

REVIEW ARTICLE

New approaches to the prevention of childhood atopic dermatitis

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Abstract

There has been a steep rise in the burden of atopic dermatitis (AD), and up to 20% of children in developed countries now suffer of the disease. At present, treatment at best achieves symptom control rather than cure, and there is a strong need to identify new methods of disease prevention. While earlier approaches focused on allergen avoidance strategies, there has been a clear shift towards attempts to induce tolerance and enhancement of skin barrier function, as skin barrier breakdown plays an important role in AD development. This article reviews the latest developments in the prevention of AD.

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With up to 20% of children in wealthy countries suffering of atopic dermatitis (1–3) (AD, syn. 'atopic eczema' and 'eczema'), the burden on healthcare resources (4–7) and patients' quality of life is significant (7–14). There is therefore a clear need to develop methods of disease prevention, partly through application of our enhanced understanding of the patho-aetiology and environmental risk factors for AD (15). Ways to reduce the incidence or severity of AD have been explored as early as the perinatal period and for many years centred around allergen avoidance (16). However, partly driven by disappointing results but also an improved understanding of the role of allergic sensitization in the development of AD, we are now moving away from strict allergen avoidance towards methods of tolerance induction. To supplement this narrative review, a systematic MedLine search was performed (which is available from the authors on request), and particular emphasis has been given to systematic reviews. This paper is one of two commissioned articles, the other one focusing on the epidemiology of AD (15).

Infant feeding and dietary allergen avoidance

There is little evidence for a protective effect of exclusive breastfeeding beyond 3 months of age on AD development (15). Although earlier studies suggested an increased AD risk in infants exposed to solid foods during the first few months of life, research published since has either shown no association or even the opposite, that is, that delayed introduction of solids was associated with a higher risk in AD development (17–22). Reverse causation has been proposed as an explanation, but no convincing evidence of parental allergy playing a role in feeding practices has been found (19). Furthermore, observational data suggest that the gradual decrease in the proportion of young infants given solids at an early age over past decades has coincided with an around threefold increase in childhood AD (23, 24). In addition, food allergies are a rare phenomenon in societies where allergenic foods, such as peanut, are introduced early into infants' diets, compared with settings where allergenic foods are introduced later (25), and a

randomized controlled trial (RCT) is currently underway in the UK to test whether the introduction of allergenic foods plus concomitant breastfeeding from 3 months of age is able to reduce the risk of developing food allergies and AD compared with exclusive breastfeeding for 6 months (Enquiring About Tolerance Study, <http://www.eatstudy.co.uk>).

Along the lines of food allergen avoidance, partially and extensively hydrolysed (hypoallergenic) formulas have also been studied, and it has been suggested that prolonged feeding with a hydrolysed formula, compared with a cow's milk formula, may result in an around 50% reduction in infantile AD in at risk children (26–29). The most substantial of these studies ($n = 2252$), the German Infant Nutritional Intervention Study, reported a significant risk reduction in AD (including more severe disease) up to age 10 for those who had been fed either extensively hydrolysed casein formula (RR = 0.72, 95% CI 0.58–0.88) or partially hydrolysed whey formula (RR = 0.82, 95% CI 0.68–1.00) (26, 30). Although these findings seem at odds with those supporting early weaning, it may be that low-level exposures, such as with hydrolysed proteins, enable the immune system to develop tolerance, rather than sensitization, especially in children with a positive family history of allergic disease (28).

Even if strict allergen avoidance does not convincingly work in infants, does maternal dietary antigen avoidance during pregnancy have a role to play in AD prevention? This was certainly recommended for years in many countries. However, a recent Cochrane review concluded that even in high-risk children, evidence of a protective effect of maternal dietary antigen avoidance was lacking (16).

