Effectiveness of probiotics in the prophylaxis of necrotizing enterocolitis in preterm neonates: a systematic review and meta-analysis
Bernardo WM, Aires FT, Carneiro RM, Sa FP, Rullo VE, Burns DA

CRD summary
This review concluded that food supplementation, with probiotics, reduced the incidence of severe necrotising enterocolitis, and its complications, in premature babies. The review was vulnerable to bias (publication and language), did not clearly report details of the included trials and review processes, and the statistical synthesis may have been inappropriate, so the authors’ conclusions may not be reliable.

Authors’ objectives
To assess the effectiveness of probiotics for the prevention of necrotising enterocolitis, and its complications, in preterm babies.

Searching
MEDLINE, EMBASE, and LILACS were searched to May 2012; search terms were reported. The reference lists of selected studies and reviews were handsearched for additional studies. Language restrictions were not applied, but some Chinese studies were excluded due to their language of publication.

Study selection
Randomised controlled trials (RCTs) of probiotic supplementation to enteral nutrition, with human milk, formula, or both, for premature babies, delivered at less than 34 weeks of gestation, very low birth weight babies (less than 1.5kg) regardless of gestational age, or both, were eligible for inclusion. Trials had to have a control group, in which babies received only enteral nutrition with human milk, formula, or both. The outcomes of interest were the incidence of necrotising enterocolitis at Bell stage II or higher, overall mortality, mortality from necrotising enterocolitis, incidence of sepsis, time to reintroduction of oral feeding, and hospitalisation.

The included trials used the probiotic agents: Lactobacillus rhamnosus GG, Bifidobacteria infantis, Bifidobacteria bifidum, Streptococcus thermophilus, Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus rhamnosus, Bifidobacteria longum, Bifidobacteria lactis, Bifidobacteria breve, or Lactobacillus sporogenes. Dose and duration were presented. In some trials, all babies received human breast milk, while in others, they received human breast milk, formula, or both.

The authors did not state how many reviewers assessed trials for inclusion in the review.

Assessment of study quality
The quality of the included trials was assessed using the Jadad scale. Those with a score of less than 3 out of 5 were excluded from the review.

The authors did not state how many reviewers assessed quality.

Data extraction
Mean differences between treatment groups were extracted from the included trials. Those that did not provide results as means, with standard deviations, were excluded from the analyses.

The authors did not state how many reviewers extracted the data.

Methods of synthesis
A fixed-effect model was used to pool the trial data to create weighted mean differences, with 95% confidence intervals. The number needed to treat, and number needed to harm, were calculated. Heterogeneity was assessed using $\chi^2$ and $I^2$. A sensitivity analysis was performed by excluding trials that had less than 80% power.
Results of the review
Of the 18 trials that met the inclusion criteria, two were excluded because they scored less than 3 on the Jadad scale, and four were excluded because they were published in Chinese, leaving 12 included RCTs, with 2,907 participants.

There was a statistically significant 4% reduction in the risk of necrotising enterocolitis at stage 2 or more, in the probiotic group, compared with the control group (WMD -0.04, 95% CI -0.06 to -0.02; 11 RCTs), heterogeneity was not considered to be significant ($I^2=37\%$). It was necessary to treat 25 patients for one to benefit.

There was a statistically significant 3% reduction in the risk of death, in the probiotic group, compared with the control group (WMD -0.03, 95% CI -0.05 to -0.01; 11 RCTs), but there was significant heterogeneity ($I^2=59\%$). It was necessary to treat 34 patients for one to benefit. There was no statistically significant difference between groups, in mortality due to necrotising enterocolitis (five RCTs).

There was a trend for a lower incidence of sepsis in the probiotic group, compared with the control group, but the difference was not statistically significant (WMD -0.03, 95% CI -0.05 to -0.00; 12 RCTs). There was significant heterogeneity ($I^2=52\%$). Removal of the trial that generated the heterogeneity did not alter the result.

Babies who received probiotics were reintroduced to oral feeding on average three days (95% CI 2.78 to 3.69; eight RCTs) earlier than those in the control group. There was significant heterogeneity ($I^2=94\%$). Babies who received probiotics stayed in hospital on average six days (95% CI 5.12 to 7.09; four RCTs) less than those who did not. There was significant heterogeneity ($I^2=88\%$). The results of the sensitivity analysis were presented.

Authors’ conclusions
Food supplementation with probiotics reduced the incidence of severe necrotising enterocolitis, and its complications, in premature babies.

CRD commentary
The review question and inclusion criteria were clear. Three relevant databases were searched, but no attempts were made to identify unpublished trials, and some trials were excluded based on their language of publication, so publication bias and language bias may have been present. It was unclear whether attempts were made to minimise error and bias in the selection of trials, data extraction, or quality assessment.

The quality assessment results were not reported; trials that scored less than 3 out of 5 on the Jadad scale were excluded from the review. Few trial details were presented, particularly for patient characteristics and control treatments, making it difficult to assess whether pooling their data was appropriate, or whether differences between trials made pooling inappropriate. The data were pooled using a fixed-effect model, which may not have been appropriate. Where statistical heterogeneity was identified, it was not explored further.

The review was vulnerable to bias (publication and language), did not clearly report details of the included trials and review processes, and the statistical synthesis may have been inappropriate, so the authors’ conclusions may not be reliable.

Implications of the review for practice and research
Practice: The authors stated that probiotics were a useful tool in paediatric clinical practice.

Research: The authors stated that research was required to assess the best preparation methods and doses, as well as the types of probiotics that work best. Four clinical trials were in progress, and their results should be included in an update of the available data.

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