

# Food Allergy in Atopic Dermatitis

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## 1. Introduction

Atopic dermatitis (AD) is a form of allergic skin inflammation characterized by late eczematous skin lesions [1]. These skin lesions occur through non-Immunoglobulin E (non-IgE)-mediated immune responses, and therefore, AD can be regarded as a non-IgE-mediated allergic inflammatory skin disease [2]. Many causes, including inhalant allergens, food allergens, and other factors, have been implicated in AD [1]. In addition to information about the causes, knowledge of the immunologic nature of AD is extremely important in order to understand AD. Without an understanding of the immunologic nature of AD, the cause of food allergy in patients with AD may be wrongly identified. Because of this confusion in establishing the cause of a food allergy in AD, the role of food allergy in AD remains poorly understood [2]. However, with the recent advance in the diagnosis and treatment of food allergy, it is necessary inevitably to distinguish between IgE- and non-IgE-mediated food allergies that co-exist with AD in order to better understand and control AD [2].

It is well-known that food allergy is an important cause of atopic dermatitis [3]. Although food allergies can be either IgE- or non-IgE-mediated, due to a lack of diagnostic modalities such as laboratory tests to diagnose non-IgE-mediated food allergy [4], it is difficult to clarify the nature of the food allergy, leading to confusion about role of food allergy in AD. Tests that determine IgE levels cannot predict the likelihood of an eczematous reaction because eczematous reactions are the result of non-IgE-mediated food allergies [2].

Until recently, discrimination of IgE-mediated and non-IgE-mediated food allergies was not considered necessary for diagnosis or treatment. Therapeutic modalities, including tolerance induction for food allergy (TIFA), have been developed for patients with food allergy [5,6]. However, the principles for diagnosing and treating IgE-mediated or non-IgE-mediated food allergies are quite different [7]. Presently, a differential diagnosis is absolutely necessary for relevant, proper, and successful treatment of IgE-mediated and non-IgE-mediated food allergies, independently. Clinical approaches to treat food allergy in AD patients, including laboratory tests and diagnosis, should consider the conceptual differences between IgE-mediated and non-IgE-mediated food allergies.

In the past, avoidance has been suggested as the main principle for treating food allergies [8]. More recently, however, the clinical and laboratory characteristics of IgE-mediated and non-IgE-mediated food allergy in atopic dermatitis have been well-characterized, and the

relevant treatment techniques, including tolerance induction for food allergy (TIFA), have been markedly advanced and well-established [7]. In this chapter, updates on the diagnosis and relevant treatments for food allergy in AD are described

## 2. Atopic dermatitis

### 2.1 Definition

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease [1] that is characterized by non-IgE-mediated allergic skin inflammation, in which allergen-specific Th2 cells play a major role in the pathogenesis of the inflammation [2]. The appearance of atopic dermatitis is characterized by late eczematous reactions, which result from an allergen-specific Th2 immune response.

### 2.2 Immunopathogenesis of AD with food allergy

The immunologic phases of food allergy in AD include a sensitization phase and an effector phase (Fig. 1) [2]. During the sensitization phase, the tolerance of a subject to a specific allergen is determined. Response to that allergen, either allergic or tolerant, occurs in the effector phase.

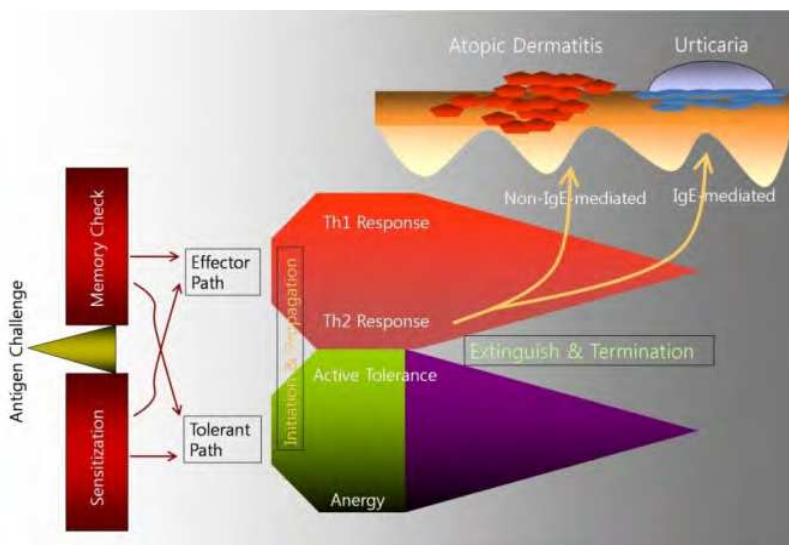


Fig. 1. Scheme of immunopathogenesis of food allergy in atopic dermatitis. When allergen is challenged, the immune system check the memory. In the neosensitization, immunologic memory of allergy is induced in the Th2 polarized status, or tolerized in normal status. In the immunologic process, IgE-mediated allergy or non-IgE-mediated allergy is formed when food allergen is to be memorized to react as allergic reactions. If food allergen is re-challenged, atopic dermatitis is appeared by non-IgE-mediated food allergy or IgE-mediated allergy including urticaria to anaphylactic shock occurred. If allergen is memorized being tolerant, there is no reaction even by any further challenge by allergen. IgE-mediated food allergy and non-IgE-mediated allergy is apparently different in the immunopathogenesis as well as clinical manifestations.

Humans are continually challenged by foreign particles, including pathogens and foods. Protection from these foreign substances is mediated by effective immune responses (effectors). Protection from immune responses directed against food occurs by an immune tolerance response (tolerance). Allergy is one type of effector immune response that is the consequence of allergic sensitization. Allergic sensitization occurs from a Th1/Th2 imbalance [9]. There are 2 classes of allergic effector mechanisms: IgE-mediated and non-IgE-mediated allergic reactions. An IgE-mediated allergic response occurs if allergen-specific IgE is activated after exposure to the specific allergen. IgE-mediated immune reactions include urticaria, asthma, and rhinitis.

IgE has been positioned at the center of focus in allergy and allergic disease research. However, a major characteristic of AD is its non-IgE-mediated response.

### **3. Clinical characteristics of food allergy in AD**

#### **3.1 Clinical features of AD**

The clinical phenotype of AD varies with age and course of the disease [10]. The eczematous lesions may present as acute (oozing, crusted, or eroded vesicles or papules on erythematous plaques), subacute (thick and excoriated plaques), or chronic (lichenified, slightly pigmented, or excoriated plaques) forms. Furthermore, xerosis and a lowered threshold for itching are usual hallmarks of AD. Pruritus attacks can occur throughout the day and worsen at the night, causing insomnia, exhaustion, and a substantial impairment in quality of life. To date, the symptoms and signs of AD have been listed horizontally. However, the primary clinical manifestations of AD include eczematous skin lesions and itching caused by allergen-specific Th2 immune responses. Some clinical manifestations of AD, including papule, plaque, and xerosis, are descriptions of skin manifestations; some manifestations, including excoriation, are related to the primary AD symptoms and signs; and some manifestations, including viral infection and impetigo, insomnia, and exhaustion, are secondary to the primary symptoms and signs.

