Evaluation of Food Allergy in Patients with Atopic Dermatitis

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Atopic dermatitis (AD) is a common skin disease characterized by inflammatory, chronically relapsing and pruritic eczematous flares. Its estimated incidence is 10% to 30% in children. Food allergy has been well documented in approximately one-third of children with a moderate-to-severe AD. Cow's milk, hen's egg, peanut, wheat, soy, nuts, and fish are responsible for >90% of food allergy in children with AD. The incidence and type of food can vary with age. In infants, cow's milk, hen's egg, peanut, and soy and, in older children, wheat, fish, tree nuts, and shellfish are the most common food allergens. Birch-associated foods have also been described as potential triggers of AD in children as well as in adults. The diagnosis of food allergy in AD is currently based on the clinical history, skin prick tests, or blood test screening, followed by an elimination diet and/or standardized oral food challenge. Once an underlying food allergy is confirmed, the avoidance of the incriminated food is generally recommended and usually leads to an improvement of the AD. Follow-up clinical evaluation with a detailed history and tracking of the level of specific IgE to implicated foods are typically used to evaluate the development of clinical tolerance, further confirmed by an oral food challenge. © **2013 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol: In Practice 2013;1:22-8)**

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Childhood eczema has been well known for centuries but remained until recently a purely descriptive clinical entity. During the 20th century, the association of eczema with hay fever and asthma was acknowledged, leading to define the so-called "atopic triad." In 1933, Wise and Sulzberger[1] used for the first time the term atopic dermatitis (AD), referring to a common skin disease characterized by inflammatory, chronically relapsing and pruritic eczematous flares. The adjective *atopic* refers to the underlying presence of elevated total IgE and frequent sensitization to aeroallergens or food allergens, with AD often the first manifestation of the "atopic march."[2]

AD affects a large number of children in industrialized countries with an incidence of 10% to almost 30%, according to published data.[3,4] Its onset is typically in early infancy even though some patients may develop AD later in life. The incidence of AD is estimated to be 1.7% in adolescents, 47.6% of them with first symptoms in early childhood.[5] The reason for persistence of AD into adulthood has not been established, but a genetic predisposition is suspected. Adult-onset AD is rare, occurring in 9% to 14% of cases.[6,7]

Non-AD (not related to IgE-type sensitization) is more common in preschool children or adults with a prevalence of 45% to 64% in children[8,9] and 40% in adults.[10] Children with non-AD have been reported to have a lower risk of developing asthma than atopic children.

Several studies have shown that allergens participate actively to cause inflammation after ingestion of specific food in children with AD.[11,12] Indeed, food allergy (FA) has been well documented in approximately one-third of children with moderate-to-severe AD as a participating trigger of the inflammation, thus influencing the severity of the disease.[13] Cow's milk, hen's egg, soy, and peanut are the most commonly associated allergens in young children. They seem to play a minor role in older children or adults in whom allergy to pollen-related foods, mostly to apple, carrot, celery, and hazelnut, are more frequently involved as triggering factors.[14,15]

In this review, we describe the role of food allergens as triggering factors of AD and elaborate on recommendations for adequate management which are based on the most recent published data.

WHERE ARE WE IN UNDERSTANDING MECHANISMS LINKING FA TO AD?

AD arises from a complex pathologic interaction between several factors, including a genetic predisposition that leads to a defective skin barrier and a dysregulated immune response, as well as environmental triggers that include allergens, irritants, and microbes. Various stressors can also contribute to eczema flares. A number of studies have provided better understanding of the pathogenesis of AD and FA, focusing on the structural abnormalities of skin barrier and the involved immunologic pathways. We describe these briefly and refer to previous reviews for further details.[16,17]

A genetic predisposition clearly plays a role in the pathogenesis of AD.[18,19] Various genes have been identified, mostly coding for proteins involved in skin barrier function as well as in innate and adaptive immune responses.[20] Genetic mutations of the gene encoding filaggrin (*FLG*), an epidermal structural protein, have

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Abbreviations used
AD- Atopic dermatitis
APT- Atopy patch test
FA- Food allergy
FLG- Filaggrin
OFC- Oral food challenge
SCORAD- SCORing Atopic Dermatitis
SPT- Skin prick test

been found as a key defect that leads to epidermal dysfunction and are strongly associated with increasing the risk of AD.[21,22]

