

Eczema and Food Hypersensitivity

David M. Fleischer and Donald Y.M. Leung

KEY CONCEPTS

- Food allergy plays a role in the pathogenesis of atopic dermatitis (AD) in a subset of patients.
- Approximately one-third of children with moderate to severe AD are affected by food allergy. Studies in adults with AD have not clearly shown a significant role for food allergy.
- Eighty percent of food allergy diagnosed by food challenge in children with AD is caused by milk, egg, and peanut. The most common food allergens in adults are peanut, tree nuts, fish, and shellfish.
- By correctly diagnosing food allergy and eliminating the offending food allergen(s), eczematous lesions can significantly improve and even clear in children with AD and food allergy.
- Infants and children with AD and food allergy are at high risk for the development of allergic rhinitis and asthma.

Introduction

Atopic dermatitis (AD) is one type of eczema that usually begins in early infancy and is typified by extreme pruritus, a chronic relapsing course, and a distinctive pattern of skin distribution. AD is a global problem that affects a large number of children and adults around the world [1]. Prevalence of AD ranges from 1% to 20% based on data from the Global International Study of Asthma and Allergies in Childhood trial, with the highest prevalence in Northern Europe [2]. The most recent data from school-aged children in the United States indicate that the prevalence in this population approaches 17% [3]. The onset of AD occurs during the first 6 months of life in 45% of children, during the first year of life in 60%, and before the age of 5 years in 85% of affected individuals [4]; only approximately 17% of adults with AD have onset after adolescence [5,6]. AD is often the first step in the atopic march, with more than 50% of affected children developing asthma and allergic rhinitis [7,8].

Numerous triggers for AD have been identified over the past few decades, including food allergens, inhalant respiratory allergens, irritant substances, and infectious organisms such as *Staphylococcus aureus* [9] and *Malassezia furfur* [10] (Table 9.1). Food allergy has been strongly correlated with the development and persistence of AD, especially in infants and young children. In this chapter, we will focus on how

Table 9.1 Allergic triggers of AD (Reproduced from Leung D. *Pediatric Allergy: principles and practice*. St. Louis: Mosby, 2003, with permission from Elsevier.)

<i>Food allergens (most common)</i>	<i>Microorganisms</i>
Cow's milk	Bacteria
Egg	<i>Staphylococcus aureus</i>
Soy	<i>Streptococcus</i> species
Wheat	Fungi/yeasts
Peanut	<i>Trichophyton</i> species
Tree nuts	<i>Malassezia</i> (formerly known
Fish	as <i>pityrosporum orbiculare/</i>
Shellfish	<i>ovale</i>) species
Aeroallergens	<i>Candida</i> species
Pollen	
Mold	
Dust mite	
Animal dander	
Cockroach	

the ingestion of certain foods can trigger AD. Laboratory and clinical investigations that demonstrate how food hypersensitivity plays a pathophysiologic role in AD will be reviewed. The epidemiology, diagnosis, management, natural history, and prevention of food hypersensitivity with respect to AD will also be discussed.

Immunopathophysiology of atopic dermatitis

The pathophysiology of AD involves an intricate interaction between various susceptibility genes, host environments,

infectious agents, defects in skin barrier function, and immunologic responses. It also involves multiple cell types including T-lymphocytes, dendritic cells (DCs), macrophages, keratinocytes, mast cells, and eosinophils. While a full understanding is not yet complete, some important insights into the allergic mechanisms involved in the initiation and maintenance of skin inflammation in AD have been elucidated [11–13].

Acute AD skin lesions are associated with an increased number of T_H2 cytokines, notably IL-4 and IL-13. IL-4 and IL-13 mediate antibody isotype switching to IgE synthesis and upregulation of adhesion molecules on endothelial cells. T-lymphocytes in chronic AD lesions express increased IL-5, which is involved in eosinophil development [14], as well as IFN- γ , which potentiates effector function of pro-inflammatory cells. The maintenance of chronic AD also involves increased production of GM-CSF [15], IL-12 [16], and IL-18, as well as several remodeling-associated cytokines IL-11, IL-17, and TGF- β 1 [17]. The T_H2 cytokines help promote recruitment and subsequently allergic inflammation by upregulating adhesion molecules on vascular endothelial cells, such as vascular adhesion molecule-1 (VCAM-1), E-selectin, and intercellular adhesion molecule-1 (ICAM-1) [18,19]. Studies have shown that adhesion molecules are not expressed in the skin of non-atopic individuals; however, they are expressed in normal-appearing skin of patients with AD and are markedly upregulated in lesional skin or upon epicutaneous application of allergen in sensitized AD patients [20].

Increased expression of chemokines such as CCL5 (RANTES), CCL13 (monocyte chemoattractant 4), and CCL11 (eotaxin) contribute to the infiltration of T-cells, macrophages, and eosinophils into AD skin [21]. IL-16, produced by epidermal Langerhans' cells (LCs), is a cytokine that induces chemotactic responses in $CD4^+$ T-cells, monocytes, and eosinophils [22,23].

Serum IgE levels are elevated in approximately 85% of patients with AD, and often contain food-allergen-specific and aeroallergen-specific IgE antibodies [24]. Some patients have IgE sensitization to microbial antigens, such as *Staphylococcus aureus* [9] enterotoxins and *Candida albicans* or *Malassezia sympodialis* [10]. The role of allergen-specific IgE in the pathogenesis of AD involves a number of cell types. LCs in AD lesions have allergen-specific IgE antibodies on their surface [25], and this makes them 100- to 1000-fold more efficient at presenting allergen to T-cells than LCs which do not express the high-affinity IgE receptor (Fc ϵ RI) [26,27]. T_H2 cytokines upregulate Fc ϵ RI on LCs and other antigen-presenting cells (APCs), and promote local IgE synthesis [28]. IgE-bearing Fc ϵ RI $^+$ inflammatory dendritic epidermal cells (IDECs) are prominent in chronic AD skin lesions. It is believed that IDECs are not only involved in cell recruitment and IgE-mediated antigen presentation to T-cells, but that they also release IL-12 and IL-18 and promote T_H1 cytokine production by priming naive T-cells

into IFN- γ -producing T-cells, which together may lead to the switch from an initial T_H2 -type immune response to a T_H1 -type immune response [29].

AD is associated with abnormalities in keratinocyte differentiation. This results in skin barrier dysfunction and frequent skin infections. Microarray analysis demonstrated that decreased expression of a group of antimicrobial genes, including human β -defensin, IL-8, and inducible nitric oxide synthetase, occurs as the result of local upregulation of T_H2 cytokines and the lack of elevated amounts of TNF- α and IFN- γ under inflammatory conditions in AD skin. This could explain the increased susceptibility of AD skin to microorganisms [30]. Reduced expression of skin barrier genes, such as filaggrin and lipids, may account for the characteristic skin dryness found in AD [12].

Eosinophils are thought to play a significant role in AD [13]. Inhibition of eosinophil apoptosis in AD, probably mediated by an autocrine release of IL-5 and GM-CSF, appears to be a mechanism for the eosinophil accumulation in AD [31]. Several studies indicate that eosinophils are recruited to and activated at tissue sites by T_H2 cytokines, such as IL-5 and IL-13 [32]. Once activated, eosinophils are capable of releasing an arsenal of potent cytotoxic granule proteins and chemical mediators, which contribute to tissue inflammation, as shown by the deposition of eosinophil products in the inflamed skin [32,33]. One of these products is eosinophil major basic protein (MBP), which is known to damage skin epithelial cells [34] and promote mast cell degranulation [29,35].

Role of food allergy in atopic dermatitis

The causal link between food allergy and AD has been the subject of debate for many years and still remains controversial [36]. There is, however, a large and growing body of evidence that supports the pathogenic role of food allergy in AD in at least a subset of patients, particularly in children (Table 9.2). Three patterns of cutaneous reactions to food may occur in patients with AD: (1) immediate-type allergic reactions, such as urticaria and angioedema, which occur within 2 hours after food ingestion, and suggests an IgE-mediated mechanism; (2) pruritus within 2 hours soon after food ingestion, which also suggests an IgE-mediated mechanism, with subsequent scratching leading to an AD exacerbation; and (3) delayed reactions with AD exacerbations that occur after 6–48 hours, either with or without a previous immediate-type response, suggestive of a non-IgE-mediated reaction or a cutaneous late-phase reaction of IgE-mediated hypersensitivity [37]. The following sections will review the evidence and methods used to evaluate the role of food allergy in AD.

Clinical evidence

Recent clinical evidence supporting the pathogenic role of food allergy in AD is based on three areas of clinical

Table 9.2 Association between AD and food allergy (Modified from Sicherer SH and Sampson HA [46], with permission from the American Academy of Allergy, Asthma and Immunology.)