#### **3.2 Clinical features of food allergy in AD**

The clinical manifestations of IgE-mediated food allergy (IFA) are uniform in AD and in the absence of AD; they include dermatologic manifestations, such as immediate urticaria and rashes, as well as other cardiovascular and respiratory symptoms and signs [2].

The clinical manifestations of non-IgE-mediated food allergy (NFA) are not uniform. Although IFA has been described as a central immunopathogenesis of atopic dermatitis, the symptoms and signs of IFA do not correspond to those of atopic dermatitis. Rather, the symptoms and signs of NFA are those of atopic dermatitis itself.

Food allergies have clinical manifestations on the skin as well as gastrointestinal and respiratory systems. Cutaneous reactions have been categorised as non-eczematous versus eczematous and early versus late [11]. Non-eczematous reactions tend to occur immediately after exposure to the food, usually immediately or within less than 1 hour. The typical reactions include pruritus, urticaria, angioedema, and diffuse morbilliform erythema. These reactions do not cause immediate exacerbations of AD, and they are commonly associated with gastrointestinal or respiratory symptoms. Acute urticaria and angioedema are among the most common symptoms, and acute contact urticaria or allergy can also occur. One-half of the reactions after the ingestion of milk are not mediated by specific IgE antibodies to

milk protein and are lost by the age of 3 years. Eczematous reactions has been regarded as occurring less frequently. They usually manifest as a late event, generally defined as occurring 2 to 6 hours or more after exposure to the food. As has already been shown, eczematous reactions can develop infrequently as an early event or in combination with non-eczematous reactions.

The symptoms and signs of NFA are not uniform; they vary according to subjects and foods [2]. In addition, in one subject, various symptoms and signs often develop according to the food ingested. The onset time of symptoms and signs of NFA ranges from 2 hours to several days, up to even a week, after intake [12]. Because it is very difficult to predict the onset time of NFA symptoms, physicians should observe patients long enough to cover the maximum onset time following challenge or intake during daily life. The clinical manifestations of NFA show patterns of their own with respect to onset time, the severity of clinical manifestations, and type of allergy.

It should be kept in mind that AD patients, as well as other food allergy patients, may be allergic to multiple food allergens [13]. These patients may also have multiple types of food allergy, such as IFA and NFA, together. However, when this is the case, patients will not necessarily have both IFA and NFA simultaneously to the same food. The diagnosis, management, and treatment of food allergy in AD should be approached keeping in mind that subjects may have food allergies to multiple foods and that they may exhibit multiple types of food allergies including both IFA and NFA.

### **3.3 Types of foods that cause atopic dermatitis**

Based on OFC outcomes, the most common food allergens in the United States, accounting for the vast majority of food allergies in patients, are known as cow's milk, hen's eggs, peanuts, soy, wheat, tree nuts, and shellfish [14]. Although some children prove to be truly allergic to meats, fruits, vegetables, or other grains, the vast majority have negative OFCs for these foods.

As confirmed in several studies, cow's milk, hen's eggs, wheat, soy, and peanuts are responsible for approximately 75% of food-associated AD [15,16] in IFA, whereas for NFA, meats as well as cow's milk, hen's eggs, soy and wheat were the major causes of AD [13].

In Western country, Hen's eggs and cow's milk are significantly more likely to result in IFA and are associated with elevated food-specific IgE [11]. Soy and wheat are more likely to cause late eczematous flares, but reactions to cow's milk were also observed. Although some of these reactions are observed in the context of elevated food-specific IgE, some also occur in the absence of food-specific IgE.

The same food can provoke IFA and NFA. In recent studies, foods were mapped according to the kinds of food allergy (IFA or NFA) and severity [7]. Such mapping is necessary for the proper management of food allergy in atopic dermatitis.

### **3.4 Mixed-type allergy: The simultaneous presence of two different types of food allergy, IFA and NFA, in AD**

Because IFA and NFA are present together in atopic dermatitis, the characteristics of AD that result from each of these two types of food allergy should be clarified [7]. It is generally understood that IFA, rather than NFA, plays a central role in the immunopathogenesis of AD until recently [12]. Immediate reactions in IFA often lead to increased scratching and, eventually, secondary exacerbation of eczematous lesions [11], whereas direct exacerbation

of AD with development of new eczematous outbreaks tends to occur as a late reaction and infrequently as an early reaction. However, in its clinical and immunopathogenic aspects, NFA is similar to AD. With the advent of successful treatments for food allergy, IFA is less so. In this chapter, AD are described, especially in the viewpoint of non-IgE-mediated food allergy.

### **3.5 Multiple food allergies in AD**

#### **Multiple sensitisation to foods in IFA**

Multiple sensitisation with foods has not been generally considered a possible cause of AD; this is another point that can easily confuse clinicians and patients. The prevalence of data describing multiple food allergies in published studies provides an estimate of multiple food allergy prevalence [7, 13]. In a study of food allergies in a highly atopic group of children, all of whom had atopic dermatitis and 50% of whom had concurrent asthma or allergic rhinitis, 57% reacted to two or three foods during double-blind, placebo-controlled food challenges [17]. Most children in this subset had positive skin prick tests (SPTs) to several foods, although only approximately one third of positive tests correlated with positive food challenge [13]. However, few children reacted to more than three foods [18]. Five foods (eggs, peanuts, milk, wheat, and soy) accounted for approximately 60% of the positive clinical responses in this study [19].

More than 500 random serum samples were evaluated for specific IgE against six common food allergens (milk, eggs, wheat, soy, peanuts, and cod) [17]. They addressed that having evidence of IgE-mediated sensitisation to a food does not necessarily imply a true food allergy. This study found that 27% of children were sensitised to more than one of the six foods. The main limitation of this retrospective study was that information regarding clinical reactivity to foods was not available; therefore, it is not known how many of these patients were truly allergic to more than one food.

A recent study examining the prevalence of multiple food allergies found that most (>70%) food-allergic children were allergic to or were avoiding multiple foods [17]. On average, each child was avoiding three or four foods or food groups. These children were generally very atopic, with 56% showing atopic dermatitis, 47% having allergic rhinitis, and 38% having asthma. Thus, highly atopic children may be at greater risk for allergies to multiple foods.

#### **Sensitisation to multiple foods in AD**

Although food allergies are not the only cause of AD, in many cases AD is caused by multiple food allergies. Over 50% of AD patients also exhibited NFA to a mean of 2.8 food items [18]. Moreover, IFA co-exists simultaneously with AD and NFA [7]. Interestingly, in most cases, patients with isolated IFA did not have AD. From these results, it seems clear that NFA is the major type of food allergy in AD, although IFA is the aggravating cause of AD.

