Probiotics for allergy prevention

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Received: 10 June 2015/ Accepted: 23 October 2015
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Abstract

Probiotics, given either as a supplement or in infant foods, have been evaluated in randomised controlled trials for allergy prevention. Here, the aim is to give an overview of the results from these primary prevention studies and to discuss current strategies. In most studies, single strains or a mixture of strains of lactic acid bacteria and bifidobacteria have been used – prenatally, postnatally or perinatally. Several meta-analyses have reported a moderate benefit of probiotics for eczema prevention, and the most consistent effect has been observed with a combined perinatal intervention in infants at high risk of allergic disease due to familial predisposition. In a recent meta-analysis, the use of multi-strain probiotics appeared to be most effective for eczema prevention. No preventive effect has been shown for other allergic manifestations. As long-term follow-up data on later onset allergic conditions (asthma and allergic rhinitis) are available only from a few of the initiated studies, reports from ongoing follow-up studies that are adequately powered to examine long-term outcomes are anticipated to provide more insight. Arguably, the differences in many aspects of study design and the use of different probiotic strains and combinations have made direct comparison difficult. To date, expert bodies do not generally recommend probiotics for allergy prevention, although the World Allergy Organization (WAO) in their recently developed guidelines suggests considering using probiotics in pregnant women, during breastfeeding and/or to the infant if at high risk of developing allergic disease (based on heredity). However, in concordance with other expert bodies, the WAO guideline panel stressed the low level of evidence and the need for adequately powered randomised controlled trials and a more standardised approach before clinical recommendations on specific strains, dosages and timing can be given.

Keywords: asthma; children; eczema; microbiota; probiotic

1. Introduction

Over the last decades there has been a dramatic increase in the prevalence of allergic diseases and the disease burden is enormous in a global perspective (Pawankar, 2014). The earliest manifestations are commonly atopic eczema and food allergy and children with a family history of allergic disease have the highest risk. Studies have reported a prevalence of atopic eczema in infants ranging between 10-30%, with marked differences between countries (Draaisma et al., 2015). The risk of developing allergic disease is influenced by a complex interplay between genetic predisposition and many environmental exposures, reviewed by (Harb and Renz, 2015; Hoffjan and Stemmner, 2015). Consequently, the triggers of the allergy epidemic have been sought in our modern way of living; one of these is the general microbial deprivation characterising our modern lifestyle. This led to the hypothesis that the changes in our indigenous microbiota impair immune regulation and tolerance development to increase allergy risk (Haahreta et al., 2013; Hanski et al., 2012). As the development of the gut-associated lymphoid tissue (GALT) and tolerance is shaped by exposure to microorganisms in the gut, summarised by (Renz et al., 2012), there has been much interest in strategies to modulate the gut microbiota for allergy prevention. These strategies include administration of probiotics, i.e. ‘live microorganisms, which when administered in adequate amounts, confer a health benefit on the host’ (FAO/WHO, 2001).

Here, the aim is to give an overview of the results of randomised controlled trials (RCTs) using probiotics for primary prevention of allergic disease and to discuss current recommendations. RCTs using a prenatal, postnatal or
combined perinatal probiotic intervention are included in this review.

2. Gut microbiota and immune programing

Approximately two thirds of the body’s immune cells are located in the GALT, and there is ‘cross-talk’ between intestinal microorganisms and the immune system. In germ-free murine models, it has been shown that gut microbiota impact both local and systemic immune responses with potential to modify the propensity for development of sensitisation and allergy risk, and that intestinal colonisation in early life is needed for normal immune system maturation and immune regulation (Gaboriau-Routhiau et al., 2009; Sudo et al., 1997). If such an early critical window is relevant to the human setting is not definitely shown, but could be consistent with reports on intestinal dysbiosis and reduced gut microbial diversity in infancy to be associated with increased risk for subsequent allergic manifestations in childhood, which is recently reviewed elsewhere (West et al., 2015a,b). Early studies reported differences in gut microbiota composition and lower counts of bifidobacteria and lactobacilli in the infant gut to precede the onset of allergic manifestations (Björkstén et al., 1999, 2001; Kalliomäki et al., 2001a). Together with reports of immunomodulatory capacities of specific probiotic strains (Cross and Gill, 2001) and preliminary results of a therapeutic effect of probiotics in the treatment of eczema (Isolauri et al., 2000), this laid the ground for probiotics for allergy prevention. Further support was then provided from a large-scale pregnancy cohort study reporting associations between probiotic milk consumption in pregnancy and childhood, and a reduced relative risk of reported atopic eczema and allergic rhinoconjunctivitis at three years of age (Bertelsen et al., 2014).