Clinical studies

- Appropriate dietary elimination leads to improvement in AD
- Double-blind, placebo-controlled food challenges reproduce skin symptoms
- Breast-feeding for at least 3–4 months decreases the risk of the development of AD in high-risk infants
- The use of a hydrolyzed formula compared to a cow's milk formula in high-risk infants who are not able to be completely breastfed reduces infant and childhood allergy and infant cow's milk allergy

Laboratory studies

- Presence of elevated total IgE and food-specific IgE antibodies
- LCs bear high-affinity IgE receptors and can present allergen to T-cells
- Food allergens can activate skin mast cells after ingestion
- Plasma histamine elevation during positive OFCs
- Elevated histamine releasing factors in children when consuming diet with allergenic food
- Increased spontaneous basophil histamine release while ingesting causal food
- AD lesions contain eosinophil products: MBP and eosinophil cationic protein
- Eosinophils are activated during positive food challenge
- T-cells, cloned from active lesions of AD, can react to food allergen
- Children allergic to milk with AD have CLA+, milk-reactive T-cells.

investigation: elimination diet studies, oral food challenge (OFC) studies, and preventive studies of AD. Multiple clinical studies have shown that elimination of pertinent food allergens can lead to improvement in AD symptoms, that repeat oral challenge with the offending food(s) can lead to redevelopment of skin symptoms, and that AD and food hypersensitivity can be partially prevented by prophylactic elimination of highly allergic foods from infant diets and possibly from diets of breast-feeding mothers.

Elimination diet studies

Numerous studies have addressed the therapeutic effect of dietary elimination on the treatment of AD. Atherton *et al.* [38] showed that 14 of 20 subjects (70%) with AD between the ages of 2 and 8 years showed significant improvement after completing a 12-week, double-blind, controlled, cross-over trial of an egg and cow's milk (CM) exclusion diet. However, there were notable problems in this study, including 16 of the 36 subjects who did not complete the study (44% dropout) and poor control of confounding variables such as environmental factors and other triggers of AD. Neild *et al.* [39] studied 53 subjects with AD in another trial using a similar design as Atherton and colleagues. Forty of the 53 subjects (75%) complied adequately with the trial regimen, but only 10 of the 40 subjects benefited from the egg and CM exclusion diet, yielding a response rate to the

diet that was not statistically significant. Juto *et al.* [40] studied 21 infants with AD, of which only 20 were treated with a strict elimination diet for up to 6 weeks. Seven infants had complete resolution of their rash, 12 had some skin improvement while on the diet, and the remaining infant had no change in skin condition. While the cumulative results of the above studies provide support for the role of food allergy in AD, most of the trials failed to control confounding factors such as other potential AD triggers, placebo effect, or observer bias.

In one of the original prospective follow-up studies of the natural history of food hypersensitivity in children with AD, Sampson and Scanlon [41] studied 34 subjects with AD, of whom 17 had food allergy diagnosed by double-blind, placebo-controlled food challenges (DBPCFCs). These 17 subjects were placed on appropriate elimination diets and experienced significant improvement in their clinical symptoms. Comparisons made at 1–2-year and 3–4-year follow-ups with 12 control subjects who did not have food allergy and 5 subjects with food allergy who were non-compliant with their diet showed that the 17 food-allergic subjects with appropriate dietary restriction demonstrated highly significant improvement in their AD compared with the control groups. The amount of time for resolution of their food hypersensitivity was also reduced.

Lever *et al.* [42] performed a randomized, controlled trial of an egg exclusion diet in 55 children who presented to a dermatology clinic with AD and possible egg sensitivity identified by radioallergosorbent (RAST) testing before randomization. True egg sensitivity was confirmed by DBPCFC after the trial. The 55 children were randomized either to a 4-week regimen in which mothers received general advice on the care of AD and additional specific advice from a dietitian about an egg elimination diet (diet group), or to a control group in which only general advice was provided. There was a significantly greater mean reduction in surface area affected by AD in the diet group (from 19.6% to 10.9% area affected; $p = 0.02$) than in the control group (from 21.9% to 18.9%). There was also significant improvement in symptom severity scores from 33.9 to 24.0 ($p = 0.04$) for the diet group, compared with a decrease from 36.7 to 33.5 in the control group.

Oral food challenge studies

For almost 30 years, researchers have used OFCs to demonstrate that food allergens can cause symptoms of rash and pruritus in children with food-allergy-associated AD. Bock *et al.* [43], in their studies of children with suspected food and respiratory allergies, reported that 4 of 7 children with a history of developing eczematous reactions to food developed skin rashes within 2 hours of a DBPCFC. In two studies, Burks *et al.* [44,45] also used the DBPCFC to study 165 children with mild to severe AD who presented to university allergy and dermatology clinics. Sixty percent

of the subjects with AD had a positive skin prick test (SPT) to at least one of the following foods: milk, egg, soy, wheat, peanut, cashew, and codfish. They performed 266 DBPCFCs, and 64 subjects, 38.7% of the total group with AD, were found to have food allergy. Using a similar challenge protocol, Sampson and colleagues have studied over 600 subjects who were referred for evaluation of severe AD, and have performed more than 2000 OFCs [46].

Sampson and Scanlon [41], Sampson and McCaskill [47], Sampson and Metcalfe [48] and Eigenmann *et al.* [49] published a number of articles spanning over 17 years using DBPCFCs to identify foods that are trigger factors of AD. In the initial evaluation of 470 subjects with a median age of 4.1 years (range 3 months to 24 years), serum total IgE concentration was elevated in 376 subjects (80%), with a median of 3410 IU/ml and range of 1.5–45,000 IU/ml. Foods used in the DBPCFCs were selected based on skin and RAST testing results and/or a clinical history suggestive of food allergy, and these foods were eliminated from the subject's diet for at least 7–10 days prior to admission. A total of 1776 DBPCFCs were performed during the studies and 714 (40%) were positive and 1062 were negative. Cutaneous reactions during challenges developed in the vast majority of subjects (529 [74%] of the 714 DBPCFC-positive cases). The cutaneous reactions comprised a pruritic, erythematous, macular, or morbilliform rash that occurred primarily in previously affected AD sites. The development of skin symptoms only occurred in 214 (30%) of the positive reactions, and typical urticaria were rarely seen, and if present, consisted of only a few lesions. However, intense pruritus and scratching often led to superficial excoriations and occasionally bleeding.

Almost all symptoms during the DBPCFCs began between 5 minutes and 2 hours after starting the challenge. Immediate-type response symptoms generally occurred abruptly and lasted 1–2 hours. A few patients had a delayed second episode of pruritus, scratching, and transient morbilliform rash 6–10 hours after the initial challenge. This morbilliform rash may represent the acute phase of AD, and it is induced in the OFCs by acute consumption of a food that previously caused symptoms on a chronic basis [50]. Clinical reactions to milk, egg, soy, and wheat accounted for nearly 75% of the reactions in the studies. Some subjects had repeated reactions during a series of daily OFCs and subsequently had an increasingly severe AD exacerbation. This data provide further evidence that ingestion of a causal food can trigger itching, scratching, and the reappearance of typical AD lesions.

Prevention of food hypersensitivity and atopic dermatitis through diet

In addition to the above-mentioned studies that have shown that AD can improve through elimination diets of offending foods and that reintroduction of these foods

during DBPCFCs can elicit symptoms, many studies have been performed in an attempt to prevent food allergy and AD through dietary means during pregnancy, lactation, and early infant feeding. Although it can be argued that all families should practice primary allergy prevention, this method can be so difficult that it is typically recommended only for those at “high risk” for developing allergy, defined as infants with at least one first-degree relative (parent or sibling) with documented allergic disease.

Maternal and/or infant elimination diets

Studies attempting to prevent CM and egg allergies by maternal CM and egg avoidance during late pregnancy have failed to show a reduction in food allergy, any other atopic disorder, or sensitization from birth through age 5 years. Additionally, maternal weight gain during pregnancy was negatively affected by these dietary restrictions. A recent Cochrane meta-analysis [51] confirmed the above findings, and the authors concluded that the prescription of an antigen avoidance diet to a high-risk woman during pregnancy is unlikely to substantially reduce the child's risk of atopic diseases, and such a diet may adversely affect maternal or fetal nutrition, or both. Another recent review of this issue by Muraro *et al.* [52] stated that there is no conclusive evidence for a protective effect of a maternal exclusion diet during pregnancy. Therefore, both the American and European guidelines do not recommend maternal avoidance diets that exclude essential foods during pregnancy.

Breast-feeding

For quite some time, it has been suggested that the presence of food antigens in breast milk might sensitize an infant if the mother does not avoid these foods in her diet during lactation. However, results of studies during the 1980s and 1990s examining this hypothesis have been contradictory. These contradictory studies, along with consideration of many others, led both a Cochrane analysis [51] and a recent meta-analysis [52] to conclude that while the prescription of an antigen avoidance diet to high-risk women during lactation may reduce the child's risk of developing AD, there is insufficient conclusive evidence to show a preventative effect of maternal diet during lactation on atopic disease in childhood. Furthermore, one cannot state for certain whether food antigens in breast milk will induce allergy or be immunoprotective in any given recipient [53].

