



Bacterial lysates in food allergy prevention

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Purpose of review

In the concept of food allergy prevention, no successful strategy could be identified until now. Although interventional trials using probiotics, prebiotics, hydrolyzed formula and bacterial lysates early in infancy were found to reduce the incidence of atopic dermatitis, no effect on food sensitization and allergy could be shown.

Recent findings

Studies in a farming environment showed that early contact to livestock, bacteria and moulds may upregulate the immune responses regulated via Toll-like receptors and thus prevent allergy. There is increasing evidence that the unbalanced composition of the human microbiome on human skin and mucosal surfaces may be a key player in the development of inflammatory diseases like allergy and asthma. However, during the last 5 years, this concept could not yet be verified in the interventional trials. There are few studies using bacterial lysates, for example, *Escherichia coli* plus *Enterococcus faecalis* in ProSymbioflor and heat-killed *Bifidobacterium breve* and *Streptococcus thermophilus*; however, food allergy prevalence could not be reduced by these interventions.

Summary

During the last 5 years, new interventional trials addressed the use of bacterial lysates. There was only an effect on eczema in the ProSymbioflor trial, whereas the trial using *B. breve* and *S. thermophilus* in a cow's milk formula showed a slight reduction of food sensitization at the age of 12 months. However, these strategies need further investigation and success seems to be restricted to certain subpopulations.

Keywords

bacterial lysate, food allergy prevention, human microbiome

INTRODUCTION

The human microbiome and early contact with environmental microbial compounds are very important for a healthy development of the immune system and especially for tolerance towards food proteins [1].

Recent trials try to analyse the human microbiome on the skin and mucosal surfaces as a potential cause and target of unbalanced immune responses. The stool flora of atopic and nonatopic individuals were 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 and rhinitis), but not for asthma and atopic eczema at school age [2]. The major determinant for the microbiome of the neonatal gut is the maternal vaginal and gut flora. A caesarean section turns out to be a risk factor for atopy and asthma in many epidemiological trials [3].

In search of protective factors, epidemiological studies reliably showed that continuous exposure to microbial compounds (e.g. lipopolysaccharides, LPS, of Gram-negative bacteria) during pregnancy

and early infancy was associated with a lower prevalence of atopy and asthma in children, especially in rural areas (farm effect) [4], and also in other populations [5]. As a proof of this concept, animal models confirmed that prenatally initiated LPS exposure decreased the allergic sensitization and airway inflammation [6]. The consumption of raw milk in the farming community [7,8] and the exposure to compounds of Gram-negative bacteria like *Acinetobacter lwoffii* already *in utero* facilitates the protection against atopy and asthma later [9,10,11]. Obviously, maternal exposure to an environment rich in microbes upregulates the receptors of innate immunity, the so-called Toll-like receptors (TLRs), especially TLR2 and TLR4. Thus,

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KEY POINTS

- Interventional trials on the significance of the human microbiome in infancy and later atopy and asthma are ongoing.
- Studies until to date using orally applied bacterial lysates as primary prevention measures showed no reduction of food allergy in populations at risk.
- Further studies are necessary to evaluate the potentially beneficial effect of bacterial lysates on the development of food allergy and other atopic outcomes.

the infantile immune system is directed to a Th1-type like affinity and tends to gradual inhibition of Th2 phenotype, and finally to postnatal induction of tolerance [12]. Further, in a recent birth cohort study, maternal contact with farm animals and cats during pregnancy had a significantly protective effect on the manifestation of atopic dermatitis during the first 2 years of life, associated with elevated gene expression of TLR5 and TLR9 in cord blood. A significant interaction between polymorphism in TLR2, which binds particularly peptidoglycan of Gram-positive bacteria, and prenatal cat exposure was additionally observed [13]. In a mouse model, feeding with *Clostridium leptum* increased the percentage and total number of Tregs in the spleens and mediastinal lymph nodes, and attenuated allergen-induced airway hyperresponsiveness and inflammation by inhibiting inflammatory cytokine production but enhancing IL-10 and TGF- β 1 production in the lungs [14]. In the serum of rats that received a bacterial lysate (*Escherichia coli* Enterococcus faecalis) in addition to ovalbumin sensitization, the levels of allergen-specific IgE and IgG were significantly reduced compared with the animals which were not exposed to the bacterial lysate. This was accompanied by an elevated cytokine production of IL-10 [15]. In light of these intriguing data, it is reasonable to mimic this protective effect of microbial exposure in an interventional approach.

Oral application of bacterial lysates (*E. coli* and *E. faecalis*) in infancy decreases the risk of atopic dermatitis in children with one atopic parent in a randomized placebo-controlled trial [16] – the Prevention of Atopic Dermatitis in infants with atopic parents using ProSymbioflor (PAPS) study.

