

Probiotics, Prebiotics & Food allergy Prevention: Clinical Data in Children

Alessandro Fiocchi, Valentina Pecora,
and Lamia Dahdah

ABSTRACT

Purpose of review: there are accruing evidences on the role of the intestinal microbiota in the development of allergic diseases among infants. Elaborating on this theoretical basis, studies did assess the possibilities to prevent allergic diseases in infancy through manipulation of the intestinal microbiota. We review here such studies.

Recent findings: interventional studies led to conflicting conclusions on the possible role of probiotics and prebiotics in allergy prevention. Two meta-analyses published in 2015 did reconcile all data. Guidelines have been predicated on such studies using the GRADE methodology.

Summary: the guidelines for allergy prevention suggest for the first time the use of probiotics and prebiotics. The existing evidences stand for a use of such supplementation in particular for the prevention of eczema. As there is no evidence so far of superiority of one probiotic strand over the others, they should be considered as class and not as individual products.

Key Words: Food allergy, Guidelines, Meta-analysis, Probiotics

Abbreviations: AD, atopic dermatitis, GLAD-p, GuideLines on Allergic Disease-prevention, LGG, *Lactobacillus GG*

INTRODUCTION

Allergies are more common today among the inhabitants of affluent countries than they were 70 years ago; yet remain uncommon in poorer nations (1). There are probably hundreds of explanations for this phenomenon, but there may be bacteriological possibilities worthy of investigation. The kinds and amounts of microbes (particularly parasitic worms) that babies are exposed to now may differ compared to 60 years ago. This possibility cannot be determined scientifically, but comparisons of bowel microbiota of infants born in countries with low or high prevalence of allergies have been reported to show differences (2). The exposure of infants to different kinds of microbes in different geographical regions is influenced by ethnicity and maternal diet, different hygiene standards, different obstetrical practices, and the amount of use of antibiotics. Therefore, a connection between the composition of the microbiota in early life, the programming of the immune system in terms of later response to environmental allergens, and predisposition of the child to allergies, is a rational proposition (3).

Probiotics, Prebiotics and Food Allergy Prevention: Clinical Data

The 'hygiene hypothesis' proposes that, as result of modern public health practices, individuals experiencing a relative deficiency in immune stimulation by microbes become vulnerable

to the development of allergic hypersensitivities and their associated diseases. Working on this concept, studies aiming to evaluate the effect of probiotic administration on the development of various aspects of allergic disease in children have been developed in the last 15 years. If they were demonstrated able to exert local and systemic immunological effects (4), their administration may provide a tool to probe the relationship between specific microbial exposures and allergies.

The first preventive study hypothesizing that probiotics can reduce food allergy and thus atopic dermatitis (AD) assessed 159 pregnant women with history of atopy in the foetus' parents or siblings. At 2–4 week pre-natally and for 6 months during lactation, mothers were given a placebo or *Lactobacillus GG* (LGG, 10,000 CFU daily). Non-breastfed infants were given the material directly orally. The infants were followed for several years. Among 132 children who completed the follow-up, AD incidence – but not food allergy incidence – in the probiotic group was one-half of that in the placebo group (5).

After this seminal study, many others elaborated on the topic of allergy prevention. The interventions were the administration of probiotics, prebiotics or symbiotics. Their outcomes included AD, food allergy, paediatric asthma and allergic rhinitis, yielding conflicting results. Non-systematic reviews casted doubts on the real effects of these approaches³, and guidelines remained sceptical about the real opportunity to suggest the use of probiotics or prebiotics for allergy prevention (6). The basic problem posed by supplementation of probiotic species remains to durably modulate the autochthonous microflora towards treatment applications in the allergy setting. The effect of supplemented probiotic bacteria on the evolutionarily conserved homeostatic mechanisms, however, is only initially been addressed³.

