



What is new in the prevention of atopy and asthma?

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Purpose of review

Increasing understanding of mechanisms and influencing factors in the development of uncontrolled inflammatory responses in atopy and asthma should serve for the introduction of new preventive measures. This review tries to present the current state of the art and resumes that until now, no really effective concept can be offered to families at risk.

Recent findings

In addition to modified feeding regimes (hydrolysed formula feeding in infancy), timing of the introduction of solids (avoidance of allergens versus early induction of tolerance), immune modulation using prebiotics or probiotics, a new target of potential intervention could be the human microbiome as a key player in the development of inflammatory diseases such as allergy and asthma. However, during the last 5 years, this concept could not yet be verified in interventional trials. There are new trials ongoing, studying the effect of microbial compounds in early infancy, vitamin D and polyunsaturated fatty acid supplementation during late pregnancy and the effect of azithromycin in children with recurrent wheeze. Results are to be expected within the next couple of years.

Summary

New data on multifaceted intervention and the analysis of the human microbiome are to be expected. The recommendation for atopy and asthma prevention still focuses on avoidance of tobacco smoke exposure and food allergens during the first 4 months of life and feeding of hydrolysed formula if breast-feeding is not possible in high-risk infants, potentially early feeding of prebiotic sugars and/or certain strains of probiotic bacteria or bacterial compounds in certain subpopulations.

Keywords

atopy and asthma prevention, bacterial compounds, human microbiome, nutrition

INTRODUCTION

Epidemiological studies indicate that in certain populations allergy and asthma are less frequently found [1], indicating that lifestyle factors, for example in a farming community or in areas with higher sunlight exposure, may provide a certain protection against unbalanced immune responses. Nutrition, exposure to bacterial compounds and the composition of the human microbiome, infections, smoking and many other factors are influential and may modify epigenetic factors and, thus, inflammatory responses. In Berlin, Germany, migrants of Turkish origin keeping a fairly traditional lifestyle were found to have less atopy and asthma at age 6–7 years compared with the children with a German descent [2]. It is still unknown which protective factors in the Turkish population mediate the prevention; however, nutrition differs and orofecal infections such as hepatitis A, salmonella and helicobacter are more frequent compared with the German population.

Cohort studies tried to identify risk factors which should be avoided and protective factors which should be introduced early in life [3]. There have been numerous interventional trials targeting primary prevention in infancy. The majority of trials focus on high-risk populations. Most recent publications, often controversial, can be found on nutrition such as supplementation of polyunsaturated fatty acids (PUFA), antioxidants (vitamin C and E), vitamin D, prebiotics, probiotics and microbial compounds (lysate of *Escherichia coli* and *Enterococcus faecalis* or *Bifidobacterium breve* and *Streptococcus*

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KEY POINTS

- The current recommendations for asthma and atopy have not changed dramatically during the last 5 years. Breast-feeding and avoidance of cow's milk formula during the first 4–6 months, feeding of hydrolysed formula if breast-feeding is not possible during the first 4 months and avoidance of tobacco smoke exposure during pregnancy and lactation. Oral application of bacterial lysates, synbiotics and a Mediterranean diet containing sea fish, olive oil and fresh vegetables and fruits seem to be of some protective effect.
- Interventional trials on the significance of the human microbiome in infancy and later asthma are ongoing.
- Whether early introduction of solids such as peanut and hen's egg will provide a better development of tolerance to allergenic foods will be shown in ongoing studies.
- Early viral infections like RSV are risk factors for later asthma. New vaccinations could be a useful tool in prevention.
- Controversial data are seen for the preventive effect of probiotics and the supplementation with n3-PUFA, antioxidants and vitamins. Further studies with mixtures of probiotic strains and better characterization of the immunological properties are needed.

thermophilus). Furthermore, ongoing studies analyse the effect of early introduction of solids containing highly allergenic proteins like, for example, peanut [Learning Early About Peanut (LEAP) study] [4²²]. Recent trials try to analyse the human microbiome on the skin and mucosal surfaces as a potential cause and target of unbalanced immune responses. However, the maternal environment, genetic and epigenetic factors are key players in the development of atopic and asthmatic diseases; therefore, intervention has to start very early.

As phenotypes and, therefore, risk factors are numerous, most publications report on prediction, asthma control, modifying disease activity and prevention of asthma exacerbations [5¹].

