Common Non-Pharmacologic Interventions in the Prevention of Pediatric Atopic Dermatitis

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Abstract
At the incidence of pediatric atopic dermatitis (AD) continues to increase, dermatologists may find themselves talking to concerned parents about strategies for disease prevention. In this article, we present the current evidence for options that may help decrease a child’s risk of developing AD. Specifically, we address whether maternal antigen avoidance, probiotic supplementation, vitamin D supplementation, and emollients are effective in preventing AD in the pediatric population.

Introduction
Atopic dermatitis is a chronic disease that affects more than 20% of children and may continue into adulthood.1 If persistent, the disease may cause significant irritation in daily life, financial burden, and social stigmatization. There is no cure for atopic dermatitis, and current therapies only provide symptomatic relief. Although the cause of atopy is not completely understood, it has a multifactorial etiology. The environment, barrier dysfunction, genetics, and an altered pro-inflammatory immune response have all been implicated. Despite the best efforts of dermatologists, the prevalence of atopic dermatitis in the developed world has risen over the last few decades.2 This problem has led countless parents to seek the advice of dermatologists in an effort to prevent the development of atopy in their child.

Common questions that dermatologists encounter from parents with a family history of severe atopy or from mothers breast-feeding infants with AD are whether maternal antigen avoidance, probiotic supplementation, vitamin D supplementation, or emollients can reduce the risk of developing this disease. Parents also ask if AD is associated with their child developing behavioral disorders such as attention deficit hyperactivity disorder (ADHD) or autism spectrum disorder (ASD).2

Because of the substantial increase in pediatric atopic dermatitis (AD) cases over the last three decades, there is a necessity to determine if any preventative measure can reduce the incidence of disease. This editorial briefly summarizes the best available evidence to assist busy dermatologists in providing practical, cost-effective solutions for parents who want to decrease their child’s risk of developing AD.

Evidence of Prevention
Antigen Avoidance
Expectant mothers should be advised against antigen avoidance. In a 2014 Cochrane review, five trials that included 952 patients found that maternal avoidance of milk, eggs, and other potentially “antigenic” foods during pregnancy, breast-feeding, or both does not prevent childhood AD (Table 1).3 Of importance, one trial found that women who avoided eating these foods gained significantly less weight during pregnancy (mean difference -3.00, 95% CI -5.21 to -0.79), which raises the possibility of adverse nutritional effects on the mother or fetus.4 Further concerns associated with maternal antigen avoidance include a higher (but statistically unstable) risk of preterm birth (RR 10.06, 95% CI 0.53 to 192.26) and a possible adverse effect on mean birthweight (MD -83.45, 95%CI -221.87 to 54.97).5 Conversely, they should be made aware that a maternal diet that is rich in wheat, dairy products and calcium might reduce the risk of atopy and infantile eczema.6,7

Vitamin D
There is currently insufficient evidence to recommend the use of vitamin D supplementation during pregnancy. Although controversial, one study found that higher maternal intake of vitamin D increased the risk of infantile eczema.6 This is counterintuitive to the recent association of low levels of vitamin D in the cord blood and AD.8,9 Furthermore, vitamin D supplementation may have a therapeutic role in the treatment of AD.10-11 Larger trials over a longer time period with supplementation for both mother and infant are necessary to determine if vitamin D truly has a protective effect against AD.

ADHD and ASD
Atopy has previously been linked to an increased incidence of attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). However, the relationship was mostly temporal, and until recently, there were no large longitudinal studies that addressed this claim. The largest study to date involved 14,812 subjects with any atopic disease and 6,944 non-atopic subjects without history of atopy. The subjects were born between 1997 and 2000 and were followed through December 31, 2010. The study concluded that children who developed atopic disease before age 3 had an increased risk of developing ADHD (hazard ratio [HR]: 1.97) and ASD (HR: 3.40) in later life.2 This finding further substantiates the significance of atopic disease prevention for infants and children.

