



Atopic dermatitis and allergy in children: A dynamic relationship

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ABSTRACT

Atopic dermatitis (AD) is the most common chronic skin disease in children. The defective barrier function of the skin in patients with AD allows foreign proteins to enter the body and interact with components of the innate and adaptive immune systems. The immune response characteristic of AD is complex with the majority of patients making IgE in response to ingested and/or inhaled antigens. Although IgE-mediated mechanisms may represent initial immune responses, they are only one element of a biphasic inflammatory response. Identifying the role of specific allergens in a patient's skin disease is critical yet difficult because diagnostic tests are often not able to distinguish asymptomatic sensitization from true clinical allergy.

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1. Introduction

Atopic dermatitis (AD) is an intensely pruritic, chronically relapsing inflammatory skin disease affecting up to 10% of children (Spergel et al., 1999; Hamid et al., 1994). It is often the first manifestation of the “allergic march” and approximately 80% of young children with AD later develop allergic rhinitis or asthma (Burks et al., 1998). Because the majority of children with AD demonstrate elevated serum immunoglobulin E (IgE) levels and positive immediate skin test reactions to allergens, IgE-mediated immune responses are thought to be instrumental in the development of AD. However, the pathogenesis is more complex, involving susceptibility genes, environmental trigger factors, and altered immune responses (Hamid et al., 1994). Optimal therapy of AD requires a comprehensive approach, including identifying high-risk infants, avoiding known triggers, and judicious use of anti-inflammatory medications.

2. Clinical features

A hallmark feature of AD is *alloknesis*, an abnormal response to most stimuli with the sensation of itch (Heyer and Hornstein, 1999). Typically innocuous stimuli that elicit an urge to scratch in patients with AD include sweat and air coming into contact with

the skin after undressing. A complete list of triggers is listed in Table 1. After the skin is scratched, an eczematous rash erupts and initiates an itch–scratch cycle that is difficult to interrupt. AD typically appears only in areas that have been scratched and the distribution varies according to age: face, scalp, and extensor surfaces of extremities during infancy, flexural folds of extremities in older children and adolescents, and the hands of adults Leung and Bieher (2003).

The well-described features of AD permit the diagnosis to be made clinically. Hanifin and Rajka propose three essential diagnostic criteria: pruritis (*alloknesis*), the characteristic distribution of a chronic or relapsing eczematous rash, and personal or family history of atopy (Hanifin and Rajka, 1980). Other minor features of AD are listed in Table 2.

3. Immunopathology

Inclusion of the modifier “atopic” in the name implies that patients with the diagnosis of AD have a predisposition to produce IgE antibody in response to foreign proteins. In fact, approximately 80% of patients with AD have the “extrinsic” form of the disease which is characterized by IgE-mediated sensitization (Johansson et al., 2004; Sampson, 2001a; Bunikowski et al., 1999). The remaining patients have “intrinsic” AD and lack IgE-mediated sensitization but both variants are characterized by peripheral blood eosinophilia.

3.1. Biphasic T-cell inflammatory response

CD4⁺ T lymphocytes may be divided into one of two distinct phenotypes, Th1 or Th2, which differ in their cytokine profiles (Grewe et al., 1998). Th1 cells produce high levels of IFN- γ and

Abbreviations: AD, atopic dermatitis; APC, antigen presenting cell; CLA, cutaneous lymphocyte antigen; ECP, eosinophil cationic protein; EDN, eosinophil-derived neurotoxin; IDEC, inflammatory dendritic epidermal cells; LC, Langerhans' cell; MBP, Major basic protein; MDC, macrophage-derived chemokine; TARC, thymus and activation-regulated chemokine; TSLP, thymic stromal lymphopoietin; VCAM, vascular cell adhesion molecule.