Although to date, *FLG* mutations are the strongest genetic risk factor for AD, the full implications of *FLG* defects are not completely understood. In fact, not all patients with AD have *FLG* mutations, and, conversely, not all subjects with *FLG* mutations have AD. Of note, patients with FLG mutations and AD tend to have early onset, severe, and persistent skin disease and are more likely to have asthma and allergic sensitizations.[23-25] It is noteworthy that the odds ratio for *FLG* mutations and peanut allergy appears to be even stronger than for AD (5.3 vs 3.1).[26] The association between *FLG* mutations and peanut allergy provides a strong link between the disruption of the epithelial barrier and the pathogenesis of peanut allergy.[27]

Thus, a defective epidermal barrier function is an important hallmark of AD. Beside increased transepidermal water loss, it allows the penetration of various environmental triggers (microorganisms, irritants, allergens) to interact with the immune system, thus participating in the pathogenesis of atopic diseases.

Several immunologic alterations have been reported in patients with AD and food allergy. The paradigm of the inflammatory response in the skin after exposure to allergens involves epidermal antigen-presenting cells (dendritic cells and Langerhans cells) that express high-affinity IgE receptors binding the antigen and presenting it to T cells, mainly T_H2, leading to local inflammation.[28] Regulatory T cells and more recently regulatory B cells of various subtypes have been described as playing a role in pathogenesis of AD and FA as well as the development of tolerance to implicated foods.[29-38]

THE ROLE OF ALLERGENS IN THE PATHOGENESIS OF AD

Although the role of aeroallergens has been highlighted in several studies,[39] food allergens have been identified as the main external triggers in AD, definitely contributing to the inflammatory response in selected patients.

Sensitization occurs classically through the gastrointestinal tract, because of gut barrier dysfunction and consecutive facilitated absorption of food protein, leading to the development of FA in patients with AD.[40,41]

In addition, Lack et al[42] have shown that sensitization can be achieved before ingestion, also by application of peanut oil on inflamed skin. Similarly, Fox et al[43] described a dose-dependent association between household peanut exposure and the risk of developing a peanut allergy. These findings suggest that sensitization and development of FA might occur by contact of the specific food with the inflamed skin even before its ingestion.

FOOD-TRIGGERING AD: CLINICAL EVIDENCE

The first observations that relate foods to skin diseases go back to antiquity. However, in 1978 Atherton et al[44] showed for the first time in a well-designed trial an improvement in eczema after an elimination diet of cow's milk and hen's egg in 14 of 20 children with AD.

The role of food allergens in AD, based on standardized oral provocation tests, was first established by Sampson in 1983.[11] Twenty-six children aged 16 months to 19 years were tested and those with a clear diagnosis were put on an elimination diet. The most frequently tested foods were cow's milk, hen's egg, soy, and peanut. Of this group, 15 children had 23 positive challenge tests, mainly characterized by erythematous or maculopapular rashes 2 hours after ingestion of the food. The confirmation of an allergic mechanism was further substantiated by the same investigators by showing increased plasma histamine levels in a similar group of patients.[45] In addition, increased spontaneous basophil histamine release was shown in children chronically ingesting foods they were allergic to compared with control subjects.[46]

After these seminal investigations, further studies have examined the prevalence of FA in AD. In 1988, Burks et al[47] studied 46 patients with eczema referred for an allergy work-up. Patients were skin tested and underwent oral challenges with 33% reacting to food allergens, most frequently cow's milk, hen's egg, and peanut.

The first evaluation of the "true and unbiased" prevalence of FA in patients with eczema not referred to an allergist, was published in 1998 and showed that 37% of children with moderate-to-severe AD had food allergy, confirmed by oral food challenge (OFC).[13] A similar prevalence was found 2 years later in Europe among 74 Swiss children.[48]

In contrast, Rowlands et al[49] performed 91 food challenges in 17 hospitalized children with severe AD, refractory to multiple therapies after strict elimination diets. Challenges included highly suspected foods (hen's egg, cow's milk, wheat, soy) as well as other foods with a low potential allergenicity. Only 3 positive OFCs with immediate reaction were observed and no delayed eczematous-type reactions, suggesting a low incidence of FA linked to AD flares. However, because of differences in selection criteria, it is difficult to compare these results with the previously cited studies.