3. Probiotics in clinical allergy prevention studies

Probiotics, given either as a supplement or in foods, have been evaluated in randomised double-blind controlled trials for primary prevention of allergic disease (Table 1). There are also two open, controlled trials that have assessed the efficacy of an Escherichia coli strain and a combination of two bifidobacterial strains for allergy prevention, respectively. In the former, 0.8×10⁹ lyophilised E. coli was administered orally to the infant within 48 h and then three times a week for the first month of life (Kocourkova et al., 2007). An allergy-preventive effect (the type of manifestation was not specified) was observed at 2 and 5 years, compared to controls (Kocourkova et al., 2007; Lodinova-Zadnikova et al., 2010). In the latter, a combination of two bifidobacterial strains was given to mothers one month prior to delivery and then postnatally to their infants for 6 months. The risk of developing eczema in the first 18 months of life was reduced in the probiotic group compared with a control group that did not receive any intervention (Odds ratio (OR) = 0.231; 95% confidence interval (CI): 0.084-0.628) (Enomoto et al., 2014).

As displayed in Table 1, single strains or a blend of strains of lactic acid bacteria or bifidobacteria have been used for allergy prevention. The effect has been variable, however, several meta-analyses have reported a moderate benefit of probiotics for eczema prevention (Cuello-Garcia et al., 2015; Foolad et al., 2013; Pelucchi et al., 2012; Zuccotti et al., 2015) and the most consistent effect has been observed with a combined perinatal intervention in infants at high risk of allergic disease due to familial predisposition (Foolad et al., 2013). In a very recent meta-analysis including 4,755 children (17 trials) where probiotic supplementation was initiated in pregnancy or within the first month of life, there was a significantly lower risk ratio (RR) for eczema in the probiotic compared with the control group (RR=0.78; 95%CI: 0.69-0.89, P=0.0003). Notably, the benefit was particularly evident in those supplemented with a combination of probiotic strains (RR=0.54; 95%CI: 0.43-0.68, P<0.00001) (Zuccotti et al., 2015). This could be an indication that multiple strains are more effective, at least the combinations that have been evaluated. There is some support for this concept as synergistic effects have been reported, including increased mucus binding of bifidobacteria by probiotic lactobacilli (Ouwehand et al., 2000).

No preventive effect has been shown for other allergic manifestations (Table 1), but to date, long-term follow-up data are only available from eight of the initiated studies (Abrahamsson et al., 2013; Jensen et al., 2012; Kalliomäki et al., 2007; Kuitunen et al., 2009; Loo et al., 2014; Simpson et al., 2015; West et al., 2013; Wickens et al., 2013). This restricts an overall evaluation of later onset allergic manifestations, such as asthma and allergic rhinitis. In a meta-analysis evaluating the preventive effect of probiotics on asthma, including 3,257 infants (nine trials), the RR of doctor diagnosed asthma in participants randomised to receive probiotics was 0.99 (95%CI: 0.81-1.21) (Azad et al., 2013). However, the authors underscored that the trials were variable in type and duration of probiotic treatment, length of clinical follow-up and that none of the included studies were sufficiently powered for asthma as a primary outcome (Azad et al., 2013). Long-term follow-up data of already initiated large-scale probiotic studies are anticipated to provide more insight.

4. Strain specific effects

Even though the effects of probiotics are viewed upon as strain specific, few studies have directly compared the efficacy of different probiotic strains (Table 1) (Rautava et al., 2012; Wickens et al., 2008). Wickens and coauthors (2008) randomly assigned pregnant women at 35 weeks
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Table 1. Summary of randomised controlled trials using probiotics for primary prevention of allergic disease.

