Are probiotics useful for treating or preventing eczema?

Robert J Boyle
Department of Paediatrics, Imperial College
London
United Kingdom
Correspondence: r.boyle@nhs.net

Figure 1. Elie Metchnikoff, Nobel laureate and founder of probiotic science ‘The precocious old age of ruminants... coincides with an extraordinary richness of the intestinal flora’ (1)
INTRODUCTION

Probiotics in the form of *Streptococcus thermophilus* and *Lactobacillus bulgaricus* in fermented milk have been ingested by humans for thousands of years, and fermented milk products have long been believed by some to have health benefits. For example in Persian tradition Abraham owed his fertility and longevity to the regular ingestion of yoghurt. However it was not until the early 20th century that probiotics excited interest in the scientific community. The Russian immunologist Elie Metchnikoff, better known for his Nobel prize winning work on phagocytosis, proposed that lactic acid bacilli may have beneficial health effects (Figure 1). In recent years the belief that ingestion of live microbes may have health benefits has become more widely held, and has undergone increasingly rigorous scientific evaluation. Probiotics have become an important commercial commodity, and their efficacy in the treatment of infectious diarrhoea is now well established (2). In this article we will review the evidence that probiotics have a role in treating or preventing eczema, and provide some suggestions for the direction of future research in this area.

RATIONALE FOR USING PROBIOTICS TO TREAT OR PREVENT ALLERGIC DISEASE

Probiotics are live micro-organisms that when administered in adequate amounts confer a health benefit on the host (3). In the 1990s it was noted that the composition of the intestinal microbiota is different in infants with and without eczema, and this finding has spurred investigators to evaluate the use of non-pathogenic microbes for treating and preventing allergic disease, particularly eczema (4). The specific changes seen in the intestinal microbiota of those with eczema are inconsistent between studies, and this suggests that the altered microbiota may be reflective of an abnormal intestinal mucosa, without necessarily playing an important part in disease pathogenesis itself (5-9). The association between food allergy, gastrointestinal inflammation and eczema further supports the importance of intestinal mucosal abnormalities in the pathogenesis of eczema (10, 11). Probiotics are effective treatments for some gastrointestinal disorders characterized by a disturbed intestinal mucosa (2, 12). They may therefore have health benefits for those with eczema and associated allergic intestinal pathology such as food allergy, eosinophilic disorders and increased intestinal permeability. A role for probiotics in eczema is supported by the frequent observation in cross-sectional studies that unpasteurized cow’s milk ingestion is associated with markedly reduced risk of eczema (13). Differences between unpasteurized and pasteurized milk include the presence of live probiotic bacteria in the former but not the latter. There is thus a good theoretical rationale for using probiotics in eczema management, especially where there is evidence of intestinal pathology. There is less theoretical support for using probiotics in asthma or rhinitis, where abnormalities of intestinal microbiota or inflammation are not usually found, and the protective effect of unpasteurized milk exposure is less consistent (7).

ARE PROBIOTICS EFFECTIVE FOR TREATING ECZEMA?

Twelve randomised controlled trials have been published to date investigating the use of probiotic bacteria to treat established eczema. All studies focused on children, 11 used a *Lactobacillus* species either alone or in combination with other probiotics and 5 of the studies evaluated infants with suspected cow’s milk allergy in addition to their eczema. No study investigated the effects of probiotic treatment over a period longer than 3 months, so the treatment studies have very much focused on the effects of short term intervention rather than longer term probiotic exposure. In a systematic review of these 12 studies, meta-analysis of patient orientated outcomes was possible for 5 of them (309 participants) and showed no significant difference in eczema symptoms in favour of probiotic treatment [Figure 2 (14)].
Figure 2. Effect of probiotic bacteria for treating established eczema. Data shown are mean differences between probiotic and placebo treated patients in scores on a visual analogue scale of itch and sleep loss (range 0-20).