Great debate exists today regarding the degree to which breast-feeding prevents, reduces, delays, or increases the development of allergic disease. Some trends can be observed and conclusions drawn from a review of the literature on the effects of human milk and breast-feeding on AD and food allergy. Of the many studies regarding the association between breast-feeding and AD, some have shown a protective effect [54,55], whereas others have shown a lack

of association [56], and some have even shown a positive association [57]. To assist in sorting out the discrepancies in the above studies, Gdalevich *et al.* [58] performed a systematic review and meta-analysis of prospective studies in developed countries that compared breast-feeding with CM formula feeding on the development of AD. Statistical analysis revealed a significant overall protective effect of breast-feeding for 3 months on AD, with an OR of 0.68 (95% CI, 0.52–0.88) in the cohort as a whole. The effect was even stronger in children with a family history of atopy (OR, 0.58; 95% CI, 0.41–0.92). No protective effect was demonstrated in children without at least a first-degree relative with atopy (OR, 1.43; 95% CI, 0.72–2.86). In summary, despite contradictory study results, the preponderance of evidence suggests that exclusive breast-feeding for at least 3–4 months decreases the risk of the development of AD in high-risk infants. Based on the current data, there is lack of evidence that this statement holds true for infants not at risk for atopy.

The effect of breast-feeding on the development of food allergy is difficult to determine, as both AD and asthma are closely associated with the development of food allergy. There are a limited number of studies that have examined breast-feeding's role on the outcomes of specific food allergies, and the results may be affected by other dietary variables such as the length and extent of exclusivity of breast-feeding. After reviewing the existing studies, Muraro *et al.* [52] determined that exclusive breast-feeding for at least 4 months is related to a lower cumulative incidence of CM allergy until 18 months of age. However, no firm conclusions about the role of breast-feeding in either the primary prevention of or delay in onset of other specific food allergies can be made at this time.

Infant formula selection

Many studies have been performed exploring the use of various infant formulas, including conventional CM formula, partial whey hydrolysate formula (pHF), extensive casein hydrolysate formulas (eHF), and soy-protein-based formulas in the prevention of allergy. A recent Cochrane review [59] determined that there is no evidence to support prolonged feeding with a hydrolyzed formula to prevent allergy in preference to exclusive breast-feeding. In high-risk infants who are not able to be completely breastfed, there is evidence that the use of a hydrolyzed formula compared to a CM formula reduces infant and childhood allergy and infant CM allergy. Although some studies show a slight benefit of eHFs compared with pHFs, there is inconclusive evidence at this time to determine whether feeding with an eHF has any advantage over a pHF [60]. There is convincing evidence that feeding with a soy formula is not recommended in high-risk infants for the prevention of allergy [61]. Amino-acid-based formulas have not been studied in the primary prevention of allergy.

Introduction of solids

Early studies regarding the timing of solid food introduction demonstrated some benefit in delaying early solid food introduction [62,63], but more recent studies have shown a lack of protective effect [64]. The conflicting data from the studies taken as a whole does not currently allow an authoritative statement regarding the relation between the introduction of solids and the development of allergy to be made. Therefore, the advantage of delaying highly allergic solid food introduction beyond 4–6 months is unconfirmed. Delaying solid food introduction may even increase the risk of allergy (e.g. wheat allergy [65]).

Laboratory evidence

There are several other lines of laboratory evidence in addition to those presented previously in the immunopathophysiologic role of allergy in AD section that provide support for the role of food-specific IgE in the pathogenesis of AD. To show that food antigen ingestion led to IgE-mediated reactions, Sampson and Jolie [66] sought markers of mast cell activation in 33 subjects with AD who underwent DBPCFCs to evaluate the role of histamine in food hypersensitivity by monitoring changes in circulating plasma histamine. Only the group of subjects with positive DBPCFCs demonstrated a significant rise in plasma histamine, from 296 ± 80 pg/ml before challenge to 1055 ± 356 pg/ml ($p < 0.001$); subjects who consumed placebo or had negative DBPCFCs showed no demonstrable rise in plasma histamine. The rise in plasma histamine that was observed implicated the role of mast cell or basophil mediators in the pathogenesis of food allergy in AD.

Mechanisms that involve IgE antibody, other than direct IgE-mediated activation of cutaneous mast cells, may also play a role in the inflammatory process in AD. Sampson *et al.* [67] studied 63 subjects with AD and food hypersensitivity documented by DBPCFCs, 20 subjects with AD but no food allergy based on negative DBPCFCs, and 18 normal controls. Subjects with AD and food allergy had higher rates of mean spontaneous histamine release than the other two subject groups: $35.1\% \pm 3.9\%$ versus $1.8\% \pm 0.2\%$ (AD, no food allergy) and $2.3\% \pm 0.2\%$ (controls); $p < 0.001$. The high rate of histamine release appeared to depend on continued ingestion of the offending food, because once a subject was placed on the appropriate elimination diet for 9–12 months, the spontaneous histamine release returned to normal levels. Another important finding was the identification of spontaneously produced cytokines called histamine releasing factors (HRFs) from peripheral blood mononuclear cells (PBMCs) of food-allergic subjects with high spontaneous histamine release. HRF *in vitro* could activate basophils from other food-allergic subjects, but not from non-food-allergic subjects. Normal controls did not produce HRFs, and subjects with food allergy who adhered to an elimination diet had a decrease in the rate of spontaneous HRF production. The HRF was found to activate basophils

through surface-bound IgE. Several different forms of IgE have been identified [68], and it has been proposed that HRFs may interact with certain of these IgE isoforms.

Basophil histamine release (BHR) had been proposed as an *in vitro* correlate to *in vivo* allergic responses [69]. BHR as a method of diagnosing food allergy was reported by Nolte [70] to correlate well with SPTs, RASTs, and open OFCs, but not with histamine release from intestinal mast cells obtained by duodenal biopsy in children. Another study by Sampson and Ho comparing BHR, SPTs, and DBPCFCs, however, showed that the BHR assay was no more effective in predicting clinical sensitivity than SPTs [71]. The clinical application of BHR is further complicated by several factors: it is not a widely available test, blood needs to be processed within a certain amount of time for cells to be viable, and there are no standardized methods for performing BHR. BHR assays are now primarily used in research settings.

A relatively new technique used to study the mediator effects of basophils, the basophil activation test (BAT), has the potential to overcome the pitfalls of BHR. The emerging ability to measure basophil activation as an assay for immediate hypersensitivity has the potential to provide diagnostic or prognostic utility in food allergy [72]. Allergen desensitization in studies has been shown to induce basophil hyporesponsiveness to allergen-induced degranulation [73,74], and *in vivo* constitutive activation of basophils correlates with CD203c expression measured directly *ex vivo* by flow cytometry [72]. Some have found that CD203c is expressed at very high levels in patients with AD and food allergy [72]. The assessment of BAT as a clinical diagnostic tool for food allergy in AD is still in its early stages, however. Monitoring the BAT for patients with food allergy on various elimination diets or following OFCs with subjective or late-phase reactions may also prove to be an important clinical tool, but further studies are needed.

Other data support a key role of eosinophils in the pathogenesis of food-sensitive AD, particularly in the late-phase IgE response. Studies of the late-phase reactions after the initial mast cell activation have shown that the terminal stages of IgE-mediated allergic reactions are characterized by infiltration of inflammatory cells, including eosinophils [75,76]. Although blood eosinophilia is common in AD patients, increased numbers of activated eosinophils have not always been found in biopsies of AD lesions. However, eosinophil degranulation and release of potent mediators clearly occurs. Leiferman *et al.* [77] found extensive dermal deposition of eosinophil-derived MBP in lesional biopsies of 18 subjects with AD but not in normal-appearing skin in affected subjects, suggesting that the assessment of eosinophil involvement cannot be based simply on the eosinophil numbers in tissue. Suomalainen *et al.* [78] studied 28 challenge-proven CM-allergic subjects and showed increased levels of eosinophil cationic protein (ECP) in the subjects with cutaneous symptoms only, which indicated

that ingestion of an offending food in an allergic patient can lead to activation of circulating eosinophils that may then infiltrate the skin of AD patients. Another study confirmed the finding of significantly elevated plasma ECP levels in subjects with AD [79].

Several important studies have helped clarify the role of food-allergen-specific T-cells in the underlying inflammatory process in AD, showing that cell-mediated immunity also occurs in patients with food-sensitive AD in addition to IgE-mediated hypersensitivity. Food-antigen-specific T-cells have been isolated and cloned from active AD lesions [80–82]. Researchers have also been able to routinely identify food-antigen-specific T-cells from peripheral blood in subjects with food-allergy-associated AD [81–83]. There has been disagreement in the literature, though, about the validity of *in vitro* T-lymphocyte proliferation responses to specific foods in AD. Kondo, Agata, and colleagues [84,85] demonstrated that proliferative responses of PBMCs to the offending food antigen in subjects with non-immediate types of food allergy (rash developing at least 2 hours after OFC) were significantly higher than those of healthy controls and subjects with immediate types of food allergy, respectively, indicating that the proliferative response of PBMCs to food antigens is specific to each offending food antigen in non-immediate types of food-allergy-related AD. On the other hand, others have found increased lymphocyte proliferative responses to relevant foods also in subjects with immediate reactions [82]. Overall, the clinical utility of lymphocyte proliferation assays in food-allergic patients is considered marginal due to considerable overlap in individual responses to the test, as Hoffman *et al.* [86] found them to be neither diagnostic nor predictive of clinical reactivity in individual subjects with milk allergy because lymphocytes of many control patients were highly responsive to milk antigens, and lymphocytes of many subjects with milk allergy were not.

