Probiotics for necrotizing enterocolitis: a systematic review
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CRD summary
This well-conducted review concluded that the evidence appeared to lend support to the use of oral probiotics for the prevention of necrotising enterocolitis in pre-term infants less than 33 weeks’ gestation and infants with very low birth weight, but data were insufficient to comment on the safety of probiotics. The authors’ conclusions are likely to be reliable.

Authors’ objectives
To assess the safety and effectiveness of oral probiotics for the prevention of necrotising enterocolitis in pre-term infants and those with very low birth weight.

Searching
MEDLINE and CINAHL were searched to December 2006; search terms were reported. Citation searches were performed on potential studies using MEDLINE, CINAHL and Web of Science, and reference lists of all reviewed studies were checked for additional relevant studies. In addition, the proceedings of the Society for Pediatric Research and European Society for Paediatric Research were hand searched. No language restrictions were applied.

Study selection
Randomised controlled trials (RCTs) and quasi-RCTs of oral probiotics for infants at high risk of necrotising enterocolitis (born at less than 33 weeks or with birth weight less than 1,500g) were eligible for inclusion. Probiotics were defined as bacteria that will modify colonic microflora to give a predominance of non-pathogenic organisms. The outcomes of interest were incidence of necrotising enterocolitis diagnosed by Bell classification, severity of necrotising enterocolitis defined by Bell stage 2 or 3, requirement for surgery, mortality attributed to necrotising enterocolitis, overall mortality and adverse events attributed to probiotics (defined as episodes of sepsis with positive blood culture containing probiotic strain or delay in tolerance of enteral feeds).

Most trials included infants under 1500g birth weight, but one trial included all infants of 28 to 32 weeks gestation (with some infants that weighed more than 1,500g). Some trials excluded infants with congenital malformation, antibiotic administration, death within seven days or two weeks of life, or necrotising enterocolitis within seven days. One trial excluded breast-fed infants, whilst in two trials all infants received maternal or donor breast milk. The probiotics used were Lactobacillus GG, Saccharomyces boulardii, Lactobacillus acidophilus plus Bifidobacterium infantis, and B. bifidus plus Streptococcus thermophilus plus B. infantis. Control groups received placebo. The included trials were carried out in Italy, Greece, China and Israel.

Two reviewers assessed studies for inclusion.

Assessment of study quality
Two reviewers, who were blinded for study outcome, independently assessed trial quality using the Jadad scale. Trials that scored less than 3 out of 5 were excluded from the review.

Data extraction
Data were extracted on the incidence and severity of necrotising enterocolitis, requirement for surgical intervention, mortality, and adverse events attributed to probiotics.

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

Methods of synthesis
Results of studies were described narratively.

Results of the review
Five RCTs (1,267 participants), that scored 3 or more out of 5 on the Jadad quality assessment scale, were included in...
the review (one trial was excluded as it scored less than 3). Randomisation was computer generated or by sealed
evelope. Care givers were blinded in all five trials and assessors were blinded in three trials. Three trials were criticised
for being underpowered to detect changes in necrotising enterocolitis, or for not performing a power calculation.

Two RCTs found a statistically significant lower incidence of necrotising enterocolitis in the probiotic group than the
control group; they also found a statistically significant lower incidence of severe necrotising enterocolitis (Bell stage 2
or higher) in the probiotic group. The other three trials found a lower incidence of either necrotising enterocolitis or
severe necrotising enterocolitis in the probiotic group, but the difference was not statistically significant.

Two RCTs assessed requirement for surgical intervention. Both trials reported that none of the infants in the probiotic
groups required surgery, but a few infants in the control groups underwent surgery (one infant in one trial, and two
infants in the other trial).

One RCT reported a statistically significant lower overall mortality rate in the probiotic group than the control group.
Another RCT reported a statistically significant lower overall mortality rate in the probiotic group, but the difference in
necrotising enterocolitis-related mortality did not reach statistical significance. One RCT reported fewer necrotising
enterocolitis-related deaths in the probiotic group, and one RCT reported fewer deaths in the probiotic group, but
neither result reached statistical significance. One RCT did not report mortality results.

Four RCTs reported no significant difference in time to full enteral feeding between treatment groups; the other trials
did not assess this outcome. No cases of sepsis attributable to the probiotic were recorded in any of the trials.

Authors' conclusions
The evidence appeared to lend support to the use of oral probiotics for the prevention of necrotising enterocolitis in pre-
term infants less than 33 weeks' gestation and infants with very low birth weight. However, data were insufficient to
comment on the safety of probiotics.

CRD commentary
The review question and inclusion criteria were clear. The search strategy was adequate, with no language restrictions.
Limited attempts were made to identify unpublished studies. Study selection and quality assessment were undertaken in
duplicate, which reduced the potential for reviewer bias and error, but it was unclear whether the same methods were
used for data extraction. Adequate details of the included trials were presented, including the results of the quality
assessment.

In view of differences between trials in types of intervention and participant characteristics, a narrative synthesis was
appropriate, although the synthesis was limited, with most results presented separately for the separate trials.

This was a well-conducted systematic review and the authors' conclusions 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 further research was required to identify the optimal type, dose and timing of
probiotics for pre-term infants and those with very low birth weight for the prevention of necrotising enterocolitis, as
well as to assess potential adverse effects of such treatments. Future studies should have sufficient statistical power to
assess the effects of probiotics on the incidence of severe necrotising enterocolitis, requirement for surgery, mortality
attributable to necrotising enterocolitis, overall mortality and adverse events. Medium to long-term follow-up should
involve secondary outcome measures such as growth, development and general well-being. Future studies should also
have a standardised policy on breast milk donation.

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