

New visions for atopic eczema: An iPAC summary and future trends

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Atopic eczema (AE) is a chronic inflammatory skin disease characterized by pruritus, dry skin and an ongoing course of exacerbations and remissions. AE is a common disorder in children with a worldwide cumulative prevalence of 15–20% in this age group. AE has a strong familial predisposition. While AE is a complex disease with multiple gene involvement, recent interest has focused on genes involved in skin barrier/epidermal differentiation and in immune response/host defense. Recent developments and future directions on pathogenesis, diagnosis, natural course and prognosis are discussed.

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Atopic eczema (AE) is a common, intensely pruritic inflammatory skin disease that may result from complex and incompletely defined interactions between genetic susceptibility genes resulting in a defective skin barrier, abnormalities in the innate immune response and an increased immunologic response to allergens and microbial antigens (1). The prevalence of AE is high in infancy. The natural course of most of the children with AE is remission in early childhood. As demonstrated with birth-cohort studies, sensitization pattern and severity determine the prognosis and risk for development of asthma and respiratory allergies. Here we address recent developments and future directions.

Definition

The European revised nomenclature has proposed the term atopic *eczema* to replace the term atopic eczema/dermatitis syndrome (AEDS) (2). While childhood eczema has been classified into two types depending on the atopic status, there is increasing evidence for an overlap between

immunoglobulin E (IgE) and non-IgE-mediated mechanisms (3).

Epidemiology

Epidemiology of AE

AE is a chronic inflammatory skin disease characterized by pruritus, dry skin and an ongoing course of exacerbations and remissions (4, 5). AE is a common disorder in children with a worldwide cumulative prevalence of 15–20% in this age group (6). Around 50% of the cases are diagnosed by the age of 1 yr; with one-third of patients having disease which persists throughout adulthood. As demonstrated by the ISAAC study part three, the prevalence of AE is increasing, when patients are studied at 6 and 13 yr of age (7).

Epidemiology of food allergy in children with AE

The role of food allergy is greater in infants compared with adults whose eczema is rarely

influenced by dietary factors (2%) (8). The prevalence of food allergy in infants with AE has been estimated at up to 40% (9, 10). Foods may directly provoke flares of AE through non-IgE-mediated food allergy. A position paper of the EAACI and GA²LEN has been published recently to point out the role of food allergens in eczematous reactions in AE (10). In patients with AE, the flare-up of AE after hours or days can be isolated or associated with immediate IgE-mediated reactions such as urticaria, gastrointestinal, respiratory symptoms or even anaphylaxis.

Based on the literature from the past 10 yr, in which food allergies were proven by the gold standard of double-blind placebo-controlled food challenges, the prevalence of food allergy in infants with AE was reported to range from up 33% to 63% (11–18) (Table 1).

Unfortunately, published studies do not permit ready comparison owing to the various definitions used for AE (19) or atopy (use of allergy testing) or the types of study (retrospective, prospective or case-controlled studies). Birth-cohort studies are needed because they offer the strongest design to explore the temporal relationship between atopy and AE.

New insights into the etiology and pathogenesis

As the pathophysiology of AE was extensively reviewed in the PRACTALL consensus report (8), here we address only select recent developments.

Genetic factors

AE has a strong familial predisposition. Screening of families with AE has implicated chromosomal regions that overlap with inflammatory skin diseases such as psoriasis. These studies, along with candidate gene studies, have provided novel insights into the pathogenesis of AE. While AE is a complex disease with multiple

gene involvement, recent interest has focused on genes involved in skin barrier/epidermal differentiation and in immune response/host defense (20).