Further evidence of T-lymphocyte involvement in the development of AD in food-allergic patients relates to the homing of allergen-specific T-cells to the skin [81]. The extravasation of T-cells at sites of inflammation is critically dependent on the activity of homing receptors that are involved in endothelial cell recognition and binding. Two such homing receptors, cutaneous lymphocyte-associated antigen (CLA) and L-selectin, have been shown to be selectively involved in T-cell migration to the skin and peripheral lymph nodes, respectively. Significantly higher expression of CLA occurred in casein-reactive T-cells from children with milk-induced AD than *Candida albicans*-reactive T-cells from the same subjects, and from either casein- or *Candida albicans*-reactive T-cells from the control groups. In contrast, the percentage of L-selectin-expressing T-cells did not significantly differ among the three groups.

The role of non-IgE-mediated food-induced hypersensitivity in AD remains unclear [28], likely in part due to the

raging debate for several decades whether food can act as a provocation factor for late eczematous reactions. Atopy patch tests (APTs) have been proposed as a mode of diagnosis of non-IgE-mediated food allergy and in identifying allergens in delayed-onset clinical reactions. The patch test reaction seems to be specific for sensitized patients with AD, as it does not occur in healthy volunteers or in patients suffering from asthma or rhinitis [87]. The outcome of APTs in different studies shows large variations due to differences in patient selection and, more importantly, differences in methodology. These facts make interpretation of studies somewhat difficult due to reliability issues, but a number of investigators, as discussed in the diagnostic section below, have examined the use of the APTs in addition to SPTs for the diagnosis of non-IgE-mediated food allergy, primarily in patients with AD.

Epidemiology of food allergy in atopic dermatitis

The prevalence of food allergy in patients with AD differs depending on the age of the patient and the severity of AD. Burks *et al.* [44], using DBPCFCs, diagnosed food allergy in 15 of 46 children (33%) with AD ranging from mild to severe that were referred to allergy or dermatology clinics. In a larger study published 10 years later of 165 children with AD referred to the allergy clinic, Burks and colleagues [45] diagnosed food allergy in 64 children (38.7%) utilizing DBPCFCs. Ascertainment bias could have affected the results of these two studies since many of the patients were referred to an allergist, so Eigenmann *et al.* [49] addressed this potential bias by evaluating 63 unselected children referred to a university-based dermatologist for assessment of moderate to severe AD. Again OFCs were used as part of the evaluation, and ultimately 23 of 63 (37%; 95% CI, 25–50%) were found to have clinically significant IgE-mediated food hypersensitivity. In an epidemiologic study of IgE-mediated food allergy in 74 Swiss children with AD referred to an allergist or dermatologist, Eigenmann and Calza [88] found that 25 of the 74 children (33.8%) were food allergic using OFCs and other tests. While the above studies did not stratify children by the severity of AD [44,49,87] or demonstrate a direct relationship between severity of AD and presence of food allergy [45], Guillet and Guillet [89] attempted this in a study of 250 children with AD. They found that increased severity of AD and younger age of children directly correlated with the presence of food allergy. Finally, two more studies, neither of which performed OFCs, looked at the prevalence of food allergy in two prospective birth cohorts in Australia. In the first, Hill *et al.* [90] found a cumulative prevalence of AD of 24%. The contribution of IgE food sensitization to the burden of AD was calculated as an attributable risk percent; this calculation estimated that IgE food sensitization was responsible for 65% and 64% of

AD in the at-risk cohort at 6 and 12 months, respectively. In the second study, Hill and Hosking [91] discovered a cumulative prevalence of AD of 28.9%. The association between IgE-mediated food allergy and AD was assessed using only SPT cut-offs and was stratified by groups of AD severity. As the severity of AD increased, so did the frequency of IgE-mediated food allergy and reported adverse food reactions, from 12% in the least severe AD group, up to 69% in the most severe AD group.

Epidemiologic studies of food allergy in adults with severe AD are comparatively limited, which may in part be due to the fact that most food allergy is outgrown in children, with the notable exceptions of peanut, tree nuts, fish, and shellfish. In a double-blind, controlled study using an antigen-free formula (Vivasorb) compared with placebo diet in 33 severe AD adults, Munkvad *et al.* [92] found that food allergy played little role in the etiology of AD in adults because the antigen-free diet did not significantly reduce symptoms. de Maat-Bleeke de De and Bruijnzeel-Koomen [93] also failed to discover a significant role of food allergy in adult AD. However, one study from Japan found that 44% of the 195 adults with AD had positive challenges to foods, although the causative foods listed were uncommon allergens, including chocolate, coffee, and rice [94]. Finally, a recent German study by Worm *et al.* [95] found that certain adult subjects were sensitized to pollen allergens, and according to those pollen allergens, also sensitized to pollen-associated food allergens; this trend was not frequently found though.

Diagnosis of food hypersensitivity in patients with atopic dermatitis

General approach

The diagnosis of food allergy (Fig. 9.1) must first begin with a careful medical history since the information gathered will be used to guide the best mode of diagnosis, or it could lead to dismissal of the problem by history alone. In fact, it is well documented in several studies where DBPCFCs were used to diagnose food allergy that only about 40% of patient histories of suspected food-induced allergic reactions could be verified [96]. The history should focus on the food(s) and quantity of food suspected of provoking the reaction, the type of symptoms attributed to food ingestion (acute versus chronic), the timing between ingestion and onset of symptoms, patterns of reactivity, the most recent reaction, and whether other associated activities play a role in inducing symptoms (e.g. exercise, alcohol ingestion). When gathering the history, one must also be aware of other foods eaten at the same time, potentially contaminated foods that may have been packaged on non-dedicated lines, and hidden sources of ingredients.

Once a symptom history is established, the search for a food-related etiology needs to be put in context with the

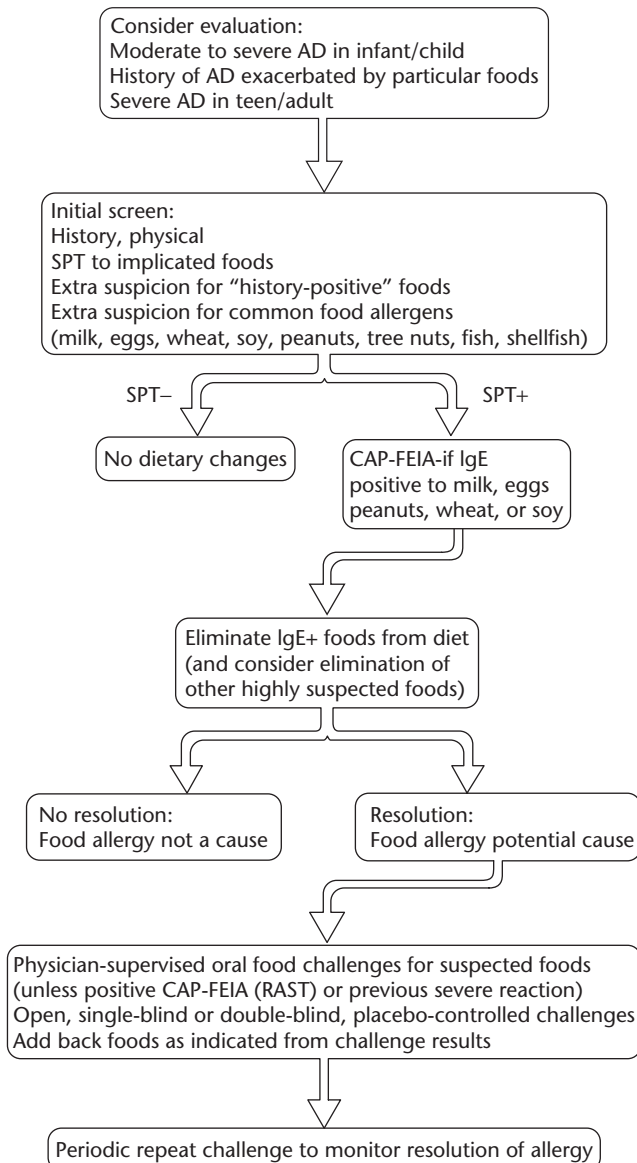


Figure 9.1 General approach to the evaluation of food allergy in AD. (Reproduced from Leung D. *Pediatric Allergy: Principles and Practice*. St. Louis: Mosby, 2003, with permission from Elsevier.)

prevalence that food allergy is implicated as the causative factor. The prevalence of food hypersensitivities is greatest in the first few years of life, affecting about 6% of children less than 3 years of age, then decreasing to a steady prevalence of 3.7% by late childhood through adulthood [97]. Furthermore, although any food could theoretically cause an allergic reaction, a small number of foods account for about 90% of verified food reactions: milk, egg, soy, wheat, peanut, tree nuts, and fish in children; and peanuts, tree nuts, fish, and shellfish in adults.

