Allergic Triggers in Atopic Dermatitis

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KEYWORDS

• Atopic dermatitis • Eczema • Allergic trigger
• Food • Aeroallergens

Atopic dermatitis (AD) is an inflammatory, chronically relapsing, and intensely pruritic skin disease. Numerous names have been used for this most frequent inflammatory disease in childhood, reflecting different approaches and definitions. The local inflammation of the skin has always been described as dermatitis. The term ''eczema'' has been suggested to describe a variety of skin diseases with common clinical characteristics, all involving a genetically determined skin barrier defect.[1] In children and young adults with atopy, the underlying inflammation is dominated by high serum IgE levels and IgE-antibody–associated reactions, which allows use of the term atopic eczema or AD. This terminology suggests a potential role for allergens as triggers in this disease.

AD affects a large number of children and adults in industrialized countries. More than 10% of all children are affected at some time during childhood.[2] The onset of AD occurs during the first 6 months of life in 45% of children, during the first year of life in 60% and before the age of 5 years in at least 85% of affected individuals.[3] Patients with severe AD and early sensitization to allergens typically have a persisting illness, sometimes lasting for a lifetime. Childhood AD can be a very disabling disease with an important impact on the quality of life of the children and their parents (see the article by Chamlin and Chren elsewhere in this issue for further exploration of this topic).

Nonatopic dermatitis (non-IgE mediated) is more common in preschool children and adults. Studies have shown a prevalence of 45% to 64% in children,[4,5] but even in adults, figures as high as 40% have been reported.[6] Nonatopic children with eczema have been reported to have a lower risk of developing asthma than atopic children with eczema. It is noteworthy that nonatopic dermatitis in children may evolve into AD.

This review focuses on AD, which by definition is associated with elevated IgE. The authors define the role of allergens in the pathogenesis of AD, comment on the various

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potential allergen triggers of eczema, their clinical consequences, and the impact on diagnosis and treatment of AD.

ROLE OF ALLERGENS IN AD

AD is a paradigmatic skin disease that is the product of a complex interaction between various susceptibility genes, defects in skin barrier function, a specific immunologic response, and a clear interaction with infectious agents and the host environment (**Fig. 1**).[7] Although the exact mechanisms of the disease are still not fully elucidated, extensive research in recent years has shed light on the role of allergens in AD. At cellular and molecular levels, evidence strongly implicates an allergic component in AD, primarily in children. A multitude of allergens has been incriminated (**Table 1**), and the largest part of the studies have focused on food allergens. The role of aeroallergens has been investigated to a lesser extent, and is discussed in the second part of this article.

Genetically predisposed patients with AD have an epidermal barrier dysfunction mainly caused by decreased ceramide levels and loss of the function of filaggrin, which is a crucial protein in the cutaneous barrier function; this results mostly in enhanced transepidermal water loss.[8] In addition, the partial loss of the barrier function can facilitate the penetration of environmental allergens and promote allergic skin inflammation. Environmental allergens potentially include aeroallergens,[9] as well as in some cases food allergens.[10] A recent study showed that children who have never been exposed to peanut during the prenatal period and with negative tests for peanut-specific IgE in the cord blood were sensitized to peanut allergens as a result of application of skin preparations containing peanut oil on inflamed skin.[10] This result suggested that a primary sensitization to a food allergen occurred before ingestion of the implicated food through a route of sensitization other than the oral route.

For food allergens, sensitization occurs mostly via the gastrointestinal tract. The absorption of unaltered proteins into the circulation is a normal, physiologic phenomenon occurring in nonatopic as well as atopic individuals of all ages.[11,12] Similar to the altered skin barrier, gut barrier dysfunction might play a role in patients with AD and food allergy.[13,14] Studies have shown that patients with AD have a facilitated absorption resulting from IgE molecules present on gut epithelial cells, followed by increased

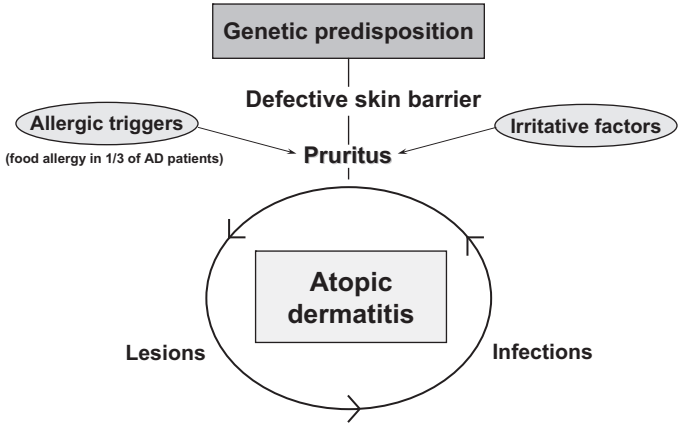

Fig. 1. Interaction of the different triggers incriminated in the pathogenesis of atopic dermatitis (AD).

