

ATOPIC ECZEMA: GENETICS OR ENVIRONMENT?*

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Abstract: Atopic eczema (AE) is a multifactorial skin disease caused by a variety of factors such as genetic conditions, altered skin structure, immunologic deviations and environmental factors, among others. There are two main subtypes of AE, i.e. the IgE-associated ("atopic eczema") and the non-IgE-associated type ("nonatopic eczema") with different prognosis concerning the development of respiratory diseases ("atopy march"). Recently, it was demonstrated that Filaggrin (= filament-aggregating protein, FL) is a major gene for atopic eczema. Filaggrin binds to and aggregates the keratin cytoskeleton in the epidermis. Homozygous *FLG* mutation leads to complete loss of filaggrin expression in skin. Half or more of children with moderate to severe AE carry *FLG* mutations. Moreover, filaggrin loss-of-function mutations predispose to phenotypes involved in the atopy march. The altered skin structure and a deficiency in antimicrobial peptides favour colonization with *Staphylococcus aureus* and yeasts (*Malassezia* sp.). Sensitization to the yeast occurs almost exclusively in AE patients. *S. aureus* enterotoxins with superantigenic activity stimulate activation of T cells and macrophages. So far, AE skin lesions are orchestrated by the local tissue expression of proinflammatory cytokines and chemokines with activation of T lymphocytes, dendritic cells, macrophages, keratinocytes, mast cells, and eosinophils which lead to the skin inflammatory responses. From the therapeutic point of view, besides emollients and local corticosteroids, topic immunomodulatory drugs (tacrolimus and pimecrolimus) have substantially improved the treatment of AE.

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INTRODUCTION

Atopic eczema (AE) or atopic dermatitis (AD) is a chronic relapsing, inflammatory skin disease, characterized by typical distributed eczematous skin lesions, dry skin, intense pruritus and a wide variety of pathophysiologic aspects [4, 21, 22, 55]. Its worldwide prevalence is 10-20% in children and 1-3% in adults [33, 44, 48, 53]. During the past few years, an increased prevalence in highly industrialized countries has been recognized, particularly in the upper social

classes and in urban regions [12, 33, 44]. The manifestations of AE result from a complex interaction between environmental factors, pharmacological abnormalities, skin barrier dysfunction, susceptibility genes and immunological phenomena [4, 21, 22, 33, 45, 55]. Among several contributing factors, cutaneous hyperreactivity, inappropriate immune response to various bacteria, fungi and other microorganisms, and secondary infections appear to play an important role, not only in the underlying pathology but also as a factor responsible for sustained disease activity [31, 45].

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Two subtypes of atopic eczema

Although most patients with AE have high concentrations of total and allergen-specific serum IgE levels and positive skin prick and intracutaneous test reactions of the immediate type to common environmental allergens, a subgroup of AE patients, both children and adults, suffer from a skin disease which clinically resembles the skin lesions and distribution pattern of AE, but is not associated with sensitization to aero- or food allergens. As main clinical characteristic, these patients suffer from a “pure” type of AE, without previous or actual associated respiratory diseases [33, 53]. More than 20 years ago one of the authors (BW) was the first who recognized this clinical entity, and in analogy to the “extrinsic” and “intrinsic” types of asthma he proposed the term “intrinsic” type of AE as a counterpart to allergic, “extrinsic” type of AE [46, 47, 52]. Meanwhile, these two main subtypes are recognized by the allergists community. In a recent study, 259 adult patients with AE were investigated in order to reassess the prevalence and associated factors of these different forms [11]. After a thorough diagnostic workup there were 18 patients (6.9%) who fulfilled the criteria of “intrinsic” AE. After follow-up, four additional patients had developed respiratory allergies or IgE-mediated sensitizations resulting in an overall proportion for “intrinsic” AE of only 5.4%. In general, the prevalence rates of the non-IgE-associated AE tended to be higher in younger individuals when compared with adults. It might well be that in very young children a transient form of eczema exists for which the relatively high percentage of 15-45% iAE might be true. According to the new WAO nomenclature, the term “eczema” should be now used as the “umbrella” term to cover all different subtypes of atopic dermatitis, i.e. the IgE-associated (“atopic eczema”) type, and “nonatopic eczema”, the non-IgE-associated one [20]. In a European multicenter study focused on atopy patch testing (APT) with aeroallergens and food allergens in a total of 314 patients with AE in remission, clear-cut positive APT with all SPT and sIgE testing negative was seen in 7% of the patients, whereas a positive APT without SPT or sIgE for the respective allergen was seen in 17% of the patients [7].