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Table 1

The full spectrum of triggers of itch in AD

Xerosis	
All irritants	Lipid solvents (soaps, detergents) Disinfectants (chlorine in swimming pools) Occupational irritants Household fluids (juices from fresh fruits, meats)
Contact and aeroallergens	Dust mites (contact > aero) Furry animals (cat > dog) Pollens (seasonal) Molds Human dander (dandruff)
Microbial agents	Viral infections (especially upper respiratory infections) <i>Staphylococcal aureus</i> (either as a superantigen or pathogen) <i>Malassezia</i> yeast <i>Candida</i> (rarely) <i>Dermatophytes</i> (rarely)
Others	Foods (as contact irritants > vasodilators > allergens) Psyche Climate Hormones (menstrual cycle)

Not all patients with AD will be triggered by every stimulus. There will be subsets of patients with AD who will experience exacerbations by some triggers and not others (Beltrani, 1999).

Table 2

Minor features of AD (Boyano et al., 2001)

Xerosis	
Ichthyosis/palmar hyperlinearity/keratosis pilaris	
Immediate skin test reactivity	
Elevated serum IgE	
Early age of onset	
Tendency toward cutaneous infections (esp. <i>S. aureus</i> and <i>Herpes simplex</i>)/ impaired cell-mediated immunity	
Tendency toward non-specific hand or foot dermatitis	
Nipple eczema	
Cheilitis	
Recurrent conjunctivitis	
Dennie–Morgan infraorbital fold	
Keratoconus	
Anterior subcapsular cataracts	
Orbital darkening	
Facial pallor/facial erythema	
Pityriasis alba	
Anterior neck folds	
Itch when sweating	
Intolerance to wool and lipid solvents	
Perifollicular accentuation	
Food intolerance	
Course influenced by environmental/emotional factors	
White dermatographism/delayed blanch	

interleukin (IL)-2 which promote cell-mediated immune responses to intracellular pathogens and suppress Th2 responses. Th2 responses enhance humoral immune responses to extracellular organisms and also provide support for eosinophils and mast cells. Atopic patients favor a Th2 phenotype, characterized by secretion of IL-4, IL-5, and IL-13 and IgE antibody production in response to foreign proteins.

The immunopathology of extrinsic AD has been described in detail and varies according to the acuity of the individual lesions. Although the non-inflamed skin of patients with AD may appear grossly normal, it is hyperkeratotic, responds abnormally to various stimuli, and has a perivascular lymphocytic infiltrate not observed in normal skin (Leung and Bieber, 2003). The lymphocytes in unaffected skin of patients with AD demonstrate a Th2 phenotype, expressing more IL-4 and IL-13 when compared to non-atopic controls while expression of IL-5 and IFN- γ is low in both (Hamid et al., 1994, 1996) (Table 3).

Acute eczematous lesions appear erythematous, papular or papulovesicular, and weepy; they demonstrate epidermal hyperplasia and spongiosis with a CD4+CD45RO+memory T-cell infiltrate (Hamid et al., 1994). Acute lesions demonstrate a more pronounced Th2-induced inflammation. More cells in the acute lesions express IL-4 and IL-13 when compared to unaffected AD skin and more expressed IL-5 when compared to both unaffected AD skin and normal skin (Hamid et al., 1994, 1996). IFN- γ and IL-12 expression is low and does not differ between acute AD lesions, unaffected AD skin and normal skin.

The lesions of chronic AD appear much different, grossly and histologically, than acute lesions. The lichenified, thickened plaques are the result of excessive scratching; chronic lesions demonstrate acanthosis with minimal epidermal infiltration (Hamid et al., 1994). IL-4 and IL-13 expression in chronic lesions is lower when compared with acute lesions but still higher than that in unaffected AD skin and normal skin (Hamid et al., 1994). Additionally, chronic lesions have higher numbers of cells expressing IL-5 as compared with normal skin, unaffected AD skin, and acute lesions. As expected with increased IL-5 expression, lesions of chronic AD had greater numbers of EG2+ (activated) and MBP+ (total) eosinophils as compared with acute lesions while no EG2+ cells were detected in unaffected AD skin or controls.

Other cytokines with increased expression in chronic as compared with acute lesions of AD are of the Th1 type: IFN- γ , IL-12 and GM-CSF with IL-12 being instrumental for a transition to a Th1 response (Grewe et al., 1998). Generally, it is believed that Th2 cytokines initiate the acute inflammation of AD but Th1 cytokines are instrumental in maintaining chronic inflammation.