## **4. Diagnosis of food allergy in AD**

The diagnosis of food allergy should be made following the discrimination of IgE- and non-IgE-mediated allergies. Diagnostic protocols for IFA have been proposed by various researchers, institutes and academic societies; however, the concept of dosage

quantitation, along with the measurement of clinical severity changes on the basis of discrimination of IgE- and non-IgE-mediated food allergy, has clearly become the most important point in successful immunotherapy [7]. Because both the diagnostic and the therapeutic protocols for IgE- and non-IgE-mediated food allergies differ greatly, the major points in these protocols should be revised.

The two most important points regarding diagnosis of food allergy in atopic dermatitis are as follows: 1) distinction should be made between IFA and NFA and 2) the treatment dosage must be calibrated and the clinical severity assessed for the purposes of therapy and follow-up [7].

#### **4.1 Allergy history**

A detailed clinical history is the key first step in the diagnosis of potential food allergy, followed by skin testing and immunoassay testing when indicated by the history [14]. Ultimately, however, in cases of non-anaphylactic reactions and especially non-IgE-mediated food allergies, OFCs may be required for an accurate diagnosis.

Parents often consider their child's AD as an "allergic" manifestation of a presumed food allergy [11]. Although the influence of the media and popular culture may play a role, parents also receive differing opinions from primary care providers and dermatologists [11]. Greater than 90% of parents and 60% of primary care providers may suspect food allergy as the cause of AD, resulting in referrals to allergists and extensive testing.

Food allergies should be suspected from the patient's history of experiences of allergy provocation, especially in case of IgE-mediated food allergy [7]. However, apart from major immediate anaphylactic reactions, patient history has proven to be an unreliable way to diagnose food allergies [3]. A poor correlation between food allergy and medical history, with only 25%-48% sensitivity overall and a 72%-97% specificity for IFA, has been reported. Moreover, in NFA it is more difficult for patients and parents to recognise the relationship between the ingested food and allergy provocation because of the difficult clinical characteristics as well as delayed reactions of this condition, and a history of NFA is inconsistent with the final diagnosis of NFA [18]. The additional possibility of exercise-induced food allergy should be considered and excluded by history.

#### **4.2 Laboratory approaches to food allergy in AD**

##### **Blood eosinophil numbers**

Increases in blood eosinophil counts due to NFA provocation by OFC have been demonstrated and blood eosinophilia is useful simply as a clue in the diagnosis of allergy [20]. The level of blood eosinophils has clinical significance as a predictor of the efficacy of IFN- $\gamma$  therapy in atopic dermatitis [21].

##### **Total IgE**

Although not all patients with AD have elevated IgE, as many as 40% to 80% [11] have been found to have high food-specific IgE levels. Total IgE does not seem to be associated with current allergic disease activity.

##### **ECP**

Eosinophil cationic protein (ECP) is produced by activated eosinophils [22]. Food additives were shown to elevate blood ECP in atopic dermatitis [23]. Interestingly, ECP is

elevated without the elevation of blood eosinophil numbers in AD patients and even in normal subjects in recent studies conducted [24]. In this report, food additives were shown to provoke xerosis (dry skin) and resultant pruritus consistent with AD. Among patients suspected to have AD, over 30% showed pseudoallergies to food additives [25]. The signs and symptoms caused by food additives can interfere with the interpretation of OFC and with the therapeutic process. ECP is specifically elevated in patients who ingest artificial chemical food additives [24] and elevated ECP has been used as a marker of pseudoallergic reactions due to food additives, particularly when blood eosinophil numbers are normal.

#### **Skin prick test and specific IgEs in IFA**

IFA is approached initially by tests for allergen-specific IgE. The skin prick test (SPT) has a high negative predictive value (approximately 95%) and is most informative when it is negative; the positive predictive value ranges between 30% and 50% [3]. Therefore, SPT is useful for excluding IFA, but a positive result may only be suggestive of IFA. Laboratory testing for food-specific IgEs also has a high negative predictive value, estimated to be 75%, but its positive predictive value is low, ranging from 20% to 60%. Recently, the diagnostic levels of food-specific IgEs have been determined. The presence of specific IgEs at or above these levels offers a positive predictive value of approximately 95% for IFA. Although skin prick tests and serum IgE measurements can confirm sensitisation, neither of these tests can on its own prove clinical allergy to a specific food with reliability or consistency. Moreover, IgE-based laboratory tests will only predict IFA; IgE-based tests are not useful for the diagnosis of NFA in AD [18].

In spite of the extremely high specific IgE and strong SPT usually associated with HDM, HDM rarely induces anaphylactic reactions following exposure. In contrast, food-induced IgE-mediated allergies, including systemic urticaria and anaphylactic allergic reactions, can occur when a patient has high specific IgE levels or strong skin reactivity for a food allergen.

#### **Interpretation of polysensitisation from the results by the SPT or allergen-specific IgE**

Polysensitisation to multiple allergens as the result of allergen-specific IgE and skin prick tests, especially to multiple food allergens, may be embarrassing to the physician. Sensitisation of the skin caused by the skin prick test and the presence of specific IgE do not indicate the presence of allergy [2].

In cases of skin sensitisation, patients often show similar reactions (itching, rash, or urticaria) to contact with allergen in the skin prick test. Therefore, patients should avoid allergens which are positive by the skin prick test. Sensitisation to specific allergens by allergen-specific IgE does not always provoke allergy. Based on the level of allergen-specific IgE, IgE-mediated allergy can be predicted, especially for food allergens. Therefore, physicians should just consider IgE-mediated food allergy if patients have high food-specific IgE.

#### **Allergy patch test**

The immunopathogenesis of eczematous allergic reactions to food that occurs in non-IgE-mediated food allergy is similar to that of allergic contact dermatitis in that it is T lymphocyte-mediated and associated with food-specific T lymphocytes [3]. For these reasons, atopic patch testing (APT) has been used to investigate food-induced eczema.

### Laboratory follow-up

Blood eosinophils provide information on current disease activity of the non-IgE-mediated type [20]. For the evaluation of disease progress and continuing disease activity and for the effective management of non-IgE-mediated allergy including NFA, blood eosinophil levels are tested repeatedly on a regular schedule.

Serum ECP should also be followed to determine changes in the disease activity of non-IgE-mediated allergy and the effectiveness of an elimination diet for food additives in atopic dermatitis.

The interpretation of the results of allergen-specific tests, such as the skin prick test and allergen-specific IgE, is often complicated because the number of positive SPT responses, the spectrum of IgE sensitisation and even the results for the same allergen often change in the same individual over time [26]. This variability may be related to the number of allergens tested and the age at which the measurements are performed. The most common food allergens determined with the SPT are soy, cow's milk, peanuts, carrot, hen's eggs whites, wheat, and corn [27].