Once a thorough history has been obtained, the physical examination should focus on detecting other atopic features,

which are more commonly found in patients with IgE-mediated allergic reactions. After completing the history and physical, the physician should determine whether the patient's findings implicate a food-induced disorder and whether an IgE-mediated or non-IgE-mediated mechanism is most likely responsible. When food allergy has been identified as the likely cause of symptoms, confirmation of the diagnosis and identification of the implicated food(s) can begin. A number of tools exist that aid in the diagnosis of food allergy. In general, laboratory tests are more useful in delineating the specific foods responsible for IgE-mediated reactions, whereas they are of limited or no value in non-IgE-mediated disorders. Available studies include *in vivo* tests such as SPT, OFCs, elimination diets, and APTs, and *in vitro* tests such as quantification of food-specific IgE and the BAT (discussed previously). The utility of these test modalities will be briefly discussed.

***In vivo* and *in vitro* laboratory testing**

SPTs are commonly used to screen patients with suspected IgE-mediated food reactions. When an SPT is positive, it indicates the possible association between the food tested and the patient's reactivity to that food because the positive predictive accuracies of SPTs are less than 50% compared to DBPCFCs. However, a positive SPT may be considered diagnostic in patients who have experienced a systemic anaphylactic reaction to an isolated food. On the other hand, negative responses virtually exclude the possibility of an IgE-mediated reaction because their negative predictive value (NPV) exceeds 95% [98]. The accuracy of SPTs varies depending on which food antigen is being studied, the quality of the food extract, and the technical skills of the tester. As a result of a study by Bock *et al.* [99], intradermal skin tests (ISTs) to food extracts were found to have no positive advantage over SPTs, and it was concluded that the increased sensitivity of ISTs would lead to even more false-positive tests than seen with the prick technique [100]. Fresh food skin prick tests (FFSPTs) may be performed because some commercially prepared extracts frequently lack the labile proteins that are responsible for IgE-mediated sensitivity to many fruits and vegetables because they are degraded or lose allergenicity during extract preparation [101]. Negative SPTs with commercially available extracts that contradict a convincing history of a food-induced allergic reaction should be repeated with the fresh food before concluding that food-specific IgE is absent [102].

Another way to identify food-specific IgE that is more widely available to the general practitioner is the CAP-System fluorescent-enzyme immunoassay (FEIA), although the sensitivity is slightly less than SPTs. The development of the CAP-System FEIA allowed better quantitation of food-specific IgE antibodies, which have been shown in key studies to be more predictive of symptomatic IgE-mediated food hypersensitivity. In a retrospective study on 196 children

and adolescents (mean age 5.2 years) with AD, Sampson and Ho [71] compared the food-specific IgE levels with the results of DBPCFCs and found that concentrations of $6\text{ kU}_A/\text{l}$ or greater for egg, $32\text{ kU}_A/\text{l}$ or greater for CM, $15\text{ kU}_A/\text{l}$ or greater for peanut, and $20\text{ kU}_A/\text{l}$ or greater for codfish were 95% predictive of an allergic reaction. Therefore, a patient with a food-specific IgE level greater than the 95% positive predictive value (PPV) could be considered reactive and an OFC would not be warranted. If, however, the food-specific IgE level was less than the 95% PPV, a patient may be reactive but would need an OFC to confirm the diagnosis. There are several caveats with this study that affect its use in the general population: first, all patients had AD, and these patients tend to have higher IgE levels; and second, this group of patients had a much higher prevalence of food allergy than is seen in most populations. Because of these factors, Sampson performed a prospective study of 100 children (median age 3.8 years) not selected for AD (only 61% had this disorder) with similar results except the 95% PPV cut-off was lower for milk at $15\text{ kU}_A/\text{l}$ [100].

APTs have been proposed as a mode of diagnosis of non-IgE-mediated food allergy and in identifying allergens in delayed-onset IgE-mediated clinical reactions. A number of investigators have examined the use of the APTs in addition to SPTs and food-specific IgE levels by CAP-System FEIA for the diagnosis of non-IgE-mediated food allergy, primarily in patients with AD. Roehr *et al.* [103] performed 173 challenges in 98 patients with AD and used APTs, SPTs, and food-specific IgE levels to CM, egg, soy, and wheat to see if the combination of a positive APT result plus a positive food-specific IgE level, a positive SPT, or both would make DBPCFCs unnecessary. Positive APT results alone correlated with high PPVs for CM (95%), hen's egg (94%), and wheat (94%), but with only a 50% PPV for soy (only 4 children reacted to soy). Combining the APT with proof of specific IgE for CM ($>0.35\text{ kU}_A/\text{l}$) and for egg ($>17.5\text{ kU}_A/\text{l}$) increased the PPVs to 100%, thus making DBPCFCs superfluous. Adding SPTs to the other two tests did not further improve results. More recent studies [104,105], however, have not been able to duplicate the results from Roehr and colleagues, finding that APTs had poor reliability, added only minimal predictive value, and were inferior to DBPCFCs in evaluation of food allergy. In a recent review of literature on APT since 2004, Turjanmaa [106] stated there is accumulating evidence that a small subset of patients with AD shows positive APTs when specific IgE to the same allergen is negative, but that is because the APT lacks standardization and until the methodology improves, the specificity, sensitivity, and PPVs and NPVs cannot be calculated properly.

One must be extremely careful in interpreting tests for food-specific IgE antibodies as clinical errors occur when the above tests are overinterpreted or various limitations are not fully appreciated, such as not considering the medical history, epidemiology of food allergy (causal foods, cross-reactivity,

and age), and specific test limitations (sensitivity, specificity, technique, and reagents). One must also appreciate that the results from studies like Sampson's [71,100] and others may not be applicable beyond the specific food, the test studied, and the characteristics of the study population (e.g. children). Another common pitfall is the assumption that a negative test result indicates a lack of allergy, which was noted by Sampson [100] and has been shown numerous times not to be the case [107].

Elimination diets and oral food challenges

The purpose of an elimination diet is to determine if a patient's symptoms will resolve when foods are restricted from the diet. Once certain foods are suspected of being responsible for a food-induced allergic disorder, an elimination diet is started as an attempt to support the diagnosis. If a patient's symptoms persist despite a very strict avoidance diet, it is unlikely that the food accounts for the patient's complaints [108]. The type of diet chosen will depend on the clinical presentation being evaluated and the results of IgE antibody tests. Elimination of one or more foods may be the obvious course of action and therapeutic in the case of an acute reaction to a food and the presence of a positive test for IgE to that food. It may also be especially helpful in evaluating infants who are on a very limited diet. In an oligoantigenic diet, a large number of foods suspected to cause chronic problems are removed, and the patient is given a list of allowed foods. This type of diet is useful for evaluation of chronic disorders such as AD. In the most extreme diet, the elemental diet, a hydrolyzed formula provides all the nutrition. This diet may be necessary when the other diets mentioned above have failed, but the suspicion for food-related illness remains high. If a patient's symptoms do not disappear on an elemental diet, then it is very unlikely that ingested substances are the problem [108,109].

If symptoms resolve on an elimination diet, some form of OFC is generally warranted, especially in chronic disorders such as AD. OFCs are performed by feeding suspected foods in gradually increasing amounts over hours or days under the supervision of a physician. OFCs can be done openly, single-blind, or double-blind and placebo-controlled. The DBPCFC is considered to be the "gold standard" for the diagnosis of food allergy, and it is the least prone to bias and confounding factors [71,109]. OFCs can be used to assess any kind of adverse response to foods. If an elimination diet did not alleviate symptoms and suspicion is still high for a food-related cause, then the OFC may be needed to resolve the issue. For non-IgE-mediated reactions, OFCs are often the only means of diagnosis [110].

The decision to perform OFCs should not be taken lightly as severe anaphylactic reactions can occur, and they are time consuming, cost intensive, and stressful to the patient and families. In the patient with a convincing history of anaphylaxis and a positive test for specific IgE to the causal

food, an OFC is generally not needed as it places patients at risk for severe reactions [110]. Given the risk of anaphylaxis during an OFC, the physician must be comfortable with a potential severe reaction and be prepared to treat it with emergency medications and equipment. As a general rule, challenges should not be done at home [110]. OFCs are usually done in a graded fashion with dose increases every 15–60 minutes and a period of observation once the OFC is finished. If a patient has tolerated all the food in the challenge, then clinical reactivity has generally been ruled out in that a negative OFC has a high NPV [111]. However, for blinded challenges, all negative challenges should be confirmed by an open feeding of the suspected food made in its commonly prepared state and served in normal meal-size quantities under medical supervision to exclude the rare false-negative challenge response [108].