In summary, during the last 5 years interesting new aspects in the understanding of the pathogenetic mechanisms in allergic and asthmatic immune responses have emerged; however, the recommendations for children and parents at risk for asthma and allergy have not yet been improved.

NUTRITION

Our so-called modern lifestyle, which has mainly been influenced by the 'American way of life' during the last 60 years, introduced several factors: improved hygiene (better living conditions,

improved housing, use of antibiotics and vaccines), fast food, lack of physical exercise with increasing mobility, media consumption, decrease of family size and several other factors.

In areas in Europe, where nutrition remained more traditional, for example in the Mediterranean countries, the prevalence of asthma and allergy is lower compared with English-speaking countries. A diet rich in sea fish (thus, omega-3-fatty acids), olive oil and fresh vegetables and fruits seems to be protective [6]. Supplementation of vitamins alone did not show the same effect. Children of mothers receiving vitamin C and E during pregnancy were not found to have wheezy bronchitis less frequently compared with control children [7]. Another study [8] showed that the natural intake of vitamin E and betacarotin was preventive in terms of sensitization at age 5 years. In the Prevention of Allergy among Children in Trondheim interventional trial [9] performed in Trondheim, Norway, cod liver and fat sea fish consumed during the first 2 years of life were found to decrease the incidence of atopic eczema during the first 2 years of life [10]. In the second phase of the International Study on Allergies and Asthma in Childhood study [11], the consumption of green vegetables and fish turned out to be protective against asthma, but not against allergic sensitization. Fruit intake was identified to be protective against allergic asthma.

In a double-blind randomized controlled trial [12] 420 infants at risk for atopy received a daily supplement of fish oil containing n3-PUFA from birth to 6 months of age; the controls received olive oil. Although fish oil supplementation improved the n3 status of infants, no prevention of eczema, food allergy, sensitization and wheeze was observed up to age 12 months.

The significance of vitamin D in the modulation of immune responses has been reported. Vitamin D is a hormone and seems to have an influence on the adaptive immune response [13]. However, whether supplementation during pregnancy and early infancy is protective against allergy and asthma remains controversial. A low vitamin D serum level during pregnancy and early infancy was associated with an increased risk of asthma [14], whereas others reported that in high-risk infants the supplementation with vitamin D is a risk for atopic eczema [15]. Another interventional trial [16] supplementing vitamin D during pregnancy found increased levels of immunoglobulin-like transcripts (ILTs) ILT3 and ILT4 in cord blood indicating increased tolerogenic dendritic cells. Low vitamin D levels are associated with higher sensitization rates in the U.S. National Health and Nutrition Examination Survey [17]. On the contrary, Rothers *et al.* [18] report that both low

and high vitamin D serum levels in cord blood were associated with increased aeroallergen sensitization in children at age 5 years in Tuscon, Arizona.

The introduction of solids is still a controversial issue. The German guidelines now recommend an introduction of solids after the completed 4 months of life [19]. An Australian cross-sectional study (HealthNuts) [20] showed that the risk for sensitization to hen's egg was three-fold increased if hen's egg was introduced to the child's diet after 10 months of life compared with infants receiving hen's egg between 4 and 6 months of life. The PIPO study (Prospective Study on the Influence of Perinatal Factors on the Occurrence of Asthma and Allergies) [21] from Belgium reported that the introduction of solids during the first 4 months of life was decreasing the risk of infantile eczema in infants of atopic parents. Without atopic family history the timing of the introduction of solids was not relevant.

A recent review summarizes [22[¶]] that the existing scientific evidence is unable to recommend any primary preventive measure in the general population or in different population subgroups.

BREAST-FEEDING

Atopic parents tend to breast-feed longer than non-atopic parents, expecting a protective effect that was reported 30 years ago by the Finnish group of Ulla Saarinen [23,24]. The Swedish BAMSE study (Barn Allergi Milio Stockholm Epidemiologi) [25] showed that a period of 4 months of breast-feeding is protective against later asthma compared with children being breast-fed for a shorter period. A study from New Zealand [26] reported that each month of exclusive breast-feeding was associated with significant reductions in current asthma from 2 to 6 years. Also pooled data of a Swedish and an Australian cohort study [27] found a reduced risk of asthma at age 4, 5 and 8 years if children with a family history of asthma were breast-fed. Although a Dutch study [28] found an inverse association between the duration of breast-feeding and asthma, possibly mediated by the prevention of lower respiratory tract infections, the Danish Copenhagen Prospective Studies on Asthma in Childhood (COPSAC) study [29] showed that prolonged breast-feeding may increase the risk of infantile eczema but reduce the risk for asthma or wheeze during the first 2 years of life. Interpretation of data in cohort studies can be complicated owing to the effect of 'reverse causation'. Mothers in the German MAS (Multicentre Allergy Study) [30] tended to prolong breast-feeding and delay the introduction of solids if the first signs of atopic eczema occur.