The atopic march: atopic eczema and the development of asthma and hay fever

Studies of well-defined cases suggest that most cases (70%) become manifest within the first 5 years of life [44]. According to the medical literature, 30-60% of children with atopic eczema will develop respiratory diseases such as bronchial asthma, hay fever, or perennial allergic rhinitis at later age, the so-called atopic march [50]. The time course of the 3 main atopic diseases is also interesting in that it may inform about possible environmental exposures and possible time windows for subsequent allergic disease prevention [50]. Åberg and Engstrom’s study of 1,335

14-year-old children in the community with a past history of asthma, allergic rhinitis, or atopic eczema, suggested that eczema was the first disease to become manifest, followed closely by asthma (41% within a 2-year interval) [1].

Children with the non-IgE-associated variety of atopic eczema rarely get asthma

In the ETAC study, 34% of the children with eczema were not atopic in terms of IgE not being greater than 30 kU/l and negative skin prick tests to the tested allergens [9]. The ETAC multicenter double-blind, randomized, placebo-controlled trial with cetirizine set about comparing the incidence of symptoms of asthma in 817 atopic eczema infants aged 1-2 years with a history of atopic diseases in parents or siblings, who took daily cetirizine or placebo for 18 months. Although there were no differences in the cumulative prevalence of asthma between active and placebo treatment in the intention-to-treat population ($p=0.7$), those infants with sensitivity to grass pollen, house dust mite, or both, who were treated with cetirizine were significantly less likely to have asthma compared with those treated with placebo for 18 months ($p=0.005$ and 0.002 , respectively) [9, 41]. In the 18 months of posttreatment follow-up, this favourable effect was sustained for the grass pollen-sensitized infants over the full 36 months ($p=0.008$). In the house dust mite-sensitized group, there was a gradual narrowing of the difference between active and placebo treatment in terms of cumulative prevalence of asthma at the end of 36 months but no evidence of a rebound immediately after the treatment stopped ($p=0.04$). In the placebo population, there was a significantly higher risk of developing asthma in those sensitized at baseline to egg (relative risk 1.4; 95% CI 1.1-1.7), house dust mite (relative risk 1.6; 95% CI 1.3-1.9), grass pollen (relative risk, 1.7; 95% CI 1.4-2.17), or cat (relative risk 1.5; 95% CI 1.2-1.9). Earlier and persistent sensitization conferred a higher risk than transient or later sensitization. Caution has to be exercised in interpreting such *post hoc* subgroup analyses, but the magnitude of the benefit (relative risk for developing asthma when treated with cetirizine 0.6, 95% CI 0.4-0.9) for those infants sensitized to house dust mite or grass pollen was impressive, and certainly warrants further testing in future trials to substantiate this finding [41].

Two other studies suggested that children with this non-atopic variety of atopic eczema at age 2 rarely get asthma [25, 51]. Novembre *et al.* evaluated 77 children who had atopic eczema at the age of 2 years; 9 years later, at the age of 11, 64% belonged to the early atopic group (EA), i.e., they were already sensitized at the age of 2 years, 21% developed atopy later, at age 11 (late-onset atopic, LOA), and 15% remained an “intrinsic” type (“non-IgE-associated”) (IAE) [25]. The persistence of atopic eczema at the follow-up was 67% higher in the IAE than in the EA (43%) or LOA (44%) ($p<0.0002$) group. The prevalence of bronchial asthma at the follow-up was with 60% higher in the

EA group compared with 25% in the LOA group. None of the nonatopic children developed asthma by age 11. In our follow-up study on 22 children with atopic eczema seen at the age of 2-4 years, at re-evaluation 8 years later, 68% of the children still suffered from atopic eczema, 45% from asthma, and 41% from seasonal rhinoconjunctivitis [51]. The percentage of IE sensitization against common inhalant allergens (Sx1, CAP) increased from 50-80% and against food (fx5, CAP) the percentage decreased from 41-27%. Four of the 7 children with intrinsic atopic eczema were still without any detectable sensitization, but 3 had evolved to an extrinsic type of atopic eczema. One of them developed asthma; however, the risk of developing asthma is much higher in the extrinsic type (9/15; 60%) than in the intrinsic type at age 2 years (1/7; 14%).

