Probiotics for prevention of necrotizing enterocolitis in preterm infants (Review)

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ABSTRACT

Background
Necrotizing enterocolitis (NEC) and nosocomial sepsis are associated with increased morbidity and mortality in preterm infants. Through prevention of bacterial migration across the mucosa, competitive exclusion of pathogenic bacteria, and enhancing the immune responses of the host, prophylactic enteral probiotics (live microbial supplements) may play a role in reducing NEC and associated morbidity.

Objectives
To compare the efficacy and safety of prophylactic enteral probiotics administration versus placebo or no treatment in the prevention of severe NEC and/or sepsis in preterm infants.

Search strategy
The standard search strategy for the Cochrane Neonatal Review Group was performed by two review authors. Searches were made of MEDLINE (1966 to December 2006), EMBASE (1980 to December 2006), Cochrane Library Controlled Trials Register (CENTRAL, The Cochrane Library Issue 3, 2006), and abstracts of annual meetings of the Society for Pediatric Research (1995 - 2006). The authors of published articles were contacted.

Selection criteria
Only randomized or quasi-randomized controlled trials that enrolled preterm infants < 37 weeks gestational age and/or < 2500 g birth weight were considered. Trials were included if they involved enteral administration of any live microbial supplement (probiotics) and measured at least one prespecified clinical outcome.

Data collection and analysis
Standard methods of the Cochrane Collaboration and its Neonatal Group were used to assess the methodologic quality of the trials. Retrieved articles were assessed for eligibility and data abstracted independently by two review authors. Where data were incomplete, the primary investigator were contacted for further information and clarification. Where appropriate, data of individual trials were combined using meta-analytic techniques to provide a pooled estimate of effect assuming a fixed effect model.

Main results
Nine eligible trials randomizing 1425 infants were included. Included trials were highly variable with regard to enrollment criteria (i.e. birth weight and gestational age), baseline risk of NEC in the control groups, timing, dose, formulation of the probiotics, and feeding regimens. Data regarding extremely low birth weight infants (ELBW) could not be extrapolated. In a meta-analysis of trial data, enteral probiotics supplementation significantly reduced the incidence of severe NEC (stage II or more) [typical RR 0.32 (95% CI 0.17, 0.60)] and mortality [typical RR 0.43 (95% CI 0.25, 0.75]. There was no evidence of significant reduction of nosocomial sepsis [typical RR 0.93 (95% CI 0.73, 1.19)] or days on total parenteral nutrition (TPN) [WMD -1.9 (95% CI -4.6, 0.77)]. The included trials reported

no systemic infection with the probiotics supplemental organism. The statistical test of heterogeneity for NEC, mortality and sepsis was insignificant.

Authors' conclusions
Enteral supplementation of probiotics reduced the risk of severe NEC and mortality in preterm infants. This analysis supports a change in practice in premature infants > 1000 g at birth. Data regarding outcome of ELBW infants could not be extracted from the available studies; therefore, a reliable estimate of the safety and efficacy of administration of probiotic supplements cannot be made in this high risk group. A large randomized controlled trial is required to investigate the potential benefits and safety profile of probiotics supplementation in ELBW infants.

PLAIN LANGUAGE SUMMARY

Necrotizing Enterocolitis (NEC) is a serious disease that affects the bowel of premature infants in the first few weeks of life. Although the cause of NEC is not entirely known, milk feeding and bacterial growth play a role. Probiotics (dietary supplements containing potentially beneficial bacteria or yeast) have been used to prevent NEC. Our review of studies found that the use of probiotics reduces the occurrence of NEC and death in premature infants born less than 1500 grams. There is insufficient data with regard to the benefits and potential adverse effects in the most at risk infants less than 1000 grams at birth.

BACKGROUND

Necrotizing enterocolitis (NEC) is the most common serious acquired disease of the gastrointestinal tract in preterm infants (Lee 2003). It is characterized by bowel wall necrosis of various length and depth. Bowel perforation occurs in one third of the affected infants (Kafetzis 2003). Although 5 - 25% of cases occur in term infants, it is primarily a disease of preterm infants, with the majority of cases occurring in very low birth weight infants (infants with birth weight < 1500 g) (Kosloske 1994). NEC is categorized into three different stages, with clinical symptoms varying from feeding intolerance to severe cardiovascular compromise, coagulopathy, and peritonitis with or without pneumoperitoneum (Bell 1978).

