

REVIEW ARTICLE

Recent advances in epidemiology and prevention of atopic eczema

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Abstract

Atopic dermatitis (AD), named also atopic eczema, is a chronic relapsing inflammatory skin disease with a considerable social and economic burden. The *primum movens* of AD is in most cases a genetic and/or immune-supported defect of the skin barrier, facilitating penetration and sensitization to food or airborne allergens, as well as infections by *Staphylococcus aureus*, *herpes simplex virus*, or other microbes. New pathogenetic concepts have generated new approaches to prevention and therapy of AD. In particular, the daily use of emollients in newborns at high risk of AD has shown interesting results, with a reduction in the cumulative incidence of AD ranging from 32% to 50% of the treated infants. On the other hand, the AD preventive efficacy of food and/or inhalant allergen avoidance has been questioned, and supplementation strategies (vitamin D, probiotics, or other compounds) need to be further investigated.

Epidemiology

Atopic dermatitis (AD) is a relapsing inflammatory skin disease with a considerable social and economic burden. In children, the disease is frequently associated with other allergic conditions, in particular asthma and rhinoconjunctivitis. The prevalence of childhood AD has increased up to 20% in some developed countries (1), while a plateau has been eventually reached in some westernized countries (e.g., France, Switzerland) (2–4), but not in others (e.g., Ireland) (5). AD typically appears in the first years of life and tends to disappear at school age in over 70% of the cases (6). An American national questionnaire-based survey assessed a prevalence of AD in children of almost 13%, with mild cases accounting for 67% of the total, moderate for 26%, and severe for 7% (7). Variations in the epidemiology and clinical expression of allergic diseases and eczema in the last decades have increased the interest of researchers in identifying etiologic factors to provide new strategies of prevention and intervention (8). In line with the so-called hygiene hypothesis, AD is less frequent in rural (vs. urban) populations (9). Moreover, late beginning of nursery school and higher and middle socioeconomic status both are risk factors for atopic eczema and other allergic diseases, while having parents working as self-employed farmers and having older siblings are protective factors (10–12). Similarly, AD and

other allergic diseases continue to be less frequent in Eastern than in Western European countries (9), confirming the east–west gradient previously described (13, 14).

Skin barrier defects and immunity: the complex interactions driving AD

Both gene–gene and gene–environment interactions affect the expression of the epidermal proteins and of AD (15). As Palmer et al. (16) found a strong association between loss-of-function mutations of the filaggrin gene (FLG) and AD, the concept of a skin barrier genetic defect causing AD has replaced the ‘inside–outside’ hypothesis. Accordingly, several later studies proved that inflammation in AD results from both inherited and acquired insults and is consequent to skin barrier impairment (17). However, additional genetic defects have been recently associated with AD. These include more proteins (e.g., involucrin, loricrin, and hornerin) of the so-called epidermal differentiation complex encoded by a gene cluster located on chromosome 1q21 (18) and lipids contributing to the skin barrier (e.g., ceramides) (19), as well as protease inhibitors (e.g., LEKTI or SPINK5, cystatin A, KLK7) (20, 21). AD also has been associated with genetic defects of the claudins family (claudin-1, ZO-1, E-caderin). These proteins are essential for the function of tight junctions of keratinocytes

in the stratum granulosum. A defect in claudins' function allows the paracellular penetration of environmental antigens and the activation of the immune system's response by antigen-presenting cells (APC) (22). Genetic defects of the skin barrier may also allow an increased transepithelial water loss, which causes dry skin and facilitates the penetration of allergens and therefore allergic sensitization. However, FLG or FLG-like proteins' loss-of-function mutations are insufficient to explain the pathogenesis of AD in all patients.