Manipulating the gut flora – pre- and probiotics

The role of the microflora (or microbiota) of the gut in the development of AD has recently been subject of much investigation, and there is mounting evidence to suggest that children who develop AD have a reduced diversity in the gut microbiota (15). Probiotics, supplements containing microorganisms with the intention of conferring a health benefit on the host, have the potential to realize their intended purpose through altering the gut microbiota (31). A variety of probiotics, such as strains of lacto- and bifidobacteria, used individually or in combination during the prenatal and postnatal periods, have consequently been studied in RCTs. Some authors describe impressive findings, and a recent meta-analysis of 13 studies associated the use of probiotics during pregnancy and in early life with a relative risk reduction for AD of 21% (RR = 0.79, 95% CI 0.71–0.88) (32). However, the heterogeneity in methodology and diagnostic criteria has undermined the impact of these results (33), and it has been difficult to replicate findings from individual studies (31, 34–37). Furthermore, oral bacterial lysates have been tested in a placebo-controlled RCT, but a beneficial effect on AD risk up to 3 years of age was only seen in the subgroup of children with a history of paternal atopy (RR = 0.52, 95% CI 0.30–0.90) (35).

Another method with which the gut flora could be stimulated is through the intake of food components that are suitable substrates for nonpathogenic bacteria and hence promote their growth and activity, so-called prebiotics (e.g., fructo- and galacto-oligosaccharide). A recent Cochrane review and meta-analysis of four RCTs that used prebiotics in the postnatal period suggested a reduction in the risk of developing AD by around 30% up to 2 years of age (RR = 0.68, 95% CI 0.48–0.97) (38), and follow-up data from one of its component studies have implied that a significant benefit may remain up to 5 years of age (39).

Although such results are encouraging, the literature on the use of pro- and prebiotics to prevent AD is hampered by significant heterogeneity in study methodologies, in particular the use of different strains, combinations and doses of organisms either during pregnancy and/or breast-/bottle feeding and the use of different markers of response, making direct comparisons between studies and meaningful meta-analysis very difficult. As a result, the World Allergy Organization has been cautious in a recent position paper, suggesting that further research is needed, before pre- and/or probiotics can be routinely recommended as an effective means to prevent AD (33).

Dietary supplementation

In established AD, patients will frequently ask whether dietary supplements may improve their skin. With the recent surge in interest in the immuno-modulatory effects of vitamin D in allergic disease, this has inevitably been studied in the AD context. While animal research suggests that systemic vitamin D may improve disease severity (40) and oral vitamin D appears to enhance antimicrobial peptide expression in human skin (41), epidemiological studies have shown conflicting evidence between vitamin D levels in cord blood and AD risk (42, 43). There is currently also no convincing evidence that vitamin D supplementation is an efficacious method to prevent AD (44–47).

Based on a number of observational studies which suggested that a high fish intake during pregnancy lowers AD risk in the offspring (48–50) (15) and similar risk reductions in children with a high fish intake during late infancy (51, 52), the effect of fish oil supplementation, rich in anti-inflammatory n-3 polyunsaturated fatty acids (n-3 PUFA), has been tested. Although such supplementation significantly increases n-3 PUFA serum levels, a double-blind RCT among 420 high-risk infants did not show a protective effect on AD development (46, 53).

Numerous other supplements have been studied, including vitamin E, vitamin C, pyridoxine, evening primrose oil, borage oil, zinc and selenium, as have a variety of exclusion and elemental diets, but there is insufficient evidence to routinely advocate any of these (46).

House dust mite avoidance

A considerable number of AD patients show sensitization to house dust mites (HDM), experimental cutaneous HDM

exposure can induce AD flares in the atopy patch test, and inhalation of house dust mite allergen can provoke eczematous skin lesions in predisposed patients (54). In addition, AD risk and severity are related to the level of HDM exposure (55). However, allergic sensitization is most likely a consequence of skin inflammation, facilitated by antigen-presenting cells in the epidermis, rather than a primary cause, and it is therefore not surprising that even the most rigid methods to reduce house dust mite exposure have not shown a convincing effect on disease activity, even in sensitized individuals (56). Somewhat paradoxically, a longitudinal study showed that children with allergic mothers who were randomized to receive mite-allergen-impermeable mattress covers actually had a higher occurrence of AD than those without (57). While it is possible that other features of the mattress cover exacerbated AD in this study, there is no evidence to support routine use of HDM-proof bed covers for AD prevention. Interestingly and consistent with work on endotoxin and parasite exposure, there is also evidence that high environmental HDM levels in early life reduce AD risk (15, 58).