Table 1
Allergic triggers of AD

Food Allergens	Microorganisms	Aeroallergens
Cow's milk	Bacteria	Pollen
Egg	*Staphylococcus aureus*	Mold
Soy	*Streptococcus species*	Dust mite
Wheat	Fungi	Animal dander
Peanut	*Trichophyton*	Cockroach
Tree nuts	*Malassezia*	
Fish	*Candida*	
Shellfish		

Data from Leung D. Pediatric allergy: principles and practice. St Louis: Mosby; 2003.

antigen transfer across the gut barrier. Rapidly absorbed food proteins circulate throughout the body, and can then initiate and perpetuate immune responses in the skin.

The immune response to an allergen in the skin of AD patients is complex and involves both IgE-mediated immediate immune responses and T-cell–mediated delayed immune responses.[15]

Many studies addressing the pathophysiology of AD have focused on serum IgE, with titers above the normal range in approximately 85% of patients with AD.[16] Approximately 85% of these patients have positive specific IgE antibodies to foods and inhalant allergens.[6,16,17] Receptors for IgE antibodies have been identified on dendritic cells, T cells, B cells, monocytes, macrophages, eosinophils, and platelets.[18–20]

Langerhans cells (LC), bearing allergen-specific IgE antibodies on their surface, are more numerous in AD lesions and appear to play an important role in cutaneous allergen presentation to T-helper 2 (Th2) cells. The LC-bound IgE facilitates capture and internalization of allergens prior to their processing and antigen presentation to T cells. Normal individuals and patients with respiratory allergy have low-level surface expression of FcεRI on their LC, whereas FcεRI is expressed at high levels in the inflammatory environment of AD. IgE-bearing LC are 100- to 1000-fold more efficient at presenting allergen to T cells (primarily Th2 cells) and activating T-cell proliferation.[21] After capture of the allergen, activated dendritic cells activate memory Th2 cells in atopic skin, but they may also migrate to the lymph nodes to stimulate naïve T cells to further expand the pool of systemic Th2 cells.

T lymphocytes play a key role in AD. This idea was initially supported by the observation that patients with primary T-cell immunodeficiency disorders frequently have increased serum IgE level and eczematous skin lesions, which clear after bone marrow grafting.[17,22] The observation was reinforced by the fact that eczematous rashes do not occur in the absence of T cells in animal models.[23] Food antigen–specific[24] and aeroallergen-specific[25] T cells have been cloned from active skin lesions and as well as from normal skin in patients with AD. Food antigen–specific T cells have been isolated in peripheral blood from individuals with relevant food protein–induced AD.[26–28] These specific cells express the cutaneous lymphocyte antigen (CLA), involved in the recruitment of allergen-specific T cells to the skin, which has not been observed in patients with other allergic diseases such as asthma or gastrointestinal allergies.[28,29]

In acute skin lesions, infiltrating T lymphocytes predominantly express Th2 cytokines, interleukin (IL)-4, and IL-13, whereas T cells in chronic lesions predominantly express IL-5 and IL-12. Hence, cytokines expressed in lesions of AD

reflect the characteristics of a typical allergic milieu. Th2-type cytokines promote chronic allergic inflammation by up-regulating adhesion molecules on vascular endothelial cells including vascular cell adhesion molecule 1 (VCAM-1), E-selectin, and intercellular adhesion molecule 1 (ICAM-1),[30] by up-regulating high-affinity receptors for IgE antibodies on LC and other antigen-presenting cells through recruiting inflammatory cells to the site, and by promoting local production of IgE antibodies.[21,31] Adhesion molecules are not typically expressed in the skin of nonatopic individuals but are expressed in nonlesional skin of AD patients, and are markedly up-regulated in skin lesions or following epicutaneous application of allergens in sensitized AD patients.[32]

T regulatory cells have been described as a further subtype of T cells that can play a role in AD. This proposal is supported by the observation that patients with immune dysregulation, polyendrocrinopathy, enteropathy X-linked (IPEX) syndrome characterized by high IgE levels, food allergy, and eczematous lesions have mutations in FOXP3, a nuclear factor expressed in regulatory T cells.[33]

In addition to T cells, eosinophils have been implicated in the pathogenesis of AD. Although eosinophils are not prominent in histologic sections of AD lesions as in allergen-induced asthma, immunohistochemical staining of AD skin has revealed prominent deposits of the eosinophil major basic protein and eosinophil-derived neurotoxin in active eczematous lesions.[34,35] Major basic protein is a cytolytic protein secreted almost exclusively by eosinophils that is capable of damaging skin epithelial cells and promoting mast cell degranulation. These deposits are not found in uninvolved skin sites in AD patients.[36] The role of eosinophils was confirmed by oral food challenges (OFC) in food-allergic AD patients. A marked increase in plasma histamine concentrations,[37] activation of plasma eosinophils,[38] and infiltration of eosinophils and elaboration of eosinophil products in skin lesions were observed after the challenge test.[16,36,39] Eosinophils are part of the late phase response that was regulated by Th2 cytokines (IL-4, IL-5, IL-13) and eotaxin-1.[40,41] These studies provide further evidences of an allergic component in a subgroup of AD patients.

