Atopic eczema: what’s new?
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Abstract

Atopic eczema (AE) is a chronic inflammatory skin disease characterized by recurrent intense pruritus and a typical age-related distribution of skin lesions. Several new aspects with regard to the pathogenetic background as well as strategies for prevention, diagnosis and treatment of AE have emerged. There are ongoing studies on genetic susceptibility loci, as well as environmental and nutritional factors associated with an increase or a decrease of AE lesions. The atopy patch test is now available for identification of allergens in aeroallergen-triggered AE. New topical therapies, such as the calcineurin inhibitors, have broadened the therapeutic armamentarium substantially. In order to increase knowledge and coping strategies, patient education programs have been launched.

Learning objective Upon completing this paper, the reader should be aware of new developments in AE, especially on nomenclature, prevention strategies, diagnostic tests, as well as therapeutic options.

Introduction

Atopic eczema (AE; synonymous to atopic dermatitis) is defined clinically as an inflammatory, chronically relapsing, itching skin disease with typical age-related distribution of lesions.1 Often, but not always, an occurrence of IgE-mediated sensitivity to allergens is found.2 Approximately, two out of three AE cases start in childhood under 5 years of age.3 AE is sometimes difficult to diagnose because of its variable course in regard to age, morphology and distribution. Nevertheless, the main clinical criteria used for diagnosis of AE have been provided, for instance, by Hanifin & Rajka,4 Williams and coworkers5 as well as Ring.6

Prevalence of AE has been increasing worldwide during the last decades, especially in industrialized countries.7–12 Among children from these areas, the current lifetime prevalence is estimated to be 10–20%.13 So far, reasons for this increase are largely unexplained.14 In support of these data, a recently published questionnaire study of a defined school population (mainly aged 9–12 years) repeated over 35 years in Aberdeen, UK documented prevalence rates of 5%, 12%, 18% and 21% in 1964, 1989, 1994 and 1999, respectively.15

Several genetic analyses have identified different chromosome regions with a linkage to AE features: Th2 cell cytokine genes on 5q31–33, as well as regions located on 1q21, 3q21, 17q25 and 20p, which are closely coincident with some major psoriasis loci.16–19 Additionally, further genetic regions associated with AE features include gene polymorphisms in the signal transducer and activator of transcription (STAT)-6, the proximal promoter of regulated on activation, normal T-cell expressed and secreted (RANTES), interleukin (IL)-4, IL-4Rα and transforming growth factor (TGF)-β.20–23 Very recent findings of Weidinger et al.24 showed an association of one intron 2 polymorphism (rs324011) with total serum IgE and a STAT 6 risk haplotype for elevated IgE in white adults.

This Continuous Professional Development paper will focus on some new developments.

Nomenclature

Terminology of AE is controversial with many different names in different countries (e.g. atopic dermatitis, neurodermitis constitutionalis atopica). Some years ago, the European Academy of Allergy and Clinical Immunology proposed a new term ‘atopic eczema/dermatitis...
syndrome’ (AEDS). This new syndrome should be further divided into non-allergic and allergic AEDS, the latter was further subdivided into ‘IgE-associated AEDS’ and ‘non-IgE-associated allergic AEDS’.

On a global level, the World Allergy Organization has recently published a revised nomenclature where the problem of combining laboratory and clinical definitions of ‘atopy’ and AE has been solved in a way that only the IgE-associated forms of the disease will be called AE. In the future, the term ‘eczema’ will replace the current term AE or atopic dermatitis. Other forms of dermatitis (e.g. contact dermatitis) will remain unaffected. It remains open whether this consensus will be accepted in daily life.

Diagnostics

Atopy patch test

It has long been known that environmental substances such as aeroallergens as well as food allergens can produce flares in some patients with AE. The atopy patch test (APT) has been advocated as an instrument to evaluate the relevance of IgE-mediated sensitizations for skin disease.

An international multicentre trial studied the correlation of positive APT reactions with history, skin prick test (SPT), and specific IgE (sIgE) in serum. Three hundred and fourteen patients with AE were tested with house dust mite (Dermatophagoides pteronyssinus), cat dander, grass pollen, birch pollen, hen’s egg, celery and wheat flour. APT, SPT and sIgE results showed significant agreement with history of AE aggravation by contact with grass pollen and ingestion of hen’s egg. Further significant correlations of APT results and patient’s history were shown in a previous study.