As discussed next, loss-of-function mutations of the epidermal barrier protein, filaggrin, have been demonstrated to be a major predisposing factor for AE (21). The filaggrin gene is found on chromosome 1q21 which also contains genes of the epidermal differentiation complex that are expressed during the terminal differentiation of the epidermis. Genes for loricrin and S100 calcium-binding proteins are also found here. Patients with AE have been shown to have upregulation of S100 calcium-binding proteins and downregulation of loricrin and filaggrin. However, filaggrin mutations can occur in patients with ichthyosis vulgaris who do not have AE and the majority of patients outgrow their skin disease, thus other gene and their products must be involved in the pathology of AE. Candidate gene approaches have implicated variants in the *SPINK5* gene expressed in the uppermost epidermis where its product, LEKT1 inhibits two serine proteases involved in desquamation and inflammation, stratum corneum tryptic enzyme (SCTE) and stratum corneum chymotryptic enzyme (SCCE). SCTE and SCCE expression is increased in AE and an imbalance of protease vs. protease inhibitor activity may contribute to skin inflammation in AE (22).

Chromosome 5q31-33 contains a clustered family of functionally related cytokine genes expressed by Th2 cells including interleukin (IL)-3, IL-4, IL-5, IL-13 and GM (Granulocyte macrophage)-colony-stimulating factor (CSF). A case-control comparison has suggested a genotypic association of the T allele of the –590C/T polymorphism of the IL-4 gene promoter region with AE. Because the T allele is associated with increased IL-4 gene promoter activity when compared with the C allele, this suggests that genetic differences in transcriptional activity of the IL-4 gene influence AE predisposition. In addition, the observed association of AE with a gain-of-function mutation in the alpha subunit of the IL-4 receptor provides additional support for the role of IL-4 gene expression in AE. Functional mutations in the promoter region of the C–C chemokines, RANTES and eotaxin, as well as variants in IL-13, the beta subunit of FcεR1, the high-affinity receptor for IgE on basophils and mast cells suggest common genetics with other atopic diseases. Finally, association of AE with polymorphisms of the *NOD1* gene which encodes cytosolic pathogen recognition receptor

Table 1. Prevalence of food allergy in children with eczema (food allergy proved by double-blind placebo-controlled food challenge)

Authors	Year	n	Food allergy (%)
Sampson (11)	1985	113	56
Burks (12)	1988	46	33
Sampson (13)	1992	320	63
Eigenmann* (14)	1998	63	37
Burks (15)	1998	165	39
Niggemann (16)	1999	107	51
Eigenmann* (17)	2000	74	34
Breuer (18)	2004	64	46

*Unselected children with atopic eczema.

and Toll-like receptors suggest an important role for host defense genes in the pathogenesis of AE.

Skin barrier function abnormalities

AE is associated with a number of abnormalities in skin barrier function owing to the mutations in cornified envelope genes, reduced ceramide levels, increased levels of endogenous proteolytic enzymes and enhanced transepidermal water loss (23, 24). Several recent studies have now shown that mutations in the gene encoding the filaggrin protein are a major predisposing factor for atopic dermatitis (AD; 21, 25). Filaggrin is a key epidermal protein, essential for the formation of a normal skin barrier. While these mutations were originally reported in European Caucasian patients, other mutations have been identified in Asian patients with AE (26). These mutations may predispose a subset of patients to early onset, severe and persistent AE (27, 28). Of note, mutations in filaggrin have also been associated with increased risk for asthma, but only in patients with AE (29). As most AE patients studied to date do not have identified filaggrin mutations, other mutations in the filaggrin gene or other barrier protein-related genes will likely be identified. Furthermore, many patients' AE has a later onset and a number of patients appear to outgrow their AE. A recent study showed that Th2 cytokines IL-4 and IL-13 can downregulate filaggrin protein expression in patients with AE (30).

In addition, abnormalities in stratum corneum chymotryptic enzyme, a serine protease localized in the extracellular space of the stratum corneum specific for keratinizing cells undergoing desquamation have also been demonstrated in AE (22). This results in increased production of the stratum corneum chymotryptic enzyme protease and premature breakdown of the skin barrier. Soaps and detergents can increase skin pH, leading to increased activity of endogenous and exogenous proteases from dust mites or *Staphylococcus aureus*, which can also contribute to epithelial damage. Importantly, the abnormal epidermal barrier may play a critical role in allergic sensitization, allowing allergen penetration through the skin, as well as microbial colonization, eliciting a cascade of immune responses (31). In a significant number of children with AE, these abnormalities precede the development of asthma and allergic rhinitis in the 'atopic march' (32). Thus, early intervention strategies to protect or repair the epidermal barrier may be important not only for optimal management of AE but also to prevent the

subsequent development of asthma and allergies in at-risk patients.