Probiotics and Prebiotics
The American Academy of Pediatrics (AAP) last updated its stance on the use of probiotics and prebiotics in November 2010. The AAP states that, “Although the results of some studies support the prophylactic use of probiotics during pregnancy and lactation and during the first six months of life in infants who are at risk of atopic disorders, further confirmatory evidence is necessary before a recommendation for routine use can be made.”2 Since that time, numerous publications have suggested that probiotics are helpful in the prevention of infantile AD. A 2008 DARE review of 1,429 infants revealed a significant risk reduction for AD after probiotic supplementation in infants.12 A 2012 meta-analysis of seven randomized controlled trials (RCTs) revealed a significant risk reduction of AD in 2- to 7-year-old children after prenatal lactobacilli administration.13 These findings were further supported by a meta-analysis of 16 RCTs in which prenatal and postnatal probiotic supplementation protected against AD in both normal and high-risk infants.14 Only four studies have evaluated the long-term outcomes of using probiotics for the prevention of pediatric AD (up to 9 years of age), and they have yielded mixed results (Table 2). This finding indicates the possibility of a species-specific benefit and a lack of standardization in study design.15 Three of the four studies found that Lactobacillus rhamnosus GG (LbR) consistently reduced the incidence of AD, but despite conflicting study outcomes, a May 2015 meta-analysis concluded that probiotics likely prevent the long-term development of AD.16 Lactobacillus rhamnosus GG transfers from the mother to the child in utero, while other strains cannot.17 It appears that the strain of bacteria is important when deciding what to recommend to the patient, but further probiotic species-specific studies must be performed before drawing definitive conclusions.

There is strong evidence to support that breast-feeding during the first four months of life causes a reduction in the incidence and severity of atopic disease in patients at high risk (those with a first-degree relative with AD).18 A meta-analysis of 18 prospective studies and the German Infant Nutritional Intervention studies found decreased AD incidence in high-risk infants who were breast-fed compared to those fed cow’s milk formula.19,20 However, breast-feeding only provides a modest risk reduction

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of about 33% against AD, and it is important to note that this only applies to children who have a first-degree relative with AD.18-20 Some studies involving children with no family history of AD suggest that breast-feeding has no effect on the incidence.20 Another study of 15,430 mother-child pairs suggested an increased risk of AD in children exclusively breast-fed for the first four months who have no family history of allergy.21 However, the incidence of AD among infants who were exclusively breast-fed was still lower than those who were never breast-fed (11.6% versus 11.8%).21 There is no formal recommendation from a national organization regarding breast-feeding and AD, but the World Health Organization recommends that mothers "exclusively breast-feed their child for the first six months of life."22 More studies are needed to determine the effect of breast-feeding in children with no family history of AD.

**Emollients**

Although the literature is limited, daily application of moisturizer for the prevention of AD in neonates at high risk for AD is perhaps the most exciting positive news to date. One randomized controlled trial (n=118) found that Japanese neonates who received daily moisturizer had a 32% reduced risk of developing AD compared to control subjects (P = .012, log-rank test).21 Another study (n=124) found that the daily use of emollients provided a 50% relative risk reduction in the cumulative incidence of AD at 6 months of life (relative risk, 0.50; 95% CI, 0.28-0.9; P = .017).24 Few studies have compared the clinical effect of specific emollients, but a large review suggests that the most clinical improvement occurred with urea- and glycerin-based emollients.25 If confirmed in larger trials, the daily use of emollients following birth for infants with a high risk of AD will be a novel, simple, and safe approach to the primary prevention of AD.

**Conclusion**

Maternal antigen avoidance does not prevent

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**Table 1. Maternal antigen avoidance trials summarized in Cochrane Review (adapted from Kramer et al.3)**

<table>
<thead>
<tr>
<th>Author</th>
<th>Type</th>
<th>Participants</th>
<th>Interventions</th>
<th>Overall Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appelt 2004</td>
<td>Randomized control trial</td>
<td>497 Canadian mothers of infants from high-risk families, defined as having at least 1 first-degree relative with asthma or 2 with a history of other IgE-mediated allergy</td>
<td><strong>Experimental</strong>: complete avoidance of peanut, nuts, and fish and decreased intake of milk and eggs during the third trimester of pregnancy and while breastfeeding for up to 1 year. A partially hydrolyzed formula supplement was provided for the first year, if required. <strong>Control</strong>: usual care and diet.</td>
<td>Trial did not report on atopic eczema or other allergic disease outcomes, but found no evidence of sensitization to milk, egg, or peanut antigen on skin-prick testing at one, two, or seven years of age.</td>
</tr>
<tr>
<td>Cant 1986</td>
<td>Randomized crossover trial</td>
<td>19 U.S. mothers of infants 6 weeks to 6 months of age with atopic eczema</td>
<td><strong>Experimental</strong>: maternal exclusion of cow milk, egg, chocolate, wheat, nuts, fish, beef, chicken, citrus fruits, colorings, and preservatives, with use of soya-based milk substitute for 4 weeks. <strong>Control</strong>: same dietary exclusions for same duration (4 weeks), but substitute contained cow milk and egg. Each of the 2 interventions allocated to all subjects in randomized order.</td>
<td>Dietary antigen avoidance by mothers of infants with established atopic eczema was associated with a non-significant reduction in eczema severity.</td>
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<tr>
<td>Falth-Magnusson 1987</td>
<td>Randomized control trial</td>
<td>212 pregnant Swedish women with positive family history of allergy (herself, husband, or previous children)</td>
<td><strong>Experimental</strong>: cow milk and egg avoidance diet from 28 weeks of gestation. <strong>Control</strong>: normal diet.</td>
<td>Restricted diet during pregnancy was associated with a small but statistically significant lower mean gestational weight gain (mean difference -3.00, 95% CI -5.21 to -0.79) percentage of pre-pregnancy weight (i.e., 1.8 kg for a 60-kg woman).</td>
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<tr>
<td>Lilja 1988</td>
<td>Randomized control trial</td>
<td>171 pregnant women in Stockholm/Uppsala with a history of respiratory allergy to pollen and/or dander.</td>
<td><strong>Experimental</strong>: low-milk and low-egg diet during third trimester. <strong>Control</strong>: high-milk and high-egg diet during third trimester.</td>
<td>Cord blood IgE levels were higher in the experimental (antigen avoidance) group. Longer-term atopic outcomes not reported.</td>
</tr>
<tr>
<td>Lovegrove 1994</td>
<td>Randomized control trial</td>
<td>26 pregnant English women with atopic histories in themselves or in partners, recruited at 30 weeks' gestation</td>
<td><strong>Experimental</strong>: milk-free diet from 36 weeks' gestation and during lactation. <strong>Control</strong>: unrestricted diet.</td>
<td>No significant protective effect of maternal antigen avoidance.</td>
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Table 2. Long-term outcomes of using probiotics for the prevention of pediatric AD

