

Are avoidance diets still warranted in children with atopic dermatitis?

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Abstract

Nearly 40% of children with moderate-to-severe atopic dermatitis (AD) have IgE-mediated food allergy (FA). This clinical observation has been extensively documented by experimental data linking skin inflammation in AD to FA, as well as by food challenges reproducing symptoms and avoidance diets improving AD. Although food avoidance may improve AD, avoidance diets do not cure AD, may even have detrimental effects such as progression to immediate-type allergy including anaphylactic reactions, and may significantly reduce the quality of life of the patient and the family. AD care should focus upon optimal medical management, rather than dietary elimination. Food allergy testing is primarily indicated when immediate-type allergic reactions are a concern. In recalcitrant AD, if food is being considered a possible chronic trigger, a limited panel of foods may be tested. An avoidance diet is only indicated in patients clearly identified as food allergic by an appropriate diagnostic food challenge, and after adequately informing the family of the limited benefits, and possible harms of an elimination diet.

KEYWORDS

anaphylaxis, atopic dermatitis, avoidance diet, food allergy, IgE testing, oral tolerance induction, quality of life

1 | INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disorder that is characterized by dry skin and recurrent flares of a pruritic eczematous rash. This disease is most prevalent in young children, especially in those with a genetic pre-disposition toward atopic disease. Food allergy (FA) is a disease primarily characterized by acute, IgE-mediated allergic reactions, including anaphylaxis, but FA may also result in chronic symptoms affecting the gut or skin. A clear link between AD and FA has been well recognized.¹

Children with moderate-to-severe AD may benefit from an allergy workup including evaluation of food allergens as a trigger. In

those in whom a specific food worsens their eczema, a strict avoidance diet has been advocated for decades.² The avoidance diet may lead to an improvement of the eczema severity and the frequency of flares, but might also have detrimental effects. Benefits vs detrimental effects of avoidance need to be balanced.

Oral tolerance induction has been recently studied in rigorously designed clinical trials, both for prevention and for treatment of FA. These modalities, often undertaken in children with AD, highlight increasing equipoise about the management of AD with food allergen elimination diets.

This article discusses the current knowledge and provides an expert opinion on an approach to FA in AD.

2 | PATHOGENESIS OF AD AND FA

Nearly 40% of children with moderate-to-severe AD have clinically significant IgE-mediated FA (summarized in Figure 1), as compared to only 6% in the general population.³ Overall, the earlier the onset in the first year of life and the more severe the AD, the more likely the infant will develop FA.⁴ These observations provided one of the first lines of evidence for a strong association between AD and FA. More recent experimental models using tape stripping, which removes the stratum corneum (SC) of the skin, and application of food allergen to the skin, have provided support for the potential route of IgE sensitization being via the skin and not necessarily through ingestion (reviewed in⁵). The removal of SC in these models closely resembles the inherent skin barrier defects of AD patients. The non-lesional skin of AD patients is characterized by a significantly thinner SC and a higher trans-epidermal water loss (TEWL).^{6,7} These barrier defects can be attributed to a deficiency in the expression of skin barrier molecules including ceramides and filaggrin by keratinocytes, the main epithelial cells in the skin, of AD patients.⁸ Following barrier disruption, keratinocytes express cytokines such as thymic stromal lymphopoietin (TSLP), IL-33, and IL-25. Expression of these cytokines will be increased in eczematous skin exposed to food allergens.⁹ These cytokines activate innate lymphoid cells 2 (ILC2), dendritic cells, and basophils, leading to the activation of Th2 and Th9 cells, which produce IL-4, IL-9, and IL-13 and subsequently induce specific IgE production. The pattern of cytokine expression found in lymphocytes infiltrating acute AD lesions is predominantly those of the Th2 type and, to a lesser degree, Th22 and Th17, which contrasts with the classic type IV cellular response.¹⁰ The Th2 cytokines

generated can promote eosinophil influx, activation of eosinophils, and deposition of eosinophil products, for example, major basic protein (MCP) in lesional skin.¹¹ Furthermore, these cytokines upregulate high-affinity IgE receptors on antigen-presenting cells, including Langerhans cells, and further promote synthesis of IgE antibodies. IgE-bearing Langerhans cells, in the presence of activated keratinocytes secreting IL-25, IL-33, and TSLP, are highly efficient at traversing to regional lymph nodes, presenting allergen to naïve T cells, and activating a Th2 response.¹²

