Probiotics and eczema.

Probiotics, originally conceived for treatment of gastrointestinal diseases and later applied to allergy prevention, are increasingly proposed for the treatment of allergic disease. At the state of the art, clinical researchers need to integrate claims that probiotics affect the incidence of specific allergic manifestations. The definition of “probiotic,” a mix of Latin (pro=for, in favor of) and Greek (bios=life) was coined, as opposite to “antibiotic,” in the 1960s to define substances produced from protozoa and able to support the growth of other microorganisms. They have been defined as “Live microorganisms which, when administered in adequate amounts, confer a health benefit on the host.”

The knowledge gap is how to harness the microbiota to reverse the clinical symptoms of allergic diseases such as eczema, rhinitis, food allergy and asthma. At a time when personalised allergy and gastroenterological medicine are in the offing, we are realizing the complexity of the many-tiered microbe-host interactions. This represents a matter of concern for allergists because the translation from possible prevention effects to therapeutic efficacy remains to be demonstrated. Up to 2010 statements and scientific opinions published on the topic in Europe did focus only on the claims of specific products or areas of competence. In 2013, a metanalysis showed that probiotics in early life may reduce total IgE and protect against atopic sensitization but does not appear to protect against asthma and wheeze. Thus, eczema seems the more interesting area. There is a considerable body of literature published to date, with randomized controlled trials for treating eczema with probiotics and for preventing eczema in humans. Attempts at systematization have been thwarted by the heterogeneity of probiotic products, study protocols, and allergy markers used in analyses of the immune modulation induced by probiotics. The issue of which probiotic is used is inconsequential. It is well known that individual strains pulse dendritic cell activation differently. Thus the cytokine profile emerging in response to treatment is substantially altered, thereby confounding clinical interpretation. Critical to the endorsement of treatment with supplemented probiotics are two of the most quoted studies in the prevention literature, from which much of the rationale for treatment is derived. Both studies used the same micro-organism and similar protocols, but achieved diametrically opposite eczema outcomes: one claimed to show efficacy whereas the other showed a lack of clinical effects.
In the treatment of eczema, most studies have tested Lactobacillus species, either alone or in combination with other probiotics and/or prebiotics. One proof-of-principle study specifically targeted adults. Systematic review and/or meta-analyses of 12 of the 14 published studies have been undertaken by 3 separate groups. A Cochrane systematic review and one other meta-analysis found no evidence that probiotics are effective for treating eczema, albeit with significant heterogeneity between the outcomes of different studies. A third meta-analysis found a statistically significant effect of probiotic treatment on the mean change in SCORAD index from baseline to the end of treatment (mean difference between groups −3.01 points; 95% confidence interval, −5.36 to −0.66; \( P = 0.01 \)); however, this effect size is of limited clinical significance.

All but one preventive study evaluated lactobacilli (7 used L. rhamnosus strain GG), either alone or in combination with other probiotics and/or prebiotics. At least 10 studies limited recruitment to women carrying a fetus at high inherited risk of allergic disease. However, the studies were heterogeneous in other respects, particularly in the timing of the intervention. In 10 studies, treatment was started during pregnancy, in one during the first trimester, and in the others in the last trimester. In 3 of the last trimester interventions, maternal treatment stopped with delivery, and in 7 it was continued for some time during breastfeeding. In 10 studies, a probiotic was given directly to all infants during the postnatal period, usually commencing early, but in 3 studies administration started after 3 months. Treatment ceased within the first year in almost all studies, except for one study which continued for 2 years. No study replicated the design and intervention of a previous successful prevention trial, with the exception of the study by Kopp and colleagues, which yielded different findings to the similarly designed study by Kalliomaki et al. With these caveats in mind, a number of authors have undertaken systematic reviews and/or meta-analyses of the randomized controlled trials evaluating the probiotic effect in eczema prevention. Two meta-analyses have found no evidence that probiotics prevent the development of atopy. A Cochrane systematic review included 5 of the 14 trials in meta-analysis, finding a relative risk of 0.82 (95% CI 0.70, 0.95) attributable to probiotic treatment. A more recent meta-analysis that included 12 of the 14 trials similarly found a relative risk of 0.79 (95% CI 0.67, 0.92). Neither meta-analysis found evidence that probiotics can prevent the development of atopy. There was significant heterogeneity in study outcomes in these meta-analyses (I2, 64% and 31%). Subgroup analysis suggested that infant treatment without maternal treatment may be ineffective. The authors of the Cochrane review advised caution in interpreting the results of their meta-analysis, due to heterogeneity and high rates of loss to follow up (17–61%) in the individual trials.

Recent discoveries in the human microbiome indicate that a new page is being written involving the microfloras in the defense of the host. So far, we have not been able to link these benchside breakthroughs with applications in our daily clinical practice. For these reasons, WAO issued in 2012 a document entitled “Clinical Use of Probiotics for Pediatric Allergy” (CUPPA): the main objective of the document was to foster research efforts towards a closer allergological focus in probiotics research. The document is intended to

1. encourage translational research documents showing the achievements reached and providing guidance for future research
2. educate physicians worldwide to foreseeable applications of probiotics to treatment and prevention
3. equip physicians with the tools necessary to interpret and apply primary research in probiotic science
4. create and raise awareness in patients towards the realistic applications of probiotic containing products.

CUPPA is a state-of-the-art review outlining epistemology, proof of principle, quality of clinical studies and current microbiological and allergy research. The document defines

- knowledge base
- clinical applications
- designing a probiotic for allergy treatment
- educational modules
and provides the scientific basis on which the various regulatory bodies could base their deliberations15.

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