In comparison with patients with AD without food allergy or normal controls, children with AD and food hypersensitivity exposed to the relevant allergen were found to have high basophil histamine release in vitro.[42] When placed on an appropriate food allergen elimination diet for 1 year, the skin condition significantly improved and spontaneous basophil histamine release decreased. Peripheral blood mononuclear cells from food-allergic subjects with high spontaneous basophil histamine release were found to elaborate a 23-kDa cytokine called histamine-releasing factor (HRF) that can activate basophils from food-sensitive, but not food-tolerant, children.[43] Several isoforms of IgE are secreted, and it has been postulated that HRF interacts with specific isoforms of IgE.[44]

Microorganisms can also provide allergic triggers. Most patients with AD are colonized with *Staphylococcus aureus* and experience exacerbation of their skin disease after infection with this organism.[45] In this regard, IgE antibodies to *S aureus* exotoxins were found in close to 60% of patients with moderate to severe AD.[46] IgE to the exotoxins could not be detected in normal controls, patients with respiratory allergy, or patients with psoriasis. These exotoxins may contribute to the biphasic inflammatory response not only by allergen-specific activation of FcεRI-bearing effector cells but also in their capacity to act as superantigens by non-MHC restricted activation of large numbers of stimulated T cells.[46,47] In a similar way, IgE sensitization to *Malassezia* species is observed in patients with AD but not in those with asthma or allergic rhinitis without AD.[48,49]

AD is a complex disease involving barrier defects and chronic inflammation. As reviewed here, currently available data strongly suggest a major role for allergic triggers in AD at a cellular and molecular level.

AD AND FOOD ALLERGENS

The potential role of food allergens in AD has been long debated. As early as the beginning of the 1900s, several case reports showed an improvement of AD after avoiding specific food,[50] with reoccurrence of the lesions when the food was reintroduced. Thereafter, well-designed studies, mostly in the past two decades, clearly pointed to a pathogenic role for food hypersensitivity in a subset of children and adolescents with AD, as removal of the causative food led to improvement in skin symptoms,[51–55] introduction of the causative food provoked the disorder,[56–59] and avoidance of the causative food helped prevent the disorder.[60–62]

Prevalence of Food Allergy in Patients with AD

To provide an accurate diagnosis, the prevalence of food allergy in AD patients should be well defined in a given population. Similarly to other chronic atopic disorders such asthma, various triggers add to the difficulty of designing well-controlled prevalence studies. Nevertheless, several well-designed studies provide a good estimation of the prevalence of food allergy in AD. In westernized countries the prevalence of food allergy is estimated to be 6% to 8% in children and 2% to 3% in adults.[63] The prevalence rate is much higher in patients with AD, with age of the patient and severity of the AD both factors, as severe AD and younger age are risk factors for food allergy.[64] During the past 20 years, a large number of studies using double-blind placebo-controlled food challenges (DBPCFC) to support the role of foods as triggers of AD have been published (**Table 2**). Although the prevalence may vary between the studies, likely due to different methodology, approximately one-third of the patients with moderate to severe AD have food allergy as demonstrated by positive DBPCFC to selected food.[21] In one of the largest series supporting the link between food allergy and AD, Sicherer and Sampson[65] performed more than 2000 DBPCFC, out of which approximately 40% were positive.

Unfortunately, comparing these studies is difficult because of the various definitions used for positivity or the type of study (retrospective, prospective, or case-controlled

Table 2
Prevalence of food allergy in children with AD based on double-blind placebo-controlled food challenges[a]

Study	Years	N	Food Allergy (%)
Sampson et al	1985	113	56
Burks et al	1988	46	33
Sampson et al	1992	320	63
Eigenmann et al	1998	63	37
Burks et al	1998	165	39
Niggenmann et al	1999	107	51
Eigenmann et al	2000	74	34
Breuer et al	2004	64	46

[a] *Data from* Rance F, Boguniewicz M, Lau S. New visions for atopic eczema: An iPAC summary and future trends. Pediatr Allergy Immunol:2008;19:17–25.

studies). Another problem related to these studies is that the intensity of the eczema was not scored systematically before and on the day after the OFC, as late reactions might occur (on the day after the OFC or even later). Another point of controversy is related to a potential selection bias (patients referred to the allergist for possible food allergy), which may lead to a potential overestimation of the prevalence. When considering only the patients recruited through a dermatology clinic, the prevalence was slightly lower (27%).[66] Worthy of note is that most studies were performed in referral clinics, possibly leading to figures higher than the "true" prevalence.