Probiotics, Prebiotics and Food Allergy Prevention: Meta-analyses

Clinical studies using probiotics or prebiotics in allergy prevention are now quite numerous, allowing the production of meta-analyses. These revisions are able to overcome the difficulties in interpreting health benefits (different strains, different doses, utilization of experimental preparations instead of actual probiotic products available to the clinician, use of pro- and pre-biotics as part of the diet, variable outcomes between results from independent trials). Meta-analyses published up to 2014 revising the use of probiotics individually on the outcomes of sensitization, food allergy, rhinitis, asthma and AD conclude that probiotics may obtain a modest reduction in AD and allergic sensitization.

In 2015, two meta-analyses evaluated the issue (7,8). The first, produced by our group to inform the Guidelines on allergy prevention (GLAD-p, see *infra*), evaluated probiotics in different forms:

- direct (given to infants as an oral supplement or in the context of milk formulae in non-breastfed infants)
- indirect (given to mothers during breast-feeding or pregnancy).

It assessed the following outcomes: eczema, asthma and/or wheezing, food allergy, allergic rhinitis, adverse effects, severe adverse effects. The meta-analysis identified 29 studies corresponding to the search criteria. Only a minority gave a direct evidence, *i.e.* were exclusively targeted to the specific outcomes in a specific period: one for probiotics given in pregnancy, one for probiotics given during breastfeeding, and seven for probiotics given in infancy. The remaining 20 studies gave evidence either for pregnancy and infancy (8 studies), for pregnancy and breastfeeding

From the Allergy Department, The Bambino Gesù Children's Research Hospital, Rome Italy.

Address correspondence and reprint requests to Dr. Alessandro Fiocchi, MD, Piazza di S. Onofrio, 4 - Pediatric Hospital Bambino Gesù-00100-Rome, Italy (e-mail: allerg@tin.it).

Sponsored research in the field of probiotic by Valeas.

(4 studies), or for pregnancy, breastfeeding and infancy (8 studies). Most of the studies present a moderate-to-serious risk of bias, in particular about concealment of allocation and the number of patients lost to follow-up. That said, the effects on the development of eczema are significant for all three interventions: as seen in Figures 1–3, the administration of probiotics reduces the risk of eczema in infants:

- by 9 per 100 (RR 0.72 [95%CI 0.60–0.86]) when given during pregnancy
- by 16 per 100 (RR 0.58, [95%CI 0.47–0.72]) when given during breastfeeding
- by 5 per 100 (RR 0.82, [95%CI 0.70–0.96]) when given during infancy.

No effect was found on other allergy outcomes. Regrettably, the search found large variability in probiotics and their mixtures used in the studies, precluding any conclusions about the effects of specific strains. This gave occasion for a comment by researchers contending the fact that, as clinicians must act on precise indications, they need data on individual probiotic strains. In other words, one should refrain from pooling data on different probiotics (9). Their metanalysis on LGG in allergy prevention was coincident with our data; therefore, even if LGG is the most-studied probiotic in allergy prevention, it is not possible for the moment give a univocal indication. We agree that this is unfortunate, as the strain of probiotic may be an important factor in its preventive efficacy (10).

The other metanalysis on the effect of probiotic supplementation during pregnancy and early infancy in preventing atopic disease localized 17 studies, reporting data from 4755 children (2381 in the probiotic group and 2374 in the control group). It confirms that infants treated with probiotics had a significantly lower RR for eczema compared to controls (RR 0.78 [95% CI: 0.69–0.89], $P=0.0003$). It indicated that mixtures of probiotics might be more effective (RR 0.54 [95% CI: 0.43–0.68]). No significant differences were found for asthma (RR 0.99 [95% CI: 0.77–1.27]), wheezing (RR 1.02 [95% CI: 0.89–1.17]) or rhinoconjunctivitis (RR 0.91 [95% CI: 0.67–1.23])⁸.

The GLAD-p Recommendations (11)

Based on the aforementioned metanalysis, the GLAD-p recommendations for probiotics provide guidance for their use in the context of allergy prevention. The new aspect is an opening to an intervention in infants is high-risk for allergy. According to the metanalysis, ‘high-risk for allergic disease’ is defined as having a biological parent or sibling with existing or history of allergic rhinitis, asthma, eczema, and/or food allergy. If this risk is extant, the WAO guideline panel suggests using probiotics in the following situations:

- pregnant women at high risk for allergy in their children
- women who breastfeed infants at high risk of developing allergy
- infants at high risk of developing allergies.