3.2. Other key cells

One feature of extrinsic AD that is instrumental in its pathogenesis is the upregulation of high affinity IgE receptors (Fc ϵ RI) on Langerhans' cells (LC) in the skin. The enhanced Fc ϵ RI expression by LCs is likely enabled by both increased serum IgE levels and increased synthesis of the γ chain of the receptor which is usually present in small amounts (Novak et al., 2003; Mudde et al., 1990). The main role of LCs is that of a professional antigen presenting cell (APC): to select foreign proteins, process them in a MHC II dependent manner, and stimulate a T-cell response to them, either in the skin or regional lymph nodes. This critical step mediates initial interactions between environmental allergens able to penetrate the defective skin barrier and resident LC in the skin. In AD, LCs influence the initial inflammatory response to environmental allergens by promoting a Th2 response from naïve T-cells if they are activated by allergen-specific cross-linking of IgE antibody bound to Fc ϵ RI (Mudde et al., 1990; Shibaki, 1998).

Inflammatory dendritic epidermal cells (IDEC) are another type of APC that are increased in lesional skin of AD. They are derived from monocytes and recruited from the peripheral blood by chemokines from Fc ϵ RI-stimulated LC (Novak et al., 2004). Similar to LCs, they demonstrate increased expression of the high affinity IgE receptor. However, allergen-specific cellular activation through this receptor on IDECs releases IL-12 and IL-18 which instead promote a Th1 response from naïve T-cells (Novak et al., 2004).

Table 3

Cytokine expression in AD

	IL-4	IL-13	IL-5	EG2+/MBP	IL-12	IFN- γ
Non-atopic control	–	–	–	–	+	–
Uninvolved AD skin	+	+	–	–	+	–
Acute AD	+++	+++	+	+	+	–
Chronic AD	++	++	++	++	++	+

Furthermore, IDECs stimulated through the FcεRI produce more IL-1α and MIP-1α/CCL-3 which may amplify immune-mediated reactions whereas LCs produce less pro-inflammatory cytokines and chemokines when stimulated in the same manner (Novak et al., 2004). Cutaneous APCs are ideally located to process antigens that penetrate the skin as well as those antigens that enter the circulation from respiratory or gastrointestinal mucosa and then travel to the skin. This model demonstrates how two different populations of APCs stimulated in the same manner are able to influence the biphasic or mixed inflammatory response characteristic of AD.

Tissue eosinophils as well as serum levels of eosinophil major basic protein (MBP), eosinophil-derived neurotoxin (EDN), and eosinophil cationic protein (ECP) are elevated in patients with acute and chronic AD (Kiehl et al., 2001; Pucci et al., 2000). The degree of peripheral blood eosinophilia and levels of the eosinophil granule proteins, indicating cellular activation and degranulation, correlate with disease activity as well as response to various therapies (Pucci et al., 2000; Magnarin et al., 1995; Czech et al., 1992). For example, patients with AD and food sensitization who were placed on elemental diets or total parenteral nutrition demonstrated an improvement in their rash that was accompanied by a decrease in activated peripheral blood eosinophils (Magnarin et al., 1995).

The Th2 cytokines IL-4 and IL-13 play a major role in recruiting eosinophils into inflamed tissue by upregulating vascular cell adhesion molecule-1 (VCAM-1) on the vascular endothelium, thereby allowing cellular migration into tissue (Schnyder et al., 1996). IL-4 levels and VCAM-1 expression correlate with tissue eosinophilia in patients with AD and in allergen-challenged skin chambers, supporting their contribution to the inflammatory cell infiltrate (Fernvik et al., 1999). Th2 lymphocytes also influence tissue eosinophilia by regulating IL-5, which promotes eosinophilopoiesis and inhibits apoptosis, and eotaxin, a selective chemoattractant for eosinophils. In both acute and chronic lesions, T-cells are the major source of IL-5. However, chronic lesions demonstrate greater numbers of IL-5 expressing activated eosinophils when compared to acute lesions. This relative increase suggests an autocrine effect of IL-5 in the transition from acute to chronic AD (Hamid et al., 1994).