With regard to history, the APT showed a much higher specificity (60–90%) than SPT and sIgE, while sensitivity was higher for sIgE and SPT. Thus, the APT with aeroallergens may provide an important diagnostic tool in patients with an air-exposed AE distribution pattern. Open questions concern the clinical relevance of positive APT reactions in patients with a negative history and negative SPT or sIgE, as there is no gold standard for the provocation of eczematous skin lesions in aeroallergen-triggered AE.

Avoidance strategies

Furry pets

Indoor allergen exposure seems to be a risk factor for allergic sensitization as well as elicitation of AE symptomatology, leading to the widely accepted recommendation of refraining or removal of pets from the home, at least as a step in secondary prevention.

Among various allergens, distribution of cat (Fel d 1) and dog (Can f 1) allergens was in the focus of a recently published paper. Herein, Arlian and coworkers characterized the presence of the aforementioned allergens on hard surfaces in homes with and without pets and examined the effectiveness of allergen removal strategies either by a dry dust cloth or by a vacuum cleaner with dust brush attachment.

As expected, homes with a cat had significantly more Fel d 1 than homes without cats. This is in contrast to homes with and without dogs, which showed no significant difference in Can f 1 allergen deposition. Interestingly, dusting with a dust cloth was found to be up to three times more effective than using a vacuum cleaner with a brush attachment. This article documents indoor allergen deposition, regardless of the presence of pets, and provides advice to increase quality of life for those who suffer from allergen-triggered AE for instance by use of a simple dust cloth.

In general population, pet ownership has been associated with less doctor visits and savings in health expenditure, and several authors report a lower prevalence of AE in children, who have been exposed to furry pets since birth. Nevertheless, interpretation of these studies must be done cautiously, because many families without a history of AE would be more likely to own pets, thereby generating a selection bias (‘reverse causality’). In a recent guideline on allergy prevention based on a meta-analysis, Schäfer and coworkers did not find an increased risk for dog ownership for inducing atopic disorders, whereas cat ownership seemed to be associated with an increased risk.

House dust mites

As demonstrated recently for children with asthma and house dust mite allergy in a large prospective, double-blind placebo-controlled study, encasing of mattresses and pillows has shown a reduction in house dust mite allergen concentration and severity of disease in house dust mite-allergic AE patients. In contrast are the findings by Holm and coworkers. They examined the outcome of a house dust mite-proof mattress encasement vs. a regular cotton cover in 40 adult AE patients in a placebo-controlled trial of 12 months duration. The AE severity (as measured by the Severity Scoring of Atopic Dermatitis (SCORAD) index and the patient perception of itching was significantly reduced in both the active treatment and the placebo group, regardless of sensitization and exposure to house dust mites. This unexpected finding, which is supported...
by similar results from studies from the Netherlands\textsuperscript{45} and Germany,\textsuperscript{46} can be explained by similar protection properties of the examined covers, or augmented cleaning habits in the participant’s household, hereby also reducing other allergens or irritants. For the future, studies with clear cut house dust mite-exposure-associated flares of AE in a house dust mite-enriched environment should be performed to see the effect of occlusive bedding.

**Dietary recommendations**

**Breastfeeding**

Breastfeeding might reduce AE by favouring the development of gut populations of bifidobacteria and lactobacilli, which appear to be protective.\textsuperscript{47} From previous studies, it is presumed that breastfeeding has a preventive effect on AE occurrence as compared to a cow’s milk formula diet.\textsuperscript{48} At the moment, although questioned by some,\textsuperscript{49} available data mainly support the recommendation for an exclusive breastfeeding for at least 3 months to avoid atopic disorders like AE.\textsuperscript{38,49} In a 2001 meta-analysis, Gdalevich et al.\textsuperscript{50} showed that exclusive breastfeeding in infants with atopic heredity resulted in a reduced odds ratio (OR) of 0.58 (95% CI 0.4–0.92) for AE. In support of this analysis, a randomized trial from Belarus demonstrated a significant reduction in AE prevalence among infants with initiation and maintenance of breastfeeding as compared to a control group (adjusted OR 0.54; 95% CI 0.31–0.95).\textsuperscript{51}