In adults, studies with a sufficient number of patients to evaluate the prevalence are lacking, but most investigators agree that food hypersensitivity plays a very minor role in adult AD.[21,67,68] To support this, Woods and colleagues[69] reported that prevalence of food allergy in 41 randomly selected young adults was 1.3%. Japanese investigators found a much higher prevalence of food-induced eczema (44%), although the causative foods were uncommon allergens, including chocolate, coffee, and rice, suggesting nonallergic adverse effects of foods.[70]

Foods Triggering AD

Hen's egg, milk, wheat, soy, peanut, nuts, and fish are responsible for more than 90% of food allergy in AD patients.[65] The incriminated foods vary according to the age of the patients (**Table 3**). Besides the frequently incriminated "classical" food proteins, other food components can exacerbate AD in individual patients.[71] Whether these reactions are allergic or nonimmunologic "pseudoallergic" reactions is not yet clear.[72] Sugar as a suspected food trigger plays no role according to the results of oral challenge tests and is overestimated by many patients or their parents.[73]

Patients with birch pollen sensitization can also react on OFC with cross-reacting foods, with exacerbation of eczema.[74] Triggering of AD by pollen-associated food is especially relevant in adolescent and adult patients. In an unselected population the inducibility of eczema by pollen-associated food appears to be low.[75]

Patterns of Clinical Reactions to Food in AD Patients

Based on OFC, studies with large numbers of patients have shown that cutaneous reactions occurred in 74% of the tested patients with AD, and that isolated skin symptoms were observed in only 30% of reactions.[21] Skin reactions generally consisted of pruritic, morbilliform, or macular eruption appearing on predilection sites for AD (head,

Table 3
Foods more commonly involved in food allergy, according to age

Infants	Children (2–10 Years)	Adolescents and Young Adults
Cow's milk	Cow's milk	Peanut
Egg	Egg	Tree nuts
Wheat	Peanut	Fish
Soy	Tree nuts	Shellfish
	Fish	Sesame
	Shellfish	Pollen-associated foods
	Sesame	
	Kiwi fruit	

Data from Sampson HA. Update on food allergy. J Allergy Clin Immunol 2004;113:805–19.

neck, and creases). Gastrointestinal and respiratory symptoms were less frequent, occurring in approximately 50% and 45%, respectively.[21]

Food-induced reactions in AD may occur at various times after a positive OFC.[76]

Immediate IgE-mediated reactions occur mostly within 2 hours after ingesting food. DBPCFC clearly demonstrated an immediate IgE-mediated food hypersensitivity reaction in a subset of children with AD.[21,71,74] Such distinct food-induced symptoms are rarely seen during ''natural exposure'' to foods, as foods are generally not ingested on an empty stomach following prolonged periods of food allergen avoidance,[21] because repeated ingestion of a food allergen can result in a down-regulation of the immediate response.[77]

These children typically present with urticaria or angioedema as well as other immediate-type reactions involving the gastrointestinal or respiratory tracts, or less frequently with anaphylactic shock. Some patients may present with only pruritus within 2 hours after food ingestion, suggesting an IgE-mediated mechanism, with subsequent scratching leading to an AD exacerbation.

Isolated eczematous delayed reactions, that is, flares of eczema usually after 6 to 48 hours, are suggestive of a non-IgE–mediated reaction. Late reactions to food are more difficult to detect. Only a few studies have addressed this type of reaction, showing that about 25% of these reactions appear after 2 hours.[78,79] In addition, more than 10% of the children who reacted to an OFC developed isolated eczematous reactions after 16 hours or later.[79]

A combination of early noneczematous reactions and delayed eczematous reactions was described in more than 40% of the children who reacted to OFC.[76] Late reactions can occur infrequently as isolated reactions or after a previous immediate-type reaction. Several patients experienced an episode of increased cutaneous pruritus and transient morbilliform rash 6 to 10 hours after the initial immediate reaction to a positive challenge.[21] These late symptoms were less prominent than the immediate symptoms but tended to last for several hours. This type of reaction is suggestive of the ''late phase'' of an IgE-mediated response.[21]

The Diagnosis of Food Allergy in AD Patients

In the diagnosis of food allergy in AD patients, no single investigation is fully reliable alone and a stepwise approach, similar to those for other allergic disorders, is recommended in international guidelines for the diagnosis of food hypersensitivity.[76] The diagnostic workup of suspected food allergy should start with a detailed history and physical examination of the patient. The next step may include in vitro and/or in vivo allergy tests, that is, measurement of food-specific IgE antibodies, skin-prick tests, atopy patch tests (APT), diagnostic elimination diet, and/or oral challenge (**Fig. 2**).