The major role of eosinophils in the pathogenesis of AD is the release of cytotoxic proteins, lipid mediators, oxygen metabolites, and cytokines that promote tissue injury (Shinagawa et al., 2003). A murine model of allergen-induced AD demonstrated that IL-5 knockout mice lacked skin eosinophilia and had less epidermal and dermal thickening (Spergel et al., 1999). The authors hypothesize that it is the repair processes occurring after exposure to the toxic effects of eosinophil granule proteins that lead to the tissue hypertrophy characteristic of AD. IFN-γ knockout mice also had less skin thickening suggesting that cytokines present in both acute and chronic lesions of AD, IL-5 and IFN-γ, contribute to skin repair and hypertrophy. Another key role of eosinophils in AD is the production of IL-12, a cytokine that induces the transition from a Th2 to a Th1 phenotype and helps to maintain chronic inflammation (Grewé et al., 1998).

Epidermal keratinocytes respond to mechanical trauma, such as scratching, by releasing TNF-α, a pro-inflammatory cytokine (Nickoloff and Naidu, 1994). Keratinocytes from patients with AD then produce earlier and elevated concentrations of the chemokine RANTES/CCL5 in response to TNF-α or IFN-γ when compared with non-atopic controls or patients with psoriasis (Giustizieri et al., 2001). RANTES is a key mediator for both acute and chronic lesions because it is a chemoattractant for dendritic cells, eosinophils, Th1 and Th2 memory cells. Furthermore, keratinocytes from lesional AD skin produce thymic stromal lymphopoietin (TSLP) but this is absent in normal skin, unaffected skin of patients with AD, and lesions of nickel-induced allergic contact dermatitis or cutaneous lu-

pus erythematosus (Soumelis et al., 2002). TSLP is a potent activator of dendritic cells that are able to stimulate naïve T-cells to produce a unique cytokine phenotype: high amounts of IL-5, IL-13 and TNF-α, with moderate amounts of IL-4 (Soumelis et al., 2002). Whereas most dendritic cell activators result in the production of pro-inflammatory cytokines and prime naïve T-cells to a Th1 phenotype, dendritic cells activated by TSLP produced the lowest amounts of IL-10 and IFN-γ. In addition, these dendritic cells produced thymus and activation-regulated chemokine (TARC) and macrophage-derived chemokine (MDC) which preferentially recruit Th2 cells into sites of inflammation (Soumelis et al., 2002). These results support a scenario in which keratinocytes, the cells injured from scratching and directly interacting with the environment, produce an abnormal cytokine and chemokine profile that may initiate the allergic infiltrate seen in patients with AD.

4. Triggers

Another feature of AD is an intrinsically abnormal skin barrier that is only worsened by scratching. Lesional and nonlesional skin in patients with AD is characterized by increased water loss across the epidermis and xerosis (Werner and Lindberg, 1985). To add to the problem, the skin is deficient in ceramides, extracellular lipids in the outermost layer of the epidermis that absorb water and form a protective monolayer around corneocytes (Macheleidt et al., 2002). Combined, these abnormalities result in decreased water content in the skin and compromise the barrier function of the epidermis. This allows increased exposure to environmental irritants and allergens.

4.1. Allergy

Approximately 40–80% of children with AD have elevated serum IgE concentrations and most of them demonstrate sensitization to dietary and environmental allergens by immediate hypersensitivity skin prick testing (Johnson et al., 1974). However, the precise role that allergy plays in the pathogenesis of AD is still debated. It is evident from the complex immunopathology of AD that IgE-mediated responses to allergens are not exclusively responsible for the chronically relapsing rash. Part of the difficulty in establishing a cause and effect relationship may be that the causative agents are ubiquitous dietary proteins, perennial allergens, or unseen microbial skin contaminants that do not instigate obvious or immediate symptoms but still contribute to the inflammatory response in the skin. There is laboratory-based and clinical evidence to support the relationship between allergy and AD.