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of participants</th>
<th>Age</th>
<th>Dose</th>
<th>Supplementation Timeline &amp; Overall Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kalliomaki et al.</td>
<td>116</td>
<td>7</td>
<td>1 x 10(^{10}) cfu LBR</td>
<td>From 36 weeks of gestation for mothers and during first 6 months of life for infants. Probiotics prevented pediatric AD and atopic sensitization compared to placebo group (42.6% vs 66.1%; RR, 0.64; 95% CI, 0.45–0.92)</td>
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<tr>
<td>Kuitunen et al.</td>
<td>891</td>
<td>5</td>
<td>Twice daily capsule of 5 x 10(^{3}) cfu LBR; 2 x 10(^{8}) cfu Bifidobacterium breve; 2 x 10(^{7}) cfu Propionibacterium freudenreichii. Infants received same probiotic once daily mixed with 20 drops of syrup containing 0.8 g of galactooligosaccharides</td>
<td>From 36 weeks of gestation for mothers and during first 6 months of life for infants. Probiotics reduced the incidence of atopy in high-risk children delivered by cesarean section but not in total cohort</td>
</tr>
<tr>
<td>West et al.</td>
<td>121</td>
<td>8–9</td>
<td>Lactobacillus paracasei 1x108 cfu per serving</td>
<td>No maternal supplementation. Infants supplemented from 4 to 13 months of age with Lactobacillus paracasei added to cereal. No long-term effects for preventing pediatric AD in cohorts who received Lactobacillus paracasei</td>
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<tr>
<td>Wickens et al. (3 trials)</td>
<td></td>
<td></td>
<td>A) n= 474 at 2 years</td>
<td>A) Maternal supplementation from 35 weeks gestation until 6 months if breastfeeding and infant supplementation until 2 years with LBR halved cumulative prevalence of eczema at 2 years in high risk infants compared to placebo (P = .01) (hazard ratio [HR], 0.51; 95% CI, 0.30–0.85)</td>
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<td></td>
<td></td>
<td></td>
<td>B) n= 425 at 4 years</td>
<td>B) LBR supplementation stopped at 2 years, and at age 4, cumulative prevalence of eczema was still significantly reduced (HR 0.57 (95% CI 0.39–0.83))</td>
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<td></td>
<td></td>
<td></td>
<td>C) n= 310 at 6 years</td>
<td>C) Significantly lower cumulative prevalence of eczema at 6 years (HR = 0.56, 95% CI 0.39–0.80) ***Bifidobacterium had no significant effect</td>
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</table>

AD and may have a harmful effect on the fetus. Vitamin D supplementation may have a role in the treatment of AD, but more trials are needed to evaluate the efficacy of vitamin D as a preventative measure against it. Prenatal and postnatal supplementation with probiotics, specifically with Lactobacillus rhamnosus GG, has the best evidence of preventing AD and is a relatively inexpensive option. Breastfeeding for the first four months of life only has a protective effect against AD if the child is at high-risk. Although further studies must be done to confirm early findings, the daily use of urea- or glycerin-based emollients following birth in newborns with a high risk for AD is a simple and cost-effective option for the primary prevention of AD.

References


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