In contrast to the skin, early oral exposure of food allergens generally leads to tolerance induction.¹³ The production of mucin by intestinal epithelial cells and GM-CSF by innate lymphoid cells type 3 (ILC3) primed CD103+ dendritic cells can convert naïve T cells into T regulatory cells (Treg), which suppress development of IgE and FA (reviewed in⁵). The role of early oral exposure to induce tolerance has been illustrated by the successful introduction of peanut in the Learning Early About Peanut (LEAP) study.¹⁴ The intimate link between sensitization in eczematous skin and loss of oral tolerance is best illustrated by early introduction of egg. The presence of AD strongly correlates with reaction to egg in trials where infants received early feeding of egg (summarized in¹⁵). These studies suggest that counter-regulatory mechanisms of early oral exposure against eczematous skin sensitization are required to maintain tolerance in AD patients. A break in oral tolerance may be induced by the adjuvant effects of staphylococcal enterotoxins.^{16,17} Almost all acute AD lesions are colonized by *Staphylococcus aureus* (*S aureus*). Skin barrier defects and deficiency in endogenous or exogenous antimicrobial peptides expressed by commensal bacteria such as coagulase-negative staphylococci are important factors that contribute the colonization of *S aureus* on AD lesions. The production of staphylococcal enterotoxins leads to worsening of AD symptoms and production of host-specific IgE against these toxins.¹⁸ Of interest, the presence of specific IgE to staphylococcal toxins was significantly associated with the presence of specific IgE to egg white in AD children.¹⁹ It has been suggested that successful early introduction of egg will likely require treatment or prevention of AD¹⁵ and a recent systematic review of randomized controlled trials demonstrated moderate evidence for this.²⁰ Control of AD symptoms leads to improvement of skin barrier functions and *S aureus* clearance, and therefore less likely for food allergens to sensitize via the skin. These mechanisms will need to be investigated further.

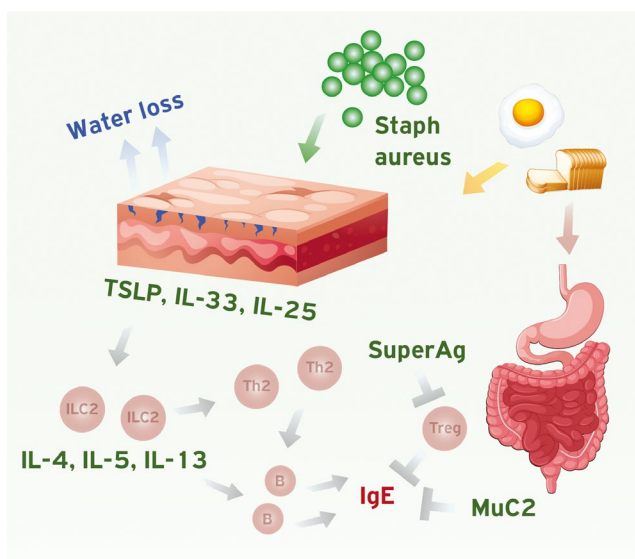


FIGURE 1 Early food allergen ingestion and intact skin barrier are required to maintain tolerance to food allergens. A breakdown in skin barrier and the presence of staphylococcal enterotoxins ("superantigens") lead to Th2 inflammation in atopic dermatitis, a loss of tolerance induction by T regulatory cells, and the development of food-specific IgE

3 | HOW THE LINK BETWEEN AD AND FA WAS ESTABLISHED?