Genetics

AE is a genetically complex disease that has a high familial occurrence. Twin studies of AE have shown concordance rates of 0.72-0.86 in monozygotic, and 0.21-0.23 in dizygotic, twin pairs, indicating that genetic factors play an important role in the development of this disease [54]. No one gene can be implicated as the gene responsible for the development of AE [8]. Genetic approaches highlight the search for disease specific AE alleles, as well as identifying overlapping genes associated with other allergic characteristics and disorders. This process has been reviewed recently [2, 6]. A European study of about 200 families with affected sibs looked at phenotypes for AD, as well as allergic sensitization, and found a region of highest linkage at human chromosome 3q2 (ref. in [2]). Another study of 148 nuclear families in which AW, as well as other intermediate phenotypes, including asthma phenotype and total serum IgE level, were examined identified association with 5 regions, including 1q21, 17q25, 20p, 16q, and 5q31 (ref. in [27]). A Swedish study of 197 affected sib pairs identified 4 phenotypes, as well as 11 locations, associated with all of the different phenotypes that ranged from severity of AD, specific IgE, and direct diagnosis of AD (ref. in [2]). Finally, a Danish study looked at a small number of affected sib pairs and found association with 3 locations within the genome [2]. However, not all of these locations are highly robust, and most of these associations from genome-wide screens might not yield effective identification of specific genes when examined in more detail [2].

Filaggrin is a major gene for atopic dermatitis and filaggrin loss-of-function mutations predispose to phenotypes involved in the atopic march

Filaggrin (filament-aggregating protein) and its gene, *FLG*, is located with many others involved in terminal differentiation, in the epidermal differentiation complex on chromosome 1q21. The initial product of the *FLG* gene, profilaggrin, is the main constituent of keratohyalin granules

and, upon terminal differentiation, is proteolytically cleaved into multiple copies of filaggrin peptide. Filaggrin binds to and aggregates the keratin cytoskeleton, which in these upper granular cells has been strongly anchored to the cell membrane by increasing numbers of desmosomal proteins. Filaggrin collapses the cytoskeleton, resulting in flattening of keratinocytes into squames [17, 19]. It was recently demonstrated that the filaggrin gene (*FLG*) is a major player in AE, showing that a heritable epidermal barrier defect (see below) is responsible in many cases of AE. [17, 19, 24, 27]. Moreover, it was also shown that *FLG* mutations are a major risk factor for eczema-associated asthma, with lower penetrance than AE alone [24]. On the basis of our current early data, the authors estimate that half or more of children with moderate to severe AD carry *FLG* mutations, and that maybe as much as 20% of all asthma involves these gene defects, but, importantly, only asthma secondary to AE.

Skin barrier dysfunction

AE is characterized by dry skin, even involving non-lesional skin and increased transepidermal water loss. In particular, ceramides serve as the major water-retaining molecules in the extracellular space of the cornified envelope, and the barrier function of these complex structures is provided by a matrix of structural proteins, which are bound to ceramides. As a result of the reduced activity of acid ceramidase and decreased levels of ceramides, there are decreased levels of sphingosine in the stratum corneum of both lesional and nonlesional skin in patients with AE [26]. A reduced content of ceramides has been reported in the cornified envelope. This favours colonization with *Staphylococcus aureus* (*S. aureus*) because under normal circumstances, sphingosine exerts a potent antimicrobial effect on *S. aureus* (see below). Moreover, changes in stratum corneum pH levels might impair lipid metabolism in the skin. Over-expression of stratum corneum chymotryptic enzyme is also likely to contribute to the breakdown of the AE epidermal barrier [2]. This would allow penetration of irritants and allergens which trigger an inflammatory response, thus contributing to the cutaneous hyperreactivity characteristic of AE. The increased susceptibility to irritants in patients with AE might therefore represent a primary defect of epidermal differentiation compounded by the presence of inflammation-induced skin damage.