Skin barrier defects contribute to the pathogenic activation of the innate immune system, leading to the typical AD lesions. APC, such as Langerhans cells, and keratinocytes play a major role in this process (23, 24) by activating pathogenic T-cell responses. In particular, cytokines produced by Th2, Th22, and Th17 cells intervene in the acute phase of inflammation (25); moreover, IL-22 and IL-17 also regulate the expression of S100A genes by keratinocytes, which encode for the proteins of the 'proinflammatory epidermal differentiation complex' (26). Overexpression of Th2 cytokines, particularly IL-4, IL-13, and IL-25, as occurs in the acute phase of AD, may inhibit, in human normal keratinocytes, the expression of FLG, but also of hornerin and FLG-2, and may determine or exacerbate the barrier impairment (27–29). Moreover, the development of skin lesions in FLG-deficient mice has shown to be dependent on adaptive immunity (30). A damaged skin barrier facilitates also colonization and invasion by bacteria (in particular *Staphylococcus aureus*) and viruses (e.g., herpes simplex virus [HSV]). On the one hand, serine proteases produced by *S. aureus* can further worsen the skin lesions (31, 32); on the other hand, a disseminated HSV infection can lead to eczema herpeticum.

Therefore, skin eczematous lesions are the result of the interaction between genetic FLG and/or FLG-like proteins' loss-of-function mutations firstly with a Th2 cytokine profile, i.e. the allergic predisposition, secondary with environmental factors such as bacteria and viruses, but also allergens and pollutants.

Prenatal and perinatal protective and risk factors

The relationship between the prenatal environment, maternal–fetal interaction, and AD in the offsprings is an object of great interest. Prenatal events, including maternal diet and stressful life events during pregnancy, gestational diabetes, and others, have been recognized as potential risk factors and targets for primary prevention of AD and atopic diseases (33–35). Preterm birth was associated with an increased risk of severe forms of AD and asthma in Norwegian children, while parity and high maternal education were associated with decreased odds of both preterm birth and AD (36). Maternal allergic manifestations during pregnancy were associated with early biomarkers of atopic diseases, such as an increased percentage of IL-4+CD4+ T cells and a reduced Treg/Th2 ratio in cord blood at the child's birth (37). Elevated maternal C-reactive protein in pregnancy was associated with a higher risk of eczema up to the age of 4 yr (38). Low levels of vitamin D in the cord blood were associated with AD and early transient wheezing in Dutch

(39) and Australian children (40). The results of ongoing randomized controlled trials of maternal supplementation of vitamin D during pregnancy may suggest whether so-called vitamin D deficiency (if any) plays a role in early life on allergic disease outcomes. Finally, yet importantly, dietary intake of common food allergens during early pregnancy may influence AD onset in the offspring. For example, a higher maternal wheat intake during the second trimester of pregnancy was associated with reduced risk of AD (OR 0.64; 95% CI) in American children, while a higher maternal intake of peanut, milk, and wheat during early pregnancy was associated with reduced odds of mid-childhood allergy and asthma (41).

A higher maternal intake of total dairy products, cheese, yogurt, and calcium during pregnancy may reduce the risk of atopic eczema and asthma, while higher maternal intake of vitamin D during pregnancy may increase the risk of infantile eczema (42).

Postnatal protective and risk factors

The exposure of the immune system early in life to a wide combination of nutrients, microbes, antigens, and allergens might drive its imbalance toward a predominant Th2 switch and the consequent development of atopic diseases (43). The protective role of breastfeeding on infants against the onset of allergic diseases has been investigated in several studies, but its role is still controversial (44). Exclusive breastfeeding was associated with sequential changes of several biomarkers of allergy (e.g., blood eosinophils, total and specific IgE levels during the first 3 yr of life) in Taiwanese children and a reduced risk of cow's milk protein sensitization during early childhood (45). The PASTURE birth cohort study showed that soluble IgA ingested in the first year of life reduced the risk of AD up to the age of 4 yr (46). A prospective birth cohort study of Dutch children showed that breastfeeding is a major determinant of innate immunity factors (RANTES, IL-10) at the age of 1 month, thus suggesting a mechanism for its infections and atopy-preventive influence (47–49). By contrast, breast milk immunomodulatory factors (TGF- β 1, sCD14, and IgA) were not associated with AD and atopic sensitization at 12 months of life in a prospective study of Australian children (50). Moreover, cross-sectional studies suggested a positive, rather than inverse association, between breastfeeding and AD among children with no parental allergic history (51–55). Finally, breastfeeding, along with other factors such as spontaneous or cesarean delivery, prenatal and postnatal exposure to antibiotics, rural animal exposure, diet, and infections, may also affect the development of AD by influencing the composition of gut microbiota (56, 57).