The pathogenic role of FA in AD has been debated for more than 100 years, ever since Schloss first reported several cases of patients who experienced improvement in their eczematous skin lesions after avoiding specific foods.²¹ Several other case reports supported Schloss' observations, but this was largely dismissed by the medical community. While AD was classically considered a type IV

TABLE 1 Summary statement

There is evidence that foods may exacerbate AD in a subset of children with AD

While about 40% with moderate-severe AD have food allergies, only a subset have AD flares from those foods, others have immediate anaphylactic reactions. Diagnostic evaluations should consider both issues

Recent prevention and treatment studies encourage ingestion of allergens and have not been associated with causing increased AD in most cases. This observation has reduced enthusiasm for managing AD by strict dietary elimination

Dietary elimination of a food carries nutritional quality of life and possible immune consequences (development of immediate-type reactions) and must be discussed and considered in shared decision-making. Skin management should be encouraged, typically as a first line approach, with food triggers considered for recalcitrant cases

Allergy testing for foods in AD has limited utility in terms of eczema symptoms, although negative tests may help eliminate suspicion. If a food is targeted for elimination, the trial should be brief and followed with oral food challenges to prove a relationship if the trial was deemed possibly successful

Although studies are lacking, a rationale to reduce rather than eliminate possible food triggers can be considered

cell-mediated disease, studies in the past few decades have demonstrated that the late stage of IgE-mediated hypersensitivity reactions are characterized by infiltration of mononuclear cells. Two main lines of evidence supported a pathogenic role for Th2/IgE-mediated food hypersensitivity in AD: [1] Food challenge studies provoked immunologic changes that were associated with the development of eczematous lesions, and [2] studies identifying and eliminating food allergens led to clinical improvement and a return of abnormal immunologic parameters to normal.

Both immediate and late-phase effects of ingested food allergens have been documented during double-blind, placebo-controlled food challenges (DBPCFCs) in children with AD.^{22,23} The pruritic, erythematous morbilliform rash, which is a hallmark of the immediate skin response, generally arose abruptly and persisted for 30-150 minutes. These "early" responses to the DBPCFCs were accompanied by sharp increases in plasma histamine, an absence of immediate activation of circulating basophils, and no significant changes in the plasma complement activation products, C3a or C5a. In addition, several lines of evidence suggested an IgE-mediated late-phase component associated with positive DBPCFC. During the post-challenge observation period, patients frequently developed diffuse pruritus and occasionally an erythematous macular rash approximately 4-8 hours following primary skin reaction. Circulating peripheral blood eosinophils decreased approximately 6-8 hours following a positive food challenge but returned to pre-challenge levels 14-16 hours later with a shift to increased numbers of activated (hypodense) eosinophils. In addition, serum ECP levels have been reported to rise following a positive food challenge with a maximum at 24 hours.²⁴ This

increase was predominantly related to eczematous reactions.²⁵ Skin biopsies obtained at the site of a food challenge-induced morbilliform lesion 10-14 hours following a positive challenge revealed eosinophil infiltration and deposition of MBP.²¹ Once recruited, eosinophils may release mediators, for example LTC₄, cationic proteins, for example MBP, ECP, and EDN, and cytokines that contribute to and perpetuate chronic inflammation. In addition, when PBMCs from patients with AD and milk allergy, milk-induced gastro-enteropathies, or normal controls were stimulated in vitro with casein and then evaluated for expression of homing receptors,²⁶ only patients with AD and milk allergy demonstrated a significant increase in CLA + T cells, the homing receptor responsible for migration to the skin, suggesting that these antigen-specific T cells play a role in the cutaneous inflammatory response in AD. However, this increase in CLA + T cells has also been observed in patients with milk-induced urticaria²⁷