Cow's milk, hen's egg, peanut, wheat, soy, nuts, and fish are responsible for >90% of FA in children with AD,[50] with age-dependent variations in classically incriminated food. Birch pollen-related foods have also been described as potential triggers of AD in older children and adults. These include families such as the *Rosaceae*, *Umbelliferae*, and *Solanaceae*, including numerous fruit and vegetables, the most frequently consumed being apple, carrot, celery, and hazelnut. In 2004, Breuer et al[14] described a worsening of eczematous lesions after an OFC with birch pollen-related food in 5 of 12 children with AD. In contrast to oral allergy syndrome, an IgE-mediated, immediate-type localized and benign reaction that typically affects patients with pollen allergy, worsening of AD might occur even after ingesting birch pollen-related foods in cooked form.[51] Major pollen allergens involved with oral allergy syndrome are the pathogenesis-related protein family 10, such as the birch pollen allergen Bet v1. It should be stressed that oral allergy syndrome–related triggering foods are geographically restricted (eg, allergy to Bet v1 analogs such hazelnut allergens to birch endemic areas).

Prevalence of FA in AD is much lower in adults than in children,[52,53] even though studies with a sufficient number of patients are still lacking. The exact prevalence varies among studies[54,55] and cannot be clearly defined.

PATTERNS OF CLINICAL REACTIONS TO FOOD IN PATIENTS WITH AD

Three different clinical reaction patterns in patients with AD after OFC have been described, depending on the type of symptoms and their time of onset.[12,56]

Immediate-type, noneczematous reactions are usually IgE-mediated, within 2 hours, with skin manifestations such as urticaria, angioedema, flush, and pruritus or other immediate-type reactions of the gastrointestinal tract, the respiratory tract, or anaphylaxis. Various studies have reported the presence of immediate-type, IgE-mediated food hypersensitivity in children with AD.[14,56,57] Cutaneous manifestations occur in 74% of patients.[56] In addition, children might develop a transient morbilliform rash 6 to 10 hours after the initial immediate reaction, disappearing within a few hours and considered as "late-phase" IgE-mediated response.[56] Immediate reactions are barely seen during regular "natural exposure" to the implicated food. This might be explained by the difficulty to identify an immediate cutaneous reaction in an already inflamed skin or possibly also to partial clinical tolerance by continuous intake of the culprit food.[58]

Isolated eczematous *delayed-type reactions* typically occur 6 to 48 hours after OFC with flares of eczema on predilection sites of AD, suggestive for a non−IgE-mediated pattern. Only a few studies have assessed this type of reaction. According to those studies, 25% of reactions occur 2 hours and 10% of reaction at least 16 hours after OFC.[12,59]

A combination of the two above-mentioned patterns with an *immediate-type reaction followed by an eczematous delayed-type reaction* has been described in approximately 40% of children with positive OFC.[60]

FA IN AD: A DIAGNOSTIC PUZZLE

The diagnosis of FA in AD should be made in combination with a thorough clinical history, a laboratory work-up, and an elimination diet, validated if necessary by an OFC, as recommended in the published guidelines for the diagnosis of food hypersensitivity (Figure 1).[57,61]

Before considering an allergy evaluation, optimal skin care should be performed (see "Treatment of patients with AD and FA"). In an interesting observational study, Thompson and Hanifin[62] showed that parental concern about contributing FA and the number of reported reactions decreased significantly after adequate treatment of AD.

According to the recent position paper on food allergy by the International Collaboration in Asthma, Allergy and Immunology,[63] an allergy work-up should be considered in children with (1) a clinical history of immediate reaction to a single food or (2) moderate-to-severe AD despite optimal skin care and currently ingesting a potential culprit food, because this may actively contribute to inflammation (food-induced eczema). This dual approach highlights not only the role of FA as a potential trigger of eczema in moderate and severe AD but also the increasing risk of FA, independently of AD flares, in this highly atopic patient population.

A detailed clinical history may point to a relation between symptoms and a specific food in the case of an immediate-type, IgE-mediated reaction. In food-induced eczema, the positive predictive value of the history is much lower and the "cause-and-effect" relation much more difficult to establish,[12] in particular in children with severe AD. A number of other factors, including inhalant allergens, irritants, microorganisms, or physical factors such as excessive heat, can lead to an eczema flare.[12,64] Sampson[56] showed that only 35% to 50% of parent-diagnosed FA could be confirmed by a double-blind placebo-controlled food challenge.