The advent of high-throughput sequencing technology now allows detailed characterization of bacterial microbiota constituents and their modification through exposure to numerous factors (58). A more diverse intestinal microbiota in the first week of life was associated with a reduced subsequent onset of eczema in infants at risk of allergic disease (59). This suggested that interventions to enhance microbial diversity in early life may be useful in the prevention of eczema in high-risk infants

(59). A cross-sectional study investigated the relation between both tuberculosis (TB) disease and bacillus Calmette–Guérin (BCG) vaccination in early life and allergic disease, finding a uniform positive association between TB and all allergic disease outcomes, including eczema, without any association or protective effect of BCG vaccination during the first year of life (60). Some evidence of a protective effect has been provided for wild-type varicella zoster infection. Retrospective studies on children who had undergone wild varicella infection up to 8 yr of age showed a lower prevalence of atopic disorders and lower levels of total IgE compared with children who received varicella vaccine, probably due to a suppression of IgE production and allergic sensitization, as well as altered leukocyte distributions (61).

The role of vitamin D in preventing and affecting the progression and severity of AD is one of the most debated topics among interventions and prevention of the disease. Serum vitamin D levels were inversely correlated with disease severity in Turkish children with AD, but only in those with concomitant allergic sensitization (62). However, in Hong Kong Chinese children, vitamin D deficiency has been associated with AD development during childhood; meanwhile, both long- and short-term AD severity appeared to be inversely correlated with high-serum vitamin D and total IgE levels (63).

Oral ingestion of antigens may result in priming of an effector repertoire, diversification of the gut microbiota and immunoregulation, driving immune tolerance (64). Accordingly, an increased food diversity introduced during the first year of life was correlated to a reduced risk of AD, food allergy, and food sensitization (65). Then, not only microbial diversity but also diversity of food antigens may be necessary early in life to prevent AD.

A higher birth order (a well-known respiratory allergies protective factor) has been recently linked also to a smaller risk to develop food allergies and AD (66, 67). However, the prevalence of eczema in children with filaggrin deficiency increased in the presence of older siblings, emphasizing a complex interaction between environmental factors and genetic backgrounds in the onset of atopy (68). Whether this 'older sibling' effect is due to a greater exposure to infections at an early age (hygiene hypothesis) or to parity influencing the immune status of women after multiple births (prenatal hypothesis) is still a matter of debate today, as two decades ago (69).

An interesting link between AD and a variety of air pollutants, such as environmental tobacco smoke, volatile organic compounds, formaldehyde, toluene, nitrogen dioxide, and particulate matter, has also been suggested (70). These air pollutants may act as risk factors for the development or aggravation of AD by inducing oxidative stress in the skin, leading to skin barrier dysfunction or immune dysregulation (70).

Food sensitization and food allergy

Atopic dermatitis and food allergy are often associated in children. The *NIH and Clinical Excellence (NICE)* guidelines recommend considering a diagnosis of food allergy: in children with atopic eczema who had immediate symptoms at food intake and in infants and young children with moderate or severe atopic eczema not controlled by optimum skin

management, particularly if associated with gut dysmotility or failure to thrive (71). Moreover, in children with AD, the early sensitization to food allergens (in particular cow's milk and hen's egg) and/or to inhalant allergens represents a risk factor for a more persistent and severe disease and asthma development (72). The most recent advances in the pathogenesis of AD have recognized in the synergic action between a genetically determined barrier defect and alterations in the immune system Th2-oriented, the primary cause of the skin damage. Food allergy often occurs in these patients (about in one-third of them) and may both play a role as a trigger and influence the future course of AD. Indeed, atopic eczema has been associated with earlier and persistent allergic sensitization to foods (73, 74). In particular, a substantial amount of studies have indicated that transcutaneous allergic sensitization may be facilitated by null mutations in FLG (75–77) and innate immunity genes (78), which are associated with food allergy and eczema in early childhood. In an English population-based birth cohort, the early-life environmental peanut exposure (within the first year of life) was measured and was associated with an increased risk of peanut sensitization and allergy in children who carry a mutation of FLG gene (76).