Microbes and antimicrobial peptides in AE

Most patients with AE are colonized by *S. aureus*, usually by toxin-producing organisms (1). Toxins secreted by *S. aureus* have properties of superantigens, which can activate high numbers of T cells and other immune cells resulting in an exaggerated inflammatory response. Patients with AE can make specific IgE antibodies against staphylococcal toxins, which correlate with disease severity. Superantigens can subvert T-regulatory cell activity, augmenting inflammation (33) and induce corticosteroid resistance, complicating response to therapy (34).

The skin of patients with AE has been found to be deficient in antimicrobial peptides, one of the components of the innate immune response essential for host defense against bacteria, fungi and viruses (35, 36). Keratinocytes are the primary source of antimicrobial peptides in the skin and up-regulation of Th2 cytokines in AE has been shown to suppress synthesis of antimicrobial peptides by keratinocytes (35, 37). This innate immune system abnormality may explain the increased susceptibility of patients with AE to skin infections by various pathogens. Of note, patients with AE have an increased propensity towards disseminated infections with herpes simplex and vaccinia viruses (38). Even patients with past histories of AE remain at risk for eczema vaccinatum and household contacts should not be vaccinated in any pre-exposure vaccination strategy (39). As such, smallpox vaccination is contraindicated in patients with AE unless there is imminent danger of exposure to smallpox. In a recent study, the skin of patients with AE was shown to exhibit increased vaccinia virus replication and decreased expression of LL-37, an antimicrobial peptide, which can kill vaccinia virus compared with normal or psoriatic skin (40). IL-4 and IL-13 enhanced vaccinia virus replication while downregulating LL-37 in vaccinia virus-stimulated keratinocytes. Neutralizing IL-4 and IL-13 in AD skin augmented LL-37 and inhibited vaccinia virus replication suggesting new therapeutic strategies.

Interventional prevention

The primary prevention of AE requires an intervention that starts early, i.e. pre- or directly postnatally. There is evidence that avoidance of cow's milk and use of hydrolyzed formula, if breastfeeding is insufficient, during the first

4 months of life can prevent AE in predisposed children (GINI, German Infant Nutritional Intervention Program). For infants with two parents suffering from eczema themselves, only extensively hydrolyzed formula was found to significantly reduce the incidence and prevalence of early AE in the first year of life, while infants with one or two atopic parents (asthma, allergic rhinitis) were less likely to develop eczema if they were fed partially or extensively hydrolyzed formula compared with infants who received normal cow's milk formula during the first four months of life. After 3 yr, however, only an effect for extensively hydrolyzed formula was found for the reduction of eczema prevalence. No influence on asthma was observed (41). High maternal intake of margarine (odds ratio, OR 1.49; 95% confidence interval, CI 1.08–2.04) and vegetable oils during the last 4 wk of pregnancy was positively associated and high maternal fish intake (aOR 0.75; 95% CI 0.57–0.98) was inversely associated with eczema during the first years of life in the offspring (42). The introduction of solids beyond the fourth month of life for the prevention of AE is not supported by data, although it is often recommended (43).

The avoidance of mite allergens early in life does not seem to have an impact on the prevalence of eczema in the first year of life (MAAS) (44). Based on epidemiological findings the hygiene hypothesis suggested that early modulation of the immune system using the immunomodulatory capacity of probiotic bacteria may help to reduce the onset of eczema in infancy. A review by Susan Prescott published in the JACI in 2007 came to the conclusion that there are currently insufficient data to recommend probiotics as a part of standard therapy in any allergic condition (45). Furthermore, although there have been several studies to show a benefit in prevention of AE, other studies have failed to support this.

Diagnosis

Diagnosis of AE

Diagnosis of AE is based on clinical assessments such as those of Hanifin and Rajka, UK Working Party, Schultz Larsen and DARC (4, 5, 8). Assessment of severity is based on scoring such as SCORAD or EASI (46–48).