Skin infections in atopic eczema

More than 20 years ago we reported on a massive skin colonization with *S. aureus* in AE patients in comparison with healthy controls and psoriatic patients, as well as on an altered immunity to *S. aureus* in AE which lead to secondary infections (impetiginization and superficial pustules) [12, 13]. The immune response to *S. aureus* is characterized by a selective hyporesponsiveness to purified *S. aureus* cell walls in delayed type hypersensitivity skin

reaction and by the presence of IgE to cell walls and soluble antigens of *S. aureus* in patients with high IgE levels [14]. During recent years there has been considerable interest in the mechanisms and trigger factors underlying the increased microbial colonization of atopic skin [3-5, 31]. There is now evidence that *S. aureus* itself stimulates the hydrolysis of ceramides by bacterial derived ceramidase in atopic skin. Furthermore, the cell membrane of *S. aureus* contains adhesins for epidermal and dermal laminin and fibronectin. They are uncovered in lesional skin, which enhances *S. aureus* cutaneous adherence. The precise mechanism by which *S. aureus* gains access to the dermis is unknown, but it is suggested that IL-4, produced by T helper type 2 cells, induces fibronectin synthesis, which in combination with plasma exudation of fibrinogen, allows *S. aureus* to bind to the skin. *S. aureus* is able to encase itself in a kind of biofilm composed of a hydrated matrix of polysaccharides (glycocalix) and proteins, which supports cell adhesion [3]. Once having gained access to atopic skin, colonies of *S. aureus* grow in an uncontrolled manner because of the missing, naturally occurring, antimicrobial peptides such as β -defensin 2 and cathelicidin that are expressed by keratinocytes [26].

Immunologic network in IgE-associated atopic dermatitis

In patients with atopic dermatitis, T-cells in the blood show increased expression of cutaneous lymphocyte antigen (CLA) which, in conjunction with presence of T-cell attractant chemokine (CTACK), leads to a skin homing of lymphocytes. In the presence of antigen-presenting cells (APC) of the skin, i.e. dendritic cells and Langerhans cells, T-cells can be primed via presentation of processed antigens. In the following initial phase, activated T-cells express cytokines of the Th-2 class that foster, via IL-4 and IL-13, an IgE class switch; in addition, eosinophilic granulocytes can be attracted and activated via IL-5. This specific milieu leads, in turn, to reduced expression of cathelicidines and β -defensins, proteins with antimicrobial activity, allowing thus a deleterious outgrowth of bacteria, viruses, and fungi on the skin of the patient. In a later, chronic state, IFN γ is the predominant cytokine that leads to a skewing towards Th-1 milieu. IFN γ may induce apoptosis in keratinocytes which may be a key event in the eczematous process in atopic dermatitis. Importantly, Th-1 and Th-2 phases/settings are not mutually exclusive, as acute exacerbation may occur in chronic diseases of atopic dermatitis. Eosinophilic granulocytes, APC and T-cells (e.g. via IL-12) have been postulated to be involved in the switching between the two phases.

***Staphylococcus aureus* superantigens**

S. aureus produces immunomodulatory toxins such as staphylococcal enterotoxins A and B and toxic shock syndrome toxin-1 in up to 65%, which are high-molecular

weight proteins with superantigenic properties (Review in: [31]). The potent immunostimulatory properties of superantigens are a direct result of their simultaneous interaction with the V β domain of the T-cell receptor on lymphocytes and the MHC class II molecules on the surface of antigen-presenting cells (APCs) and macrophages. Superantigens also induce T-cell skin homing by an upregulation of cutaneous lymphocyte-associated antigen (CLA) and differentiation through cytokine production (IL-4 and IL-10), which may contribute to the induction or enhancement of skin inflammation. It was demonstrated that T regulatory cells (CD4+CD25+) are substantially increased in AE, but lose their immunosuppressive activity by stimulation by bacterial antigens. Such T regulatory cells might thus not function properly in skin colonized by superantigen-producing *S. aureus*, which could in addition increase other T-cell activation and the inflammatory reaction in AE. Superantigens can also induce glucocorticosteroid insensitivity, which encompasses a variety of mechanisms by which superantigens increase AE severity and may be an explanation for the difficulties in the management of AE. Moreover, *S. aureus* induces the synthesis of specific IgE antibodies directed against staphylococcal superantigens in approximately 57% of AE patients, in contrast to healthy individuals, in whom these IgE antibodies are extremely rare. Severity of disease correlates better with toxin-specific IgE levels, rather than total serum IgE levels [4, 21, 22].