Meta-analysis of investigator assessed eczema severity (SCORAD) was possible for 7 of the 12 studies (588 participants) and also showed no significant difference in eczema symptoms in probiotic versus placebo treated individuals (Figure 3). Those studies not able to be included in meta-analyses also showed no evidence that probiotics are an effective treatment for eczema. There is however substantial heterogeneity between different trials for both subjective ($I^2=77\%; P=0.002$) and objective ($I^2=76\%; P<0.001$) outcome measures, which is not easily explained. Subgroup analyses demonstrated that categorisation of individuals by disease severity, age, presence of atopy or challenge confirmed food allergy did not identify a subgroup where probiotics have a significant effect on eczema severity, and did not explain the heterogeneity between study results. However subgroup analysis by probiotic strain identified the specific strain used as a major cause of heterogeneity between the results of different studies (Figure 4). Thus while the probiotic bacteria studied to date are overall not effective for treating eczema, it is possible that novel probiotic strains developed in the future may have a small beneficial effect as eczema treatments. In particular it is possible that the study of probiotic strains administered for prolonged periods may have different results to those of the trials published to date.
Figure 3. Effect of probiotic bacteria for treating established eczema. Data shown are mean differences between probiotic and placebo treated patients in scores on a composite eczema severity scale (SCORAD; range 0-102).

Figure 4. Effect of probiotic bacteria for treating established eczema – subgroup analysis by probiotic strain used. Data shown are mean differences between probiotic and placebo treated patients in scores on a composite eczema severity scale (SCORAD; range 0-102).
ARE PROBIOTICS EFFECTIVE FOR PREVENTING ECZEMA?

Eczema often develops early – sometimes in the first weeks of life – and human immune responses and intestinal microbiota are different in early infancy to later childhood and adulthood. This has justified a focus on the early use of probiotics, in particular their use before clinical eczema has become apparent. The completed studies in this area certainly show promise, and suggest that this approach may be applicable as a public health intervention in the future [Table 2 (15)]. There is great heterogeneity between the results of different studies, and as with the probiotic treatment trials variation in the probiotic strain used is likely to be a significant cause of this heterogeneity. The timing of probiotic supplementation may also be important, and at present it is not clear whether probiotics are most effective for preventing eczema when given to women during pregnancy, to mothers during breast feeding, to infants during postnatal life or a combination of these. The identification of the mechanisms through which probiotics prevent eczema would be a useful step for optimizing this approach to disease prevention. There are 3 major mechanisms which may be important – first they may act during the prenatal period by inducing a systemic inflammatory response in the pregnant woman or foetus; so far investigators have not been able to identify immune changes in the newborn infants of probiotic treated mothers, so this is unlikely to be the major mechanism of action. Second probiotics may act in the infant intestine via local immune or microbiological effects which promote mucosal barrier function and tolerogenic immune responses – this is the most plausible mechanism through which probiotics might prevent eczema. Third probiotics may alter the composition of maternal breast milk in such a way that intestinal health and immune development in the infant is promoted – this is supported by the finding in one study that the probiotic LGG administered to breastfeeding mothers leads to increased levels of TGF-β2 in breast milk (16). The search for effective probiotic strains which can prevent eczema will be made easier as we understand more about their mechanisms of action.
Table 1. Completed trials of probiotics for the primary prevention of eczema