The history needs often to be confirmed by allergy testing. When food allergy is suspected, *in vivo* (skin prick tests; SPTs) or/and *in vitro* testing (specific IgE measurement) to explore an IgE-mediated sensitization should be performed to the suspected food(s). In a multicenter, international study that included a large cohort of children, Hill et al[65] showed that the earlier the onset of AD, the greater the frequency of associated high levels of IgE to foods, in particular milk, egg, and peanut. In fact, the frequency of food-specific IgE positivity was highest in infants whose eczema developed in the first 3 month of age (64%) and lowest in those whose eczema developed after 12 months of age. The same association was found between the severity of the eczema and the positivity to food-specific IgE tests.

The choice of food tested should be done according to the clinical history and to the most prevalent food allergy in a given population, because positive specific IgE tests to multiple food allergens are commonly found in infants with AD, most of them without any clinical relevance and related only to atopy. To reduce the number of OFCs, these should be restricted to the most likely suspected foods.

It is still controversial if infants presenting with moderate-to-severe AD should be tested for the most prevalent allergenic foods before their introduction and in case of positive results, if delayed introduction of the specific food is beneficial or not. The practical approach seems to vary, depending of referral centers, and further studies are needed to evaluate exact indication for an allergy workup in this specific situation.

In severe AD, an accurate clinical history for recurrent severe bacterial infections and physical examination for dysmorphic features are mandatory to exclude an underlying immunodeficiency.

SPTs

SPTs are usually done as first-line tests and allow detecting the presence of specific IgE to various foods. They have an excellent negative predictive value, depending on the food, in general >95%, but a low positive predictive value of approximately 40%.[11,66,67] Lemon-Mule et al[68] found that <40% of patients with positive SPTs or food-specific IgE had OFC-proven FA. According to these observations, negative prick tests can be helpful to rule out FA, but a positive test often needs to be confirmed by an elimination diet followed by an OFC to confirm the diagnosis of FA.

Serum-specific IgE

The measurement of specific IgE has been shown to be useful in the diagnosis of IgE-mediated FA and is widely used in the diagnosis of FA in children with AD for predicting clinical reactivity. Similarly to SPTs, a negative test is helpful to exclude a FA, but the positive predictive value is expectedly low.[56] Decisional cutoff values for specific IgE to a limited number of foods have been established to provide >95% confidence in

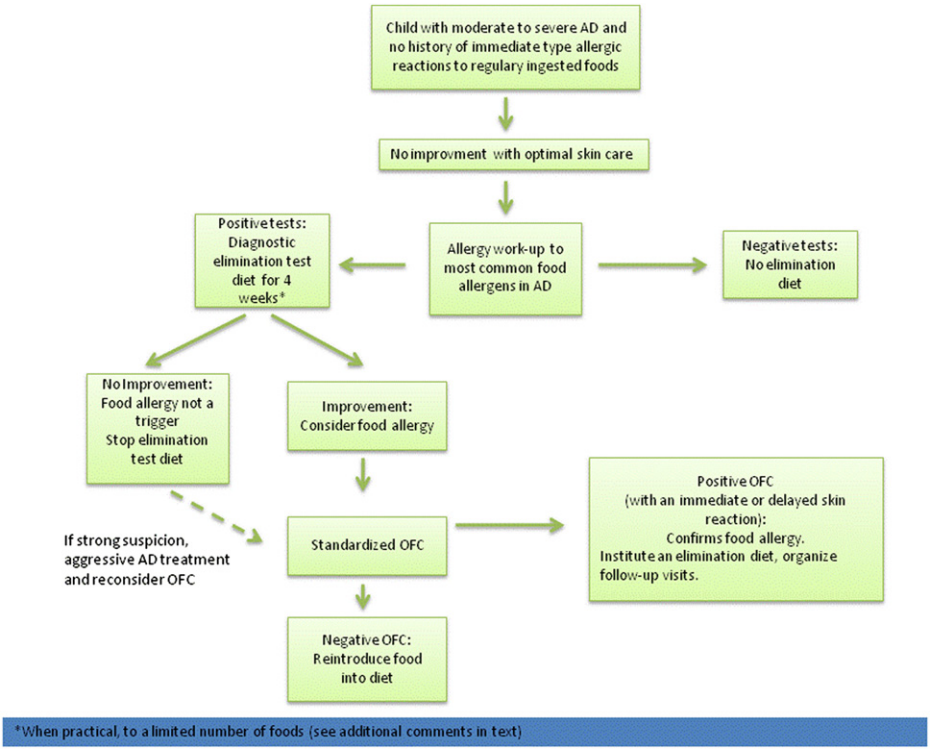

FIGURE 1. Algorithm for the investigation of foods potentially triggering eczema in a child with moderate-to-severe AD.

