Effect of *Bifidobacterium animalis* subsp *lactis* supplementation in preterm infants: a systematic review of randomized controlled trials

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CRD summary

The review concluded that evidence regarding potential beneficial effects of *B lactis* supplementation in preterm infants was encouraging. Authors' recommendations for further research appear appropriate given the limited size and quality of the evidence base. Evidence of an increased risk of nosocomial infections (although limited to one trial) means that the conclusion may not be sufficiently cautious.

Authors' objectives

To evaluate the evidence on the efficacy and safety of *B lactis* supplementation in preterm infants.

Searching

MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL) and proceedings from major paediatric conferences were searched in December 2008. There were no date or language restrictions. Reference lists from identified studies and relevant reviews were consulted. The manufacturer of *B lactis* was contacted to help identify unpublished data. Search terms were reported.

Study selection

Randomised controlled trials (RCTs) that evaluated *Bifidobacterium animalis* subsp *lactis* CNCM I-3446 (*B lactis*) supplementation in preterm infants at less than 37 weeks gestation and/or with a birth weight of less than 2,500g. *B lactis* could be administered at any dosage regimen and compared with placebo or no intervention.

Clinical outcomes of interest included anthropometric measurements, necrotizing enterocolitis stage 2 or greater, blood culture-proven sepsis, *B lactis*-positive blood cultures, antibiotics use, mortality, time to full enteral feedings and adverse events. Several non-clinical outcomes were eligible.

Only one trial included preterm infants at less than 27 weeks gestation. Mean gestational age in the other trials was 31 weeks. Interventions lasted between three and six weeks. *B lactis* was added to (and compared with) preterm formula in all trials except one where it was added to a human milk fortifier. Doses used varied across the trials.

The authors did not state how many reviewers were involved in study selection.

Assessment of study quality

Risk of bias was evaluated according to criteria for methods of randomisation and allocation concealment, blinding of investigators, participants, outcome assessors and data analysts, use of intention-to-treat analysis and loss to follow-up.

The authors did not state how many reviewers were involved in quality assessment.

Data extraction

Outcomes data were extracted to calculate risk ratios (RR), mean differences (MD) and 95% confidence intervals (CI).

The authors did not state how many reviewers were involved in data extraction.

Methods of synthesis

Where possible, studies were combined in a meta-analysis to calculate pooled risk ratios, mean differences, weighted mean differences (WMD) and 95% CI. Heterogeneity was assessed using $I^2$ and $X^2$. A fixed-effect meta-analysis was performed; a random-effects model was used where significant heterogeneity was detected ($I^2>50\%$).

Results of the review

Four studies (two of which included the same population) were included, involving a total of 324 participants. None of the trials reported an adequate method of allocation concealment. An intention-to-treat analysis was adequately
described in only one trial. All trials were described as double blinded (definition not reported). Two studies adequately described withdrawals and drop-outs.

One trial found that *B. lactis* was associated with a statistically significant increase in weight over 21 days compared to a formula-based placebo (MD 46.0g, 95% CI 16.05 to 75.95; 69 patients). Another trial found no difference in weight gain between *B. lactis* and control at 30 days and no difference in length gain but found a statistically significant improvement in head growth in the treatment arm (1.1cm/week) compared with control (0.9cm/week, p=0.001).

Pooled analyses found a statistically significant difference favouring *B. lactis* in use of antibiotics (RR 0.83, 95% CI 0.72 to 0.96; 255 patients; evidence of significant heterogeneity $I^2=92\%$). The difference was no longer significant when using a random-effects model. One trial found a statistically significant increased risk of nosocomial infections in patients who received *B. lactis* (RR 1.36, 95% CI 1.03 to 1.79; 180 patients). No statistically significant differences were found between *B. lactis* and control in the risk of necrotizing enterocolitis stage 2 or greater (three trials) and in the risk of culture-proven sepsis (two trials).

One trial found no difference between the study arms in all-cause death and death attributable to necrotizing enterocolitis. Two trials reported no significant difference in time until full enteral feedings. One trial found that none of the B-lactis positive blood cultures grew *B. lactis*. No evidence of adverse effects associated with *B. lactis* was reported. Additional non-clinical outcomes were reported.

**Authors' conclusions**
Evidence regarding the potential beneficial effects of *B. lactis* supplementation in preterm infants was encouraging. Further studies were needed to assess clinical outcomes.

**CRD commentary**
The review question and selection criteria were stated clearly. Searches were conducted without language restrictions and attempts were made to identify unpublished studies. The authors did not state whether more than one reviewer was involved in study selection, data extraction and quality assessment so reviewer error and bias could not be excluded. Quality of reporting of the trials was generally poor and the authors acknowledged that the results of the review may have been affected by various biases (including selection, attrition and/or performance bias). All trials were relatively small and the authors acknowledged that they were likely to be insufficiently powered to detect significant effects in several outcomes.

Given the limited size and quality of the evidence base, the authors' recommendations for further research appear appropriate. Evidence of an increased risk of nosocomial infections (although limited to one trial) means that the conclusion may not be sufficiently cautious.

**Implications of the review for practice and research**
**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated a need for better quality and sufficiently powered RCTs to evaluate the effect of *B. lactis* supplementation on validated clinical outcome measures (notably on the risk of necrotizing enterocolitis). Such trials should specify optimal dose and intake durations. They also stated that biomarkers of protection and inflammation should be identified.

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