However, changes in reactivity to allergens must be considered to be a natural phenomenon that is affected by the natural outgrowing of food allergy and the gradual acquisition of allergy to inhaled allergens, including house dust mites and pollen [2]. The change in the number of allergens to which a patient responds over time and the change in response to one allergen over time provides the physician with information on the progress of the disease. If the number of sensitised allergens decreases, the allergy itself may be regarded to be decreasing systemically. In addition, if the strength of SPT or the level of food-specific IgE is decreasing, the patient may be outgrowing the allergy.

### 4.3 Oral food challenge

The gold standard to confirm or disprove food allergy is the OFC, particularly double-blinded, placebo-controlled OFCs [8]. In the case of NFA, OFCs are safe, whereas in IFA, OFCs are time-consuming and carry the potential for severe reactions. They should be performed by experienced health-care professionals who have access to emergency equipment. Despite the mentioned caveats, OFCs are especially useful because observation for 24 hours or more after food exposure allows the assessment of both early and late reactions to the food and thus can detect both IgE- and non-IgE-mediated processes.

#### 4.3.1 Prerequisites for oral food challenge in atopic dermatitis

##### Evaluation of clinical severity scores

For the diagnosis of food allergy, a clinical severity scoring system is necessary. This scoring differs between IFA and NFA. The diagnosis of IFA is straight forward because of the apparent clinical manifestation following a challenge. There are several scoring systems for IFA described by Clark [28] and Noh [6]. The diagnosis of NFA is difficult due to its clinical characteristics, which are almost the same as those of atopic dermatitis, and the SCORAD index and clinical severity scoring systems for AD can be used for NFA [29]. Clinical severity scoring should be done at the initial evaluation, at every visit, and before and after every procedure.

##### 1. Diet record

A dietary diary should be kept during diagnosis and treatment [2]. In the process of management of food allergies in AD, daily diet diaries should be used to record complete



basic recipes for each meal. For the supervision of dietary management, all food should be recorded, including elimination diets, open OFCs, and tolerance induction. This is especially important for breast-feeding infants. In such cases, the diet of the mother should be recorded along with the diet of the infant, including the times of ingestion and the time of the appearance of new AD lesions or aggravation of old AD lesions.

## 2. Elimination diet

An elimination diet should precede an oral food challenge. Without complete elimination of the causes of the allergy provocation, it is difficult to interpret the results of an oral food challenge [2].

For IFA, the causative foods are typically easily recognised by parents and patients; it is therefore easy to eliminate and challenge with foods. However, it is very difficult to recognise the triggers for the diagnosis to be made in NFA. The accumulated statistics for NFA in atopic dermatitis are absolutely necessary [2]. Moreover, in cases of NFA associated with atopic dermatitis, the causative agents are more complicated and may include HDM [30]; thus, all possible allergens must be eliminated for a proper oral food challenge. Fortunately, the proper control of the causative allergens, including food and inhaled allergens, can be evaluated based on stable improvement during an elimination diet. An initial elimination diet is important as an indicator of the proper control of allergy provocation [2].

Once patients show improvement through an initial elimination diet, oral food challenges are conducted. Foods that were not addressed in the initial elimination diet should also be considered. IFN- $\gamma$  therapy can be considered when patients do not improve following the initial elimination diet [2] because IFN- $\gamma$  therapy itself does not affect allergy provocation during the next OFC [20].

## 3. Basic general management

Without basic care and the control of allergens other than foods, the precise diagnosis of food allergies may be confusing. This type of management includes the following: 1) Skin care using non-steroid drugs and emollients including moisturizer and aroma oil, 2) House dust mite and other inhaled allergen care (dander, pollen, fungi and others); patients should be tested for allergy provocation by inhaled or environmental allergens, 3) Other factors (infection control, others), 4) Discontinue all medications that affect allergy provocation (steroids, antihistamines, other immunosuppressants, drugs with unknown effects (herbal medications), etc [2].

### 4.3.2 Elimination diets as a first step in the diagnosis of food allergies

#### 1. Elimination diet and elementary diet

Diet control for the elimination of food allergy can be assessed using an elimination diet and an elementary diet. An elimination diet is a restriction of the possibly causative foods, whereas an elementary diet permits several safe foods. Both approaches require clinical data from studies [18, 19, 21]; such data are very important because if the clinical statistics are not proper, dietary restriction does not result in clinical improvement. The proper OFC then cannot be advanced further.

For an effective elementary diet, the absolutely safe foods in atopic dermatitis should be addressed. An effective elimination diet is a higher modality because it requires the accumulation of clinical data for statistics regarding the causative foods for atopic dermatitis. Noh and Lee focused on these points, and an effective elimination diet is now available for atopic dermatitis [12, 13, 18, 19, 21].

More than 50% of AD patients have NFA . Without the control of allergy provocation, AD cannot be effectively controlled [21]. As a first step in the diagnosis of food allergy, dietary restrictions should be initiated. If a patient shows improvement on an elimination diet, a food allergy to the restricted foods should be strongly suspected. An optimal elimination diet can be achieved by providing a list of the foods to be restricted, which in turn can be determined by clinical statistics.

#### 2. Breast-fed infants

In the case of breast-fed infants, maternal elimination diets are recommended. Once a maternal elimination diet is implemented, improvements are often observed in the infant [31]. If eczema improves during the elimination diet, the clinical relevance of the eliminated foods should be confirmed with standardised, physician-supervised oral food challenges to the mother.

### 4.3.3 Oral food challenge

Through OFC, the suspected foods should be listed with the classification of type of allergy, and a relevant elimination diet that eliminates only suspected foods should result in an improvement of AD symptoms [2]. The order for the OFC should prioritise NFA before IFA. Additionally, the importance of certain foods should be considered according to the patient's wishes. An OFC for NFA should generally precede an OFC for IFA. Each OFC is conducted according to the relevant protocols.

#### 1. Principle of oral food challenge in AD (Goldmann's triad): intake, elimination diet and challenge test

The diagnosis of food allergy follows the standard principle of Goldmann's triad [19]. When patients show symptoms and signs after the ingestion of suspected causative foods, an elimination diet is initiated. If the patient shows improvement with this diet, the eliminated food is strongly suspected as the cause of AD. If the patient again shows the clinical manifestation with subsequent food challenge, the challenged food is confirmed as the cause of AD.

#### 2. Proper elimination of foods as an absolute condition for OFC

An elimination diet is the first effective way to confirm a food allergy in AD. However, a proper elimination diet is necessary [2]. Unless such a diet is performed, it is likely that elimination will be ineffective. A proper elimination diet is essential and should not be omitted.