patients with OFC-confirmed FA.[69,70] The variability of results observed, mostly in relation to age and the clinical characteristics of the study populations, suggest that these tests need to be interpreted in the clinical context of a single patient. In addition, elevated serum-specific IgE titers are not necessarily a contraindication to performing OFC.[71]

New methodology that allows cloning and purifying of specific proteins (recombinant allergens) and the investigations of these specific components in the allergenicity of the food have improved the diagnosis of FA and are also increasingly used in patients with AD and associated FA.[72-74]

Although not yet fully validated, mapping procedures for IgE binding to epitopes within the peptides with the use of microarray analysis has shown promising results in differentiating allergic and tolerant patients.[75,76] These methods, however, are still under investigation.

Atopy patch test

Epicutaneous tests or atopy patch test (APT) have also been studied for their validity in diagnosis of FA in patients with AD and might be an additional tool in selected cases in which SPTs or specific IgE fail to identify a suspected food, as well as in children with multiple, mostly nonrelevant, sensitizations to identify the relevant food.[77,78] Mehl et al[79] compared, in a well-designed study, the sensitivity and specificity of APT versus SPT and measurement of specific IgE antibodies to selected foods (cow's milk, hen's egg, wheat, and soy) in 873 children with moderate-to-severe AD without a history of immediate reactions in relation to a positive OFC. APT showed greater sensitivity than SPTs and specific IgE in cases of delayed eczematous reactions and improved both sensitivity and specificity as well as the predictive value when combined with SPT and specific IgE.

Niggemann et al[80] suggest using a 1/10 dilution in saline of the fresh food, applied for 48 hours on nonlesional skin with interpretation 20 minutes and 24 hours after removal of patches. However, the reproducibility of the APT is still controversial and seems to vary according to the tested food.[81] Furthermore, APT still needs to be standardized, and, according to a recent European Academy of Allergy and Clinical Immunology position paper, it cannot yet be recommended in routine clinical practice.[77]

Elimination diet as a diagnostic tool

When a suspected food has been tested positively during the allergy work-up, a diagnostic elimination diet of 4 to 6 weeks can be a practical approach to evaluating clinical relevance. However, a successful elimination diet alone is not fully reliable because the improvement of AD might be due to other factors or may reflect a placebo effect, particularly in older children and adults.

It is not unusual to have a negative allergy work-up in patients with moderate-to-severe dermatitis. In selected patients, a diary to reports food intake and symptoms could be of help to identify the responsible food(s).[57] Prolonged unselected or elemental diets have not resulted in improving AD in children as shown in a published review.[82] In addition, such diets might induce nutritional deficiencies if applied indiscriminately and without a clear indication.[83]

THE STANDARDIZED OFC: THE "GOLD STANDARD"

The standardized OFC remains the "gold standard" for the diagnosis of FA. It should be performed to assess a clear diagnosis in patients in whom an elimination diet has improved skin symptoms.

OFCs should always be performed under medical supervision with emergency equipment available, particularly after long-lasting elimination of the culprit food.[56] Although a double-blind placebo-controlled food challenge is preferred to open food challenge in patients with active AD,[84] it may not always be the most practical approach. In the case of questionable results with an open challenge, a blinded control challenge may still need to be performed.

Practically, OFC should be performed according to standardized protocols.[71] AD should be stable off systemic drugs, including antihistamines, and the use of topical anti-inflammatory agents should be reduced to the minimum. Before and after the OFC, a physical examination should be performed. Ideally, an additional examination at least 24 hours after challenge and evaluation that use an eczema severity score [eg, by the SCORing Atopic Dermatitis (SCORAD) test; a difference of $\geq$10 SCORAD points is considered significant] can be helpful for proper interpretation.[60]

Other diagnostic tests

The basophil activation test or basophil activation assay is an *in vitro* assessment that uses flow cytometry to detect upregulation of cell surface markers (eg, CD63) after antigen stimulation. Only a few studies that explore its validity in clinical settings have been reported.[85,86]

Food-specific IgG and IgG_4 have not shown any validity in diagnosis of FA and should not be measured, because they are likely to be positive in patients with FA as well as in healthy persons, reflecting normal immune responses to foods a person has been exposed to.[87,88]

TREATMENT OF PATIENTS WITH AD AND FA

Proper skin care of AD is an essential component of managing patients while evaluating for potential triggers.[89-91] Irritants and environmental triggers should be avoided as much as possible. Microbial skin colonization and infection, particular by *Staphylococcus aureus*, needs to be addressed. If suspected, allergy testing to aeroallergens (eg, house dust mites, animal dander, pollen) should be performed, particularly in older children and adults,[92] followed by avoidance measures in patients with positive results.