The patient's history can be very helpful in identifying a potential relationship between symptoms and a specific food, especially for immediate, IgE-mediated reactions. In food-induced eczema, the predictive value of a positive case history is lower than that for food-induced immediate reactions. Parents and patients often attribute flares of eczema to the ingestion of certain foods. However, as a large number of other factors can lead to flares of eczema (*Staphylococcus* infection, irritants, heat and humidity, and so forth), the history is often not particularly informative, especially in patients with severe AD.[51,79,80] Sampson[21] showed that only 35% to 40% of parental reported suspicions of food allergy could be verified by DBPCFC.

When food allergy is suspected, in vivo tests (eg, skin-prick tests) and/or in vitro tests (eg, measurement of specific serum IgE) to assess IgE-mediated sensitization should be performed. Skin-prick tests done as first-line tests are useful for determining the presence of specific IgE antibodies to various foods. The list of tested foods should

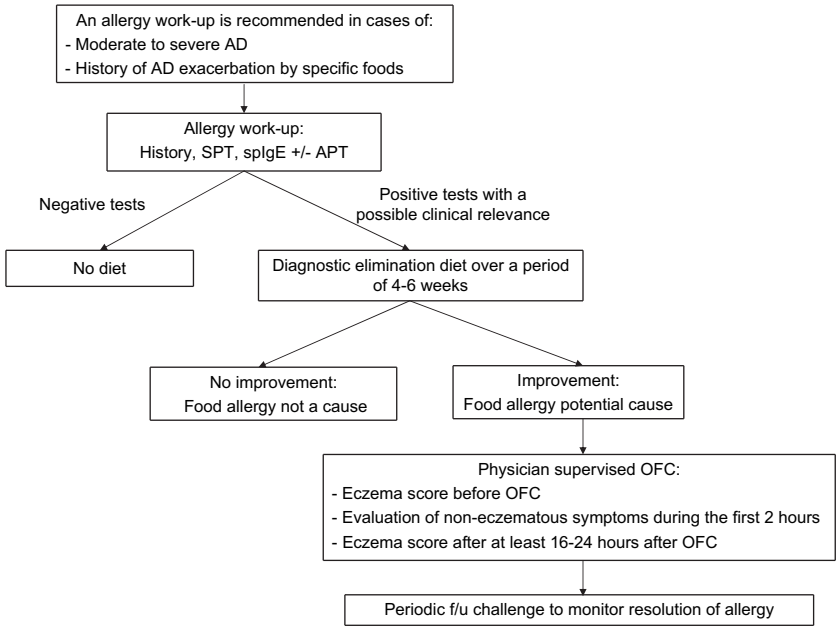

Fig. 2. Diagnostic algorithm for the identification of food allergy in AD. APT, atopy patch tests; f/u, follow-up; OFC, oral food challenge; SPT, skin-prick tests.

be adapted to the history and the age of the patient (**Table 4**). The negative predictive value of these tests is high (more than 95%), whereas the positive predictive value is low (approximately 40%).[56,57,81] This result suggests that a negative prick test can be helpful to rule out an allergy, but that a positive skin test cannot be considered to be diagnostic as such for a food allergy. Results need to be correlated with the clinical picture and, when necessary, confirmed by OFC.

Measurement of specific IgE antibodies in the blood by a standardized and validated method is also useful for detection of sensitization to food allergens, although

Table 4
Allergy testing in AD patients according to age

<3–4 Years	>3–4 Years
Foods (for AD-associated food allergy) • Cow's milk • Eggs • (Peanuts, wheat, nuts, fish, and so forth)	Foods (in case of severe persisting AD for AD-associated food allergy) • Cow's milk • Eggs • Peanuts • (Wheat, nuts, fish, and so forth)
Inhalant allergens (to test the atopic risk) • House dust mites • Cat, dog, and other furred animals • Pollens	Inhalant allergens (for allergen-associated AD) • House dust mites • Cat, dog, and other furred animals • Pollens

The allergen panel should be adjusted according to related symptomatology and local allergen exposure.

Data from Host A, Andrae S, Charkin S, et al. Allergy testing in children: why, who, when and how? Allergy 2003;58:559–69.

the sensitivity is lower. As with skin-prick tests, a negative result is helpful in excluding an IgE-mediated reaction to a specific food. A positive result has a lower specificity.[21] Quantitative measurements of food-specific IgE appear to be more useful in predicting clinical reactivity. Decision points have been established that provide greater than 95% confidence that a patient has symptomatic food allergy.[82,83] However, it has been well established that an OFC is needed to confirm food hypersensitivity when the level of specific IgE is lower than the cutoff point.

APT with common food allergens (milk, egg, wheat, and peanut) may increase the accuracy of food allergy diagnosis in patients with AD.[84–88] APT can be used as an additional diagnostic tool in specialized centers when skin-prick tests and/or specific IgE measurement fail to identify a suspected food or in patients with severe or persistent AD with a high suspicion of food allergy. APT can be also useful in patients with AD and multiple sensitizations without proven clinical relevance.[84] In these studies, children with immediate reactions generally had positive skin-prick tests whereas those with late reactions were more likely to have positive APT to the relevant foods. Studies using both skin-prick tests and APT to foods suggest that these tests are helpful in patients with delayed onset of symptoms.[84] However, APT still need to be standardized and are not yet recommended for routine clinical use.