### 4.3.4 Types of OFC

There are various types of OFC that may be clinically indicated, including open, single-blind, double-blind, and placebo-controlled trials. The choice of the type of OFC is based on a clinical assessment of the potential for bias in the interpretation of the results) [32]. Open OFC is the unmasked, unblinded administration of a food in its natural form. Open OFC is recommended for IFA because IFA is associated with a clear clinical manifestation. Moreover, in NFA, open OFC is effective in the clinical setting and can be performed on an out-patient basis. Open OFC is a cost-efficient procedure that saves substantial time and resources. It is thus considered to be a reasonable first choice for evaluating an adverse reaction to a food when the need for an OFC has been established.

Blinding and masking by mixing the challenge food with a masking vehicle or placing the food in vehicles, including opaque capsules or powders, reduces bias [32]. In the single-blind OFC, the observer but not the patient knows the food being tested. In the double-blind

OFC, the challenge material is provided by a third party, such as a dietitian, and the patient, the patient's family, and the observer are unaware of when the test food is administered. Bias is thus minimised. Placebo-controlled challenges may be administered in either a single-blind or double-blind fashion.

#### 4.3.5 Indications for an OFC

Indications for an OFC in AD are listed below [2, 20, 32]; 1) Identify foods causing AD for the initial diagnosis of a food allergy and for monitoring resolution of the food allergy, 2) Discriminate between IFA and NFA, 3) Calibrate the provoking dose and determine the clinical severity of the reaction for therapeutic purposes in IFA and in order to monitor progress in IFA treatment, 4) Expand the diet in persons who have multiple dietary restrictions because of subjective complaints, such as headaches or hyperactive behaviour, 5) Assess the status of tolerance to cross-reactive foods, 6) Assess the effect of food processing on food tolerability, e.g., fruits and vegetables that may be tolerated in cooked form in the pollen-food allergy syndrome.

#### 4.3.6 OFC procedures for IFA and NFA

The basic concept of OFC is the same for IFA and NFA. However, due to the different clinical characteristics of the two types of allergy, the OFC protocols for each differ significantly in principle and in dosage protocol [7]. OFC is conducted with relevant protocols for IFA or NFA. An OFC for IFA is relatively easy and simple, with higher risk, whereas an OFC for NFA is intricate and all aspects of this OFC should be carefully considered.

- IFN- $\gamma$  in OFC

IFN- $\gamma$  does not inhibit allergy provocation [19]; however, it does improve the pre-existing symptoms and signs of atopic dermatitis, including eczematous skin lesions and pruritus [19, 21]. The clinical characteristics of AD are of the non-IgE-mediated type, and the onset and duration of symptoms and signs are relatively longer [7]. It is difficult to handle or proceed to the next challenge when the patient shows a severe NFA reaction during the challenge. The use of steroids or antihistamines for symptomatic treatment can inhibit the allergic reaction caused by OFC or hide the symptoms of allergy provocation during an OFC.

#### 4.3.7 Clinical characteristics of OFC

##### 1. IFA and NFA

Rapid onset and apparent clinical manifestations are typical of IFA [7]. During proceeding with the OFC for food allergy, the onset time following challenge, the duration of symptoms and signs, and the various clinical manifestations should be considered. Although the diagnosis of NFA is made based on the change of clinical severity scores, expertise is necessary in the OFC for NFA because the same food may provoke variable clinical manifestations with an unexpected onset time during the challenge.

##### 2. Characteristics of OFC

The characteristics of food allergy are well described by Noh and Lee [7]. The clinical characteristics of food allergy to the same food may differ among patients and may differ in the same patient according to the type of food. Some foods, such as shrimp and mackerel, tend to provoke IgE-mediated food allergy, whereas other foods, such as milk, eggs,

soybeans and wheat, tend to provoke both IgE- and non-IgE-mediated food allergies. Other foods, such as meats, tend to predominantly provoke non-IgE-mediated food allergy. According to the characteristics of the region, the kinds of foods that cause food allergy also differ. Patients who live near the sea tend to have allergies to seafood, whereas patients who live in land tend to have less frequent allergies to seafood. Allergy to rice is less frequent in Oriental countries than in Western countries, whereas wheat allergy is more frequent in Oriental countries than in Western countries.

The statistics on food allergy are very important in clinical practice. Basically, the foods that should be restricted in the initial elimination diet for the control of food allergy in atopic dermatitis have been identified based on the statistics on food allergy [12, 13, 18, 19, 21]. The necessary statistics should be based on challenge tests conducted at least with open OFC and not on laboratory results because IgE-based tests cannot predict the presence of food allergy, particularly for non-IgE-mediated food allergy in atopic dermatitis.

Interestingly, meat (beef, chicken, pork) has not been recognised as an important cause of food allergy in atopic dermatitis because meats induce predominantly non-IgE-mediated food allergies [12, 13, 18, 19, 33]. From the statistics, fewer than 5% of patients have allergies to chicken and pork simultaneously. Therefore, if a patient shows an allergy to either chicken or pork, the physician can predict the possibility that the other may not provoke allergy in the patient. Approximately 10% of patients have allergies to both milk and eggs; thus, if a patient is allergic to either milk or eggs, the possibility that the patient has allergy to the other is less than 10%. Similar data are available for soybeans and wheat. The use of statistics is thus very helpful in managing food allergies related to atopic dermatitis.

Patients sometimes think that they may be allergic to beef if they are allergic to milk because milk comes from cows. However, this is not the case. Milk and beef have no statistical relationship as causes for food allergy in atopic dermatitis [12, 13, 18, 19, 33]. The same is the case for chicken and eggs. Physicians and dietitians should consider these points in the management of food allergy in atopic dermatitis.

#### **4.4 Diagnosis of food allergy in infants**

##### **4.4.1 Breast-feeding infants and children**

If an infant develops severe eczema while it is exclusively breast-fed, it is essential to consider a food allergy provoked by proteins in the breast milk. All food proteins can pass from the maternal diet into breast milk [31]. If an allergy due to exposure to a protein via maternal milk is diagnosed, it is necessary to modify the diet of the mother with professional dietetic support and supervision. Previously, in cases where multiple foods were implicated or there were concerns about maternal nutrition, it was appropriate to suggest the substitution of an appropriate milk formula. However, with the advent of tolerance induction, TIFA for allergenic foods is also available.

For the diagnosis of food allergy in the breast-feeding infant, OFC is performed through the mother [2]. Improvement of the baby following an elimination diet in the mother should occur before proceeding with an OFC. The mother ingests the challenge food and the baby consumes the breast milk. The baby is then evaluated following the same processes. The important point is that the baby should consume breast milk within a specified time (1-2 hours) after the mother ingests the challenge food. If the baby does not improve with the mother's elimination diet, IFN- $\gamma$  therapy can be administered to the baby to elicit clinical improvement.