Nevertheless, a recent questionnaire-based survey conducted in Sweden among 8300 families failed to show any protective effect from exclusive breastfeeding for AE development during the first year of life, even with a positive family history for AE.\textsuperscript{52} Additionally surprising, a study in small for gestational age babies from New Zealand found a higher risk of AE with longer duration of breastfeeding (OR 6.13, 95% CI 1.45–23.86 for less than 6 months; OR 9.70, 95% CI 2.47–38.15 for more than 6 months) compared to never breastfed.\textsuperscript{53}

Further detailed subgroup analyses (e.g. gestational age of the breastfed newborn, diet of mother during breastfeeding) seem to be inevitable to provide a solid basis for sound recommendations on this topic.

**Hydrolysed formula**

In the German Infant Nutritional Intervention Study (GINI), von Berg et al. assessed the preventive effect of differently hydrolysed formulas compared with cow’s milk formula in non-breastfed infants with a hereditary risk of atopy.\textsuperscript{54} At 12 months, incidence of AE was significantly reduced by using extensively hydrolysed casein formula (OR 0.42; 95% CI 0.22–0.79) and partially hydrolysed whey formula (OR 0.56; 95% CI 0.32–0.99). Future trials with more participants are necessary before any definitive recommendations in regard to hydrolysed formulas for infants at risk can be given.

**Probiotics**

According to the ‘hygiene hypothesis’,\textsuperscript{5,6,55} AE results – very much simplified – from an imbalance between Th1- and Th2-type immune responses. In this context, it is postulated that imbalances in microbial colonization of the gastrointestinal tract may also play a role in modulating the immune response in AE, e.g. by influencing interleukin (IL)-12 as well as Th1-type response. Patients with AE have shown more often *Staphylococcus aureus*-positive stool analyses and lower counts of *Bifidobacterium*, a commensal microorganism that is assumed to induce a Th1 response.\textsuperscript{47,56}

In detail, Björksten et al.\textsuperscript{57} examined a cohort of 24 Estonian infants and 20 infants from Sweden, who were followed prospectively by repetitive clinical examination, SPT and stool cultures. The authors found a reduced stool colonization with *Enterococcus* in the first months of life, and with *Bifidobacteria* during the first year of life in AE infants. Additionally, AE infants showed higher counts of *Clostridia* at 3 months, and *S. aureus* at 6 months, whereas the counts of *Bacteroides* were lower at 12 months of age.\textsuperscript{57}

Weston and coworkers\textsuperscript{58} were able to demonstrate a beneficial effect of *Lactobacillus fermentum* VRI-033 PCC in regard to extent and severity of AE in 6–18-month-old children with moderate or severe AE.

For the subgroup of cow’s milk allergic AE infants, *Lactobacillus GG* for 4 weeks resulted in a greater reduction in SCORAD than did the placebo group.\textsuperscript{59} In support for the aforementioned results, recent studies dealing with oral pre- and postpartal administration of ‘probiotics’ (e.g. *Lactobacillus GG*) were able to demonstrate at least a delay of onset of AE in infants and children.\textsuperscript{54,60–62} Definitely, larger studies are warranted before recommendations for this specialized diet during pregnancy and the postpartal period can be given.

**Cereal, starch, vegetables and other foods**

Does the intake of certain foods affect the severity of symptoms in AE? Foods as a cause or a trigger factor of AE have long been the subject of debate.\textsuperscript{63–65} Various authors have performed challenge tests with foods and reported an aggravation of AE lesions in 2–82% of patients.\textsuperscript{66–68}

To answer again that question, data of the Food and Agriculture Organization (FAOSTAT) and of the International Study of Asthma and Allergies in Childhood (ISAAC)
were combined to calculate per capita consumption of macro- and micronutrients as a percentage of total energy consumption in 721 601 children.\textsuperscript{69}

The authors were able to demonstrate a consistent decrease in symptomatology of AE with increased per capita consumption of calories from cereal, starch and vegetable nutrients.\textsuperscript{69} In particular, olive oil showed a negative association – contrary to soy oil – with AE symptomatology.\textsuperscript{69}

In partial support of this report are the findings by Uenishi \textit{et al.}\textsuperscript{70} Among 195 adult AE patients, 44\% showed a worsening of cutaneous lesions after open oral challenge with soy sauce, fermented soy beans and other foodstuff (including chocolate, cheese, coffee, yoghurt).\textsuperscript{70} An avoidance of the challenge test-positive foods for 3 months showed a marked improvement in 56\%, moderate improvement in 35\%, and a slight improvement in 9\% of AE patients.