Fungal colonization with *Malassezia*

The lipophilic yeasts *Malassezia* species, in particular *Malassezia sympodialis*, *Malassezia globosa* and *Malassezia restricta*, are found on the body surface in humans, typically predominating in seborrheic skin sites such as the head and neck, and occur in up to 90% of patients with AE in contrast to 34% in healthy controls (Review in [5, 9, 31, 34-36]). More interestingly, only AE patients (61% of 55 patients) and non-patients with either asthma, allergic rhinitis, urticaria, food allergy and healthy controls, were sensitized to *M. sympodialis* [9, 34, 36]. Therefore, IgE sensitization to *M. sympodialis* might serve as an immunologic marker for AE. The main cause for this specific sensitization may be the disrupted skin barrier facilitating allergen uptake. So far 13 allergens of *Malassezia* (Mal s1-13) have been characterized, 8 of which have been produced by recombinant technology for diagnostic purposes (rMal s1, rMal s5-11) [35, 36]. Fischer *et al.* performed SPT and APT with different recombinant allergens in AD patients, and showed that there is a preferential sensitization to rMal s5, rMal s6 and rMal s9 [9]. Interestingly, in the "intrinsic" type of AE we have also found IgE- and T cell- mediated sensitization against *M. sympodialis*: in 7 out of 15 patients (47%) by ImmunoCAP, in 5 of 15 patients by SPT and APT and in 6 out of 15 patients in peripheral blood mononuclear cell proliferation assays [9].

Autoreactivity in atopic dermatitis – induced by skin fungi?

Autoreactivity to human proteins has been postulated as a decisive pathogenetic factor for patients with AE on the basis of the detection of IgE directed against various proteins *in vitro* [23]. An essential, stress-inducible enzyme – human manganese superoxide dismutase (hMnSOD), known for its autoreactivity in allergic bronchopulmonary aspergillosis (ABPA) – was found to act also as an autoallergen in a subset of patients with AE, clearly demonstrated by eczematous reactions through atopy patch tests (APT) with the application of recombinant hMnSOD [23]. Human MnSOD also induced positive skin prick test results in 29 of 67 patients with AE in addition to IgE- and T cell-mediated *in vitro* reactivity. Such reactivity was also found in patients with non-atopic eczema and strongly correlated with disease severity. All patients reacting to hMnSOD were sensitized against the skin-colonizing yeast *Malassezia sympodialis*, known for its pathogenetic role in AE. MnSOD of fungal origin and MnSOD of human origin show a strong structural relationship. Thus, sensitization is most likely induced by exposure to environmental fungal MnSOD of *M. sympodialis*, resulting in molecular mimicry due to secondary autoreactivity with its human counterpart and might contribute to the perpetuation of the inflammatory skin reactions [23, 35].

Other triggers of atopic eczema

According to the recent Consensus Report of the EAACI, AAAAI and PRACTAL [2] the following endogenous and exogenous factors may aggravate or trigger the AE [2].

Stress. Stress-induced immunomodulation is altered in patients with AE, but the exact mechanisms are not well understood. This phenomenon might be mediated by neuroimmunologic factors, such as neuropeptides, which can be found in the blood and within the epidermal nerve fibres in close association with epidermal LCs. Increased levels of nerve growth factor and substance P can be found in the plasma of patients with AE and correlate positively with the disease activity. Enhanced levels of brain-derived growth factor can be detected in the sera and plasma of patients with AD. Brain-derived growth factor has been shown to reduce eosinophil apoptosis while enhancing chemotaxis of eosinophils *in vitro*.

Food allergens. Placebo-controlled food challenge studies have demonstrated that food allergens can induce not only immediate type I reactions, such as urticaria, angioedema, colics, asthma, anaphylaxis, etc., but also eczematous skin rashes in a subset of infants and children with AE [42]. In some patients, urticarial reactions can trigger the itch-scratch cycle that flares this skin condition. Food allergen-specific T cells have been cloned from the skin lesions of patients with AE, providing direct evidence that

foods can contribute to skin immune responses [38]. In addition, it is well established that food can exacerbate AE, both through allergic and non-allergic hypersensitivity reactions (e.g., histamine intolerance). Furthermore, direct contact with the skin (e.g., in the preparation of meals or when feeding infants) might be an important factor for the aggravation of eczema (protein contact dermatitis) [49].

Inhalant allergens. Beyond the age of 3 years, food allergy is frequently outgrown, but sensitization to inhalant allergens is common. Already in the sixties it was shown that pruritus and skin lesions can develop after intranasal or bronchial inhalation challenge with aeroallergens in patients with AE, and seasonal flare-ups of AE can be triggered by exposure to pollen [47]. Epicutaneous application of aeroallergens (e.g., house dust mites, weeds, animal danders, and moulds) by means of the APT on uninvolved skin of patients with AE elicits eczematous reactions in a subset of patients with AE [7]. In this study, previous eczema flares, after contact with specific aeroallergens, were reported in 30% to cat epithelia and in 34% to house dust (*D. pteronyssinus*) of AE patients. Seasonal flares to birch or grass pollen were reported in 17-20%. The isolation from AE skin lesions and allergen patch test sites of T cells that selectively respond to *Dermatophagoides pteronyssinus* (Der p 1) and other aeroallergens supports the concept that immune responses in AE skin can be elicited by inhalant allergens [29, 32].