Water hardness

As previous population-based cross-sectional studies suggested that AD prevalence was increased in hard water areas (36, 37, 59, 60), the Softened Water Eczema Trial (SWET), which recruited children with established moderate-severe AD, tested the hypothesis that ion-exchange water softeners plus standard treatment reduce disease severity compared with standard AD treatment alone (61). However, the study found no significant benefit of a water softener in addition to normal AD treatment after 12 weeks and therefore could not recommend their routine use. Nevertheless, the SWET study does not rule out that water hardness might play a role in the initiation of eczematous skin inflammation in early life.

Preventing skin barrier breakdown

Skin barrier dysfunction plays a major role in AD development, and dry, cracked skin is often the precursor of eczematous skin inflammation, and children with filaggrin (*FLG*) skin barrier gene inheritance show an increase in transepidermal water loss, even before AD develops (62). Intensive emollient use in early life in addition to soap and detergent avoidance may therefore be a powerful method of primary prevention, especially in children who carry skin barrier gene mutations and show early signs of skin barrier impairment. This idea has already been trialled in a pilot study with encouraging results, and a large-scale RCT is now underway ('Barrier Enhancement for Eczema Prevention' trial, 'BEEP'; <http://www.beepestudy.org/>) (63). Others are working on new barrier enhancing topical and systemic preparations to upregulate *FLG* expression in the epidermis and improve skin barrier function as a potential means of disease prevention but also treatment (64–66).

Preventing flares, skin infection and allergic sensitization

It is a common criticism that our current armamentarium against the cytokine cascade of established AD is purely symptomatic topical or systemic suppression of skin inflammation and treatment of its complications, such as skin infection. Although the majority of AD sufferers show colonization with *Staphylococcus aureus*, prophylactic topical or oral antimicrobial interventions show no efficacy outside of the context of clinical infection (67). However, proactive ('weekend') therapy is able to effectively reduce the frequency of disease flares and consequently leads to less use of topical anti-inflammatory medication (68). Importantly, there is a clear link between AD severity and the risk of allergic sensitization (69). Given the emerging role of skin inflammation in skin barrier breakdown and the aetiology of food and respiratory allergies (70), more effective AD flare and disease control might even help to prevent some children from following the so-called atopic march (71). This, in turn, could have a positive effect on AD chronicity and severity, but intervention studies are needed to prove this concept (72).

Conclusions

In summary (see also Box 1), AD prevention appears most promising well before skin barrier inflammation and breakdown have occurred, and pre- and probiotic supplementation during pregnancy and in early life and intensive emollient therapy in high-risk children are particularly promising avenues for future research. In addition, we are increasingly moving away from allergen avoidance towards tolerance induction. This will ultimately require more well-designed RCTs and interventional birth cohorts. It is important that such work recognizes the emerging endophenotypes of AD, as failure to do so previously is likely to have contributed to the heterogeneity and disappointing results of past research efforts (73). Clear, validated disease definitions are essential to aid comparability between studies, and international harmonization of AD outcome measures is important as we work towards this common goal (74).

Box 1: AD prevention – summary of main findings

- Intensive emollient therapy in early life may be a way to prevent AD or at least to reduce disease severity, and topical and systemic strategies to enhance skin barrier function are promising new avenues.
- There is no evidence that maternal dietary manipulation (e.g., peanut avoidance) has a beneficial effect on disease risk in the offspring.
- There is some evidence that pre- and probiotics during pregnancy and infancy reduce the risk of AD, but they have no significant impact on AD severity in established disease.
- House dust mite avoidance measures do not appear to reduce the risk of a child developing AD and have little impact on disease severity, even in sensitised patients.

- There is no good evidence for dietary supplements improving AD.
- Water softeners do not reduce AD severity, but data are lacking on their value as a preventative measure against AD.
- Routine antistaphylococcal measures have limited efficacy in improving AD, although it is important to treat overtly infected eczema.

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Conflicts of interest

The authors declare no conflicts of interest.

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