4.2. Foods

Casein and ovalbumin-specific T-cell clones have been generated from the peripheral blood of patients with AD and food allergy confirmed by oral food challenges (Reekers et al., 1996). All patients demonstrated a clinical deterioration of their AD after food challenge, supporting a causal relationship. Peanut-specific T-cell clones were also isolated from the skin of an infant with AD who had never knowingly ingested peanut (Van Reijssen et al., 1998). This case report illustrates the potential for atopic patients to become sensitized to peanut after unknown exposure to it, either orally or topically. The role of food allergy in AD is further supported by a pathophysiological mechanism to link food ingestion with cutaneous inflammation. In this regard, cutaneous lymphocyte antigen (CLA) is a homing receptor expressed on memory T-cells that infiltrate the skin. Stimulation of peripheral blood mononuclear cells with casein from patients with milk-induced AD or milk-induced urticaria selectively activated cutaneous lymphocyte antigen (CLA)-bearing CD4+ lymphocytes when compared with

non-atopic controls or patients with milk-induced gastrointestinal symptoms (Abernathy-Carver et al., 1995; Beyer et al., 2002). Therefore, expression of this homing receptor on antigen-specific T-cells establishes a mechanism that determines the skin as the target organ for abnormal immune responses to ingested proteins.

Not only do many patients with AD have detectable IgE antibody to food proteins, about 40% with moderate to severe disease have clinically relevant sensitization as demonstrated by positive double-blind, placebo-controlled food challenges to selected foods (Burks et al., 1998; Sampson, 1983; Sampson and McCaskill, 1985). Seventy-five to eighty percent of patients with both AD and food allergy demonstrated pruritic, morbilliform or maculopapular rashes within two hours of the food challenges and approximately half also developed gastrointestinal or respiratory symptoms. Seven foods account for almost 90% of the reactions: egg, milk, peanut, soy, wheat, fish, and cashew (Burks et al., 1998). These clinical observations support a link between food allergy and exacerbations of AD.

Although mast cells and basophils are not key effector cells for the development of AD, they may be important for those patients with both food allergy and AD. For example, plasma histamine levels were elevated in patients with AD after positive food challenges (Sampson and Jolie, 1984). Evidence to support the central role of basophils, rather than mast cells, in IgE-mediated food allergy is that basophils from patients with food allergy and AD have increased spontaneous release of histamine when compared with atopic controls without food allergy and normal controls (Sampson et al., 1989). After the causal food was restricted from the diet, the rate of spontaneous histamine release declined to control levels and the AD improved.

4.3. Aeroallergens

Foods are not the only IgE-mediated trigger for AD; sensitization to aeroallergens may also be important in the pathogenesis of AD. Patients with moderate–severe AD have a higher prevalence of IgE to dust mite, mold, and fungi (*Dermatophagoides pteronyssinus*, *Alternaria alternata*, and *Malassezia furfur*) when compared to asthmatics or non-atopic controls (Scalabrin et al., 1999). The role of dust mite allergy, after either inhaled or cutaneous exposure, has been studied in more detail. Dust mite sensitized patients with both asthma and AD developed cutaneous symptoms preceded by bronchoconstriction after double-blind placebo-controlled bronchial provocation with house dust mite (Tupker et al., 1996). Most patients developed new areas of pruritic erythema with or without new eczematous lesions while some had only exacerbations of an existing rash. Isolation of dust mite-specific T-cell lines of the Th2 phenotype from skin lesions induced by atopy patch testing provides evidence that the inflammatory response in AD may also be triggered by percutaneous exposure to aeroallergens (Van Reijsen et al., 1992).

4.4. Effect of allergen avoidance

Further evidence of the role of food allergy in the pathogenesis of AD requires improvement of the rash after dietary exclusion of causative foods. Studies to evaluate the effect of food elimination diets in AD are limited not only by study design, dietary compliance, control of environmental factors and other co-interventions, but also by the natural history of AD which is to improve over time. In this regard, many reports are favorable but not conclusive (Sampson, 1983; Sampson and McCaskill, 1985; Atherton et al., 1978; Juto et al., 1978). A randomized, blinded, controlled trial evaluated the efficacy of a four week egg-free diet in children less than two years of age with AD (Lever et al., 1998). Egg allergy was confirmed by double-blind, placebo-controlled food challenges at

the end of the trial in 22 of 32 subjects in the diet group and 20 of 30 subjects in the control group. Children following the egg-free diet demonstrated a significant decrease in affected skin and severity scores when compared with the control group. The improvement was greatest in those with more severe disease. Another prospective, randomized, double-blind controlled study evaluated the effect of dust mite avoidance on adults and children greater than seven years of age with AD (Tan et al., 1996). The investigators also demonstrated a significantly greater improvement in area affected and severity scores in the active group compared to the placebo. Taken together, these controlled studies support the role of both food and inhalant allergens in the pathogenesis of AD and avoidance of these allergens in its treatment.