Irritant factors. Frequently, rough or woolly clothing leads to mechanical irritation and exacerbation of AE. Chemical irritants like skin-cleansing agents should also be considered but can only be satisfactorily identified by means of avoidance.

Contact allergens. The role of atopic eczema (AE) as a risk factor for the development of allergic contact dermatitis is discussed controversially, as well as its influence on patch test results due to increased irritability. In a recent study, the authors analysed the pattern of positive patch test results to most frequent contact allergens in patients with AE (n=9,020) and age matched nonatopic (n=15,263) individuals [15]. The pattern and the frequencies of the observed sensitizations did not differ greatly from non-atopic individuals. Bufexamac is an exception: in AE patients sensitization is observed 3 times more often. For the other substances tested, only minor differences were detected. Moreover, the frequencies of single, double or polyvalent sensitizations were nearly identical between the 2 groups. The analysis of the anatomical sites of dermatitis shows differences between the groups: in AE patients, the face (7.2%) and hand dermatitis (6.6%) was more common, and leg dermatitis (4.0%) less common. Analysis of occupation, suspected allergen source, and accompanying factors revealed no major differences between the two groups. Therefore, the chronic and long-term exposure to external

drugs and emollients presumably carries a risk for sensitization against specific contact allergens in AE patients. However, the sensitization of contact allergens differs surprisingly little between patients with or without AE.

Therapeutic long-term options and anti-inflammatory approaches

The basic therapy for AE should comprise optimal skin care, addressing the skin barrier defect with regular use of emollients and skin hydration, along with identification and avoidance of specific and non-specific trigger factors [2]. Long-term management with topical steroids alone should be avoided because of their numerous side-effects and the high risk of *S. aureus* developing glucocorticoid insensitivity (see above). The newer calcineurin inhibitors (tacrolimus and pimecrolimus) inhibit the transcription of various T helper types 1 and 2 cytokine genes, and seem to block *S. aureus* superantigen-triggered T cells, reduce colonization with *S. aureus* efficiently, and are safe to use for facial and eyelid eczema [17-30, 39]. Topical fucidic acid reduces the prevalence and population density of *S. aureus* without increasing fucidic acid-resistant *S. aureus* [28]. A new approach to AE treatment are silver-coated textiles and a silk fabric coated with AEGIS AEM 5772/5, an antimicrobial substance, which efficiently reduce *Staphylococcus aureus* colonization in patients with AE and eczema severity [37]. Anti-fungal therapy by oral itraconazole has been demonstrated in randomized, double-blind, placebo-controlled trials in patients suffering from head and neck dermatitis [40]. This study shows that the antifungal systemic treatment has a significant Scoring Atopic Dermatitis (SCORAD) Index reduction of AE, irrespective of the presence of detectable IgE sensitization. The use of ketoconazole or itraconazole, both inhibiting IL-4 and IL-5 production and ergosterol synthesis, in AE patients may decrease *Malassezia*- and *C. albicans*-specific IgE and total IgE levels which correlate with the improvement of clinical symptoms [36]. However, although this and other studies indicate that anti-fungal treatment of both *Malassezia* and *C. albicans* may be effective in the treatment of some patients with AE, further controlled studies are needed to assess the real benefit of such therapies for generalized treatments. To date, hyposensitization is not an established instrument for the treatment of AE: double-blinded controlled trials have failed to show consistent efficacy of immunotherapy in the treatment of AD [2]. A recent randomized multicentre trial investigated the efficacy of an allergen specific immunotherapy of house dust mite preparations in patients with AD sensitized to house dust mite allergens for 1 year, and revealed a dose-dependent effect on the disease [43].

Despite the progress in pharmacologic treatment of AE, fundamentally, each patient with AE should be educated on various aspects of the disease [2]. For economic and practical reasons, structured education will target patients

with moderate and severe chronic AE and their parents. Structured patient education should enable both the patient and the parent to have realistic, short-term goals, enter a process of problem solving, accept living with their disease, appropriately use available social support, and enhance their own motivation for therapy. So far, patient education is still very important in the management of the disease since it often follows an unpredictable course [55].

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