Due to frequent skin flares and a high number of clinically nonrelevant positive tests in routine diagnostic procedures, the diagnosis of food allergy in AD patients can be difficult to establish based on skin or blood tests. Positive tests must be validated by a food elimination diet and most often by a controlled OFC.

Unfortunately, large numbers of patients with AD are started on empiric food elimination diets.[65] Although food allergens can be important triggers in AD, unnecessary elimination diets can cause malnutrition and significantly decrease the quality of life, in particular in children. Elimination diets should not be initiated based on a history-based suspicion alone. When a specific food is suspected by a positive allergy test, a diagnostic elimination diet over a period of up to 4 to 6 weeks with the suspected food items might be initiated.[76] If no food can be pinpointed by an allergy test in a patient with persistent moderate to severe AD, a diary reporting symptoms and food intake could be helpful in identifying a specific food.[21,71] If no association is found (note that this happens most of the time) and the diagnostic tests (prick tests, specific IgE $\pm$ APT) do not provide reliable information, an olligoallergenic diet over a period of 3 weeks can be helpful in patients with severe AD. In infants, an extensively hydrolyzed or amino acid formula can be used instead. Multiple dietary restrictions are rarely necessary and should be avoided.

Finally, standardized OFCs remain the ''gold standard'' for food allergy diagnosis in AD patients. If eczema remains stable or even increases in severity during a diagnostic elimination trial of 4 weeks, it is unlikely that the food is a relevant trigger of AD and an OFC is not necessary. If there is an improvement of the symptoms during a diagnostic elimination diet, an OFC should be performed, as the skin improvement may be coincidental or reflect a ''placebo'' effect, particularly in adults.[21,76] For patients with AD and prove noneczematous, immediate IgE-type reactions to a food will not need an OFC. In the investigation of active AD, a DBPCFC is highly recommended.[89] The OFC should always be performed by well-trained physicians and health personnel, and emergency equipment must be available (**Fig. 3**). Even when immediate reactions are not expected, the food must be administered with increasing doses as it may cause immediate, potentially severe symptoms, in particular in patients with AD on a long-lasting elimination of the incriminated food.[21] An OFC should only be performed in patients with stable skin condition. The extent of skin lesions should be scored, for example, by SCORAD (SCORing Atopic Dermatitis), before OFC and at least 24 hours

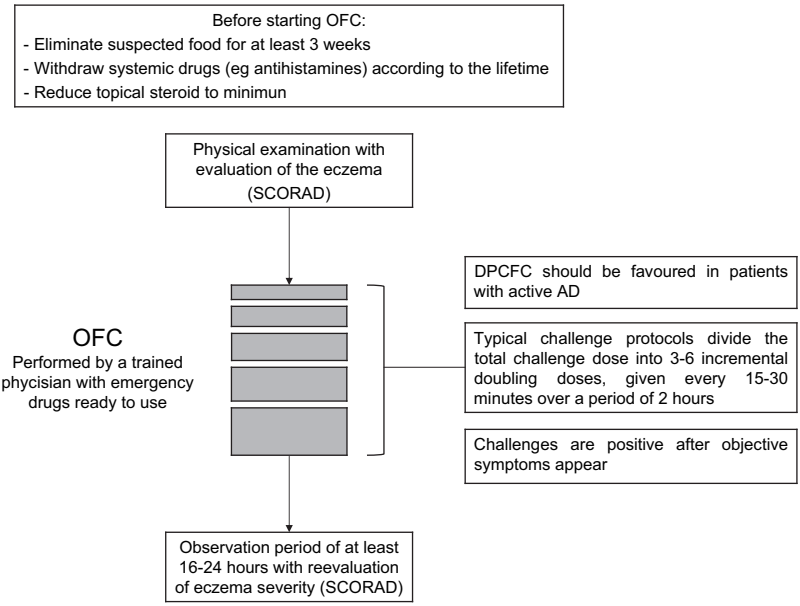

Fig. 3. Standard protocol for food challenges in patients with atopic dermatitis. OFC, oral food challenge; DPCFC, double-blind placebo-controlled food challenge.

later, as eczema flares related to the food might otherwise be overlooked. A difference of at least 10 SCORAD points is usually considered a positive reaction.[76] Other diagnostic tests, including the lymphocyte cytotoxicity test, basophil degranulation test, or measurement of food-specific IgG, are not validated and should not be used because they most often indicate a nonspecific immune reaction to the food and could be misleading.