Probiotics, prebiotics, synbiotics and the human microbiome

Probiotic bacteria such as *Bifidum* and *Lactobacilli* are more or less ubiquitous in dairy products. However, there are different strains with different immunological properties and concentrations.

The stool flora of atopic and nonatopic individuals was found to be different especially in the number of *Lactobacilli* and *Clostridia*. Furthermore, a reduced diversity of the intestinal microbiota in infancy seems to be associated with an increased risk of allergic disease (sensitization, rhinitis) but not for asthma and atopic eczema at school age [31]. The major determinant for the microbiome of the neonatal gut is the maternal vaginal flora and gut flora. It is assumed that the development of a healthy immune response and tolerance towards apathogenic proteins and glycoproteins is mediated by the microbiome of mucosal surfaces and potentially also of the skin. A caesarian section turns out to be a risk factor for atopy and asthma in many epidemiological trials [32]. Therefore, the recommendations should include avoidance of a delivery via caesarian section if possible.

A review article of 2009 [33] summarized that there is still not enough evidence to recommend probiotics to all children at risk for atopy and asthma. However, in a Finnish trial [34], a subgroup of infants after caesarian section showed a beneficial effect and less allergic sensitization up to the age of 5 years after supplementation with a mixture of probiotics in infancy. In a Dutch interventional trial [35] using three strains (*Lactobacillus lactis*, *B. infantis*, *B. bifidum*) a reduction of atopic eczema was observed during the first year of life.

For *B. infantis* 35624 it could be shown, that the oral consumption is associated with an enhanced IL10-secretion and Foxp3 expression in human peripheral blood [36].

Prebiotics, oligosaccharides, fed to infants with no atopic family history during the first year of life decreases the incidence of atopic eczema [37].

Another controlled trial [38] used heat-killed *B. breve* C50 and *S. thermophilus* 065 (HKBBST) in a nonhydrolysed fermented infant formula in children at high risk of atopy. However, the outcome 'potentially allergic adverse events' was a bit imprecise. The rate of sensitization to cow's milk was decreased in the intervention group at age 12 months.

Tobacco smoke exposure

Maternal smoking during pregnancy and nursing increases the risk for later asthma and allergic sensitization [39]. In a Norwegian study [40] parental asthma, maternal smoking and early respiratory

tract infections turned out to be the major risk factors for decreased lung function in adulthood (not increased). Maternal smoking changes gene methylation of DNA and CpG loci and may, thus, change epigenetic factors like silencing of anti-inflammatory genes [41].

Birth weight and obesity

Newborns with low birth weight (small for gestational age) have an increased risk for later asthma [42]. Obesity in childhood increases the risk for asthma: with increasing BMI point above the 50th percentile the risk increases by 6% [43]. The obesity–asthma link was mainly observed for nonatopic asthma [44]. Increasing adiposity seems to be associated with lower lung function independently of atopic status.

Early exposure to microorganisms and the human microbiome

For the maturation of the immune system the natural contact to microorganisms play a crucial role. The apathogenic contact and infections may modulate the balance of pro-inflammatory and anti-inflammatory responses. The consumption of raw milk in the farming community [45,46] and the exposure to compounds of gram-negative bacteria like *Acinetobacter lwoffii* already *in utero* facilitates protection against later atopy and asthma [47,48]. The protection against eczema is less pronounced. Arabinogalactan from cowshed and also gram-negative bacteria can induce immune modulation of allergic immune responses [49,50] and diversity of microbial exposure was inversely correlated to the risk of asthma in children in PARSIFAL (Prevention of Allergy-Risk Factors for Sensitization in Children Related to Anthroposophic Lifestyle) and GABRIELA (Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the European Community) study [51[■]]. Furthermore, the significance of early contact to infectious agents in day care is discussed [52,53].

