy.[5] The use of wheat- or peanut-containing skin products has been shown to positively correlate with the development of wheat and peanut allergy, respectively.[6]

In addition, experimental models that use skin tape stripping, which removes the stratum corneum of the skin, and application of food allergen to the skin support the skin as a potential route of IgE sensitization because removal of the stratum corneum in these models resembles skin barrier defects in patients with AD.[7] A defective stratum corneum is found in nonlesional skin of patients with AD, and, in children with AD and FA, results of studies have shown increased transepidermal water loss.[8] A deficiency in the expression of skin barrier molecules, such as ceramides and filaggrin by keratinocytes, account for barrier skin defects in patients with AD.

Keratinocytes, the skin's main epithelial cells, express cytokines such as thymic stromal lymphopoietin, interleukin (IL) 25, and IL-33 after scratching. Food allergen exposure to eczematous skin increases expression of these cytokines, which leads to action of Th2 and Th9 cells, which produce IL-4, IL-9, and IL-13. These events induce production of specific IgE and mast cell hyperplasia.[9] Th2 cytokines upregulate high-affinity IgE receptors on antigen-presenting cells, *e.g.,* Langerhans cells, promoting production of IgE antibodies. In addition, in the presence of activated keratinocytes secreting thymic stromal lymphopoietin, IL-25, and IL-33, IgE-bearing Langerhans cells traverse to regional lymph nodes and present allergen to naive T cells and activate a Th2 response.[9]

In comparison with the skin, tolerance induction generally results from early oral exposure of food allergens.[9] Mechanistically, mucin produced by intestinal epithelial cells and Granulocyte-macrophage colony-stimulating factor (GM-CSF) by dendritic cells can convert naive T cells into T regulatory cells, which prevent development of IgE and FA.[7] The role of early oral exposure inducing tolerance was demonstrated by the early introduction of peanut in the LEAP (Learning Early About Peanut) study.[10] The LEAP study, a randomized controlled trial with infants, ages 4–11 months, at high risk and with severe AD and/or egg allergy, demonstrated that the early introduction of peanut could reduce development of peanut allergy by 81%, as measured by double-blind challenge at 5 years of age.[10] The study showed that AD development preceded development of peanut allergy, which suggests that AD is involved in the causal pathway toward the development of FAs, rather than the reverse.[11]

The close association between sensitization in AD skin and loss of oral tolerance has been demonstrated by early egg introduction, in which the presence of AD had a strong correlation with reaction to egg in studies in which infants received early egg feeding.[11] Results of these trials suggest that, to maintain tolerance in patients with AD, counter-regulatory mechanisms of early oral exposure against eczematous skin sensitization is necessary.[11] The effects of staphylococcal enterotoxins may induce a break in oral tolerance because it has been shown that *S. aureus* colonizes most of acute AD lesions, with production of staphylococcal enterotoxins, which leads to worsening AD symptoms and production of specific IgE against these toxins.[12] In children with AD, the presence of specific IgE to egg white was significantly correlated with the presence of specific IgE to staphylococcal toxins.[11] Prevention and treatment of AD has been noted to be critical for successful early egg introduction, with control of AD leading to improved skin barrier function and *S. aureus* clearance, which thus makes it less likely for food allergens to cause transcutaneous sensitization.[13]

The pathogenic role of Th2 IgE-mediated FA in AD has been shown in food challenge studies in which immunologic changes were incited and associated with the development of AD lesions, and, alternately, in trials that identified and eliminated food allergens that led to clinical improvement of AD. Although experimental data linked skin inflammation in AD to FA, with food challenges that reproduce symptoms and avoidance diets improves AD, elimination diets are not known to cure AD and may have unfavorable consequences. The loss of tolerance may occur, which leads to immediate-type allergy, including anaphylaxis. Other concerns include nutritional deficiencies and growth failure as well as a reduction of quality of life for the patient and family, including increased anxiety, label reading, and impairment in school, work, travel, and restaurants.

In a randomized controlled trial, children with AD and egg allergy placed on an egg elimination diet saw a significant reduction in the surface area affected by AD and significant improvement in the AD severity score compared with the control group.[11] A Cochrane meta-analysis later revealed that there may be some benefit in an egg elimination diet in infants with suspected egg allergy who have positive specific IgE to egg, however, little evidence supports the use of various elimination diets in unselected patients with AD because they were likely not allergic to these foods.[11] An Australian population–based study (HealthNuts)[14] found that the highest risk of FA to peanut, egg, and/or sesame seed at 1 year occurred in infants with early onset (0–3 months of age) and more severe disease (which required prescription topical steroids), with 50% of these subjects with food challenge failures.