The incidence of NEC varies among countries and neonatal centers. It has been reported to affect up to 10% of very low birth weight infants (VLBW) (Kosloske 1994). VLBW infants with NEC have a mortality rate up to 20% (Caplan 2001; Holman 1997). Approximately 27 - 63% of affected infants require surgical intervention (Lee 2003). Strictures, primarily in the colon, occur in more than one third of affected infants (Ricketts 1994). Increased rate of total parenteral nutrition (TPN) related complications and extended hospitalization have been reported (Bisquera 2002). Recent data from the National Institute of Child Health and Human Development Network (NICHD) suggest an increase in neurodevelopmental impairment rates among infants with NEC and sepsis (Stoll 2004).

The pathogenesis of NEC remains incompletely understood. NEC most likely represents a complex interaction of factors causing mucosal injury (Neu 1996). It is speculated that NEC occurs with the coincidence of two of the following three pathologic events; intestinal ischemia, colonization of the intestine by pathologic bacteria, and excess protein substrate in the intestinal lumen (Kosloske 1984; La Gamma 1994). Bacterial colonization is necessary for the development of NEC (Kosloske 1990; Musemeche 1986). When compared to term infants, VLBW infants at risk of NEC have abnormal fecal colonization, demonstrate a paucity of normal enteric bacterial species, and have delayed onset of bacterial colonization (Goldmann 1978; Gewolb 1999).

Nosocomial infection is also a frequent complication in VLBW infants. Data from the NICHD Network demonstrated that as many as 25% of these infants have at least one or more positive blood cultures, and 5% have positive cerebrospinal fluid cultures over the course of their hospitalization (Stoll 1996). Late onset sepsis is associated with an increased risk of death, neonatal morbidity and prolonged hospitalization (Stoll 2002a; Stoll 2002b).

Probiotic bacteria are live microbial supplements that colonize the gastrointestinal tract and potentially provide benefit to the host (Millar 2003). The most frequently used probiotics are lactobacillus and Bifidobacterium. There is increasing interest in the potential health benefits of proactive colonization of the gastrointestinal tract of preterm infants (Millar 2003). Potential mechanisms by which probiotics may protect high risk infants from developing NEC and/or sepsis include increased barrier to migration bacteria and their products across the mucosa (Orrhage 1999; Mattar 2001), competitive exclusion of potential pathogens (Reid 2001), modification of host response to microbial products (Duffy 2000), augmentation of IGA mucosal responses, enhancement of enteral nutrition that inhibit the growth of pathogens, and up-regulation of immune responses (Link-Amster 1994). There is a theoretical risk of bacteremia secondary to enterally administered probiotics strains, though few data support this concern. Bacillus species ad-

ministered as probiotics were reported to be associated with invasive disease in target populations (Richard 1988).

OBJECTIVES

The primary objective was to compare the effectiveness and safety of prophylactic enteral probiotics administration versus placebo or no treatment in the prevention of severe (stage II or more) NEC and/or sepsis in preterm infants. The secondary objective was to conduct a subgroup analysis to investigate the effect of probiotics in extreme low birth weight infants (infants with birth weight < 1000 g).

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Only randomized and quasi-randomized controlled trials were included.

Types of participants

Preterm infants < 37 weeks and/or birth weight < 2500 g.

Types of intervention

Enteral administration of any live microbial supplement (probiotics) at any dose for more than seven days compared to placebo or no treatment.

Types of outcome measures

Primary outcomes

- Severe NEC (stage II or more) as per Bell's criteria (Bell 1978; Walsh 1986), diagnosed prior to discharge.
- Nosocomial sepsis, defined as positive blood or cerebrospinal fluid cultures taken beyond 5 days of age.

Secondary outcomes

- All cause neonatal mortality
- Any NEC (according Bell's criteria)
- The composite of nosocomial sepsis or NEC or death
- Systemic infection with the supplemented organism
- Duration of total parenteral nutrition (days)
- Time to establish full enteral feeds (days)
- Duration of hospitalization (days)
- Neurodevelopmental impairment i.e. rates of cerebral palsy , cognitive delay, deafness, blindness or their composite reported at 18 months corrected age or later.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Neonatal Group methods used in reviews.

The standard search strategy for the Cochrane Neonatal Review Group was used. Randomized and quasi-randomized controlled trials that compared enteral probiotics to placebo or no treatment in premature infants were identified from OVID MEDLINE-National Library of Medicine (1966 to December 2006) using the following subject headings (MeSH) and text word terms: "neonate(s), newborn(s), infant(s), probiotics, lactobacillus, bifidobactrium, saccharomyces and publication type 'controlled trial'. No language restrictions were applied.

Other databases were searched including: EMBASE (1980 to December 2006), Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 3, 2006). Two review authors performed the electronic database search independently. A manual search of the abstract books published from the Society of Pediatric Research (SPR) and the European Society of Pediatric Research (ESPR) for the period of 1998 - 2006 were performed. Additional citations were sought using references in articles retrieved from searches. Subject experts were contacted to identify the unpublished and ongoing studies. Authors of the published trials were contacted to clarify or provide additional information. Two review authors independently screened candidate articles to check the eligibility for inclusion in the review.