In a prospective follow-up study of 34 patients with AD, 17 children with FA who were appropriately diagnosed and placed on an allergen elimination diet experienced a marked and significantly greater improvement in their eczematous rash at 1-2 years and 3-4 years of follow-up compared with 12 similar AD patients who did not have FA and 5 children who were food allergic but did not adhere to the elimination diet.²¹ Only food-allergic children adhering to the appropriate elimination diet demonstrated long-term improvement in their AD and a significant decrease in their serum IgE concentrations over the 3-4 years of follow-up. In an additional cohort of food-allergic children with AD, lactulose absorption studies (a measure of gastrointestinal permeability) were found to abnormal prior to allergen elimination, but subsequently became normal when the responsible food allergens were eliminated from the diet.²² In a randomized controlled trial of children with AD and egg allergy, egg elimination resulted in a significant mean reduction in surface area affected by eczema and significant improvement in AD severity score in children placed on an egg elimination diet compared to the control group.²⁸ A subsequent Cochrane meta-analysis²⁹ concluded that there "may be some benefit in using an egg-free diet in infants with suspected egg allergy who have positive specific IgE to eggs," but "little evidence supports the use of various exclusion diets in unselected people with atopic eczema, but that may be because they were not allergic to those substances in the first place. Lack of any benefit may also be because the studies were too small and poorly reported." While young children with AD, especially severe AD, frequently are sensitized to a variety of food allergens (positive skin prick tests or elevated allergen-specific serum IgE), only 30%-40% reflect clinical reactivity as demonstrated by DBPCFC. Egg, milk, and peanut allergy were the most common food allergens responsible for reactions in these children, but egg and to a lesser degree milk were most commonly implicated in exacerbating AD since peanut reactions were typically anaphylactic in nature.²¹ While FA does not cause AD, it can exacerbate flares of eczema in some sensitized patients, much as aeroallergens can exacerbate asthma.

4 | BENEFITS OF A DIET IN PROVEN AD AND FA

The major expected benefit of a food avoidance diet is the reduction of severity of AD. Despite the significant number of studies discussed above showing a role for foods in the pathogenesis of AD by standardized food challenges, few studies have investigated the extent of AD improvement after a food avoidance diet. In 1978, Atherton et al conducted a double-blind cross-over trial in 36 children with AD suspected to be cow's milk or egg allergic.³⁰ The AD activity scores improved by 2.06, the area scores by 2.73, the pruritus scores by 4.49, and the sleeplessness scores by 4.95. Overall, 70% of the children who completed the trial responded to the food avoidance diet. In a small series of 21 infants, 7 were reported as having totally cleared (all were infants less than 6 months of age), while 12 improved after a period of elimination of up to 6 weeks.³¹ Half of the population were reacting to cow's milk upon challenge. In a larger sample of 59 children with severe AD, Businco et al³² observed a clinical improvement in 80% of the children after dietary exclusion of cow's milk and egg. In another small series from Finland, Broberg et al started an elimination diet excluding allergenic foods in thirteen children with severe AD during 2 to 4 weeks.³³ AD scores improved in most patients, by a mean of 60%. In a trial on hen's egg allergy, Lever et al²⁸ recruited 62 children with AD and elevated egg-specific IgE. All children were eating eggs in processed foods, but not whole egg. Children were randomized to an avoidance group or a control group after optimal skin care. More children in the diet group showed a decrease in the surface of skin affected (89% vs 59%); similarly, a decrease was seen in the severity score in the diet group. Children with AD and cow's milk allergy also significantly improved by about 50% of their SCORAD AD severity score similarly on either a diet with an amino-acid-based formula, or an extensively hydrolyzed formula.³⁴ Interestingly in this trial lasting 6 months, the author saw a gradual improvement, plateauing after only the third month of milk avoidance.

Overall, these studies confirm the clinical impression that in a subgroup of patients with AD identified as allergic to cow's milk, hen's egg, wheat, and/or possibly also soy, an avoidance diet may significantly, but most often not completely, reduce the severity of the AD.

5 | CAN AN AVOIDANCE DIET HARM?

Removal of foods from the diet can result in potential harms, including progression to anaphylactic allergy to the eliminated food, nutritional concerns, and impact on quality of life.

Various reports suggest that clinical allergy, including anaphylaxis, can arise in persons for whom dietary elimination of a previously consumed food was initiated. Such elimination has typically been undertaken due to suspicion of a role in causing AD but has