Airborne allergens sensitization

Several new concepts are rising that demonstrate the existence of a dynamic interaction between the epidermis and the immune system (79). IgE-associated AD is more frequent in childhood than non-IgE-associated AD, and these two phenotypes differ in age at onset and in remission patterns. Therefore, it is important – especially in early life – to distinguish these two phenotypes to evaluate possible allergic-related conditions and to predict the occurrence of allergic asthma later in childhood (80, 81). Actually, infant severe eczema is associated with an increased risk of asthma at 10 yr of age, and children with eczema and wheezing episodes during infancy more frequently develop asthma than infants with eczema alone (82). A recent study conducted on two Dutch birth cohorts showed that a variant of the gene encoding for protocadherin-1, an adhesion molecule expressed in the airway and skin epithelium, is associated with eczema, bronchial hyper-responsiveness, and asthma (83). In AD patients, the early epidermal barrier impairment may facilitate the epicutaneous penetration of molecules of environmental allergens (84), such as Der p 1, synergizing with their proteolytic activity. In fact, recent advances suggest that the dust mite, more than foods, is a major cause of allergic AD (85). A cross-sectional study has recently shown that early sensitization to cat among children with AD may be linked to an increased risk of sensitization to a broader spectrum of allergen components from early life (86).

Diagnosis: different phenotypes and endotypes

The pathogenetic mechanisms underlying AD are heterogeneous in different patients and may change over time even in the same patient. Therefore, many different clinical phenotypes and endotypes of AD can be observed according to the

following characteristics: (i) an onset in childhood vs. adulthood; (ii) the degree of disease severity, persistence, and duration; (iii) presence of FLG and/or FLG-like genetic null mutations; (iv) IgE sensitization to food or airborne allergens; (v) immunologic reactivity to cutaneous self-antigens (87); and (vi) colonization by microbial agents (e.g., HSV, *S. aureus*). The study of all these characteristics in the individual patient is essential to achieve a personalized preventive and therapeutic approach (88–90).

The diagnosis of AD is clinical, but searching for an associated allergic sensitization can help to identify potential allergic triggers for eczema flares in infants and children with moderate to severe, persistent eczema (91, 92). Children with early-onset persistent AD – a pattern associated with early IgE sensitization to cow's milk or hen's egg proteins or inhalant allergens – have an increased risk of later development of allergic asthma (93, 94). Then, the early identification of these children might be important to evaluate adequate prevention strategies. An updated Position Paper of the European Academy of Allergy and Clinical Immunology clarified when and how a child with skin symptoms should be tested for allergies (95). Children under 3 yr of age with moderate to severe eczema should undergo skin-prick test or IgE tests for at least hen's egg white and cow's milk, as well as for the most prevalent food allergens (grade B recommendation); nevertheless, standardized food challenges tests are then required to define diagnosis and avoid unnecessary exclusion diets. In some circumstances, especially if eczema is the only atopic symptom and/or specific cow's milk IgE antibodies are not detected, low serum levels of β -lactoglobulin-specific IgG4 may imply tolerance (96). The prevalence of food allergy decreases with age, due to the natural development of tolerance, so that older children need to be tested mainly for mite and other prevalent inhalant allergens (95).

Markers of AD severity are being actively searched. For example, IL-31 represents an interesting cytokine, especially with regard to the severity of the inflammatory process in general. IL-31 serum levels were significantly higher in German children with AD and correlated with severity, sleeplessness, IL-4, and IL-13 levels in children with extrinsic AD (97). Similarly, serum levels of the chemokine CCL18 are associated with AD severity, serum eosinophil, and IgE levels (98). In cases of chronic recurrent or therapy-resistant eczema in children, patch tests might be useful for ruling out an allergic contact dermatitis; in infancy, test reactions to nickel patch tests could be of irritant or non-specific nature, so positive reactions should be interpreted with caution (99).