Management

In addition to the medical management of AD using hydration therapy and moisturizers, topical corticosteroids, topical calcineurin inhibitors, antibiotics for secondary bacterial infections, and environmental avoidance of triggers, the only currently available treatments for food allergy are strict dietary elimination of the causative food(s) and being prepared to treat a potential reaction after accidental ingestion. The complete elimination of food proteins, though, is not an easy task, and lack of complete elimination can lead to puzzling results during dietary elimination. Therefore, with any of these diets, specific information needs to be reviewed carefully to ensure adherence, as it is common for patients to make errors. For example, eliminating egg from someone's diet means reading labels for key words such as ovalbumin, lysozyme, and globulin. However, reading labels on US food products has become an easier task since the implementation in January 2006 of the Food Allergen Labeling and Consumer Protection Act of 2004, which requires clear labels for the major food allergens (milk, egg, soy, wheat, peanut, tree nuts, fish, and shellfish). Contamination of the food being eliminated and hidden ingredients in non-labeled products such as in restaurants can still be issues that hinder strict avoidance. Organizations such as the Food Allergy and Anaphylaxis Network (<http://www.foodallergy.org>) may provide assistance for patients. When multiple foods are eliminated from the diet, it may also be necessary to consult the aid of a nutritionist to maintain a balanced diet.

Unfortunately, despite all the above precautions, accidental ingestions of known allergenic foods are relatively common. Therefore, patients, family members, and other caregivers must have an emergency action plan in place for such occasions. This plan includes readily available injectable epinephrine, oral antihistamines such as diphenhydramine, bronchodilators, and knowledge of when to seek

urgent medical attention. Patients that have had prior severe reactions, those with underlying asthma, and patients allergic to peanut, tree nuts, fish, and shellfish may be more at risk for acute, severe, or even fatal food-induced anaphylactic reactions [112]. Prompt administration of epinephrine at the initial signs of a severe reaction needs to be emphasized because reports of fatal and near-fatal reactions have been associated with delayed epinephrine use [112]. Follow-up after accidental ingestions is important to review circumstances surrounding the reaction and review the effectiveness of food allergy action plan. Routine follow-up to assess growth and nutrition and to retest for progression or possible resolution of food allergy is crucial as well.

Natural history of food hypersensitivity

Fortunately most children with food-induced eczema will lose or “outgrow” their allergies to milk, egg, soy, and wheat [113], and this usually corresponds to the resolution or improvement of their AD [46]. However, patients allergic to peanut, tree nuts, fish, or shellfish are much less likely to lose their clinical reactivity: only approximately 20% of children who have had a reaction to peanut early as a child may outgrow their peanut sensitivity [114,115], while only about approximately 10% may outgrow tree nut allergy [116]. From the Sampson and Scanlon study on the natural history of food allergy in AD [41], about one-third of children outgrew their clinical reactivity over 1–3 years with strict compliance to the elimination diet, which was believed to have helped in speedier resolution. Three factors emerged to be most important in determining the likelihood of patients losing clinical reactivity: (1) the specific food(s) to which the patient was allergic, meaning that patients allergic to milk, egg, soy, or wheat were much more likely to outgrow these allergies than those with peanut, tree nut, fish, or shellfish allergies; (2) the food-specific IgE level, that is, the higher the level of food-specific IgE, the less likely clinical tolerance will develop in subsequent years; and (3) the degree of strict adherence to the diet, that is, patients who continued to ingest small amounts of food allergen or had frequent accidental ingestions were less likely to develop clinical tolerance.

Clinical tolerance is acquired more quickly, though, than the loss of food-specific IgE measured by SPT or *in vitro* allergen-specific IgE testing [41,117], as they can remain positive for many years after the food has been reintroduced into the diet. Therefore, it is important to follow patients with food allergy regularly with intermittent OFCs when appropriate to determine if food allergy persists. Although food allergy and AD may resolve, many of these infants and children often go on to develop allergic rhinitis and/or asthma [7,8]. In one study, approximately 90% of children with egg-specific IgE and AD developed respiratory allergies and asthma [118].

Conclusions

The triggers associated with disease pathogenesis and clinical symptoms in patients with AD are numerous. Early in life, the role of allergens, especially food allergens, is clearly important. A careful history with appropriate diagnostic testing coupled with a comprehensive treatment program can alter the disease and life for patients with AD and food hypersensitivity.

References

- Williams H, Robertson C, Stewart A, *et al.* Worldwide variations in the prevalence of symptoms of atopic eczema in the International Study of Asthma and Allergies in Childhood. *J Allergy Clin Immunol* 1999;103:125–38.
- The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet* 1998;351:1225–32.
- Laughter D, Istvan JA, Tofte SJ, *et al.* The prevalence of atopic dermatitis in Oregon schoolchildren. *J Am Acad Dermatol* 2000;43:649–55.
- Kay J, Gawkrödger DJ, Mortimer MJ, *et al.* The prevalence of childhood atopic eczema in a general population. *J Am Acad Dermatol* 1994;30:35–9.
- Williams HC, Strachan DP. The natural history of childhood eczema: observations from the British 1958 birth cohort study. *Br J Dermatol* 1998;139:834–9.
- Ozkaya E. Adult-onset atopic dermatitis. *J Am Acad Dermatol* 2005;52:579–82.
- Lau S, Nickel R, Niggeman B, *et al.* The development of childhood asthma: lessons from the German Multicentre Allergy Study (MAS). *Paediatr Respir Rev* 2002;3:265–72.
- Spergel JM, Paller JS. Atopic dermatitis and the atopic march. *J Allergy Clin Immunol* 2003;112:S118–27.
- Novak N, Allam JP, Bieber T. Allergic hyperreactivity to microbial components: a trigger factor of “intrinsic” atopic dermatitis? *J Allergy Clin Immunol* 2003;112:215–16.
- Scheynius A, Johansson C, Buentke E, *et al.* Atopic eczema/dermatitis syndrome and *Malassezia*. *Int Arch Allergy Immunol* 2002;127:161–9.
- Morar N, Willis-Owen SA, Moffatt MF, *et al.* The genetics of atopic dermatitis. *J Allergy Clin Immunol* 2006;118:24–34.
- Cork MJ, Robinson DA, Vasilopoulos Y, *et al.* New perspectives on epidermal barrier dysfunction in atopic dermatitis: gene – environment interactions. *J Allergy Clin Immunol* 2006;118:3–21.
- Akdis CA, Akdis M, Bieber T, *et al.* Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergy and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report. *J Allergy Clin Immunol* 2006;118:152–69.
- Hamid Q, Boguniewicz M, Leung DY. Differential *in situ* cytokine gene expression in acute versus chronic atopic dermatitis. *J Clin Invest* 1994;94:870–6.
- Bratton DL, Hamid Q, Boguniewicz M, *et al.* Granulocyte macrophage colony-stimulating factor contributes to enhanced monocyte survival in chronic atopic dermatitis. *J Clin Invest* 1995;95:211–18.
- Hamid Q, Naseer T, Minshall EM, *et al.* *In vivo* expression of IL-12 and IL-13 in atopic dermatitis. *J Allergy Clin Immunol* 1996;98:225–31.
- Toda M, Leung DY, Molet S, *et al.* Polarized *in vivo* expression of IL-11 and IL-17 between acute and chronic skin lesions. *J Allergy Clin Immunol* 2003;111:875–881.
- Wakita H, Sakamoto T, Tokura Y, *et al.* E-selectin and vascular cell adhesion molecule-1 as critical adhesion molecules for infiltration of T lymphocytes and eosinophils in atopic dermatitis. *J Cutan Pathol* 1994;1:33–9.
- Schon MP, Zollner TM, Henning-Boehncke. The molecular basis of lymphocyte recruitment to the skin: clues for pathogenesis and selective therapies of inflammatory disorders. *J Invest Dermatol* 2003;121:951–62.
- Kallos P, Kallos L. Experimental asthma in guinea pigs revisited. *Int Arch Allergy Appl Immunol* 1984;73:77–85.
- Taha RA, Minshall EM, Leung DYM, *et al.* Evidence for increased expression of eotaxin and monocyte chemoattractant protein-4 in atopic dermatitis. *J Allergy Clin Immunol* 2000;105:1002–7.
- Laberge S, Ghaffar O, Boguniewicz M, *et al.* Association of increased CD4+ T-cell infiltration with increased IL-16 gene expression in atopic dermatitis. *J Allergy Clin Immunol* 1998;102:645–50.
- Reich K, Hugo S, Middel P, *et al.* Evidence for a role of Langerhans cell-derived IL-16 in atopic dermatitis. *J Allergy Clin Immunol* 2002;109:681–7.
- Sampson HA. Food sensitivity and the pathogenesis of atopic dermatitis. *J Roy Soc Med* 1997;90:S3–9.
- Bruynzeel-Koomen C, Van Wicker DF, Toonstra J, *et al.* The presence of IgE molecules on epidermal Langerhans cells in patients with atopic dermatitis. *Arch Dermatol Res* 1986;297:205.
- Mudde G, Bheekha R, Bruynzeel-Koomen C. Consequences of IgE/CD-23-mediated antigen presentation in allergy. *Immunol Today* 1995;16:380–3.
- Mudde G, van Reijnsen F, Boland G, *et al.* Allergen presentation by epidermal Langerhans cells from patients with atopic dermatitis is mediated by IgE. *Immunology* 1990;69:335–41.
- Sampson HA. Eczema and food hypersensitivity. In: Metcalfe DD, Sampson HA, Simon RA (eds.) *Food Allergy: Adverse Reactions to Foods and Food Additives*, 3rd edn. Malden: Blackwell Publishing, Inc., 2003:144–59.
- Novak N, Valenta R, Bohle B, *et al.* FcεRI engagement of Langerhans cell-like dendritic cells and inflammatory dendritic epidermal cell-like dendritic cells induces chemotactic signals and different T-cell phenotypes *in vitro*. *J Allergy Clin Immunol* 2004;113:949–57.
- Nomura I, Goleva E, Howell MD, *et al.* Cytokine milieu of atopic dermatitis, as compared to psoriasis, skin prevents induction of innate immune response genes. *J Immunol* 2003;171:3262–9.