Diagnosing food allergy in AE

There is no recommended diet for patients with AE. Dietary restrictions should only be recom-

mended in cases of an established diagnosis of food allergy. Allergy tests should be performed in children with moderate to severe eczema in addition to conventional treatment strategies (10, 49). Other clinical signs associated with eczema should direct the physician towards the possibility of a food allergy and thus the necessity of allergy testing. Indeed, the infant with eczema and food allergy frequently presents with gastrointestinal symptoms (vomiting, persistent diarrhea), irritability or sleep disorders.

There is no single parameter which can prove the clinical relevance of a sensitizing food in patients with AE. A stepwise procedure addressing individual factors is recommended. Basic investigation for suspected food allergies in infants with eczema include screening tests for IgE sensitization by skin prick test (SPT) and measurement of specific serum IgE concentrations to common food allergens (Fig. 1) (10). Testing should include allergens suspected by history, and known to elicit reactions most commonly according to the age (50) (Table 2). In case of negative screening test (10% of infants with food allergies and eczema), the atopy patch test performed by experienced test evaluator could enhance the diagnostic accuracy

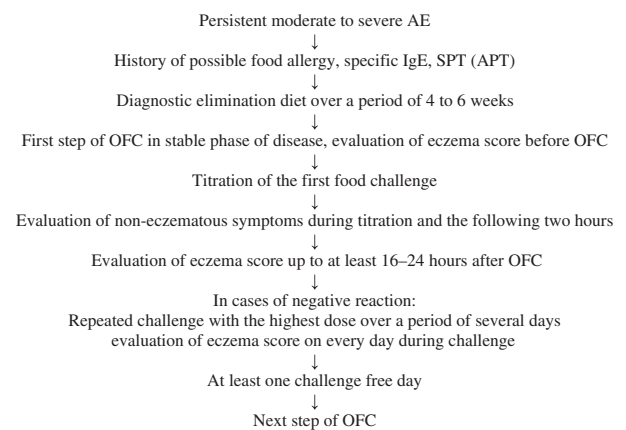


Fig. 1. Food allergy diagnosis in children with eczema (10).

Table 2. Foods account for more than 90% of the food allergies, according to the age

Infant	Children (2–10 years)	Older children
Cow milk	Cow milk	Peanut
Eggs	Eggs	Tree-nuts
Wheat	Peanut	Fish
Soy	Tree-nuts	Shellfish
	Fish	Sesame
	Shellfish	Pollen-associated foods
	Sesame	
	Kiwi fruit	

Adapted from Ref. (50).

(51–53). Atopy patch test (APT) is still not generally recommended for routine diagnoses of food-induced eczema. It was concluded from a recent evaluation of a large number of children with AE that APT does not lead to a significant reduction of the need of oral food challenge (OFC) when food-induced eczema is supposed. The APT with foods (cow's milk, hen's egg, cereals and peanut) may increase the identification of food allergy in patients with AE in the following cases: (i) suspicion of food allergy without predictive specific IgE levels or positive SPT, (ii) severe and/or persistent AE with unknown trigger factors; (iii) multiple IgE sensitizations without proven clinical relevance in patients with AE.

Positive results lead to a diagnostic elimination diet lasting 4–6 wk (maternal elimination diet for the breastfed infant). If eczema improves during the elimination diet, the clinical relevance of the eliminated foods should be confirmed by standardized, physician-supervised OFC (10). Standardized, physician-supervised food challenges provide the most accurate diagnostic tool. Finally, double-blind, placebo-controlled food challenges (DBPCFC) represent the 'gold standard' for diagnosing food allergy. The aims of controlled OFC are both to prove that a certain allergen plays a role for the individual clinical symptoms and to exclude food allergy in order to prevent the child being subjected to unnecessary or even harmful elimination diets. A position paper reviewed information relevant to the performance of double-blind, placebo controlled challenges (54). Provocation tests should always be performed by persons with experience in OFC and emergency equipment must be available at all times.

