Probiotics for prevention of necrotising enterocolitis in preterm neonates with very low birthweight: a systematic review of randomised controlled trials

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CRD summary
This review evaluated the efficacy and safety of probiotic supplementation in the prevention of necrotising enterocolitis in pre-term neonates with low birth weight. The authors concluded that the use of probiotics may lower the risk of necrotising enterocolitis and the risk of death in comparison with placebo. This review was generally well-conducted and its cautious conclusions are likely to be reliable.

Authors' objectives
To evaluate the efficacy and safety of probiotic supplements used as prophylaxis for necrotising enterocolitis in pre-term neonates weighing less than 1,500 g.

Searching
MEDLINE (from 1966), EMBASE (from 1980), the Cochrane CENTRAL Register (the Cochrane Library, Issue 4, 2006), CINAHL, and proceedings of the Pediatric Academic Society meetings (from 1980) and Pediatric Gastroenterology conferences (from 1980) were searched up to November 2006; the search terms were reported. Reference lists of relevant studies and reviews were checked for additional studies. There were no language restrictions.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were included.

Specific interventions included in the review
Studies evaluating probiotic supplementation for the prevention of necrotising enterocolitis were eligible. Probiotics were required to be administered via the enteral route, starting within the first 10 days of life and being continued for at least 7 days. The specific probiotics evaluated in the included studies were Bifidobacterium breve, Lactobacillus GG, Saccharomyces boulardii, Bifidobacteria infantis, Streptococcus thermophilus, Bifidobacterium bifidus, Lactobacillus acidophilus, Lactobacillus casei and Bifidobacterium lactis. The doses and duration of treatment varied between the studies. Some studies used combinations of probiotics. All included studies used placebo as the control treatment.

Participants included in the review
Studies including pre-term neonates of less than 33 weeks' gestation with a birth weight below 1,500 g were eligible. Neonates received mothers', donors' or formula milk.

Outcomes assessed in the review
Studies were required to report the incidence of stage 2 or greater necrotising enterocolitis, as defined by the modified Bell staging criteria. The safety outcomes were the incidence of blood culture-positive sepsis and any other reported adverse events. Secondary efficacy outcomes included the time to reach full feeds and length of hospitalisation.

How were decisions on the relevance of primary studies made?
Three reviewers independently selected the studies, with any disagreements resolved by discussion.

Assessment of study quality
Three reviewers independently assessed the quality of the studies using a modified version of the Jadad scale. The criteria evaluated were the method of randomisation, concealment of allocation, blinding of investigators and outcome assessors, and attrition bias.

Data extraction
Two reviewers independently extracted data to calculate the relative risk (RR) or weighted mean difference (WMD),
and the corresponding 95% confidence intervals (CIs). Any disagreements were resolved by discussion. When necessary, authors were contacted for additional data.

**Methods of synthesis**

How were the studies combined?
The pooled RR or WMD and their 95% CI were calculated using a fixed-effect model, with pooled estimates cross-checked by a random-effects model. Publication bias was visually assessed by means of a funnel plot.

How were differences between studies investigated?
Statistical heterogeneity was evaluated for each outcome by the I-squared statistic.

**Results of the review**

Seven RCTs (n=1,393) were included.

All included studies scored 3 or more on the Jadad scale.

Probiotic supplementation was associated with a significantly lower risk of necrotising enterocolitis in comparison with the control group (RR 0.36, 95% CI: 0.20, 0.65), with no statistical heterogeneity for this outcome across the trials (I-squared 0%; p=0.46). The authors calculated that 25 neonates (95% CI: 17, 50) had to receive probiotic supplementation to prevent one case of necrotising enterocolitis. The funnel plot for the primary outcome did not suggest publication bias.

Compared with placebo, the use of probiotics reduced the risk of all-cause mortality (RR 0.47, 95% CI: 0.30, 0.73), with no evidence of statistical heterogeneity (I-squared 0%; p=0.68). The authors estimated that 20 neonates (95% CI: 12, 50) had to receive probiotics rather than placebo to prevent one death. The incidence of blood-culture-positive sepsis and mortality due to necrotising enterocolitis were not significantly different between neonates receiving probiotic supplementation or placebo (respectively: RR 0.94, 95% CI: 0.74, 1.20 and RR 0.14, 95% CI: 0.2, 1.15). No statistical heterogeneity was detected for these outcomes.

Full feeding was reached earlier in the probiotic group (WMD -2.74, 95% CI: -4.98, -0.51), without any statistical heterogeneity between the studies (I-squared 0%; p=0.87).

**Authors’ conclusions**

Probiotic supplementation appears to reduce the risk of necrotising enterocolitis in pre-term neonates with very low birth weight. The authors suggested that these findings had to be taken cautiously, owing to the different schedules and regimens of probiotics evaluated.

**CRD commentary**

This review addressed a well-defined question in terms of the study design, participants, intervention and outcomes. The authors searched several relevant databases and made efforts to find further information by reviewing reference lists. The potential influence of publication bias was considered in the report, but no evidence of it was found for the primary outcome of the review. No restrictions on language were applied. The authors attempted to minimise bias and errors during the review by carrying out the study selection, quality assessment and data extraction processes using two or three independent reviewers.

Statistical heterogeneity was assessed. The authors stated that there was no significant statistical heterogeneity for the main outcomes, which supported the authors’ decision to pool the studies in a meta-analysis. The authors’ cautious conclusions appear appropriate and are likely to be reliable.

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

Practice: The authors did not state any implications for practice.

Research: The authors stated that the efficacy and safety of probiotic supplementation needs evaluation in large, well-
designed trials with long-term follow-up using comparable feeding regimens.

**Bibliographic details**

**PubMedID**
17499603

**DOI**
10.1016/S0140-6736(07)60748-X

**Original Paper URL**

**Additional Data URL**
http://pediatrics.aappublications.org/cgi/content/abstract/125/5/921

**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Double-Blind Method; Enteral Nutrition; Enterocolitis, Necrotizing /etiology /mortality /prevention & control; Gestational Age; Humans; Infant Formula; Infant, Newborn; Infant, Premature; Infant, Very Low Birth Weight; Meta-Analysis as Topic; Probiotics /administration & dosage /metabolism /therapeutic use; Randomized Controlled Trials as Topic

**AccessionNumber**
12007008124

**Date bibliographic record published**
04/07/2007

**Date abstract record published**
09/08/2008

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.