METHODS OF THE REVIEW

Study Quality and Data extraction

Standard methods of the Cochrane Collaboration and the Neonatal Review Group were used to assess the methodological quality (validity criteria) of the trials. For each trial, information was sought regarding the method of randomization, blinding and reporting of all outcomes of all the infants enrolled in the trial. Each criteria was assessed as yes, no, can't tell. Retrieved articles were assessed for eligibility and data abstracted independently by two review authors. Discrepancies were resolved by discussion and consensus. Where data were incomplete, the primary investigator was contacted for further information and clarification.

Data Analysis

For dichotomous outcomes, relative risk (RR) and its associated confidence interval were calculated. For continuous outcomes, treatment effect was expressed as mean difference and its calculated standard deviation. If appropriate, meta-analysis of pooled data was performed assuming a fixed effect model. Review Manager 4.2.7 software was used for statistical analysis. A subgroup analysis to investigate the effect of probiotics in extreme low birth weight (ELBW) infants was planned. A sensitivity analysis was carried out to assess the effect of trials methodological quality on results of the meta-analysis.

Heterogeneity was defined as a significant test of heterogeneity ($p < 0.1$) and differences in the treatment effects across studies. Tests for between-study heterogeneity (including the I^2 test) were applied. If noticed, possible sources of heterogeneity were examined, including differences in the type or dose of probiotics used, the population under study (VLBW vs. ELBW infants), and the quality of the study.

DESCRIPTION OF STUDIES

Initial electronic search yielded 98 MEDLINE and 93 EMBASE potentially relevant citations. After reading abstracts, 12 articles were identified as potentially relevant. Review of full text articles identified ten studies comparing probiotic administration to control treatment. Two studies (Stansbridge 1993; Agarwal 2003) were excluded since no clinical outcomes were reported. A decision regarding the inclusion of one study published in German (Uhlemann 1999) was deferred till further assessment. This study included infants between 25 - 42 weeks gestation. Attempts were made to contact the author in order to extract data relevant to preterm infants alone. Two review authors, independently checked eligibility of included studies. The inter-observer agreement was excellent (kappa = 1.0). Two studies (Stansbridge 1993; Agarwal 2003) were excluded for reasons outlined in the table below. Details of the included studies are shown in the table "Characteristics of Included Studies".

Participants
Full details of included studies are given in the table "Characteristics of Included Studies". The nine included studies reported outcomes on 717 infants treated with probiotics and 708 control infants. While all studies enrolled infants < 37 weeks and/or birth weight < 2500 g, entry criteria varied between studies. Reuman 1986, Kitajima 1997, Lin 2005, Bin-Nun 2005 and Manzoni 2006 enrolled infants based on birth weight criteria. On the other hand, Millar 1993 and Costalos 2003 enrolled infants based on their gestational age. Dani 2002 utilized both criteria to enroll infants. None of the included studies limited their enrollment to ELBW infants.

Intervention
Included studies randomized infants to different preparations and dosages of probiotics. While Reuman 1986, Millar 1993, Dani 2002 and Manzoni 2006 administered Lactobacillus species to the intervention groups; Kitajima 1997 and Li 2004 utilized the Bifidobacterium species and Costalos 2003 utilized Saccharomyces boulardii. Lin 2005 and Bin-Nun 2005 used a mixture of two to three species of probiotics (L acidophilus - B infantis, and Lactobacillus bifidus-streptococcus thermophillus-bifidobactrium infantis, respectively).

The time of initiation and duration of therapy was different among included studies. Probiotics were administered either during the first 24 h of life (Reuman 1986; Kitajima 1997; Li 2004), at the time of the first feed (Millar 1993; Dani 2002; Lin 2005), or during the first week when enteral feeds were tolerated (Costalos 2003, Manzoni 2006). The duration of probiotics administration varied from two weeks (Reuman 1986), 28 and 30 days (Kitajima 1997; Costalos 2003 respectively), or until discharge (Dani 2002; Li 2004; Lin 2005; Manzoni 2006).

Outcomes
The major outcomes reported in included studies were severe stage II-III NEC (Dani 2002; Costalos 2003; Lin 2005; Bin-Nun 2005; Manzoni 2006), all causes mortality (Reuman 1986; Dani 2002; Lin 2005; Bin-Nun 2005; Manzoni 2006) and sepsis (Millar 1993; Costalos 2003; Dani 2002; Lin 2005; Bin-Nun 2005; Manzoni 2006). Weight gain was reported in three studies (Reuman 1986; Millar 1993; Costalos 2003) using different measurement scales. Only one study reported data on apnea (Kitajima 1997). None of the studies reported data on the long-term neurosensory outcomes of enrolled infants.