An accurate diagnosis of food allergy and carefully managed dietary manipulation can improve the symptoms of eczema. Moreover, infants with early development of IgE sensitization have an increased risk for later development of allergic diseases such as asthma (55). Early identification of children with food allergy and AD may provide opportunities to prevent the progression of the allergic march. The diagnosis of food allergy in infancy is necessary to develop a suitable elimination diet. Nevertheless, dietary manipulation is only one aspect of the management of eczema, which must also consider other proven therapeutic strategies.

Diagnosing triggering factors others than food allergens

Numerous trigger factors for flare-up of AE have been identified, including allergens, irritant sub-

Table 3. Trigger factors for eczema in children

Food allergens
Inhalant allergens
Contact allergens
Bacterial colonization of the skin
Irritant substances (soap, creams, wool, perspiration, hot bath, etc.)
Cold climate
Psychological factors
Infections

Adapted from Ref. (56).

stances and infectious micro-organisms such as *S. aureus* (Table 3) (56).

Natural course and prognosis

Most of the children with AD have developed the disease in early infancy, i.e. during the first 12 months of life. Two-thirds of these infants will lose their AD within the first 3 yr of life (55). In the German Multicentre Allergy Study (MAS children), of 1123/1314 children, 13.4% had AD in the first year of life. By 2 yr of age, the life time prevalence amounted to 21.5% (241/1123). Parental atopy was significantly associated with the manifestation and severity of early AD, the effect being strongest for parental AD. Furthermore, elevated total and specific IgE at the age of 2 yr showed a strong positive association with early AD, especially with the more severe form. The association of atopic sensitization and early AD was strongest for onset of sensitization in the first year of life: whereas 48 of 117 children with sensitization at age 1 (41.0%) showed early AD, this was the case in only 15 of 66 children with onset of sensitization by age 2 (22.7%, $p = 0.012$). In contrast to total and specific IgE, elevated cord blood IgE was inversely associated with the manifestation and severity of early AD.

All other analyzed early life factors, i.e. gender, breastfeeding, age at introduction of solid foods, pet keeping, level of mite and cat allergen exposure, parental smoking, maternal smoking during pregnancy, older siblings, parental education and number of infectious diseases, did not show a significant association with the manifestation and severity of early AD.

Prognosis of early AD

Of the 192 children with early manifestation of AD and complete data on the course of AD, 43.2% were in complete remission after the age of 2 yr (55). Of these 83 children, 55.4% only had had symptoms in the first year of life. Almost one-fifths (18.7%) of all children with early AD

Table 4. Summary of suggested research topics

Research topic	Open questions	How to address it	Expected outcome
Mechanisms of AE	What is the exact role of the skin barrier in the pathogenesis of AE?	Gene studies	Better comprehension of AE
Genetics	What are the genes involved in AE?	Candidate gene study	Better comprehension of AE
The role of allergy in AE	What is the exact role of food allergy in the severity of AE? How does the severity of AE in early childhood contribute to the severity of the allergic marathon?	Prospective cohort study Prospective cohort study, intervention studies to prevent early sensitizations in patients with AE	Better prevention of food allergy Better prevention of the allergic marathon
Prevention of AE	Can AE be efficiently prevented by early nutritional intervention studies?	Birth cohort study with interventional strategies	Decreasing prevalence of AE
Diagnostic tools	Are there biochemical markers to identify AE?	Prospective cohort study	Better identification of AE
Treatment of AE	What is the treatment for severe AE?	Randomized, controlled study in patients with AE	Better recovery of AE

AE, atopic eczema.

had symptoms of AD every year up to age 7 and were thus categorized as having persistent AD. An intermittent pattern of AD up to age 7 was observed in 38.0% of the children with early AD.

The strongest risk factor for a poor prognosis of early AD was the severity: 72.2% of the children with persistent AD reported frequent scratching with early AD, whereas this was the case in only 35.6% of the children with an intermittent pattern and in only 14.5% of the children with complete remission after 2 yr of age [aCOR (adjusted cumulative odds ratio) 5.86; 95% CI 3.04–11.29].