Treatment of Food Allergy in AD Patients

In addition to management of AD with emollients, topical anti-inflammatory medications, antibiotics, and avoidance of environmental triggers, the only currently available treatment for patients with AD and food allergy is a strict dietary restriction of the causative food. As discussed earlier, long-term dietary avoidance should only be prescribed to patients with a well-documented diagnosis of food hypersensitivity. The avoidance diet needs to be thorough and carefully defined. The family and the patient must be taught how to read food labels to avoid potential sources of allergen contamination. In addition, patients and/or their parents need to be instructed to treat a potential reaction after accidental ingestion, and need to be equipped with an emergency treatment kit for anaphylaxis (antihistamines and self-injectable epinephrine) if there is a risk for systemic reaction. To date, treatment of food allergy by food-specific immunotherapy has not yet been proven to be safe and effective in well-designed trials, although oral desensitization trials are currently ongoing.

Follow-Up and Prognosis

AD starting in early infancy is often the first step of later manifestations of respiratory allergy known as the atopic march (see also the article by Jonathan M. Spergel elsewhere in this issue for further exploration of this topic). Food allergy is often associated with AD in patients presenting with this allergic phenotype. Approximately

one-third of children with AD have a favorable outcome and will outgrow their food hypersensitivity over 1 to 3 years, depending on the food they are allergic to.[42] Allergy to egg white, cow's milk, or wheat is short lasting in most patients, whereas allergy to peanuts, nuts, fish, and shellfish may be long lasting. Children with AD-associated food allergy should be regularly reevaluated for persistence of allergy, for example, at intervals of 12 to 18 months, for milk or egg allergy. Peanut and tree nut allergies are most often long lasting and may need less frequent reevaluations. Measuring the level of serum-specific IgE for follow-up can be very helpful. Patients with an initial low level of specific IgE are more likely to outgrow their allergy than patients with a higher level. Following the positivity of skin-prick tests is not helpful, as they can remain positive for several years after the child has outgrown his food allergy. It has been suggested that patients who do not strictly avoid the offending food are less likely to lose their allergy.[21] To date, "no patients have experienced a recurrence of allergic symptoms or worsening of eczema once food hypersensitivity was lost."[21]

AD AND AEROALLERGENS

After the age of 3 years, the prevalence of food allergy decreases; however, sensitization to inhalant allergens becomes more common. It has been observed that patients with moderate or severe AD more often have positive IgE tests to house dust mites (HDM), molds, and fungi (eg, *Alternaria*) and yeasts (eg, *Malassezia*) than asthmatics or nonatopic controls.[48] The exact role of these sensitizations in the pathogenesis of AD remains controversial. However, in some patients contact with certain aeroallergens, such pollen or HDM, may trigger eczematous skin lesions.

Evidence Supporting the Role of Aeroallergens as AD Triggers

The role of aeroallergens in AD has not been investigated as extensively as food allergens. In 1918, Walker[90] observed that some of his AD patients had skin flares after contact with aeroallergens (horse, ragweed, timothy). Subsequently, Tuft found that most adult patients with AD displayed positive skin tests to HDM. He demonstrated that intranasal application of aeroallergens could exacerbate AD and that environmental avoidance of HDM would improve skin symptoms.[91,92] Later, Tupker and colleagues[93] reported that bronchoprovocation with a standardized HDM extract in a double-blind, randomized, placebo-controlled way can result in new-onset AD skin lesions and exacerbation of previously existing skin lesions. Together, these studies suggest that the respiratory route could be important in the induction and exacerbation of AD by aeroallergens.

Patch testing has been most extensively studied for inhalant allergens in AD. Epicutaneous application of aeroallergens on uninvolved skin of patients with AD by APT elicits eczematous reactions in a subset of patients.[48,94–98] Positive reactions have been observed to HDM, pollens, animal dander, and molds. In contrast, patients with respiratory allergy and healthy volunteers rarely have positive APT.[99] Positive APTs support a role for contact hypersensitivity to aeroallergens in AD. There are no definitive data to support either a primary role for aeroallergen sensitization through direct skin contact or indirectly by inhalation.[99]

At a cellular level, evidence supporting a role for aeroallergens in AD includes the presence of both allergen-specific IgE antibodies and allergen-specific T cells in the skin.[100] A recent study found that 95% of AD patients were positive for IgE to HDM as compared with 42% of asthmatic patients.[48] Moreover, the HDM-specific IgE titers were usually at least 20-fold higher in AD than in asthma patients. Evidence of HDM (and other aeroallergen)–specific T cells in lesional skin and at the site of positive

HDM patch test supports the concept that immune responses in AD skin can be elicited by percutaneous exposure to aeroallergens.[25] Using the APT, Langeveld-Wildschut and colleagues[101] showed that positive reactions to HDM were associated with IgE-positive LC in the epidermis of AD patients. Together, these studies support, at the clinical and cellular levels, the importance of aeroallergens in a subgroup of patients with AD.