In a randomized placebo-controlled trial (Prevention of Atopic Dermatitis using ProSymbioflor PAPS) including 606 newborns with at least single heredity for atopy infants were treated orally with bacterial lysate containing heat-killed gram-negative *E. coli* and gram-positive *E. faecalis* or its placebo from week 5 until the end of month 7. Children were followed until 3 years of age. Primary endpoint was atopic dermatitis at the end of the treatment phase. There was no difference in the primary outcome between the active and placebo groups in the total study group. Atopic dermatitis prevalence was significantly reduced at the end of the intervention phase (31 weeks of age) in the subgroup of infants with

single heredity for atopy [relative risk (RR) 0.52; 95% confidence interval (CI) 0.29–0.93]. Ten percent of infants in the active group had developed atopic dermatitis (15/154) compared with 19% (27/145; $P < 0.03$) in the placebo group. This was more pronounced in the group of infants with paternal heredity for atopy (11 versus 32%; $P < 0.004$; RR 0.34; 95% CI 0.17–0.68). Feeding of this bacterial lysate may have prevented the development of atopic dermatitis especially in children with paternal atopy, possibly indicating a preventive property only in individuals with a limited risk for atopy [54].

Early lower respiratory tract infections, especially respiratory syncytial virus (RSV) and rhinovirus, but also bacteria may increase the risk for acute and later asthma [55–58]. The development of effective and well tolerated vaccines could reduce dramatically the incidence of wheezy bronchitis early in life and later asthma. Furthermore, the COPSAC indicates that the frequently observed coinfection with bacteria and virus in young children with wheezy bronchitis may justify an antibiotic therapy.

The human microbiome, being like a fingerprint, may be a prerequisite for dysregulation of the immature immune system facilitating chronic inflammatory diseases such as asthma and allergy. Ongoing studies may identify microorganisms on mucosal surfaces like the bronchi being a risk and others being protective. So further phenotyping will be possible and potential targets for intervention may be identified [31].

Even in mild asthmatic patients an altered microbial composition is reported, which is similar to that observed in patients with more severe asthma. In induced sputum samples of nonasthmatic and asthmatic adults Firmicutes, Proteobacteria, Actinobacteria, Fusobacterium and Bacteroidetes were the major bacteria. Whereas Proteobacteria were more frequent in asthmatics, Firmicutes and Actinobacteria were more frequent in nonasthmatic individuals [59[■]]. This altered composition could be a potential target for therapy.

Pet keeping

The potentially beneficial harmful or protective effect of pet keeping in urban societies has been discussed controversially. Recent data of a pooled analysis of 11 European birth cohorts indicate neither an increase nor a reduction in the risk of childhood asthma [60]. However, new data emerged, indicating that an increased vaginal *E. coli* colonization in women living with a cat or a dog was associated with an increased rate of urinary tract infections and an increased rate for oral antibiotics. This can affect the commensal vaginal flora and is of particular concern [61[■]].

Allergen avoidance

The Isle of Wight study [62] has reported about the long-lasting asthma-preventive effect of a multifaceted approach of allergen avoidance (house dust mite, food allergens early in life) in infants at risk. At age 18, there was still a lower prevalence of asthma in the prevention group compared with the control group (odds ratio 0.23; 95% CI 0.08–0.7; $P=0.01$). Other trials using multifaceted approaches of allergen avoidance (inhalant and food allergens) were not found to be successful in the prevention of allergic asthma, although the exposure was significantly reduced in the PREVASC study (Prevention of Asthma in Genetically Susceptible Children) [63].

CONCLUSION

Increasing understanding of the development of immune responses and dysregulated inflammatory responses helps to develop new targets for intervention. Although the effect of the early microbial environment and the human microbiome is still under investigation, it will take a while until new interventional trials will enable us to develop new prevention guidelines for young children. First results on prebiotics, probiotics and other bacterial compounds seem to indicate that effects are not observed for every population and further phenotyping will help to develop tailored intervention and prevention measures. The same is true for recommendations targeting nutrition during pregnancy and early in life.

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Conflicts of interest

SymbioPharm Herborn, supported the PAPS interventional trial but was not involved in writing this manuscript. There are no conflicts of interest.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 219–220).

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