Probiotic supplement reduces risk of necrotizing enterocolitis and mortality in preterm very low-birth-weight infants: an updated meta-analysis of 20 randomized, controlled trials

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CRD summary
The authors concluded that probiotic supplement could reduce the risk of necrotizing enterocolitis and mortality in preterm very low-birth-weight infants. The review process may have been influenced by reviewer bias and error, but the conclusion appears to reliably reflect the evidence presented.

Authors' objectives
To assess the benefits of probiotic supplementation for preterm very low-birth-weight infants.

Searching
PubMed, EMBASE and the Chinese Biomedical Literature Database were searched from January 1985 to March 2011 without language restrictions (search terms were reported). Reference lists of identified studies and key review articles were handsearched to locate further studies.

Study selection
Eligible studies were randomised controlled trials (RCTs) with preterm infants of very low-birth-weight (gestation less than 34 weeks or birth weight of less than 1500g), that reported stage 2 or greater necrotizing enterocolitis (defined by the modified Bell staging criteria) and enteral administration of any probiotic, started within the first ten days of life and continued for seven days or more. The primary eligible outcome was prevention of stage 2 or greater necrotizing enterocolitis. Secondary eligible outcomes included rates of mortality and culture-positive sepsis.

Probiotics investigated included: bifidobacteria; lactobacillus; lactobacillus and bifidobacteria; and saccharomyces. Most studies defined low birth weight as being less than 1500g (where reported). Two studies defined low birth weight as being in the range of 750g to 2000g or 1000g to 1800g.

Although not stated, it appeared that multiple reviewers were involved in the study selection process; discrepancies were resolved by discussion among all authors.

Assessment of study quality
Study quality was assessed according to randomisation, blinding and accountability of all participants (drop-outs and withdrawals) using the Jadad Scale; total scores for this scale range from 0 to 5, with total scores from 3 to 5 indicating high quality.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Data were extracted to calculate risk ratios (RRs) for incidence of mortality, necrotizing enterocolitis, and sepsis, along with 95% confidence intervals (CIs). Data were extracted separately for probiotic groups versus placebo groups.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Risk ratios were pooled using a fixed-effect or random-effects model according to the level of statistical heterogeneity indicated by the Cochran Q and I² statistical tests. Pooled results were estimated using 95% confidence intervals. Statistically significant heterogeneity was investigated by application of meta-regression analysis to analyses of total studies and subgroups (by probiotic agents). Publication bias was assessed using a funnel plot and the Egger linear regression test.

Results of the review
Twenty RCT studies were included (3,816 participants). The Jadad score for individual trials ranged from 3 to 5.

Risk of necrotizing enterocolitis was statistically significantly lower for probiotic groups versus placebo groups (RR 0.33, 95% CI 0.24 to 0.46; 20 trials, I²=0%). The risk remained significantly lower in subgroup analyses by probiotic agent: bifidobacteria (RR 0.30, 95% CI 0.16 to 0.58; eight trials; I²=0%), lactobacillus (RR 0.37, 95% CI 0.19 to 0.73; four trials; I²=0%), and both bifidobacteria and lactobacillus (RR 0.33, 95% CI 0.19 to 0.58; six trials; I²=0%).

Risk of mortality was statistically significantly lower for probiotic groups versus placebo groups (RR 0.56, 95% CI 0.43 to 0.73; 13 trials; I²=0%). The risk remained significantly lower in subgroup analyses for lactobacillus (RR 0.61, 95% CI 0.38 to 0.97; four trials; I²=0%), and both bifidobacteria and lactobacillus (RR 0.47, 95 CI 0.26 to 0.87; five trials; I²=49%). The risk of mortality remained lower for bifidobacteria versus placebo, but was not statistically significant (RR 0.74, 95% CI 0.18 to 2.97; three trials; I²=0%).

No statistically significant differences for risk of culture-positive sepsis were found between probiotic groups and placebo groups (RR 0.90, 95% CI 0.71 to 1.15; 14 trials; I²=56%). Differences in risk for sepsis remained non-significant in the three subgroup analyses (reported in paper).

Meta-regression analysis suggested that major sources of heterogeneity between studies might be type of probiotic agent and eligibility criteria for inclusion of pre-term very low-birth-weight infants. No evidence was found for publication bias (reported in paper).

Authors' conclusions
Probiotic supplement could reduce the risk of necrotizing enterocolitis and mortality in preterm very low-birth-weight infants.

CRD commentary
The review question was clear and inclusion criteria appeared sufficient for replication. Relevant electronic and manual data sources were searched, and attempts were made to minimise language, location and publication biases. Details of the review process itself were not reported, so the presence of reviewer bias and error is unclear. A suitable quality assessment tool was employed; results suggested that all of the included studies may have been of high quality. Study details were well presented, methods of synthesis seemed appropriate for the data presented, and statistical heterogeneity was accounted for. Although the review process may have been influenced by reviewer bias and error, the authors' conclusion appeared to reliably reflect the evidence presented.

Implications of the review for practice and research
Practice: The authors stated that the robustness of the meta-analysis evidence suggested that probiotic supplement should be offered as a routine therapy for pre-term infants.

Research: The authors stated that the optimum strain and dose of probiotic supplement and their long-term effects required more investigation, preferably using individual patient data to ensure uniformity in defining infant characteristics and outcome measures.

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