Chronic allergic diseases, such as AD and asthma, can have a serious impact on the quality of life not only of the affected child but of the whole family (100). When AD is associated with food allergy, the elimination diet and other factors could contribute to the impairment of quality of life (101); this point is very important for the patient and should be considered in a proper diagnosis. Many AD-specific questionnaires or quality of life scales have been developed: The Paediatric Food Allergy Quality of Life Questionnaire was the first tool targeted to assess quality of life in children with food allergy (102).

Preventive approaches

A large array of preventive measures, including food and/or inhalant allergen avoidance, and supplementation strategies (vitamin D, probiotics, or other compounds), have been investigated in the last decades (103).

- **Skin barrier care improvement:** The hypothesis that a genetic dysfunction of the epidermal barrier contributes to AD and allergic sensitization offered a rationale to test the primary preventive efficacy of early emollient therapy. Two prospective, randomized, and controlled trials demonstrated that the daily use of a moisturizer prevents AD in 32% of Japanese (104) and 50% of Anglo-American (105) high-risk newborns. If confirmed in larger trials, the daily use of emollients since birth in newborns with a high risk of AD will be a novel and simple approach to AD primary prevention. A retrospective follow-up study has been suggested that the improvement of the skin management in children with AD can reduce or delay the appearance of allergic respiratory diseases (72).
- **Formulas:** Extensively hydrolyzed as well as partially hydrolyzed formulas have the potential for primary prevention in high-risk children (106–110); several meta-analyses and systematic reviews have investigated the role of these formulas separately, but, due to methodologic differences, a direct comparison between their outcomes is difficult (111). The German Infant Nutritional Intervention (GINI) compared the preventive effect of three hydrolyzed formulas with cow's milk formula. Two hydrolyzed formulas appeared to be cost effective or even cost saving (112) with promising results up to the age of 6 yr, whereas subsequent results have shown little evidence of an ongoing preventive effect between the ages of 7 and 10 yr (113). The American Academy of Allergy Asthma and Immunology recently stated that partially hydrolyzed whey formulas and extensively hydrolyzed casein formulas appear to offer advantages to prevent AD and cow's milk protein allergy when used instead of intact cow's milk protein formula, but evidence is not conclusive to support the use of such formulas in those infants at increased risk of allergic disease who cannot be exclusively breast-fed for the first 4–6 months of life (114). In a study from the UK, an extensively hydrolyzed formula was cost effective when compared with an amino acid formula in infants with cow's milk allergy younger than 1 yr of age, as the patients showed similar times of symptoms resolution but with lower management costs (115). The diagnosis of cow's milk allergy in this study was not based on objective measures; hence, further studies performed with double-blind, placebo-controlled food challenges are needed (116). The use of hydrolyzed formulas also reduces the intake of lactose and oligosaccharides components provided by breastfeeding, thus implying disadvantageous consequences for the development of a healthy gut microbiota. Therefore, lactose may facilitate the acquisition of oral tolerance (117). Interestingly, dietary supplementation with arachidonic acid/docosahexaenoic acid and galactooligosaccharide/polydextrose has shown to improve symptoms of allergen-induced dermatitis in an experimental model (118).