There is a widely accepted general recommendation to delay the introduction of solid foods until after the age of 6 months with a more strict delay until age 2–3 years for highly allergenic foods (egg, peanuts, tree nuts and fish).\textsuperscript{71} A missing protective effect of late introduction of solids for the development of AE in 642 children recruited before birth and followed to the age of 5 years was reported by Zutavern and coworkers.\textsuperscript{72} On the contrary, there was a statistically significant increased risk of AE in relation to late introduction of egg (adjusted OR 1.6, 95\% CI 1.1–2.4) and milk (adjusted OR 1.7, 95\% CI 1.1–2.5).

In summary, individual diagnosis – including double-blind, placebo-controlled food challenge is required, before any specialized diet recommendation can be given to AE patients.

**Therapy**

**Topical immunomodulators (TIMs) (calcineurin inhibitors)**

The new TIMs tacrolimus and pimecrolimus are potent anti-inflammatory substances without steroid side-effects. They inhibit Th1 and Th2 cytokine production as well as mediator release from mast cells and basophils.\textsuperscript{71–75} Both compounds have shown to be both effective and safe for children and adults with AE.\textsuperscript{75–80}

In clinical trials, tacrolimus was found to be more effective than placebo, 1\% hydrocortisone acetate (0.03\% tacrolimus ointment) and as effective as a mid-potency topical corticosteroid (0.1\% tacrolimus ointment).\textsuperscript{75–77,81,82} Although topical corticosteroids are still the standard of care in AE,\textsuperscript{83} several situations may favour the first line use of a topical calcineurin inhibitor (e.g. treatment of eye-lid dermatitis and other facial regions, patients with steroid phobia).\textsuperscript{84}

In a recent paper by Reitamo \textit{et al.},\textsuperscript{78} children suffering from severe AE benefited more from a twice daily application of 0.03\% tacrolimus ointment, compared to a once daily application ($P = 0.001$). As children with moderate AE experienced little difference in efficacy between once- or twice-daily application, the authors recommend once-daily application for this group of patients.\textsuperscript{78} Further studies may show, whether once-daily application of a calcineurin inhibitor can be reduced further with time as AE lesions improve, until only intermittent treatment would be sufficient. This regime will also help to reduce considerably the cost of treatment, although in a recent analysis, tacrolimus ointment was more cost-effective than high-potency topical corticosteroids in adults suffering from moderate to severe AE.\textsuperscript{85}

In March 2005, the Food and Drug Administration issued an alert to health-care professionals concerning a potential link between TIMs and cancer (mainly lymphoma and skin cancer) on the basis of studies in animals, case reports and knowledge of how these drugs work.\textsuperscript{86}

The alert emphasizes the importance of using these preparations only as labelled and when first-line treatment has failed or cannot be tolerated.\textsuperscript{87}

**Leukotriene receptor antagonists**

Leukotriene receptor antagonists (as montelukast and others) have recently been approved for the treatment of asthma. Some reports have suggested effectiveness in other atopc disorders, such as seasonal allergic rhinitis.\textsuperscript{88–93} The role of leukotrienes in the pathogenesis of AE is not fully elucidated. Available for clinical use are two leukotriene receptor antagonists (montelukast is approved in asthma for patients older than 6 years, and zafirlukast is approved in AE as well as asthma for adolescents and adults).\textsuperscript{88–89}