- 31 Wedi B, Raap U, Lewrick H, *et al.* Delayed eosinophil programmed cell death *in vitro*: a common feature of inhalant allergy and extrinsic and intrinsic atopic dermatitis. *J Allergy Clin Immunol* 1997;100:536–43.
- 32 Simon D, Braathen LR, Simon HU. Eosinophils and atopic dermatitis. *Allergy* 2004;59:561–70.
- 33 Kapp A. The role of eosinophils in the pathogenesis of atopic dermatitis – eosinophil granule proteins as markers of disease activity. *Allergy* 1993;48:1–5.
- 34 Gleich G, Frigas E, Loegering DA, *et al.* Cytotoxic properties of eosinophilic major basic protein. *J Immunol* 1979;123: 2925–7.
- 35 O'Donnell MC, Ackerman S, Gleich G, *et al.* Activation of basophil and mast cell histamine release by eosinophil granule major basic protein. *J Exp Med* 1983;157:1981–91.
- 36 Rowlands D, Tofte SJ, Hanifin JM. Does food allergy cause atopic dermatitis? Food challenge testing to dissociate eczematous from immediate reactions. *Dermatol Ther* 2006;19:97–103.
- 37 Wuthrich B. Food-induced cutaneous adverse reactions. *Allergy* 1998;53:S56–60.
- 38 Atherton DJ, Sewell M, Soothill JF, *et al.* A double-blind controlled crossover trial of an antigen-avoidance diet in atopic eczema. *Lancet* 1978;1:401–3.
- 39 Neild VS, Marsden RA, Bailes JA, *et al.* Egg and milk exclusion diets in atopic eczema. *Br J Dermatol* 1986;114:117–23.
- 40 Juto P, Engberg S, Winberg J. Treatment of infantile atopic dermatitis with a strict elimination diet. *Clin Allergy* 1978;8: 493–500.
- 41 Sampson HA, Scanlon SM. Natural history of food hypersensitivity in children with atopic dermatitis. *J Pediatr* 1989;115:23–7.
- 42 Lever R, MacDonald C, Waugh P, *et al.* Randomised controlled trial of advice on an egg exclusion diet in young children with atopic eczema and sensitivity to eggs. *Pediatr Allergy Immunol* 1998;9:13–9.
- 43 Bock S, Lee W, Remigio L, *et al.* Studies of hypersensitivity reactions to food in infants and children. *J Allergy Clin Immunol* 1978;62:3327–34.
- 44 Burks AW, Mallory SB, Williams LW, *et al.* Atopic dermatitis: clinical relevance of food hypersensitivity reactions. *J Pediatr* 1988;113:447–51.
- 45 Burks AW, James JM, Hiegel A, *et al.* Atopic dermatitis and food hypersensitivity reactions. *J Pediatr* 1998;132:132–6.
- 46 Sicherer SH, Sampson HA. Food hypersensitivity and atopic dermatitis: pathophysiology, epidemiology, diagnosis, and management. *J Allergy Clin Immunol* 1999;104:S114–22.
- 47 Sampson HA, McCaskill CC. Food hypersensitivity and atopic dermatitis: Evaluation of 113 patients. *J Pediatr* 1985;107: 669–75.
- 48 Sampson HA, Metcalfe DD. Food allergies [Review]. *JAMA* 1992;268:2840–4.
- 49 Eigenmann PA, Sicherer SH, Borkowski TA, *et al.* Prevalence of IgE-mediated food allergy among children with atopic dermatitis. *Pediatrics* 1998;101:e8.
- 50 Sicherer SH, Sampson HA. Role of food allergens. In: Leung DY, Greaves MW (eds.) *Allergic Skin Disease: A Multidisciplinary Approach*, 1st edn. Philadelphia, PA: Marcel Dekker, Inc, 2000: 403–422.
- 51 Kramer MS, Kakuma R. Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. *Cochrane Database Syst Rev* 2003;4: CD0001333.
- 52 Muraro A, Dreborg S, Halken S, *et al.* Dietary prevention of allergic diseases in infants and small children. Part III. Critical review of published peer-reviewed observational and interventional studies and final recommendations. *Pediatr Allergy Immunol* 2004;15:291–307.
- 53 Friedman NJ, Zeiger RS. The role of breast-feeding in the development of allergies and asthma. *J Allergy Clin Immunol* 2005; 115:1238–48.
- 54 Kull I, Bohme M, Wahlgren C-E, *et al.* Breast-feeding decreases the risk for childhood eczema. *J Allergy Clin Immunol* 2005;116: 657–61.
- 55 Laubereau B, Brockow I, Zirngibl A, *et al.* Effect of breast-feeding on the development of atopic dermatitis during the first 3 years of life – results from the GINI-birth cohort study. *J Pediatr* 2004;144:602–7.
- 56 Ludvigsson JF, Mostrom M, Ludvigsson J, *et al.* Exclusive breast-feeding and the risk of atopic dermatitis in some 8300 infants. *Pediatr Allergy Immunol* 2005;16:201–8.
- 57 Pesonen M, Kallio MJ, Ranki A, *et al.* Prolonged exclusive breastfeeding is associated with increased atopic dermatitis: a prospective follow-up study of unselected healthy newborns from birth to age 20 years. *Clin Exp Allergy* 2006;36: 1011–8.
- 58 Gdalevich M, Mimouni D, David M, *et al.* Breast-feeding and the onset of atopic dermatitis in childhood: a systematic review and meta-analysis of prospective studies. *J Am Acad Dermatol* 2001;45:520–7.
- 59 Osborn DA, Sinn J. Formulas containing hydrolyzed protein for prevention of allergy and food intolerance in infants. *Cochrane Database Syst Rev* 2006;4:CD003664.
- 60 von Berg A, Koletzko S, Filipiak-Pittroff B, *et al.* Certain hydrolyzed formulas reduce the incidence of atopic dermatitis but not that of asthma: three-year results of the German Infant Nutritional Intervention Study. *J Allergy Clin Immunol* 2007;119:718–25.
- 61 Osborn DA, Sinn J. Soy formula for the prevention of allergy and food intolerance in infants. *Cochrane Database Syst Rev* 2006;3:CD003741.
- 62 Fergusson DM, Horwood LJ, Shannon FT. Early solid feeding and recurrent childhood eczema: a 10-year longitudinal study. *Pediatrics* 1990;86:541–6.
- 63 Kajosaari M. Atopy prophylaxis in high-risk infants: prospective 5-year follow-up study of children with six months exclusive breastfeeding and solid food elimination. *Adv Exp Med Biol* 1991;310:453–8.
- 64 Zutavern A, Brockow I, Schaaf B, *et al.* Timing of solid food introduction in relation to atopic dermatitis and atopic sensitization: results from a prospective birth cohort study. *Pediatrics* 2006;117:401–11.