In confirmed food-exacerbated AD, an elimination diet of the causative food will lead to improvement of AD. In these patients, the indication for a strict diet is still actively debated and its duration not well defined. It has also been reported that after a food elimination, patients might change their patterns of reactivity by developing potentially severe IgE-mediated reactions on accidental exposure.[93] To avoid this, the continuous intake of the implicated food, in a tolerated amount in combination with an adequate treatment of the AD, has been suggested, although the scientific evidence for this approach is lacking. Thus, the potential benefits (decreased AD severity and improved quality of life) and potential disadvantages (decreased quality of life because of need for food avoidance and risk of anaphylactic reactions to a food) of an elimination diet need to be evaluated and discussed with the family.

FA AND AD: THE NATIONAL JEWISH HEALTH ATOPIC DERMATITIS PROGRAM EXPERIENCE

One of the authors of this review (M.B.) works at a tertiary national referral center where typically, children with severe recalcitrant AD are sent for a 2-week program of intensive therapy and evaluation of potential triggers.[89] An all too common problem encountered in this population is that of a diagnosis of "multiple food allergy" that is based on allergic sensitization to multiple foods, often the result of an overly zealous diagnostic response to suboptimal clinical outcomes. This can then lead to a cycle of frustration and nutritionally unsound dietary restrictions. A retrospective study from our center evaluated 125 children aged 1 to 19 years (median age, 4 years) who were evaluated for FA and who underwent an OFC.[94] Ninety-six percent of this selected cohort had a diagnosis of AD with 42% classified as severe. A total of 364 OFCs were performed on foods avoided before evaluation at our center, of which 325 (89%) were negative. In this population, cow's milk, hen's egg, peanut, soy, wheat, tree nuts, and shellfish accounted for most of the clinically relevant FAs. The 95% predictive decision points for food-specific IgE were useful for milk, egg, and peanut. Of note, this was a retrospective analysis in patients without a history of anaphylactic reactions, and the nature of the design did not allow for OFCs on all suspected foods.

FOLLOW-UP AND PROGNOSIS

Approximately one-third of children with AD will outgrow their food hypersensitivity 1 to 3 years after the diagnosis, depending on the causative food.[46] Allergy to cow's milk, hen's egg, wheat, or soy is short lasting in most patients.[95,96] Recent data show that the rate of resolution of some FAs may be much slower than initially reported.[97] Regular follow-up visits at 12- to 18-month intervals may be required. Food-specific IgE levels are helpful in determining the likelihood that the child has outgrown the FA,[98] but, because clinical reactivity is lost over time more quickly than serum-specific IgE testing, OFCs are often needed to assess the current status of clinical reactivity.

Patients allergic to peanut, nuts, fish, and shellfish are less likely to lose their clinical reactivity with time.[99,100] These patients need less frequent reevaluations. Fleischer et al[101] showed in 278 children with tree-nut allergy that only 9% will outgrow their allergy. These data may underestimate the natural resolution of nut allergy and need to be confirmed in further studies.

SPTs are not as helpful in the follow-up of patients with FA, because they can remain positive for several years after the child has outgrown the allergy. However, properly done negative tests would have a high predictive value as discussed earlier.

CONCLUSIONS

AD is a common skin disease, particularly in early childhood, with a significant effect on the quality of life of patients and their families. New insights into both skin barrier and immune abnormalities point to a complex pathophysiology. Increased allergen absorption through a defective skin barrier and genetically determined immune dysregulation can contribute to skin changes in AD and also in other target organs. FA has been well documented in approximately one-third of children with a moderate-to-severe AD, and an allergy workup should be performed in this selected group of patients. The diagnosis is currently based on SPTs and blood test screening, followed by an elimination diet and OFC. Rationale for testing, as well as limitations of testing, should be discussed with patients and caregivers before initiating an evaluation of patients with AD. Once an underlying FA is confirmed, the avoidance of the incriminated food is generally recommended and usually contributes to an improvement of the AD. Regular clinical follow-ups, including a detailed history that searches for intercurrent accidental

exposures and measures of specific IgE level, can be useful in evaluating the development of clinical tolerance, which will ultimately be determined by an OFC followed by successful reintroduction of the food into the patient's diet.

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