Common Aeroallergens Incriminated in AD

As discussed above, aeroallergens can exacerbate AD either by inhalation or by direct contact with the skin. Relevant allergens include HDM (most frequently incriminated), animal dander, and pollen. Fungus and cockroach have been suspected as well.[102,103] However, well-controlled clinical studies have validated only HDM as a clear trigger for AD.

Diagnosis of Aeroallergen Allergy in AD Patients

Similarly to food allergy, the diagnosis is based on a sequential allergy workup. History can be particularly helpful to identify pollens (seasonal flares) or animal dander allergens as triggers of AD. In a second step, skin-prick tests or measurements of specific IgE antibodies are useful to detect sensitization to aeroallergens. Allergens should be selected according to the history and the age of the patients (see **Table 4**). Similarly to foods, the severity of AD has been correlated with the degree of sensitization to aeroallergens.[104]

In addition to skin-prick tests and specific IgE, APT can be used to assess a skin-specific response to various aeroallergens, including HDM, pollen, animal dander, and molds. Patch testing elicits eczematous reactions in 15% to 100% of patients with AD, according to patch test materials and test modalities.[94–98] Based on the history of aeroallergen-triggered AD flares, APT has proved to have a higher specificity but lower sensitivity than skin-prick tests or specific IgE.[105] In 2003, Kerschenlohr and colleagues[106] reported positive APT in patients with nonatopic eczema,[106] suggesting that aeroallergens might also be relevant triggers for nonatopic eczema, even in the absence of detectable aeroallergen-specific serum IgE and with negative skin-prick test (SPT) results.

Recently, the European Academy of Allergy and Clinical Immunology (EAACI) suggested the following indications for APT[84]:

- Suspicion of aeroallergen-related symptoms in absence of positive specific IgE and/or a positive SPT
- Severe and/or persistent AD with unknown triggering factors
- Multiple IgE sensitizations without proven clinical relevance in patients with AD.

APT might become an important diagnostic tool, especially in patients with nonatopic eczema in whom SPTs and serum IgE tests fail to identify relevant allergens. The major problem with APT is the variability of methods and results among investigators.[107,108] Thus, standardization of the procedure is needed. Although hampered by the absence of a gold standard for aeroallergen-induced eczema diagnosis, specific avoidance measures should be considered in patients with positive APT.

Treatment of Aeroallergen Allergy in AD Patients

Several studies have examined whether avoidance of aeroallergens may improve AD. Most of these studies have focused on HDM allergy and have shown a positive effect of HDM avoidance measures.[105] These reports are mostly uncontrolled trials in which

patients were in dust mite–free environments, such as hospital rooms, or by use of acaricides or dust mite–proof encasing. All these measures have led to improvement of AD.[99] A double-blind, placebo-controlled study using a combination of effective mite reduction measures in the home showed that lower levels of HDM are associated with significant improvement of AD.[109] By contrast, other studies have found no clinical benefit from HDM avoidance,[110,111] even though encasing resulted in a significant decrease in HDM allergen levels.

In addition to avoidance, specific immunotherapy (SIT) could be an effective therapeutic intervention. A potential role of SIT in environmental allergen-triggered AD has been shown in several case reports and smaller cohort studies,[112] as well as recently in a multicenter trial with HDM immunotherapy involving 51 patients.[113] As a result of these studies, it became clear that SIT used for treatment of patients with allergic rhinitis and/or asthma can also be used in patients with AD, as eczema was not worsened during or after SIT. This finding suggests a potential benefit of SIT for AD in patients primarily treated for allergic rhinitis or mild asthma. However, even if there are several studies showing a positive effect of SIT on AD, no definite conclusion on the efficiency of SIT in AD can be drawn at present.[112] Prospective studies involving larger numbers of patients are currently being performed, which may answer the question of whether AD alone could be an indication for the initiation of SIT.

DIRECT ALLERGEN SKIN CONTACT

AD patients were previously thought to be less prone to develop contact allergy, although it is known today that the prevalence of delayed-type sensitization to common allergens (fragrances, latex and rubber accelerators, lanolin, and formaldehyde) in AD patients is as frequent as in nonatopic individuals[114,115] (see the article by Fonacier and Aquino elsewhere in this issue for further exploration of this topic). Therefore, preventive measures should begin early in life to avoid contact with common sensitizers. Contact dermatitis should always be considered as a potential flare-up trigger in AD. Patch tests to common allergens (including topical medications), cosmetic products (emollients), and even corticosteroids should be performed when suspected in AD patients.

SUMMARY

After years of debate and uncertainties, it is now clear that allergens may play a significant pathogenic role in a subgroup of patients with AD and can be considered as specific triggers of AD. Therapeutic measures, such as elimination of the incriminated allergen(s), can lead to marked improvement of AD; this is particularly true for food allergens but also for inhalant allergens. Patient care should include early allergy diagnosis by SPTs, specific IgE test and/or APT, and when necessary, OFC.

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