In these situations, infants would profit of a net benefit resulting primarily – but not exclusively – from prevention of eczema. All recommendations are conditional, and thus non-mandatory.

The recently published GLAD-p guideline on prebiotics is based on a metanalysis of 18 interventional studies, all performed by the administration of prebiotics in formulae. None of the studies was performed in pregnant or in breastfeeding mothers. The results indicate a risk reduction for developing eczema, but the estimate is not precise and does not exclude the possibility of no effect with a risk ratio (RR) of 0.57 [95% CI: 0.30 to 1.08]. Two studies evaluated the risk for development of asthma or wheezing showing a decrease in the risk (RR: 0.37, 95% CI: 0.17 to 0.80). Only one study assessed the risk of developing food allergy and reported a reduced risk that was also estimated imprecisely, not excluding no effect (RR: 0.28, [95% CI: 0.08 to 1.00]). Twelve studies measured nutritional status (weight gain in most studies) and found no difference between prebiotics and control groups (SMD: 0.06, 95% CI: -0.02 to 0.15). According to these data, the WAO guideline panel chose to provide no recommendation for pregnant and breastfeeding mothers, owing to lack of experimental and observational studies in which prebiotic supplements would be used in such settings. For infants, prebiotic

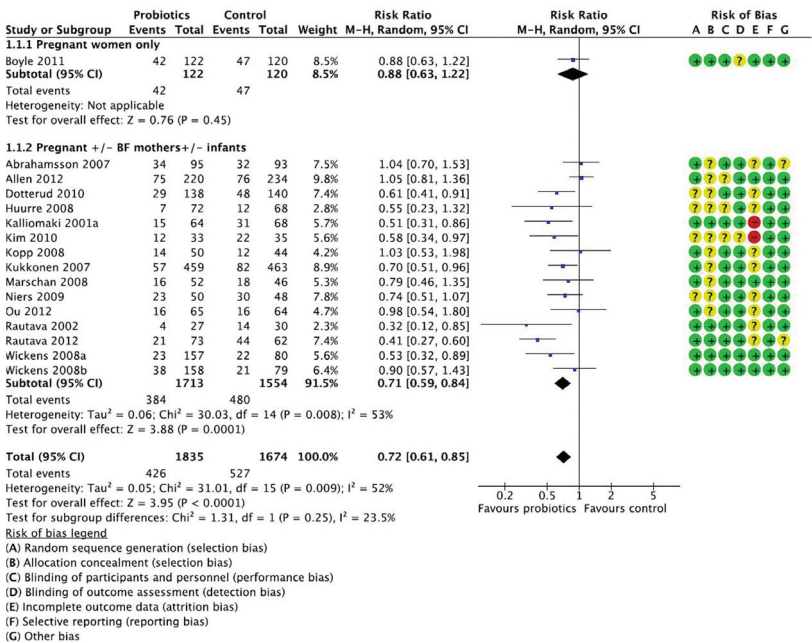


FIGURE 1. Probiotics in pregnancy and eczema⁷.