4.5. *Staphylococcus aureus*

The role of *S. aureus* in the pathogenesis cannot be overlooked. Greater than 90% of patients with AD are colonized with these bacteria on their skin compared to only 5% of controls (Leung et al., 1993). Additionally, IgE antibody to *S. aureus* exotoxins was found in almost 60% of patients with moderate to severe AD (Leung et al., 1993). No IgE to the exotoxins was detected in normal controls, patients with respiratory allergy, or patients with psoriasis. Furthermore, detectable *S. aureus* exotoxins and the degree of sensitization to *S. aureus* exotoxins correlated with disease activity in children and adults (Bunikowski et al., 1999; Breuer et al., 2000). The exotoxins may contribute to the biphasic inflammatory response not only by allergen-specific activation of FcεRI-bearing effector cells but also in their capacity to act as superantigens for non MHC restricted activation of large numbers of activated T-cells (Leung et al., 1993; Bunikowski et al., 2000). Further evidence supporting bacterial infection in the pathogenesis of AD is clinical improvement after eradication with appropriate antibiotic therapy in patients who are infected with *S. aureus* (Boguniewicz et al., 2001).

5. Diagnosis

Skin biopsies are typically not necessary to diagnose AD because they fail to distinguish it from the many other rashes characterized by spongiosis. However, they may be useful to rule out non-eczematous lesions such as cutaneous T-cell lymphoma. Although the diagnosis of AD may be made clinically with a history and physical examination, the diagnosis of food allergy requires further investigation. Histories of food allergy are often unreliable and subject to observer bias (Sampson, 1983; Sampson and McCaskill, 1985). The clinical diagnosis of food allergy as a trigger for exacerbations of AD is especially complex because the rash is prone to wax and wane, often without identifiable triggers or changes in therapy. Additionally, frequent ingestions of common dietary proteins such as milk or egg may result in subclinical or mild symptoms. Both factors may mask the immediate cause and effect relationship between food ingestion and exacerbation of the rash. Furthermore, although these patients generate high total serum IgE levels, this only supports the diagnosis of AD, not food allergy. Tests that detect food-specific IgE, either allergy skin tests or serum levels, are difficult to interpret in the face of very elevated total serum IgE levels because IgE may cross-react with related foods or pollens rendering them clinically irrelevant. Therefore, clinical correlation or oral food challenges are required to distinguish between asymptomatic sensitization, detectable food-specific IgE in the absence of adverse reactions, from true clinical allergy.

Due to the high rate of asymptomatic sensitization, testing all children with AD for food allergy is not likely to be beneficial. When testing for foods is pursued, it should be limited to those foods historically associated with adverse reactions or to the seven

Table 4
Diagnostic food allergen-specific IgE levels (CAP FEIA System®)

Food	kU _A /L	Positive predictive value (%)
Egg	7	98
Infants ≤ 2 years	2	95
Milk	15	95
Infants ≤ 2 years	5	95
Peanut	14	100
Fish	20	100
Tree nuts	~15	~95

Adapted from Sampson (2004).

main food allergens. For children with moderate to severe AD or those with suspected food triggers, tests to detect food-specific IgE are a highly sensitive method for the initial evaluation. However, their poor specificity limits their usefulness as a single test to diagnose food allergy. In this regard, negative allergy skin prick tests or radioallergen sorbent tests (RAST) generally rule out food allergy but positive tests correlate poorly (about 50%) with results of double-blind, placebo-controlled food challenges, the gold standard for diagnosing food allergy (Sampson and Albergo, 1984). A modified, quantitative, *in vitro* assay, CAP System FEIA (Pharmacia Diagnostics; Uppsala, Sweden) is more sensitive and diagnostic levels have been established for a few foods (egg, milk, peanut, fish) that correlate well with positive outcomes on oral food challenges (Sampson and Ho, 1997; Boyano et al., 2001; Garcia-Ara et al., 2001; Sampson, 2001b) (Table 4).