Because of its nutritional purpose, this process is designed to identify completely safe foods rather than allergenic foods [2]. According to the OFC protocol for breast-fed babies, it is very important to list the foods that can be ingested by the mother that are completely safe for the baby. The primary purpose of the diagnosis of food allergy is to provide safe recipes for the infant and the mother. Subsequently, the test results will be applied to the infant during the phase of solid food introduction. Safe foods will be introduced with priority. An OFC is conducted on the mother using normal protocols; the sole difference is that the food is given to the mother and reactions are observed in the infant.

#### **4.4.2 Formula-feeding infants**

In formula-feeding babies, the OFC is simpler than in breast-feeding infants [2]. The primary purpose of treatment is to set up safe formula feeding with casein hydrolysate, soy formula or other foods. To rule out milk allergy, challenge with casein hydrolysate will be performed for the diagnosis of allergy, especially to casein. If the infant improves with casein hydrolysate, he or she is allergic to casein and casein hydrolysate formula is used until weaning.

If the baby does not improve on casein hydrolysate formula, it is subsequently challenged with amino acid-based formula. If the baby improves, the baby is allergic to components other than casein in milk or together with allergic to casein. The baby can then be fed the amino acid-based formula or be tested on soy formula. If the baby cannot tolerate the amino acid-based formula and has an allergy to casein hydrolysate, or if the parents wish to feed the baby soy formula, a soy formula challenge can be performed. If the baby improves with the soy formula, the baby is allergic to milk and can be fed with soy formula until weaning.

TIFA for any formula is indicated when the baby does not improve with either soy formula or casein hydrolysate or when the baby does not tolerate amino acid-based formula [2]. Parents can select the kinds of foods (milk or soy) to be tolerated. After tolerance induction for formula, the baby is fed the tolerated formula until weaning.

#### **4.4.3 Mixed-feeding baby (breast-feeding with formula feeding)**

An initial elimination diet for the mother is conducted with simultaneous feeding of a safe formula, as described above [2]. After initially setting the baby up with safe formula feeding and diet restriction of the mother, an OFC of the mother for the diagnosis of food allergy in the infant should be performed as described above.

#### **4.4.4 Solid food introduction for baby (approximately 5-12 months)**

The primary purpose of diagnosis is to set up a safe recipe for the infant to prevent nutritional deficiencies due to elimination diets or food allergies [2]. Transiently, an elimination diet should be conducted in the mother and all solid foods should be stopped in the infant (elimination diet of infant and mother). Due to nutritional considerations, elimination for the infant and the mother should not be conducted for more than 3 days. If the baby does not improve, IFN- $\gamma$  therapy for the baby is indicated during subsequent OFCs of the baby. If the baby improves following an elimination diet of the mother and baby with or without IFN- $\gamma$ , sequential introduction of solid foods may be performed according to the weaning schedule. However, the sequence of foods can be changed according to the circumstances of the infant and the mother. The mother and infant should be simultaneously fed with the same challenge foods. In case of formula feeding infants, stop all solid foods to the infant (elimination diet in the infant) and simultaneously set up a safe

formula feeding during the elimination diet in the infant, as described above. Sequential introduction of solid foods should be performed according to the weaning schedule. Nutritional care for the infant is essential.

## 5. Immunotherapy for food allergy in AD

Presently, there are 3 therapeutic approaches for food allergies. In all cases, the allergen should be avoided until proper treatment is administered [9]. In infants and young children, the allergenic food(s) should be excluded from the diet until the allergy is outgrown unless exclusion results in nutritional deficiency or the allergen cannot be avoided; in such cases, active treatment, such as tolerance induction for food allergy (TIFA), is performed [2]. If exclusion cannot be practiced, patients may experience discomfort caused by non-IgE-mediated food allergy and atopic dermatitis or reactions as serious as anaphylaxis from repetitive ingestion of the allergenic food(s). However, with the recent advent of TIFA treatment, management of atopic dermatitis has improved remarkably [7].

Clinical tolerance can develop over time; this process is also called “outgrowing” the allergy. Allergies to milk and eggs are common food allergies that are outgrown: 80% of children with milk and egg allergies show tolerance by the age of 3 to 5 years [8]. In contrast, only about 20% of young children develop tolerance to peanuts, and less than 10% outgrow an allergy to tree nuts. However, the persistence of food allergy is variable and depends on the specific food allergen.

### 5.1 Specific Immunotherapy for food allergy

Allergen-specific therapies have been investigated to achieve desensitization and/or tolerance to an allergen [34]. Desensitization is defined as a change in the threshold dose of ingested food allergen necessary to cause allergic symptoms. Tolerance is the induction of long-term immunologic changes associated with the ability to ingest a food without showing symptoms and without ongoing therapy. In a recent pilot study [35], subcutaneous immunotherapy (SCIT) was well tolerated in children with milk allergy. Despite its efficacy in treating food allergy as well as allergic rhinoconjunctivitis and venom hypersensitivity, this traditional approach to allergen immunotherapy is impractical and unsafe for the treatment of food allergies because of an unacceptably high rate of anaphylactic reactions in IgE-mediated food allergy [34]. Sublingual immunotherapy (SLIT) has a broad efficacy for the treatment of inhalant allergies. SLIT has been used to treat hazelnut allergy and a life-threatening kiwi allergy. Currently, trials are in progress to evaluate the efficacy of SLIT in treating other food allergies. Traditional Chinese Medicine represents an innovative approach with the potential to treat food allergies although this approach is not allergen-specific. Food Allergy Herbal Formula (FAHF-2) is reported to promote tolerance and protection from anaphylaxis in mouse models. Further, human clinical trials are just beginning and hold promise for future clinical efficacy. Omalizumab is a recombinant, humanized, monoclonal anti-IgE antibody that was demonstrated to significantly increase the threshold peanut protein dose necessary for allergic response in oral food challenge, thereby providing potential protection from accidental peanut ingestion. Clinical trials are in progress to evaluate both anti-IgE monotherapy for food allergy and the use of omalizumab as an adjunct to oral immunotherapy. While this therapy is suitable for IgE-mediated food allergy, it is not applicable for treatment of non-IgE-mediated food allergy. Protection from peanut allergic response has also been demonstrated in a report where rectal immunization with mutated peanut protein allergens protected mice from

anaphylaxis, Peptide immunotherapy has also been investigated using the immunodominant epitopes of ovalbumin.

### **5.2 Oral immunotherapy for food allergy: Tolerance induction for food allergies (TIFA) or specific oral tolerance induction (SOTI)**

Oral immunotherapy appears to be effective in inducing desensitization in most patients, as well as oral tolerance in a subset of patients with food allergy [34]. Oral immunotherapy was officially introduced in 1996 in "Monographs in Allergy" [36, 37]. Noh & Lee reported the first successful use of oral immunotherapy for food allergy [38]. They used IFN- $\gamma$  as the adjuvant for oral immunotherapy for food allergy and named this therapy "specific oral tolerance induction (SOTI)" in 2003. SOTI was attempted for IgE-mediated food allergy in humans by several investigators [5, 34, 39-43]. The complete SOTI protocol for IgE-mediated food allergy was accomplished by also using IFN- $\gamma$  in 2009 by Noh & Lee [6].

