Updated meta-analysis of probiotics for preventing necrotizing enterocolitis in preterm neonates

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CRD summary
This review concluded there was evidence of significant benefits of probiotic supplements in reducing death and the risk of necrotising enterocolitis in premature newborn babies of very low birth weight; there was no evidence of a reduced risk of late onset sepsis. The authors' conclusions reflect the evidence presented and are likely to be reliable.

Authors' objectives
To update a previous systematic review (see Other Publications of Related Interest) of probiotics for preventing necrotizing enterocolitis in pre-term neonates with very low birth weight.

Searching
MEDLINE, EMBASE, CINAHL and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched to March 2009 with no language restrictions; search terms were reported (in an online appendix). Proceedings of the Pediatric Academic Society meetings and gastroenterology conferences were searched for additional articles. Reference lists of identified studies and key review articles were scanned.

Study selection
Randomised controlled trials (RCTs) that evaluated the efficacy of any probiotic supplementation for the prevention of necrotizing enterocolitis in pre-term very low birth weight neonates were eligible for inclusion. Probiotics were required to be administered via the enteral route within the first 10 days of life and to be continued for at least seven days. Pre-term very low birth weight neonates were defined as neonates under 34 weeks gestation with a birth weight lower than 1,500g.

The primary outcomes were efficacy of probiotic supplementation in preventing stage 2 necrotizing enterocolitis or higher (as defined by modified Bell staging criteria), safety (incidence of blood culture-positive sepsis), and other adverse events. Secondary outcomes included time to reach full feeds and duration of hospital stay.

Probiotic interventions in the included trials were Bifidobacterium bifidus, B. breve, B. infantis, B. lactis, B. longum, Lactobacillus, L. acidophilus, L. casei, Saccharomyces boulardii and Streptococcus thermophilus. Doses and duration of treatment varied between trials. Some trials used combinations of probiotics. All trials used placebo as the control group. Neonate participants received mothers’, donors’ or formula milk.

All reviewers independently assessed studies for inclusion, differences were resolved through discussion.

Assessment of study quality
Quality assessment was conducted using the Jadad Scale. Criteria evaluated included randomisation, blinding and withdrawals/drop-outs. The maximum score was 5 points.

All reviewers independently assessed validity, differences were resolved through discussion.

Data extraction
Data were extracted to calculate the relative risk (RR) or weighted mean difference (WMD), together with corresponding 95% confidence intervals (CIs). Authors were contacted for additional data, where necessary.

Two reviewers independently extracted data, differences were resolved through discussion.

Methods of synthesis
The pooled relative risks and weighted mean differences, with their corresponding 95% confidence intervals were calculated using a fixed-effect model; pooled estimates were cross-checked by using a random-effects model. Heterogeneity was assessed using the $\chi^2$ test and $I^2$ statistic. The number needed to treat (NNT) was also calculated. Trial sequential analysis methods were used to evaluate whether findings from the meta-analysis was conclusive.

Publication bias was assessed by visual inspection of a funnel plot.

**Results of the review**

Eleven RCTs (n=2,176 neonates) were included in the review. Four RCTs scored a maximum of 5 points on the Jadad scale, four RCTs scored 4 points and three RCTs scored 3 points.

Probiotic supplementation was associated with a lower risk of necrotising enterocolitis compared with placebo (RR 0.35, 95% CI 0.23 to 0.55; NNT=25; 11 RCTs). There was no evidence of statistical heterogeneity for this analysis ($I^2=0\%$).

The use of probiotics reduced the risk of all-cause mortality compared with control (RR 0.42, 95% CI 0.29 to 0.62; NNT 20; nine RCTs). There were no significant differences between groups in the risk of mortality resulting from necrotising enterocolitis (five RCTs). There was no evidence of statistical heterogeneity for either of these analyses ($I^2=0\%$).

There were no significant differences between groups for the risk of blood culture positive sepsis, but there was evidence of moderate heterogeneity (10 RCTs; $I^2=52.1\%$).

Full feeding was reached earlier in the probiotic group (WMD -5.03 days, 95% CI -5.62 to -4.44; five RCTs; fixed-effect model), although there was evidence of moderate heterogeneity for this analysis ($I^2=83.3\%$); this difference was not significant when analysis was conducted using a random-effects model.

Sensitivity analyses did not significantly alter the results.

The results of the trial sequential analysis did not alter the conclusion.

The funnel plots showed no evidence of publication bias.

**Authors' conclusions**

The results confirmed the significant benefits of probiotic supplements in reducing death and the risk of necrotising enterocolitis in pre-term neonates of very low birth weight. There was no evidence of a reduced risk of late onset sepsis.

**CRD commentary**

The review addressed a clear question with appropriate inclusion criteria. Several relevant sources were searched, with no language restrictions; efforts were made to locate unpublished data, so the potential for publication and language bias was reduced. Formal assessment found no evidence of publication bias. Appropriate methods were used to reduce the potential for reviewer error and bias throughout the review process. The method of synthesis was appropriate. Statistical heterogeneity was assessed.

The authors' conclusions reflect the evidence presented and are likely to be reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that, given the significant benefits in critical areas that outweigh the potential adverse effects, probiotics should now be offered as a routine therapy for pre-term neonates weighing under 1,500g. However, selection of a safe and suitable product with documented probiotic properties and close monitoring of the target population are essential before offering the therapy as routine in high-risk populations.

**Research:** The authors stated that, considering the robustness of the evidence provided in the review, additional placebo-
controlled trials are not warranted. Although rigorous evaluation of a potentially suitable, but as yet untested product, may possibly be the only role for additional RCTs administration in this high-risk population. Further studies such as well-designed, tightly controlled prospective, observational studies or heat-on-trials are also required to answer questions of product/strains, dosage, duration and practicalities of administration.

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