Furthermore, early atopic sensitization played a major role for the prognosis of AD. Sensitization to food allergens, especially the less prevalent types such as wheat (aCOR 7.43; 95% CI 2.21–25.02) and soy bean (aCOR 4.46; 95% CI 1.34–14.87) sensitization, showed the strongest associations. The magnitude of early atopic sensitization, i.e. the sum of the measured concentrations of specific IgE, was strongly associated with the prognosis of AD; however, no cut-off achieved a satisfactory positive or negative predictive value for a sufficiently accurate prognosis (data not shown).

A parental history of AD was associated with the prognosis of AD, although not quite reaching statistical significance. However, a strong atopic family history, defined as two or more atopic family members, remained a significant predictor of poor prognosis even in the adjusted model (aCOR 2.40; 95% CI 1.29–4.48). Furthermore, children with concomitant early wheeze had a significantly poorer prognosis. A cat in the home in early childhood increased the risk of persistent AD, although not significantly so (aCOR 2.33; 95% CI 0.85–6.38). However, when analyzing the level of cat allergen in the children's homes, no

association of cat exposure and pattern of AD was observed (aCOR 1.23; 95% CI 0.44–3.39, for highest vs. lowest quartile). None of the other analyzed early life factors, i.e. gender, older siblings, breastfeeding, age at introduction of solid foods, dog keeping, level of mite allergen exposure, parental smoking, maternal smoking during pregnancy, parental level of education and number of infectious diseases showed a significant association with the prognosis of early AD.

Children with a manifestation of disease in the first year of life were not at risk for a poorer prognosis than children with a manifestation of disease in the second year of life: equal proportions of children with onset in the first and in the second years had complete remission, intermittent and persistent AD (43.3%, 35.0%, 21.7% with onset in the first year of life and 43.1%, 43.1%, 13.9% with onset in the second year of life, $p = 0.50$).

Treatment of AE

Treatment of AE is reviewed extensively in Ref. (8). It is important to approach treatment of patients with AE in a comprehensive manner, incorporating principles of skin barrier repair and skin hydration, with anti-inflammatory therapy, antipruritic measures, identification and elimination of flare factors including irritants, allergens, infectious agents and emotional stressors, as well as education. A step-care approach with basic skin care measures at each step was stressed in the PRACTALL consensus report (Fig. 2; fig. 5 in PRACTALL, Ref. 8). This includes skin hydration and use of emollients along with avoidance of irritants and allergens. Further treatment includes topical corticosteroids of increasing potency and/or topical calcineurin inhibitors, remembering that topical

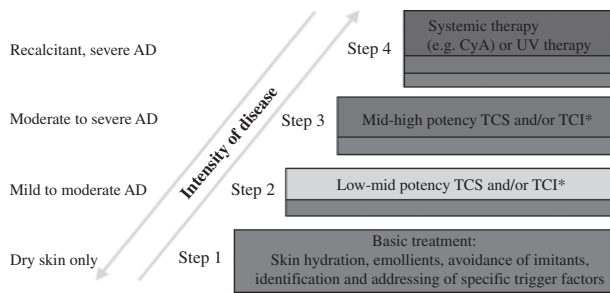


Fig. 2. Stepwise approach to management of children with atopic eczema. TCS, topical corticosteroids; TCI, topical calcineurin inhibitors; CyA, cyclosporine A. *Over the age of 2 years (fig. 5 from PRACTALL; Ref. 8).

calcineurin inhibitors are currently indicated for children aged 2 yr or older. Systemic therapy includes ultraviolet light therapy and cyclosporine A, although most children with AE can be managed without these step 4 measures. Investigational therapy for AE includes intravenous immunoglobulin (57), omalizumab (58) and allergen desensitization, both subcutaneous (59) and sublingual (60).

Conclusions

Recent studies improve the development and the outcome of AE including the understanding of skin barrier, immunity, nutrition and other exposures, allergenic or not. Genetic factors are not yet very well defined. More studies are needed as well defining specific biochemical markers for AE. Multicenter birth-cohorts should be developed to identify early risk or protective factors of AE (Table 4). Results should be expected before submitting new preventive or therapeutic strategies.

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