also been demonstrated in cases where food is eliminated inappropriately for identified sensitization (positive skin prick tests or serum food-specific IgE) or other reasons. In 1984, TJ David observed that among 80 patients with AD on various elimination diets, while they re-tried eliminated foods, 4 of them experienced anaphylaxis.³⁵ Flinterman et al³⁶ described 11 children with acute allergic reactions upon food challenge to milk. These 11 children had tolerated cow's milk without acute symptoms but had milk eliminated for AD, without improvement, for a median of 2.3 years. Larramendi et al³⁷ described 7 atopic children noted to be fish sensitized who were instructed to avoid fish. Following avoidance from 2 to 10 years, they experienced acute allergic reactions. A fatality from milk allergy was reported in a girl who had accidentally ingested milk years after it was removed from her diet at age 11 for persistent eczema.³⁸ Nachshon et al culled data on 23 patients with FA to previously consumed foods, including one who had a fatal milk reaction.³⁹ Of these, 19 had started an elimination diet (12 based on advice from a healthcare professional) before allergic symptoms were identified on re-exposure (median avoidance 45 weeks, range 1 week to 23 years). Seven had severe AD, including a 28-year-old who died from milk ingestion 10 months after dietary elimination. These examples likely represent the loss of a desensitized state following a period of no oral exposure, similar to what is observed when oral immunotherapy is withdrawn and sustained unresponsiveness is monitored.⁴⁰ However, there is also a suggestion in the literature that delaying introduction of foods or removal of them from the diet even without prior sensitization may result in new-onset sensitization and allergy.⁴⁰⁻⁴²

The degree of risk related to removing foods from the diet has not been well-delineated. A study by Chang et al focused on patients who had acute reactions to foods eliminated to treat AD.⁴³ They began with a chart review of 298 patients and noted 19% of sensitized children without a history of acute reactions developed new-onset allergy (30 percent of those with anaphylaxis). Overall, these observations and studies underscore the need to consider this potential risk during allergen elimination for AD.

The nutritional risks of dietary avoidance for treatment of FA are well described.⁴⁴⁻⁴⁷ Those with milk allergy or multiple food allergies are at highest risk for growth failure and nutritional deficiencies.^{48,49} National FA guidelines recommend nutritional counseling and growth monitoring for children on elimination diets for FA.⁵⁰⁻⁵² One may hypothesize that children with severe AD could have growth failure caused by increased metabolic needs of the skin damage. However, in a study of a referral population with moderate-to-severe AD, it was noted that the children with comorbid AD and FA were at significant risk of growth deficiency (particularly if avoiding milk) and those with AD and no FA were actually more likely to have an elevated weight.⁵³ These distinctions were not explained by the severity of the AD. Overall, dietary elimination, especially milk or multiple foods, poses a nutritional concern that should be addressed during management.

Removing foods from the diet requires attention to label-reading for ingredients, discussions in restaurants about ingredients

and cross-contact, home management, and managing these issues for celebrations, travel, work, and school among other situations.⁵⁴ It is therefore not surprising that FA carries significant impact on health-related quality of life and may cause anxiety.⁵⁴⁻⁵⁹ The emotional ramifications related to dietary elimination are another potential harm that should also be discussed when considering the option of avoidance.

6 | WHAT LEAP HAS BROUGHT TO CURRENT KNOWLEDGE AND TO PREVENTION OF FA?

The LEAP (Learning Early About Peanut allergy) study was a randomized controlled trial that demonstrated in a high-risk atopic cohort of infants aged 4-11 months with severe eczema and/or egg allergy that early introduction of peanut could reduce the development of peanut allergy overall by 81% as measured by double-blind challenge at 5 years of age. What is clear from the LEAP study is that the development of eczema preceded the development of peanut allergy. This together with a growing body of evidence suggests that eczema is involved in the causal pathway toward the establishment of food allergies rather than the reverse. It should be noted that in the LEAP study, the introduction of peanut protein in the intervention arm did not alter the trajectory of eczema over time.⁶⁰ SCORAD was recorded prospectively in the LEAP study, and it is clear that SCORAD levels over time, resolution of eczema, and persistence of eczema in the intervention and control arms were identical despite a high proportion of infants already sensitized to peanut at baseline (see below).

A striking finding of the LEAP study is that 17% of children at enrollment, who were skin prick test (SPT) negative, had specific IgE (sIgE) to peanut ≥ 0.35 kU_A/L and 28% had sIgE ≥ 0.1 kU_A/L.⁶¹ Furthermore, 69% (25/36) of infants in the SPT avoidance arm who became allergic to peanuts by 5 years of age already had sIgE to peanut ≥ 0.1 kU_A/L at study enrollment at which time they were tolerant to peanuts (with a baseline peanut SPT size of ≤ 4 mm).