Young patients with AD, particularly severe AD, are often sensitized to a variety of food allergens with a positive skin-prick test result or an elevated allergen specific serum IgE level; however, only 30–40% reflect clinical reactivity as documented by double-blind, placebo controlled food challenges.[11] In a study that recruited 62 children with AD and an elevated specific IgE level to egg, children were randomized to an egg elimination group and to a control group that continued egg after optimization of skin care. In this study, it was shown that 89% of children in the elimination diet group had a decrease in the surface area of the skin affected (versus 59% of the control group) and a decrease in the AD severity score in the elimination diet group.[15] Thus, although FA does not cause AD, it may exacerbate flares of AD in some patients with AD and who are sensitized, and, therefore, in a subgroup of patients with AD identified as food allergic, there may be a reduction in AD severity with an elimination diet.

Exacerbation of AD, however, can be inaccurately attributed to foods in individuals with AD with positive testing results, who are able to tolerate the food. Testing for FA is recommended if, from a detailed clinical history, immediate-type allergic symptoms occur with ingestion of food or in infants with AD who do not improve with very aggressive skin care. Unwarranted FA testing of tolerated foods can lead to unnecessary food elimination diets. In a retrospective chart review of individuals referred for evaluation of AD and FA, the outcome of oral food challenges in patients placed on elimination diets based primarily on positive specific IgE immunoassay results was assessed.[16] It was found that 93% of the foods being avoided were able to be returned to the diet after oral food challenge, which indicates that the majority of foods being restricted could be tolerated, which reflects overreliance on serum immunoassay test results as the primary indicator for food elimination diets.[16]

In these patients, negative oral food challenge meant that patients with AD did not experience worsening of their AD beyond the 2-hour observation period when IgE-mediated symptoms are expected to occur. In addition, in a study of 186 unselected children with AD (mean age, 45.8 months), 24% were on a milk elimination diet (87% physician prescribed, 53% positive blood test result), with 8.9% of patients on the milk elimination diet (2% of all patients) found to be milk allergic by food challenge.[17] This study revealed that the actual prevalence of allergy to cow's milk in patients on a milk elimination diet (4%) was significantly lower than the number of patients on an elimination diet (24%), which suggests that a milk elimination diet was being overprescribed. An unnecessary prescription of elimination diets can have the detrimental consequence of promoting FA and preventing development of oral tolerance, and, in infants, may lead to a delay in the introduction of foods into the diets, which may prove more injurious than good.[18] Nutritional risks of elimination diets for treatment of FA have been described, with those with milk allergy or multiple FA at highest risk for growth failure and nutritional deficiencies.[11]

Thus, the NIAID Expert Panel 2010 Food Allergy Guidelines Testing for FA in AD has outlined that, in children < 5 years old with moderate-to-severe AD, FA evaluation can be considered for milk, egg, peanut, wheat, and soy if at least one of the following conditions are met: (1) the child has a reliable history of an immediate reaction to ingestion of a specific food, such as hives, swelling, itching, sneezing, coughing, wheezing, vomiting, or low blood pressure, and/or (2) the young child has persistent AD despite optimized management and topical therapy.[19] AD management should initially focus on skin care before undertaking allergy evaluation, with the elimination diet considered in individuals with a clinical history and clearly apparent FA by appropriate diagnostic food challenge.

Given the nutritional risks of elimination diets for treatment of FA and the potential detriment in removing foods, such as progression to FA and anaphylaxis to the eliminated food, optimized skin care with aggressive skin hydration, optimal use of topical anti-inflammatories for rescue and proactive therapy, an adequate anti-itch plan, and systemic treatment, if indicated, should be addressed at the forefront, with optimal skin care often minimizing the role of foods in AD. For infants with an early onset of severe AD, particularly with *S. aureus* and who do not improve with aggressive skin care, FA testing can be considered. When warranted, FA testing should be to a limited number of foods, and food challenges should be offered in an expedited fashion. If a food elimination diet is warranted, then parents should also be informed of the harms of an elimination diet and that removal of food will not cure AD. If food elimination is pursued, then the patient should be reassessed in 4 weeks to determine if the skin changes warrant continued elimination.

## CLINICAL PEARLS

- Patients with AD have an increased risk of FA; analysis of data shows that allergic sensitization occurs through an impaired and inflamed skin barrier.
- FA testing is recommended if (1) allergic symptoms occur with ingestion of the food or in (2) infants with AD who do not improve with very aggressive skin care.
- Peanut in an appropriate form should be introduced to infants with mild-to-moderate AD at 4 to 6 months of age; for infants with severe AD, testing

should be performed first and then introduced based on skin test results per guidelines.[20]

- False-positive testing may lead to unnecessary removal of food from the diet; elimination diets for children with AD should be recommended very rarely and with caution because these children may develop type-1 IgE-mediated food reactions, including anaphylaxis, as well as nutritional deficiencies and growth failure, and/or reduction of quality of life.

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