Yanase and David-Bajar demonstrated little success with montelukast when it was used as an adjunctive agent in patients with chronic AE.\textsuperscript{92} A small trial showed rapid and significant alleviation of symptomatology with zafirlukast monotherapy in adults with AE.\textsuperscript{93} In a larger, double-blind, placebo-controlled crossover pilot study, the efficacy of the leukotriene receptor antagonist montelukast in moderate to severe AE in 195 adults suffering from severe AE was examined.\textsuperscript{94} Participants received 5 mg montelukast or placebo per day for 4 weeks. Eleven patients completed the study with six individuals in the placebo-first group, and five in the drug-first group. The drug-first group showed a significant decrease in disease severity during the drug phase and an increase in disease severity during the placebo phase. The placebo-first group had a decrease of AE severity both in placebo and in drug phase.\textsuperscript{94}
In another study, Silverberg and Paller administered 5 mg montelukast daily (3 children aged 4, 6 and 8 years), 10 mg montelukast daily (one 15-year-old girl), 20 mg zafirlukast daily (3 adults aged 18, 42 and 65 years), respectively, all suffering from a severe AE affecting more than 90% of the body area.95 Beside temporary partial improvement in two patients (relief of pruritus (both patients), abatement of erythema (one patient), the other AE patients failed to show any benefit from leukotriene receptor antagonist treatment.95

A reduction in total SCORAD scores in five of seven children (age range 3–16 years) by 30–84% with constant scores in two patients after body-weight-adapted initiation of montelukast (5 mg per day for children < 12 years of age; 10 mg per day for children ≥ 12 years of age) was reported in a recent paper by Hon et al.96 Nevertheless, the future role of leukotriene receptor antagonists remains controversial. Especially patients with asthma and AE may experience some improvement of both disorders with this treatment modality.

### Silver-coated textiles

Skin colonization with *S. aureus* is known to be an important factor for the maintenance of skin inflammation and acute exacerbations of AE.2,97,98 The degree of colonization is assumed to be associated with disease severity.99–101 Antibiotic, as well as antiseptic substances with antistaphylococcal activity, has been well established in the treatment of AE together with anti-inflammatory therapy.102–106 A new strategy is the use of special textiles.

Metallic silver has broad antibiotic properties without the risk of emerging resistance.100 In an open-labelled, controlled side-to-side comparative trial, Gauger and coworkers found a highly significant decrease of *S. aureus* colonization together with clinical improvement of eczematous lesions covered with silver-coated textiles (PadycareTM) compared to cotton textiles in 15 AE patients.107

Interestingly, the reduction of *S. aureus* colonization persisted even after removal of the silver-coated textile,107 which is in contrast to colorings with anti-*S. aureus* activity (e.g. gentian violet).105 The authors speculate whether an overnight wearing of silver-coated textiles might be able to sustain a constant *S. aureus* reduction, thereby enhancing the efficacy of anti-inflammatory treatment.107 The question of possible silver absorption in patients wearing silver-coated textiles needs to be further investigated.

### Unconventional therapies

A long list of procedures and treatments can be found under this topic, including Chinese herbal therapy, homeopathy, biofeedback therapy and massage therapy.108–111 Beside of concerns regarding the toxicity of Chinese herbal medicine, more clinical research is needed to adequately assess the value of complementary therapies.108

In an effort to fill this gap, adult AE patients received in a randomized, controlled, observer-blinded trial either single person hypnotherapy (*n* = 15) or no hypnotherapy (*n* = 18) in addition to their pre-existing dermatological treatment, which had to be continued throughout the study period of 3 months.112 Values of SCORAD improved after hypnotherapy on an average of 40%, whereas without hypnotherapy values deteriorated on an average of 32%.112 The Dermatological Life Quality Index (DLQI)113 demonstrated a significant improvement in life quality in the hypnotherapy group; the control group showed a significant decrease.112 Although these preliminary results are encouraging, a selection bias by persons interested in hypnotherapy cannot be excluded. Furthermore, a detailed list of the dermatological treatment modalities – which were in use throughout the study – is missing. Much more clinical research is needed before any recommendations for the use of complementary therapies can be given.