- *Supplementing breastfeeding*: Prolonged breastfeeding (up to 6 months) is still encouraged, but unable to completely prevent the development of allergy (119). Taking inspiration from the hygiene hypothesis, empiristic AD prevention studies were based on bacterial products in at-risk children or their breastfeeding mothers. A randomized, placebo-controlled trial on the prevention of AD by oral supplementation of a bacterial lysate between week 5 and the end of month 7 explored the association between infant gut microbiota and the development of AD. A statistically significant indirect effect via *Clostridium* cluster I colonization was demonstrated in the active treatment group in association with AD. Moreover, a correlation between older siblings and microbiota composition was observed, suggesting that microbiota may be one of the biologic mechanisms underlying the sibling effect (120). A Norwegian study examined the associations between the consumption of probiotic milk products in pregnancy and infancy and risk of atopic eczema, rhinoconjunctivitis, and asthma onset in early childhood in a large population-based pregnancy cohort (121). A reduced incidence of atopic eczema and rhinoconjunctivitis was associated with probiotic milk products consumption, but no association was seen for incidence of asthma by 36 months of age (121). In a randomized, double-blind, placebo-controlled study supplementation with probiotic *Lactobacillus plantarum* CJLP133 for 12 wk (in children aged 12 months to 13 yr with AD) was shown to improve the severity score and lead to a decreased eosinophil count, IFN- γ , and IL-4 levels but without significant differences in the total use of topical corticosteroids (122). The role of probiotics in the prevention of allergic disease is still not clear; efficacy – if any – may depend on the timing, dose, duration, and specific probiotic used. In low-atopic-risk formula-fed infants, the supplementation with prebiotic and immunoactive oligosaccharides showed to reduce the early occurrence of AD with similar results if compared with breastfed infants (123).
- *Vitamin D supplementation*: The expression of antimicrobial peptides, such as human β -defensins 2 and 3 and cathelicidin LL-37, is lower in patients with AD due to a relative defect in innate immunity. The observation that antimicrobial peptide cathelicidin expression in human subjects is induced by 1,25-dihydroxyvitamin D₃ offers a new perspective for vitamin D supplementation in patients with AD, as recently reviewed (124). A randomized, double-blind, placebo-controlled trial of Mongolian children with winter-related AD aged 2–17 yr showed that daily supplementation with oral cholecalciferol (1000 IU/day) for 1 month improved skin symptoms during winter (125). The current practice parameter states that patients with AD might benefit from supplementation with vitamin D, particularly in the case of documented low serum levels (126).
- *Mite avoidance*: Two RCTs in children (127, 128) and one involving children and adults (129) suffering from AD considered the effectiveness of house dust mite avoidance, providing some evidence that house dust mite avoidance strategies in children and adults led to greater

improvements in atopic eczema severity than placebo after 2–6 months. However, there is a growing body of evidence suggesting that excessive avoidance of natural exposure to allergens without justification can lead to impaired immunologic tolerance and a poorer quality of life of children and their families (130).

- *Specific immunotherapy*: The efficacy of immunotherapy in patients with atopic eczema has been poorly investigated in the past years. If type I sensitizations are present, studies suggest the efficacy of allergen-specific immunotherapy in improving the course of atopic eczema not only in house dust mite allergy but also in patients with birch or grass pollen sensitization (131). However, a review by Compalati et al. (132) showed that no long-term studies have been conducted to determine its disease-modifying potential in the context of the ‘allergic march’.
- *Functional textiles*: Several functional textiles may have antimicrobial and antipruritic properties and have been used as a complementary treatment in AD. A recent systematic review showed that silver and silk fabrics were associated with an improvement in SCORAD and symptoms but not in quality of life, so that more studies are needed before recommending a systematic use of these fibers (133). Multidisciplinary education programs and new effective strategies for the treatment of subjective symptoms such as antipruritic techniques have been developed and have been shown to be effective in improving both AD severity and patients’ and families’ quality of life (134, 135).

Conclusions

Atopic dermatitis is often associated with multiple comorbidities, such as asthma, hay fever and food allergy. The association is more frequent in severe cases, and additionally, the severity of eczema is directly related to that of the comorbidities (7). The American National Survey of Children’s Health, a prospective questionnaire-based study of 91,642 children aged 0–17 yr, showed the association of atopic eczema not only with other allergic comorbidities but also with sleep impairment, healthcare utilization, recurrent ear infections, and visual and dental problems (7). Psychologic and educational interventions have been used as an adjunct to conventional therapy for children with atopic eczema to enhance the effectiveness of topical therapy and to improve their quality of life (136). A better control of the skin to preserve the cutaneous barrier’s efficiency with a daily use of emollient, but also – in the presence of flares – with topical steroids, seems to be a promising option to improve AD than to reduce the development of allergic sensitization. The new advances in AD have led to re-evaluating many of the older dogmas in the treatment and management of the affected children; the available evidence about food allergy issues, allergic sensitization, and the efficacy of the preventive interventions is still insufficient to give definitive recommendations (137, 138). Despite intense ongoing research, several aspects of the pathogenesis of AD and of the development of allergic sensitization are still poorly understood, with consequent limitations in planning new preventive and therapeutical approaches.

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