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention Period</th>
<th>Active intervention</th>
<th>Outcome (1 or 2 year)</th>
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<tbody>
<tr>
<td>Kalliomaki</td>
<td>Prenatal: final 2-4 weeks pregnancy</td>
<td>LGG 2x10^{10} CFU/day (1x10^{10} CFU/day to infants)</td>
<td>RR eczema 0.51*† RR atopic eczema not reported</td>
</tr>
<tr>
<td>n=159</td>
<td>Postnatal: to breastfeeding mother/ formula fed infant 6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kukkonen</td>
<td>Prenatal: final 2-4 weeks pregnancy</td>
<td>Probiotic mix* and galacto-oligosaccharide prebiotic</td>
<td>RR eczema 0.81*† RR atopic eczema 0.70*†</td>
</tr>
<tr>
<td>n=1223</td>
<td>Postnatal: to infant for 6 months</td>
<td></td>
<td></td>
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<tr>
<td>Abrahamsson</td>
<td>Prenatal: from 36 weeks gestation</td>
<td><em>Lactobacillus reuteri</em> 10^{8} CFU/day</td>
<td>RR eczema 1.04 RR atopic eczema 0.61*†</td>
</tr>
<tr>
<td>n=232</td>
<td>Postnatal: to infant for 12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prenatal: final 4-6 weeks pregnancy</td>
<td>LGG 10^{10} CFU/day</td>
<td>RR eczema 1.03 RR atopic eczema not reported</td>
</tr>
<tr>
<td>Kopp</td>
<td>Postnatal: to breastfeeding mother/ formula fed infant 3 months, then infant until 6 months</td>
<td></td>
<td></td>
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<tr>
<td>n=105</td>
<td></td>
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<td></td>
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<tr>
<td>Taylor</td>
<td>Prenatal: Nil</td>
<td><em>L. acidophilus</em> LAVRI-A1 3x10^{9} CFU/day</td>
<td>RR eczema 1.10 RR atopic eczema 1.87*†</td>
</tr>
<tr>
<td>n=231</td>
<td>Postnatal: to infant daily from &lt;48 hours age to 6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolauri</td>
<td>Prenatal: from first trimester</td>
<td>LGG and <em>B. lactis</em> Bb12 each at 10^{10} CFU/day</td>
<td>RR atopic eczema 0.55 RR eczema not yet reported</td>
</tr>
<tr>
<td>n=140</td>
<td>Postnatal: to mother until the end of exclusive breastfeeding</td>
<td></td>
<td></td>
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* = LGG 10^{10} CFU/day, *L. rhamnosus* LC705 10^{10} CFU/day, *B. breve* Bb99 4x10^{8} CFU/day, *Propionibacterium freudenreichii, spp. shermanii* JS 4x10^{9} CFU/day; † = P<0.05
SAFETY OF PROBIOTICS

Several human safety assessments of probiotics have demonstrated that they are generally safe for use in most human populations, but there are recognised risks of both sepsis and bowel ischemia in certain patient groups (17, 18). In view of these risks, probiotic treatment should be avoided where possible in certain patient groups (Table 3).

Table 2. Relative contraindications to probiotic treatment

**MAJOR RISK FACTORS**

- Immune compromise including debilitated state/malignancy
- Premature infants

**MINOR RISK FACTORS**

- Central Venous Catheter *in situ* (where probiotic sachets are opened nearby)
- Increased risk for bacterial translocation eg intestinal inflammation, pancreatitis
- Administration of probiotic by jejunostomy
- Treatment with broad spectrum antibiotic to which probiotic is resistant
- Probiotics with properties of high mucosal adhesion or known pathogenicity
- Cardiac valvular disease (*Lactobacillus* probiotics only)

The presence of a single major or more than one minor risk factor merits caution in using probiotics.

**CONCLUSIONS**

Probiotics are not an effective treatment for established eczema, and their use cannot be recommended for this indication outside of clinical trials. They carry a significant risk of adverse events in some specific groups of patients. Some probiotics appear to be effective for the prevention of eczema, however there is variation between studies and the optimum strain(s) and timing of supplementation are unknown at present. The ongoing global allergy epidemic makes it a research priority that we investigate the mechanism of action through which probiotics prevent eczema, with a view to developing improved probiotic strains for use in future clinical trials. Probiotic treatment is likely to play a significant role in future strategies to prevent the development of allergic diseases, particularly those that are associated with intestinal pathology.
REFERENCES


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