Several terms are used to describe oral immunotherapy for food allergy. These terms are based on an escalating dosage of orally ingested foods or food protein to induce immune tolerance for allergenic food(s). Tolerance induction for food allergy (TIFA) was first coined by Noh & Lee in 2003 [38]. Specific oral tolerance induction (SOTI) is currently the more precise term to describe oral tolerance induction for specific allergens in food allergy, and this term, SOTI, was also used first by Noh in 2003 in a report on milk-specific oral tolerance induction for non-IgE-mediated food allergy in atopic dermatitis. Tolerance induction for food allergy (TIFA) is a similar term that has a broader immunologic meaning: to induce immune tolerance for allergenic foods by any method.

### **5.3 IFN- $\gamma$ in food allergy and AD**

IFN- $\gamma$  was introduced for the correction of Th1/Th2 imbalance, which is the basic immunologic mechanism in allergies, including food allergy [21]. As expected, desensitization for house dust mites was successful when IFN- $\gamma$  was used, but was ineffective without IFN- $\gamma$  [30]. Moreover, IFN- $\gamma$  seemed to show tolerogenic effects in addition to its corrective effects in Th1/Th2 imbalance [7]. Especially, IFN- $\gamma$  was absolutely necessary for TIFA for non-IgE-mediated food allergy. Other than SOTI, effective treatment methods for non-IgE-mediated food allergy by using IFN- $\gamma$  have not been established. Without IFN- $\gamma$ , tolerance is not induced in non-IgE-mediated food allergy.

### **5.4 Indication for SOTI**

Tolerance induction for food allergy is indicated when (1) nutritional deficiency is expected, (2) the patient is inevitably unable to avoid the allergen (e.g., wheat allergy in a baker), (3) an infant displays allergy to all available formulae, and (4) the patients or parents want an improved quality of life [2].

## **6. Prevention of food allergy**

### **6.1 Breastfeeding for the prevention of food allergy**

Breast milk is the gold standard for protective nutrients fed to newborn infants, and present clinical evidence supports the strong protective effect of breast milk against age-related infectious gastroenteritis [44]. An important function of early breastfeeding is its anti-inflammatory effect on the immature, excessive inflammatory response in newborns.

Several components of breast milk, including transforming growth factor (TGF)- $\beta$ , interleukin (IL)-10, erythropoietin, and lactoferrin, can reduce the inflammatory response to stimuli in the newborn intestine. Although, historically, there has been widespread support for the concept that breast-feeding is protective against atopic disease in general, breastfeeding could facilitate food allergies in certain cases by allowing transfer of the allergens from the mother's diet through breast milk. Exclusive breastfeeding for 4 months should be recommended to prevent atopic disease; however, there is no evidence to support the protective effect of exclusive breastfeeding beyond this period. Mixed feeding should be encouraged until 6 months of age.

## **6.2 Delayed introduction to solid foods to prevent the development of food allergy**

An additional question regarding food allergy and AD is whether delaying the introduction of solid foods to infants at a high risk for AD can delay or prevent the development of AD. The most recent clinical report states that exclusive breast feeding for 4 to 6 months for infants who are at a high risk for AD (i.e., positive family history) can help prevent or delay AD; furthermore, cow's milk should not be introduced until 2 years of age in order to prevent allergy [11]. No convincing evidence exists to delay the introduction of any solid food beyond 4 to 6 months of age. In contrast, dairy products are recommended to be introduced at 12 months; hen's egg at 24 months; and peanuts, tree nuts, fish, and seafood at 36 months.

Attempts to avert the development of food allergy through primary prevention strategies such as early restriction of dietary allergens and modified timing of complementary solid food introduction to infants have proven to be frustrating and possibly counter-productive. Early dietary restriction of peanuts is recommended to avoid sensitization [34]. However, early consumption of food proteins and subsequent oral tolerance induction in infants and children may be a key element in preventing the development of food allergies. In another study, neither the diversity nor the timing of introduction of complementary foods had any association with development of eczema. The most recent recommendations for high-risk infants do not endorse restriction of maternal diet during pregnancy and lactation or restriction of allergenic foods in infants after 4–6 months of age.

Elimination of highly allergic foods is plausible to prevent the development of food allergy [34]. Concerning the timing of solid food introduction, a delay does not seem to prevent the development of food allergy, but it may enhance sensitization to some foods. Introducing solid food at 4–6 months might result in the lowest allergy risk and the recommended duration of exclusive breast feeding and age of introduction of solids were confirmed to be 6 months [46]. Exclusive breastfeeding for at least 4 months for infants at a high risk of developing atopic disease but no current convincing evidence that delaying solid food introduction, including fish, eggs, and foods containing peanut protein, beyond 4–6 months of age had a significant protective effect on the development of atopic disease [47]. In contrast, early introduction of peanuts during infancy, rather than avoidance, was reported to prevent the development of peanut allergy [48]. Their data might be a good example of oral immune tolerance in a human model.

In contrast, some reports have suggested that delaying the introduction of hyperallergenic solid foods during weaning is not effective in preventing the development of food allergy. A new concept about the timing of weaning and the introduction of solid foods was suggested



[49]. Avoidance of highly allergenic foods beyond 4–6 months might not be effective in preventing the development of food allergy in most children, and the effect of specific early introduction of allergenic foods was being investigated. Significantly, delaying the introduction of solid foods until 4 to 6 months of age in infants at a high risk for atopic disease appears to reduce the incidence of AD [11].

### **6.3 Elimination of hyperallergenic foods from the diet of prenatal or breastfeeding mothers**

Opinions about a mother's diet during breast feeding differ. Whether a mother should follow an elimination diet for hyperallergenic foods to prevent food allergy remains a matter of debate [2]. From prenatal development studies, however, there is no evidence to support the assumption that an elimination diet can prevent food allergy because the mother's immune system protects the fetus from foods ingested by the mother.

### **6.4 Correction of Th1/Th2 imbalance**

The development of food allergy is related to Th2-deviant immune status in the sensitization phase of AD [9]. Although IFN- $\gamma$  has tolerogenic effects on pre-existing food allergy, the development or prevention of a food allergy is primarily associated with sensitization. IFN- $\gamma$  plays a role in preventing food allergy by correcting the Th1/Th2 imbalance [21].

### **6.5 Prevention of allergy provocation**

The diagnosis of food allergy and subsequent elimination diet of all possible allergenic foods is important to prevent further sensitization from repetitive allergy provocation. Repetitive allergy provocation and the resultant further Th2-polarization make patients more likely to develop additional allergies [2]. Sensitization to more food allergens, as well as aeroallergens, can occur with repeated allergy flares. It follows that allergy provocation by known allergens should be avoided to prevent further sensitization. For this reason, AD should be evaluated for repetitive allergy provocation and not simply the severity of AD. Furthermore, patients with mild AD should be treated early to prevent repeated allergic responses.