In a randomized placebo-controlled trial including 606 newborns with at least single heredity for atopy, infants were treated orally with bacterial lysate containing heat-killed Gram-negative *E. coli* Symbio and Gram-positive *E. faecalis* Symbio or its placebo from week 5 until the end of month 7. Children were followed until 3 years of age. Primary

outcome was atopic dermatitis at the end of the treatment phase at 7 months of age. Secondary endpoints were atopic dermatitis at later age, food sensitization and wheezy bronchitis. There was no difference in the primary outcome between the active and placebo groups in the total study group. However, there was a significant difference in the atopic dermatitis prevalence at the end of the treatment period (31 weeks of age) in the subgroup of infants with single heredity for atopy. Whereas 10% of infants in the active group had developed atopic dermatitis [15 of 154 Intention to treat (ITT) analysis], 19% (27 of 145; $P=0.03$) had developed atopic dermatitis in the placebo group [relative risk (RR) 0.52; 95% confidence interval (CI) 0.29–0.93]. This was even more pronounced in the group of infants with only paternal heredity for atopy (11 versus 32%; $P=0.004$), showing a reduction of the RR for atopic dermatitis of almost 70% (RR 0.34; 95% CI 0.17–0.68). In this subgroup, the significantly different prevalence rates were also observed after the intervention phase at 1 year of age ($P=0.020$) and remained borderline until the end of the follow-up phase. In the ITT analysis, in order to prevent one case of atopic dermatitis, 11 children with single heredity or 5 with paternal heredity had to be treated with the study medication. Mean survival times without eczema at the end of the treatment phase were 34.8 weeks in the treatment group and 34.3 weeks ($P=0.035$) for the placebo group in children with single atopic family history for atopy. For children with atopic fathers, the mean survival times were 31.7 and 30.6 weeks at the end of the treatment phase ($P=0.003$) and 135 and 114 weeks at the end of the follow-up phase ($P=0.003$), respectively.

The treatment effect was strongest for infants with a single parent suffering from allergic rhinitis ($P=0.001$; data not shown). If allergic asthma was present in a single parent, the effect was significant, but weaker ($P=0.040$). No effect was seen if a parent showed atopic dermatitis or a combination of atopic symptoms. In the subgroup with paternal atopy only, less parental eczema was reported than in the other subgroups (13% compared with 37% in the group of double heredity and 26% in the group of maternal heredity).

There was no difference in specific serum IgE levels between intervention and placebo groups at any time (total study group). A total of 121 infants in the placebo group and 114 infants in the active group showed elevated levels of serum IgE to food allergens, whereas 3 infants in the placebo group and 4 in the active group already were found to have elevated levels of serum IgE to inhalant allergens at the age of 7 months. The most frequent sensitizations observed at the end of the treatment phase

were against cow's milk, hen's egg and peanut. Median total IgE concentration in serum was 5 kU/l for both treatment groups at the age of 7 months ($P=0.820$), 14.95 kU/l in the active group and 16.5 kU/l in the placebo group ($P=0.740$) at the age of 24 months and 24.3 versus 22.9 kU/l at the age of 36 months ($P=0.02$). In the group with single heredity for atopy, only at age 36 months, there was a slightly significant difference between active and placebo group (11.8 versus 17.9 kU/l; $P=0.020$). There was no effect on the prevention of food allergy during the first 3 years of life.

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 [16].

A NONHYDROLYZED, FERMENTED MILK FORMULA REDUCES DIGESTIVE AND RESPIRATORY EVENTS IN INFANTS AT HIGH RISK OF ALLERGY

Another multicentre, randomized, double-blind controlled trial used heat-killed *Bifidobacterium breve* C50 and *Streptococcus thermophilus* 065 (HKBBST) in a nonhydrolyzed fermented infant formula in children at high risk of atopy [17]. Primary outcome was the incidence of 'allergy-like events' during the first 2 years of life. Infants used HKBBST or a standardized formula (SIF) since birth until 1 year of age, and were followed at 4, 12 and 24 months after birth. Skin prick tests for six foods and six aeroallergens were systematically performed and adverse events were recorded. In case of potentially allergic adverse events (PAAEs), allergy could be further tested by skin prick tests, patch tests and quantification of specific IgEs. If cow's milk allergy was suspected, an oral challenge could also be performed. The study included 129 children, 63 randomized to SIF and 66 to HKBBST. The use of HKBBST did not alter the proportion of cow's milk allergy, but decreased the proportion of positive skin prick test to cow's milk (1.7 versus 12.5%; $P=0.03$). There was a tendency that potentially allergic digestive and respiratory symptoms were reduced in the prevention group at 12 and 24 months of age; however, at the age of 12 and 24 months, wheeze is usually virally induced and not allergic.

CONCLUSION

The effect of the early microbial environment and the human microbiome is still under investigation. First trials investigating bacterial lysates in the prevention of eczema, food allergy and wheeze showed different results. Whereas the PAPS study [16] showed only effects in subpopulations, mainly on eczema but not on food allergy, the study [17] using

nonhydrolyzed fermented formula only showed differences in cow's milk sensitization and viral wheeze, but no effect on cow's milk allergy and eczema. Further investigations are necessary in order to elucidate the underlying mechanisms.

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None.

Conflicts of interest

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 319).

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