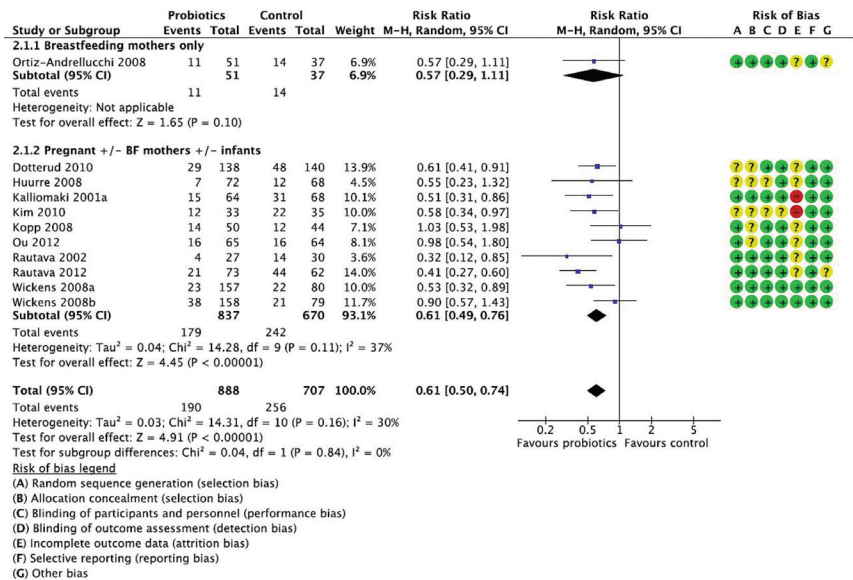


FIGURE 2. Probiotics in breastfeeding and eczema ⁷.

supplementation was conditionally suggested in all not-exclusively breastfed infants, both at high and at low risk for developing allergy (low certainty of evidence) (12).

Of course, the question of the use of pro- and pre-biotics for allergy prevention is far from being completely elucidated. A list of information is still needed, including interventional studies on

- better instruments than family history for evaluating the risk of allergy in children (it predicts only about 30% of the population risk)
- possible differences among the strains of the same probiotic species;
- the effects of probiotics in different situations (for instance, in the firstborns vs. subsequent)

- the effects of prebiotics in different situations (for instance, in pregnancy & breastfeeding).

We completely lack follow-up studies to evaluate the long-term effects of the administration of probiotics and pre-biotics. Most important, what is needed is a deeper knowledge of the microbiome in its relationship with the development of atopic dermatitis and the allergic disease. In this situation, I would expect more non-interventional studies on the microbiome of children prone to develop food allergy and/or AD vs. healthy children. The interventional studies proposing probiotics for the primary prevention of the allergic disease completely jump this step.

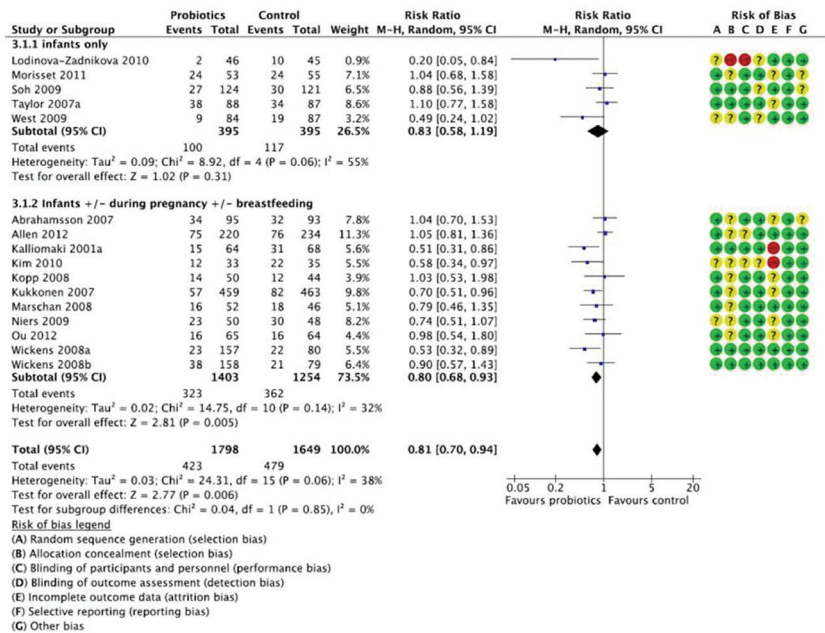


FIGURE 3. Probiotics in infancy and eczema ⁷.

CONCLUSIONS

The recent metaanalyses on the use of probiotics and prebiotics in the context of allergy prevention paved the way to new guidelines. We are more open to the use of these products than in the past, but the evidence basing the recommendations is still tiny. Currently, the main obstacle to harness the power of the microflora through supplementation of prebiotics or commercial strains of probiotics lies in our ignorance of how different microflorae interact with the host, at different stages of development, in health and particularly in allergic disease. Future studies will take stock of state-of-the-art methods for the evaluation of the microflora to better define the indications, the probiotic strains, the type of prebiotic used (13).

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