### **6.6 IL-10 for the prevention of food sensitization**

Helminths induce generation of IL-10 in the gut and prevent sensitization to foods in mice [50]. Promotion of an IL-10-rich environment in the gut was investigated for its role in preventing or even treating food allergies. The prevention of food allergies by administering either an IL-10-secreting *Lactococcus lactis* [51] or an avirulent *Salmonella typhimurium* strain that promotes IL-10 secretion in the gut [52] was demonstrated. In this study, transiently expanded IL-10-secreting T cell populations played an important role in keeping the allergen-specific effector T cell responses in check. From these results, it was possible to explain how skin exposure to high doses of allergens led to a decreased immune response with subsequent allergen exposures [53].

### **6.7 Skin hydration**

Physical injury leads to a Th2-deviant status in the local skin and resultant allergic status (Fig. 2) [54]. These changes result in sensitization to simultaneously exposed allergens as described above. Dryness is one of the main causes of itching. For all aspects of AD symptoms, skin hydration is very important to prevent further sensitization through the skin.

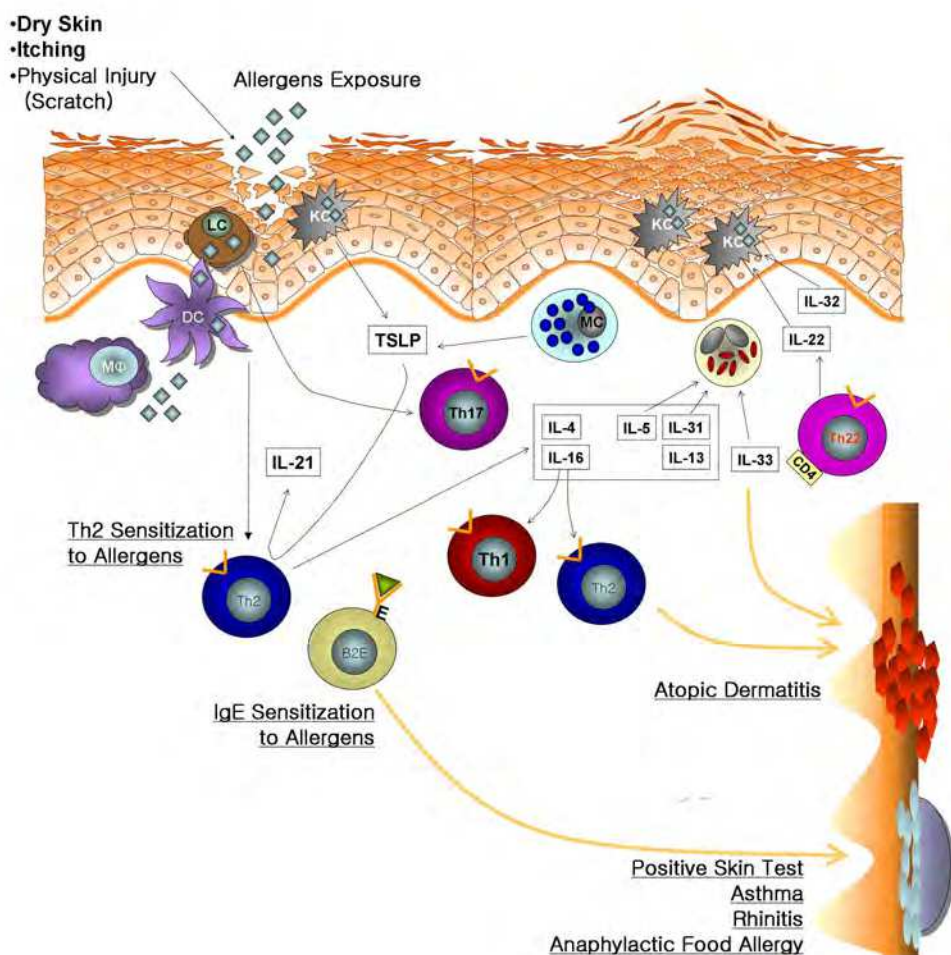


Fig. 2. Immunopathogenesis of sensitization through skin. Physical injury induced the release of thymus stromal lymphopoiectin (TSLP) in the skin and subsequently IL-21 is released from Th2 cell by TSLP. By the multiple actions of IL-21, the skin is Th2-polarized. In this process, also many Th2-related cytokines are involved including IL-4, IL-5, IL-13, IL-16, IL-31, IL-32. Any allergens exposed simultaneously in this status, are sensitized in skin. If skin is sensitized by IgE-mediated allergy, skin prick test to sensitized allergens becomes positive, while if skin is sensitized by non-IgE-mediated allergy, allergy patch test may become positive with the development of atopic dermatitis.

### 6.8 Restriction of food additives

Food additives play a role in food allergy and AD by acting as pseudoallergens [25]. Ingestion of food additives leads to dryness and itching [24]. Physical injury by scratching due to dryness and itching results in sensitization to additional allergens [54]. This cycle of

dryness and injury caused by scratching contributes to repeated allergic responses (Fig. 2). In order to prevent sensitization to multiple allergens, use of food additives should be restricted.

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## 8. Abbreviations

IFA, IgE-mediated food allergy; NFA, non-IgE-mediated food allergy; TIFA, tolerance induction for food allergy; SOTI, specific oral tolerance induction

### Keywords

Food allergy, IgE-mediated food allergy, Non-IgE-mediated food allergy, Tolerance, Oral tolerance induction, IFN- $\gamma$

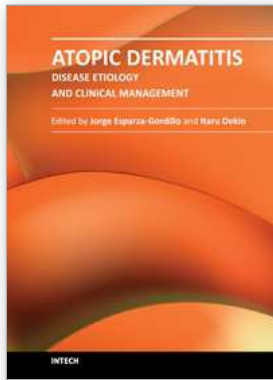
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Atopic Dermatitis is a common disease characterized by inflamed, itching and dry skin. This relapsing allergic disorder has complex etiology and shows a remarkably high clinical heterogeneity which complicates the diagnosis and clinical management. This book is divided into 4 sections. The first section (Disease Etiology) describes some of the physiological mechanisms underlying Atopic Dermatitis, including alterations in the immune system and the skin-barrier function. The important role of host-microorganism interactions on the pathophysiology of Atopic Dermatitis is discussed in the second section (Microorganisms in Atopic Dermatitis). An overview of the clinical diagnostic criteria and the disease management protocols commonly used is given in the third section (Diagnosis and Clinical Management). The last section (New Treatments) describes new therapeutic approaches that are not widely used but are currently being studied due to preliminary evidence showing a clinical benefit for Atopic Dermatitis.

### **How to reference**

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