<table>
<thead>
<tr>
<th>References</th>
<th>Study population</th>
<th>Probiotic(s) and dose</th>
<th>Benefit on eczema</th>
<th>Sustained benefit on eczema at follow-up</th>
<th>Benefit on allergic rhinitis, wheeze and/or asthma</th>
<th>Effects on objective lung function measures</th>
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</thead>
<tbody>
<tr>
<td><strong>Studies using Lactobacillus rhamnosus GG</strong></td>
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<tr>
<td>Kalliomäki et al. (2001b, 2003, 2007)</td>
<td>High risk&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Dose: 1×10&lt;sup&gt;10&lt;/sup&gt; cfu daily given to mothers 2-4 weeks before delivery and then to breastfeeding mother or directly to infant for 6 months</td>
<td>eczema reduction in the probiotic group at 2 years</td>
<td>eczema reduction in the probiotic group at 4 and 7 years</td>
<td>no reduction of IgE-associated eczema in the probiotic group at 2 years</td>
<td>lower FeNO levels in the placebo group at 4 years</td>
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<td>Kopp et al. (2008)</td>
<td>High risk&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Dose: 1×10&lt;sup&gt;10&lt;/sup&gt; cfu daily given to mothers 4-6 weeks before delivery and then to breastfeeding mother for 3 months or to infant for 6 months</td>
<td>no</td>
<td>not reported</td>
<td>no reduction of allergic rhinitis at 4 years, both probiotics; no differences between the groups in wheeze, asthma or rhinoconjunctivitis</td>
<td>no differences between the groups when evaluated by spirometry reversibility test and FeNO levels at 7 years</td>
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<tr>
<td>Boyle et al. (2011)</td>
<td>High risk&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Dose: 1.8×10&lt;sup&gt;10&lt;/sup&gt; cfu daily from 36 weeks gestation until delivery</td>
<td>no</td>
<td>not reported</td>
<td>no</td>
<td>no differences between the groups when evaluated by spirometry reversibility test and FeNO levels at 6 years</td>
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<td>Ou et al. (2012)</td>
<td>High risk&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Dose: 1×10&lt;sup&gt;10&lt;/sup&gt; cfu daily from second trimester and then 6 months to mother if breastfeeding or directly to infant</td>
<td>no</td>
<td>not reported</td>
<td>no differences between the groups when evaluated by spirometry reversibility test and FeNO levels at 8 years</td>
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<td><strong>Studies using other single strains</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
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<td>Prescott et al. (2008b); Taylor et al. (2007)</td>
<td>High risk&lt;sup&gt;2&lt;/sup&gt;</td>
<td>L. acidophilus (LAVRI-A1) 3×10&lt;sup&gt;9&lt;/sup&gt; cfu given within 48 hours, and then for six months, directly to infant</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no differences between the groups when evaluated by spirometry reversibility test and FeNO levels at 7 years</td>
</tr>
<tr>
<td>Abrahamsson et al. (2007, 2013)</td>
<td>High risk&lt;sup&gt;1&lt;/sup&gt;</td>
<td>L. reuteri 1×10&lt;sup&gt;9&lt;/sup&gt; cfu daily 2-4 weeks before delivery and then to infant for 12 months</td>
<td>no reduction of eczema, but reduction of IgE-associated eczema in the probiotic group at 2 years</td>
<td>no</td>
<td>no</td>
<td>no differences between the groups when evaluated by spirometry reversibility test and FeNO levels at 5 years</td>
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<tr>
<td>Wickens et al. (2008, 2012, 2013)</td>
<td>High risk&lt;sup&gt;1&lt;/sup&gt;</td>
<td>L. rhamnosus HN001 or B. lactis HN019 1×10&lt;sup&gt;9&lt;/sup&gt; cfu daily from 2-5 weeks before delivery and then to infant directly for 2 years</td>
<td>eczema reduction with L. rhamnosus HN001 at 2 years; no benefit of B. lactis HN019</td>
<td>eczema reduction in the group receiving L. rhamnosus HN001 at 4 and 6 years; no benefit of B. lactis HN019</td>
<td>no reduction of allergic rhinitis at 4 years, both probiotics; no differences between the groups in wheeze, asthma or rhinoconjunctivitis</td>
<td>no differences between the groups when evaluated by spirometry reversibility test and FeNO levels at 6 years</td>
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<td>West et al. (2009, 2013)</td>
<td>Mixed (2/3 high-risk)</td>
<td>L. paracasei/ ssp. paracasei F19 1×10&lt;sup&gt;9&lt;/sup&gt; cfu daily to infant (in infant cereal) during weaning from 4-13 months</td>