The diagnosis of food allergy can be made in patients with positive skin tests and diagnostic IgE levels but those with positive skin tests and/or non-diagnostic IgE levels require oral food challenges to establish the diagnosis of food allergy. To ensure that the procedure yields meaningful information, the food in question must be completely eliminated from the diet for at least two weeks prior to challenge and the patient's rash should be under good control. Oral food challenges are especially helpful for patients with AD who have many positive allergy skin tests (mean 4.3) but have clinical reactions to only one or two foods (Sampson and McCaskill, 1985). Therefore, making dietary manipulations based only results of skin or *in vitro* testing would unnecessarily limit a child's diet.

6. Treatment and prevention

Conventional medical therapy for AD revolves around topical anti-inflammatory medications, corticosteroids or calcineurin inhibitors. Increasing hydration with frequent soaking baths and emollients helps restore the normal barrier function of the skin thereby decreasing absorption of irritants and allergens (Loden, 2003). Emollients have also been shown to reduce the need for topical corticosteroids in patients with mild or moderate AD (Lucky et al., 1997). Additional treatment focuses on suppression of the itch-scratch cycle; this is desirable but often difficult to achieve. Treatment with moisturizers and topical anti-inflammatory medications all reduce pruritis and some patients may achieve additional relief from routine use of an antihistamine (Imaizumi et al., 2003; Diepgen, 2002). Those patients whose pruritis is worse at night may derive the most benefit from sedating antihistamines by decreasing the sleep latency period.

After individual triggers for AD have been confirmed, avoidance measures may provide further benefit. Compliance with a food elimination diet is time-consuming, inconvenient, and requires a great deal of education and commitment on the part of the patient and all caregivers. Parents and caregivers must scrutinize all food labels for the presence of those allergens that should be avoided. In this regard, the Food Allergy and Anaphylaxis Network (<http://www.foodallergy.org>), a non-profit patient advocacy group, and

registered dietitians are invaluable resources for parents as well as physicians.

Recommendations to decrease exposure to dust mite allergen include: (1) placing allergen-impermeable encasements on the patient's mattress, pillows, and boxspring, (2) frequently washing bed linens in hot water, (3) vacuuming carpets weekly or removing them, and (4) use of air-conditioning to reduce indoor humidity (Leung et al., 2004). Although routine treatment for *S. aureus* would not be prudent, surveillance skin cultures are useful to identify those patients who are infected or colonized and likely to benefit from antibiotic treatment (Leung et al., 1993). Lastly, avoidance of known irritants such as wool clothing, emotional stress, or getting overheated may provide additional clinical benefit.

Given the rising prevalence of AD and all allergic diseases, interest in preventing its onset is increasing among parents and practitioners. Based on interpretations of existing studies for the primary prevention of food allergy in high-risk infants, the American Academy of Pediatrics has encouraged exclusive breastfeeding for 4–6 months and supplementing with or weaning to an extensively hydrolyzed casein formula. The most consistent finding benefit from prolonged breastfeeding and hypoallergenic diets in infancy is a decrease in infantile AD and cow's milk allergy (Lucas et al., 1990; Zeiger and Heller, 1995). However, dietary manipulations after 4–6 months of age such as delaying introduction of egg, cow's milk, peanut, and/or fish, are not likely to prevent or delay the development of atopy. The use of probiotics to induce a Th1 cytokine profile is an enticing approach to preventing atopic diseases but requires further study (Kalliomaki et al., 2003).

7. Summary

AD is a common chronic skin disorder in children. The hallmark feature of AD is alopecia. Therefore, treatment plans focus on reducing triggers of itch as well as use of anti-inflammatory agents. Although most patients with AD demonstrate allergic sensitization to foods and aeroallergens, IgE-mediated immune responses represent only one component of its complex pathogenesis. Given the increasing prevalence of AD, more effective treatment and/or prevention strategies require additional insight into this multifactorial disease.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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