### Patient education programs (‘eczema school’)

In the past, educational programs for patients with chronic diseases such as diabetes and asthma have demonstrated effectiveness.114 A similar concept – combining dermatological and nutritional education with psychological behaviour training by an interdisciplinary team – has been developed for AE patients and their families in Germany (national program of the German Ministry of Health).114

The main contents are basic information on the nature and aetiopathology as well as pathophysiology of AE, as well as identification and avoidance of individual provocation factors, skin care and specific treatment options as well as discussion of unconventional therapies. A special part deals with diagnosis and treatment of adverse food reactions, and adequate nutrition in childhood. Behaviour-oriented psychological intervention is focused on interrupting the itch–scratch cycle through improved self-perception, training of alternative habits of scratching, discrimination and control of scratching stimuli and relaxation techniques. Furthermore, the training aims at reducing the negative effects of the disease on social life by development of behavioural competence for an improved coping with stress and disease-specific problems.115 The program should enable the patient (or, in case of a child, the parents) to play an active part in the management of AE in a competent manner.115 First results of a recently launched randomized prospective controlled trial (German Atopic Dermatitis Intervention Study (‘GADIS’))
showed a significant effect of the ‘eczema school’ intervention program compared to a waiting group as control.\textsuperscript{116}

**Conclusion**

In the last decade there has been major progress in understanding the complex aetiopathology of AE. At the same time new diagnostic, therapeutic and preventive strategies have been developed which will be evaluated regarding their suitability, side-effects as well as long-term effects, respectively, in the future.

**Key points**

- Probiotic treatment during pregnancy and nursing may delay onset of AE in infants and children.
- The atopy patch test is available for identification of aero-allergen involvement in AE elicitation.
- Silver-coated textiles can reduce \textit{Staphylococcus aureus} colonization of AE skin.
- Topical corticosteroids are still the standard of care in inflammatory AE lesions.
- Some situations may favour the use of a topical calcineurin inhibitor relative to a topical corticosteroid (e.g. treatment of facial regions, patients with steroid phobia), although concerns about long-term safety remain unanswered.
- Patient education programs should enable the patient (or the parents) to play an active part in the management of AE in a competent manner.
- Much more clinical research is needed before any recommendation for the use of complementary therapies in AE can be given.

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Appendix A: CME questions

1. The atopic eczema/dermatitis syndrome (AEDS) includes the following subgroup(s): (a) allergic (b) non-allergic (c) IgE-associated (d) all of the above.

2. In industrialized countries, the current lifetime prevalence of AE in children is estimated to be (a) 1–2% (b) 4–8% (c) 10–20% (d) 80–100%.

3. To remove allergen of pets (cat, dog) from hard surface at home (a) a vacuum cleaner with dust brush attachment (b) a dust cloth (c) none of the aforementioned demonstrated superiority.

4. In contrast to healthy controls, AE patients have shown (a) less often *Staphylococcus aureus*-positive stool analyses (b) higher contents of *Bifidobacterium* in stool analyses (c) none of the above.

5. Infants with a hereditary risk for atopy have demonstrated reduced incidence of AE after use of (a) cow’s milk formula (b) extensively hydrolysed casein formula (c) partially hydrolysed whey formula.

6. The atopy patch test may provide information on sensitization of (a) nickel (b) mercury (c) house dust mite (d) copper in AE individuals.

7. Silver coated textiles provide on lesional skin in AE patients (a) antibiotic properties (b) a decrease in *S. aureus* colonization compared to cotton textiles during application (c) a prolonged reduction of *S. aureus* colonization after removal (d) all the above.

8. Chromosome regions without linkage to AE include (a) 1q21 (b) 3q21 (c) 5q31–33 (d) 17q11.2

9. Lesional application of topical calcineurin inhibitors (a) are not the standard of anti-inflammatory treatment in AE (b) are approved for use in newborns (c) should be used at least three times per day on the same spot (d) are less effective than 1% hydrocortisone acetate ointment.

10. In patient education programs for AE, information is provided (a) in regard to aetiology, pathophysiology (b) for the identification and avoidance of individual provocation factors (c) for skin care and specific anti-inflammatory treatment (d) all of the above.

**Answers**

1. (d)
2. (c)
3. (b)
4. (c)
5. (b) (c)
6. (c)
7. (d)
8. (d) 17q.11.2 characterizes the chromosomal region affected in neurofibromatosis type I.
9. (a) Tacrolimus and pimecrolimus are not approved for use in children younger than 2 years of age. In most studies, tacrolimus and pimecrolimus were applied once or twice daily.
10. (d)
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