- 65 Poole JA, Barriga K, Leung DY, *et al.* Timing of initial exposure to cereal grains and the risk of wheat allergy. *Pediatrics* 2006;117:2175–82.
- 66 Sampson HA, Jolie PL. Increased plasma histamine concentrations after food challenges in children with atopic dermatitis. *N Engl J Med* 1984;311:372–6.
- 67 Sampson HA, Broadbent KR, Bernhisel-Broadbent J. Spontaneous release of histamine from basophils and histamine-releasing factor in patients with atopic dermatitis and food hypersensitivity. *N Engl J Med* 1989;321:228–32.
- 68 Lyczak JB, Zhang K, Saxon A, *et al.* Expression of novel secreted isoforms of human immunoglobulin E proteins. *J Biol Chem* 1996;271:3428–36.
- 69 Du Buske LM. Introduction: basophil histamine release and the diagnosis of food allergy. *Allergy Proc* 1993;14:243–9.
- 70 Nolte H. The clinical utility of basophil histamine release. *Allergy Proc* 1993;14:251–4.
- 71 Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol* 1997;100:444–51.
- 72 Shreffler WG. Evaluation of basophil activation in food allergy: present and future applications. *Curr Opin Allergy Clin Immunol* 2006;6:226–33.
- 73 Sobotka AK, Dembo M, Goldstein B, *et al.* Antigen-specific desensitization of human basophils. *J Immunol* 1979;122:511–17.
- 74 Satti MZ, Cahen P, Skov PS, *et al.* Changes in IgE- and antigen-dependent histamine-release in peripheral blood of *Schistosoma mansoni*-infected Ugandan fishermen after treatment with praziquantel. *BMC Immunol* 2004;5:6.
- 75 Demoly P, Piette V, Bousquet J. *In vivo* methods for study of allergy. In: Adkinson NF, Yunginger JW, Busse WW, *et al.* (eds.) *Middleton's Allergy: Principles and Practice*, 6th edn. Philadelphia, PA: Mosby, Inc., 2003:631–2.
- 76 Abramovits W. Atopic dermatitis. *J Am Acad Dermatol* 2005;53: S86–93.
- 77 Leiferman KM, Ackerman SJ, Sampson HA, *et al.* Dermal deposition of eosinophil-granule major basic protein in atopic dermatitis. Comparison with onchocerciasis. *N Engl J Med* 1985;313:282–5.
- 78 Suomalainen H, Soppi E, Isolauri E. Evidence for eosinophil activation in cow's milk allergy. *Pediatr Allergy Immunol* 1994;5:27–31.
- 79 Magnarín M, Knowles A, Ventura A, *et al.* A role for eosinophils in the pathogenesis of skin lesions in patients with food-sensitive atopic dermatitis. *J Allergy Clin Immunol* 1995;96:200–8.
- 80 van Reijssen FC, Felius A, Wauters EA. T-cell reactivity for a peanut-derived epitope in the skin of a young infant with atopic dermatitis. *J Allergy Clin Immunol* 1998;101:207–9.
- 81 Abernathy-Carver KJ, Sampson HA, Parker LJ, *et al.* Milk-induced eczema is associated with the expansion of T cells expressing cutaneous lymphocyte antigen. *J Clin Invest* 1995;95:913–18.
- 82 Reekers R, Beyer K, Niggemann B, *et al.* The role of circulating food antigen-specific lymphocytes in food allergic children with atopic dermatitis. *Br J Dermatol* 1996;135:935–41.
- 83 Werfel T, Ahlers G, Schmidt P, *et al.* Detection of kappa-casein-specific lymphocyte response in milk-responsive atopic dermatitis. *Clin Exp Allergy* 1996;26:1380–6.
- 84 Kondo N, Fukutomi O, Agata H, *et al.* Proliferative responses of lymphocytes to food antigens are useful for detection of allergens in nonimmediate types of food allergy. *J Invest Allergol Clin Immunol* 1997;7:122–6.
- 85 Agata H, Kondo N, Fukutomi O, *et al.* Effect of elimination diets in food-specific IgE antibodies and lymphocyte proliferative responses to food antigens in atopic dermatitis patients exhibiting sensitivity to food allergens. *J Allergy Clin Immunol* 1993;91:668–79.
- 86 Hoffman KM, Ho DG, Sampson HA. Evaluation of the usefulness of lymphocyte proliferation assays in the diagnosis of allergy to cow's milk. *J Allergy Clin Immunol* 1997;99:360–6.
- 87 De Bruin-Weller MS, Knol EF, Bruijnzeel-Koomen C. Atopy patch testing – a diagnostic tool? *Allergy* 1999;54:784–91.
- 88 Eigenmann PA, Calza A-M. Diagnosis of IgE-mediated food allergy among Swiss children with atopic dermatitis. *Pediatr Allergy Immunol* 2000;11:95–100.
- 89 Guillet G, Guillet M-H. Natural history of sensitizations in atopic dermatitis. A 3-year follow-up in 250 children: food allergy and high risk of respiratory symptoms. *Arch Dermatol* 1992;128:187–92.
- 90 Hill DJ, Sporik R, Thorburn J, *et al.* The association of atopic dermatitis in infancy with immunoglobulin E food sensitization. *J Pediatr* 2000;137:475–9.
- 91 Hill DJ, Hosking CS. Food allergy and atopic dermatitis in infancy: an epidemiologic study. *Pediatr Allergy Immunol* 2004;15:421–7.
- 92 Munkvad M, Danielsen L, Hoj L, *et al.* Antigen-free diet in adult patients with atopic dermatitis. A double-blind controlled study. *Acta Derm Venereol* 1984;64:524–8.
- 93 de Maat-Bleeker F, Bruijnzeel-Koomen C. Food allergy in adults with atopic dermatitis. *Monogr Allergy Basel Karger* 1996;32:157–63.
- 94 Uenishi T, Sugiura H, Uehara M. Role of foods in irregular aggravation of atopic dermatitis. *J Dermatol* 2003;30:91–7.
- 95 Worm M, Forschner K, Lee HH, *et al.* Frequency of atopic dermatitis and relevance of food allergy in adults in Germany. *Acta Derm Venereol* 2006;86:119–22.
- 96 Bock SA, Atkins FM. Patterns of food hypersensitivity during sixteen years of double-blind, placebo-controlled food challenges. *J Pediatr* 1990;117:561–7.
- 97 Sicherer SH, Sampson HA. Food allergy. *J Allergy Clin Immunol* 2006;117:S470–5.
- 98 Sampson HA. Food allergy. Part 2. Diagnosis and management. *J Allergy Clin Immunol* 1999;103:981–9.
- 99 Bock SA, Lee WY, Remigio L, *et al.* Appraisal of skin tests with food extracts for diagnosis of food hypersensitivity. *Clin Allergy* 1978;8:559–64.

- 100 Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 2001; 107:891–6.
- 101 Ortolani C, Ispano M, Pastorello EA, *et al.* Comparison of results of skin prick tests (with fresh foods and commercial food extracts) and RAST in 100 patients with oral allergy syndrome. *J Allergy Clin Immunol* 1989;83:683–90.
- 102 Eigenmann PA, Sampson HA. Interpreting skin prick tests in the evaluation of food allergy in children. *Pediatr Allergy Immunol* 1998;9:186–91.
- 103 Roehr CC, Reibel S, Ziegert M, *et al.* Atopy patch tests, together with determination of specific IgE levels, reduce the need for oral food challenges in children with atopic dermatitis. *J Allergy Clin Immunol* 2001;107:548–53.
- 104 Breuer K, Heratizadeh A, Wulf A, *et al.* Late eczematous reactions to food in children with atopic dermatitis. *Clin Exp Allergy* 2004;34:817–24.
- 105 Mehl A, Rolinck-Werninhaus C, Staden U, *et al.* The atopy patch test in the diagnostic workup of suspected food-related symptoms in children. *J Allergy Clin Immunol* 2006;118:923–9.
- 106 Turjanmaa K. The role of atopy patch tests in the diagnosis of allergy in atopic dermatitis. *Curr Opin Allergy Clin Immunol* 2005;5:425–8.
- 107 Sicherer SH, Bock SA. An expanding evidence base provides food for thought to avoid indigestion in managing difficult dilemmas in food allergy. *J Allergy Clin Immunol* 2006; 117:1419–22.
- 108 Bock SA, Sampson HA, Atkins FA, *et al.* 1988. Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: a manual. *J Allergy Clin Immunol* 1988;82:986–97.
- 109 Sicherer SH. Food allergy: when and how to perform oral food challenges. *Pediatr Allergy Immunol* 1999;10:226–34.
- 110 Sicherer SH. Food allergy. *Lancet* 2002;360:701–10.
- 111 Sampson HA. Use of food-challenge tests in children. *Lancet* 2001;358:1832–3.
- 112 Sampson HA, Mendelson LM, Rosen JP. Fatal and near-fatal anaphylactic reactions to foods in children and adolescents. *N Eng J Med* 1992;327:380–4.
- 113 Bock SA. The natural history of food sensitivity. *J Allergy Clin Immunol* 1982;69:173–7.
- 114 Skolnick HS, Conover-Walker MK, Sampson HA, *et al.* The natural history of peanut allergy. *J Allergy Clin Immunol* 2002; 107:367–74.
- 115 Fleischer DM, Conover-Walker MK, Christie L, *et al.* The natural progression of peanut allergy: resolution and the possibility of recurrence. *J Allergy Clin Immunol* 2003;112:183–9.
- 116 Fleischer DM, Conover-Walker MK, Matsui EC, *et al.* The natural history of tree nut allergy. *J Allergy Clin Immunol* 2005; 116:1087–93.
- 117 Fleischer DM, Conover-Walker MK, Christie L, *et al.* Peanut allergy: recurrence and its management. *J Allergy Clin Immunol* 2004;114:1195–1201.
- 118 Nickel R, Kulig M, Forster G, *et al.* Sensitization to hen's egg at the age of 12 months is predictive for allergen sensitization to common indoor and outdoor allergens at the age of 3 years. *J Allergy Clin Immunol* 1997;99:613–7.