<td>reduced cumulative incidence of eczema at 13 months in the probiotic group</td>
<td>no</td>
<td>no</td>
<td>no differences between the groups when evaluated by spirometry reversibility test and FeNO levels at 8 years</td>
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<tr>
<td><strong>Studies using probiotic combinations</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
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<td>Kukkonen et al. (2007); Kuutinen et al. (2009)</td>
<td>High risk&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Mix of L. rhamnosus GG and LC705 (both 5×10&lt;sup&gt;9&lt;/sup&gt;) and B. breve Bb99 and Propionibacterium freudenreichii ssp. shermani JS (both 2×10&lt;sup&gt;9&lt;/sup&gt;); given twice daily to mother 2-4 weeks before delivery and then to infant for 6 months</td>
<td>eczema reduction in the probiotic group at 2 years</td>
<td>no</td>
<td>no</td>
<td>no differences in FeNO levels between the groups at 5 years in a randomized subpopulation</td>
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<tr>
<td>References</td>
<td>Study population</td>
<td>Probiotic(s) and dose</td>
<td>Benefit on eczema</td>
<td>Sustained benefit on eczema at follow-up</td>
<td>Benefit on allergic rhinitis, wheeze and/or asthma</td>
<td>Effects on objective lung function measures</td>
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<td>Huurre et al. (2008)</td>
<td>High risk²</td>
<td><em>L. rhamnosus</em> GG and <em>B. lactis</em> Bb-12 1×10¹⁰ cfu daily from first trimester and then to breastfeeding mother until cessation of exclusive breastfeeding</td>
<td>no</td>
<td>not reported</td>
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<td>Soh et al. (2009); Loo et al. (2014)</td>
<td>High-risk¹</td>
<td><em>L. rhamnosus</em> LPR 1×10⁹ cfu and <em>B. longum</em> (BL999) 6×10⁸ cfu daily to infant (in infant formula) for 6 months</td>
<td>no</td>
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<td>Niers et al. (2009); Gorissen et al. (2014)</td>
<td>High-risk¹</td>
<td><em>Lactobacillus lactis</em> W58, <em>B. lactis</em> W52 and <em>B. bifidum</em> W23 1×10⁹ cfu daily over six weeks before delivery and then directly to infant for 12 months</td>
<td>reduced cumulative incidence of eczema in the first three months of life</td>
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<td>no</td>
<td>not reported</td>
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<tr>
<td>Kim et al. (2010)</td>
<td>High risk¹</td>
<td><em>B. bifidum</em> BGN4, <em>B. lactis</em> AD011, and <em>L. acidophilus</em> AD031 (1.6×10⁹ cfu of each daily) 4-8 weeks before delivery, 3 months to breastfeeding mother and then to infant from 4 to 6 months</td>
<td>reduced cumulative incidence and prevalence of eczema at 12 months</td>
<td>not reported</td>
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<td>not reported</td>
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<td>Dotterud et al. (2010); Simpson et al. (2015)</td>
<td>Unselected – about 2/3 with family history of allergic disease</td>
<td><em>L. rhamnosus</em> GG, <em>L. acidophilus</em> LAS, and <em>B. lactis</em> Bb-12 (5×10¹⁰ cfu of each daily) from 36 weeks gestation and then to breastfeeding mother for 3 months</td>
<td>reduced cumulative incidence of eczema at 2 years</td>
<td>reduced cumulative incidence of eczema at 6 years</td>
<td>no</td>
<td>not reported</td>
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<tr>
<td>Rautava et al. (2012)</td>
<td>High-risk²</td>
<td><em>L. rhamnosus</em> LPR and <em>B. longum</em> BL999 or <em>L. paracasei</em> and <em>B. longum</em> BL9 – each probiotic at a daily dose of 1×10⁹ cfu from two months before delivery and during two months to breastfeeding mother</td>
<td>reduction of eczema at 2 years in both probiotic groups</td>
<td>not reported</td>
<td>not reported</td>
<td>not reported</td>
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<tr>
<td>Allen et al. (2014)</td>
<td>High-risk²</td>
<td><em>L. salivaris</em> CUL61, <em>L. paracasei</em> CUL08, <em>B. animalis</em> ssp lactis CUL34 and <em>B. bifidum</em> CUL20, 10¹⁰ cfu daily in total starting 2-4 weeks before delivery and to the infant for six months</td>
<td>no reduction of eczema, but a reduction of IgE-associated eczema at 2 years in the probiotic group</td>
<td>not reported</td>
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<td>not reported</td>
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</table>