The clinical implications of these findings are 2-fold. Firstly, infants who have early evidence of sensitization to peanut are at increased risk of developing FA and should have early introduction of peanut and potentially other foods such as hen's egg (if tolerated). Secondly, atopic infants with eczema who are already consuming and tolerating a food in their diet in the first few years of life should not have SPT or sIgE testing performed to that food which they are eating. Unnecessary testing of tolerated foods remains common practice among numerous medical specialties. The consequences are potentially serious as highlighted in the previous section.

The unproven perception that ingestion of these foods will lead to worsening of eczema as a justification for the removal of these foods from the infant's diet has the potential consequence of promoting FA and preventing the development of oral tolerance.

Allergy testing in young infants is clearly important from a diagnostic perspective. However, if it is done without appropriate

reason, it may lead to a delay in introduction of foods in the infant's diet and may cause more harm than good.

7 | WHAT OIT HAS BROUGHT TO CURRENT KNOWLEDGE AND TO TREATMENT OF AD AND FA?

For decades, FA has been treated with complete food allergen avoidance without regard to the elicited symptoms or the threshold levels causing the symptoms.⁵¹ For example, infants with worsening of their eczema after the consumption of 100 mL of cow's milk are treated similarly to infants with generalized urticaria and wheezing after 1 mL of cow's milk. As described above, there is evidence that strict allergen avoidance in children previously consuming the offending allergen might lead to the development of anaphylactic reactions after re-introduction. This risk may mitigate a decision for strict allergen avoidance, if possible.

The concept of strict allergen avoidance as a management tool for IgE-mediated FA has been challenged by the efficacy of oral immunotherapy (OIT) as shown in a recently published meta-analysis.⁶² In this analysis, out of 31 included trials, 16 focused on cow's milk allergy, 11 on hen's egg, and one on wheat; foods potentially implicated in worsening of AD. Since this report, additional OIT trials have been published mostly with peanuts, a low-dose peanut OIT protocol with successful desensitization in 74% of the active group,⁶³ and very recently, a large international phase III trial with 496 children randomly assigned to receive a peanut-derived investigational oral immunotherapy drug or placebo.⁶⁴ Of these, 67.2% who received active treatment, as compared with 4.0% who received placebo, were able to ingest a dose of 600 mg or more of peanut protein, without dose-limiting symptoms.⁶⁰

Although the concept of OIT also relates to FA and AD, OIT has been developed as a more generalized concept for desensitization in patients with a clinically defined IgE-mediated FA. How AD is addressed in these studies can be highlighted in three representative studies for OIT to foods commonly linked to AD flares (cow's milk, egg, and wheat). Staden et al⁶⁵ published an early trial on cow's milk OIT with 25 children assigned to OIT and 20 to avoidance. In the group on OIT, 13 worsened their AD (3 terminated the trial for this reason), 11 developed episodes of urticaria, and 4 of angioedema. In a representative trial on egg OIT, 55 children were randomized 2:1 to receive either egg or placebo for 22 months.⁶⁶ At 22 months, 75% of the children in the egg group (30 of 40 children) successfully passed the egg challenge. No indication was given on the number of patients with AD, but eczema severity was mild in those with AD. During the 22 months of OIT, none of the withdrawals were for eczema worsening. Skin symptoms were reported in up of 8.1% of the ingested doses, mostly during the initial-day dose escalation, but without specifying the type of reaction. Overall, worsening of AD was not an issue in this egg OIT trial (personal communication of the authors).

In a very recently published trial on wheat OIT, 46 children and young adults with challenge-proven wheat allergy were randomized to

a low-dose wheat or placebo group for one year, and while the low-dose group continued with the same protocol for a second year, the placebo group switched to a high wheat dose for the second year.⁶⁷ Desensitization was obtained in about half of the patients receiving wheat, while only 13% achieved sustained unresponsiveness. In this trial, 39 in 46 subjects suffered from AD, mostly mild intermittent, and only 2 subjects from the active group had moderate persistent AD. Almost all subjects on wheat reported dosing symptoms during the trial, 85.7% related to the skin in the high-dose wheat group, and 65.2% in the low-dose group, without additional information on the type of skin symptoms. None of the patients discontinued the study for worsening of their AD.

In all the OIT trials, the measured outcomes were the allergen eliciting threshold of clinical reactivity, which did not allow an estimate of whether and how much OIT was influencing the severity or the course of AD. Nevertheless, skin rashes and AD flares were reported, but worsening of AD seemed to be mostly marginal. However, OIT studies specifically addressing AD as the prime clinical picture of FA are lacking.

OIT seems to be a promising approach for the treatment of FA, with data suggesting that an early initiation with lower OIT doses may offer good efficacy. Nevertheless, safety has been questioned in a recent meta-analysis.⁶⁸ Although the majority of the children in these OIT trials had underlying AD, worsening of eczema was very uncommon. To conclude, it is yet unclear if current findings from OIT trials will challenge the dogma of total food avoidance in children with AD and FA. Nevertheless, the concept of OIT, feed what is tolerated as it might positively influence the outcome of food allergy, suggests that complete food avoidance might not be recommendable.

8 | HOW TO ADDRESS FA IN PATIENTS WITH AD IN 2019?

It first needs to be emphasized that “one size does not fit all”; there are many different triggers in patients with AD, responses to therapies may differ, and also, the patient and family expectations when seeing an allergist are varied. However, as a common rule to all patients with AD before an allergy workup, skin care should be addressed. Does the patient benefit from optimal hydration of the skin? Are topical anti-inflammatories used optimally? Has an anti-itch plan been established? Does the patient qualify for a systemic treatment? If available, has “AD school” (skin care education programs) been offered? In many patients, the role of foods will become minor if the skin has reasonably cleared with good eczema care.

If warranted, the first step of the allergy assessment starts with a thorough discussion with the family on the various options of medical (and possibly dietary) management, including the risk/benefits of the various options. This initial discussion will establish the needs and expectations of the family and the patient. Indeed, these will vary according to the age of the patient and the severity of AD. First, the history will establish if a specific food worsens AD. Tomato,

eggplant, or parmesan cheese among others may provoke only perioral erythema. They are most likely the result of skin irritation by the food and do not warrant FA testing. If allergy tests (SPT or serum sIgE tests) are indicated, they should be restricted to the very few foods which have been identified as triggers of AD flares, for example egg, milk, wheat, and very rarely soy by allergy specialists. In young patients not having started highly allergenic foods, allergy testing will also address immediate-type allergy upon introduction (eg, for peanuts or tree nuts). The negative predictive value of these tests is sufficient to exclude FA. After maximal skin care (hydration and topical corticosteroids), a short avoidance diet (2-3 weeks in general) under continuous skin care may help assess the relevance of positive tests. Nevertheless, before considering dietary changes, a discussion with the family needs to address the pros and cons of an avoidance diet as it has been outlined above. The quality of life may diminish, in particular in older children, and a risk of “disease-switching” to anaphylactic symptoms exists. If a dietary avoidance trial has been undertaken and no improvement is seen, FA is not proven and the food can be reintroduced. If there is an improvement, a food challenge will help establish the diagnosis.

When starting an avoidance diet, one needs to consider whether strict avoidance is necessary. For example, most egg allergic patients will tolerate at least some amounts of eggs in baked products. Similarly, milk allergy patients may tolerate some amounts of baked milk products. Clinical experience shows that removing them from the diet will in most cases not further improve AD. In some centers, patients with AD would qualify for OIT. This is an additional reason for titrating the tolerated amounts of foods and keeping them in the diet. Finally, a FA diagnosis in AD patients will need a follow-up plan, as FA may spontaneously resolve, or symptoms switch to anaphylaxis during avoidance.

In conclusion, AD is a chronic inflammatory skin disease with many triggers, and FA is only one possible trigger in about one third of patients with moderate-to-severe AD. In these patients, and only after an optimal skin care treatment is established, allergy testing with a limited panel of food may be warranted. In patients with a positive test, and clinical reactivity clearly attributed to the food, an avoidance diet may be indicated. IgE testing should also aim at identifying patients at risk for immediate anaphylactic reaction to high-risk foods not yet introduced in the diet of the child. The diet should be tailored not only to improve AD severity, but also to avoid a negative impact. Table 1 provides a summary of this review.

CONFLICT OF INTERESTS

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