1 Family history of allergic disease.
2 Maternal allergic disease.
3 Probiotic strains: *L.* = *Lactobacillus*, *B.* = *Bifidobacterium*; *P.* = *Propionibacterium*.
4 FeNO = fractional exhaled nitric oxide; IgE = immunoglobulin E.
7. Current recommendations

Although several meta-analyses have shown a benefit of probiotics for eczema prevention (Cuello-Garcia et al., 2015; Foolad et al., 2013; Pelucchi et al., 2012; Zuccotti et al., 2015), it has been difficult to translate the findings into clinical recommendations. International expert bodies do not generally recommend probiotics for allergy prevention, however, very recently the World Allergy Organization (WAO) and the McMaster University set out to develop guidelines for probiotics as an allergy preventive measure (Fiocchi et al., 2015). In their report, they stated that the available evidence does not support that probiotics lessen the risk for allergic disease, although they concluded that when taking into account all the critical outcomes, there is a likely net advantage of probiotics (resulting primarily from eczema prevention). In otherwise healthy individuals, the panel suggested considering using probiotics in pregnant women and during breastfeeding in women at high risk of having an allergic child based on family history of allergic disease in a first grade relative, and in infancy if the child is at high risk of developing allergic disease (also based on family history). In their report, the WAO guideline panel also stressed that the recommendations are conditional, and based on very low quality evidence, which also restricts more specific recommendations about specific strains, optimal dosages and treatment duration (Fiocchi et al., 2015).

Others have questioned the concept of pooling data on different probiotic strains in meta-analyses as probiotic effects are considered strain-specific (Szajewska et al., 2015). A clear shortcoming to date is that study findings of specific probiotics or probiotic combinations have not been replicated in other RCTs, with the exception of L. rhamnosus GG, however, even for this strain results have been divergent (Table 1). Collectively, despite encouraging but moderate results of probiotics for eczema prevention, the evidence is not yet there to support recommendations on specific probiotic(s), dosages or timing (Fiocchi et al., 2015; Madhok et al., 2015; Szajewska et al., 2015).

8. Future strategies

Evidence of the significance of the gut microbiota in health and disease is mounting, however, we have still not detailed what constitutes a microbiota that promotes and maintains tolerance, which is key for tailoring the most effective gut microbiota modulation strategies in allergy prevention. To further add to the complexity, the effects of probiotic interventions are likely to be modulated not only by specific strain properties, but also by genetics, epigenetics (Kumar et al., 2014) and immunity – in addition to a number of pre- and postnatal environmental exposures. It is clear that if we are to translate findings from probiotic intervention studies into more decisive clinical recommendations, there is need for adequately powered studies, a more standardised approach and multi-professional collaborations (Fiocchi et al., 2015; Rijkers et al., 2010; West et al., 2015a,b,c).

References


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