METHODOLOGICAL QUALITY

Details of included studies are presented in the table "Characteristics of Included Studies". The methodologic details of the studies were extracted from the published data and by contacting the primary author. However, a response was only received from one primary author (Dani 2002).

- Bin-Nun 2005: This was a single centre study. Infants less than 1500 g were randomized to receive either probiotics mixture (Lactobacillus bifidus, streptococcus thermophillus, and bifidobactrium infantis) or placebo. Information regarding allocation concealment was not specified, intervention was masked, and blinding of outcome assessment was not specified. Of note, this trial was published in an abstract form on two previous occasions at the Society of Pediatrics Research (SPR 2003, 2005) with different inclusion criteria and clinical outcomes, which suggests a change in the *a priori* specified criteria and multiple looks at the trials results.

- Costalos 2003: This was a single center study. Infants were randomized to receive either enteral probiotics (Saccharomyces boulardii) added to preterm formula or the same formula with maltodextrins. Allocation concealment was apparently adequate. Intervention and outcome assessment were masked. All infants were accounted for in the final results. There was a discrepancy with regard to the infants enrolled in both groups (51 in the treatment group and 36 in the control). The author presented no explanation of whether this discrepancy was a result of imbalance in the randomization process or a loss to follow-up.

- Dani 2002: This was a multicenter study. Infants were randomized to receive either enteral probiotics (Lactobacillus GG) or

placebo. Allocation was adequately concealed. The intervention was masked. All enrolled infants were accounted for and outcome measurement was blinded.

- Kitajima 1997: This was a single center study. 91 infants were randomized to receive enteral probiotics (Bifidobacterium breve) or control. It was unclear whether allocation was concealed, intervention blinded, or the outcome assessment was blinded. Not all enrolled infants accounted for the final results (six infants excluded for various reasons).
- Li 2004: This was a single center study. Infants were randomized in three groups to receive either enteral probiotics (Bifidobacterium breve) (group A, B) or control (group C). Allocation concealment was not described. It was unclear whether the intervention or outcome assessment were blinded and whether all infants were included its final results.
- Lin 2005: This was a single centre study, infants less than 1500 g were randomized to either probiotics (Infloran® - L acidophilus and B infantis) or to a control group (breast milk only). Allocation was adequately concealed. Intervention was masked (except for investigators and breast milk team). All enrolled infants were accounted for. Outcomes measurement was blinded.
- Manzoni 2006: This was a single centre study, infants less than 1500 g were randomized to either probiotics (Dicoflor Lactobacillus casei) or to a control group (breast or donor milk only). Although authors utilized computer generated randomization, allocation concealment was not described. Intervention was masked from human bank and microbiology workers however unclear whether care givers are masked or not. All enrolled infants were accounted for. Blinding of outcomes measurement was reported.
- Millar 1993: This was a single center study. Twenty infants were randomized to receive either enteral probiotics (Lactobacillus GG) or control. The intervention was masked. All infants enrolled were accounted for. It was unclear whether the outcome assessment was blinded or not.
- Reuman 1986: This was a single center study. Three groups of infants were randomized to receive either enteral probiotics (Lactobacillus) or control. Randomization and allocation concealment were clearly inadequate. The intervention was double masked. All infants enrolled were accounted for and outcome assessment was blinded.

RESULTS

PROBIOTICS VS. CONTROL (COMPARISON 01):

Severe stage II-III necrotizing enterocolitis (Outcome 01.01):
Five studies reported on severe stage II-III NEC (Dani 2002; Costalos 2003; Lin 2005; Bin-Nun 2005; Manzoni 2006). The administration of prophylactic probiotics significantly reduced the incidence of severe stage II -III NEC [typical RR 0.32 (95% CI 0.17, 0.60); typical RD -0.04 (95% CI -0.06,-0.02), NNT 25]. Data pertaining to the most vulnerable infants (ELBW) could not be abstracted from the included studies.

Mortality (Outcome 01.02):
Five studies reported on mortality (Reuman 1986; Dani 2002; Lin 2005; Bin-Nun 2005; Manzoni 2006). The number of deaths was significantly lower in the probiotics group [typical RR 0.43 (95% CI 0.25, 0.75); typical RD -0.04 95% CI (-0.06,-0.01), NNT 25]. Two studies (Bin-Nun 2005; Dani 2002) reported NEC-related mortality (a post hoc analysis). A total of five deaths were attributed to NEC in the control group, while no NEC-related deaths occurred in the probiotics arm of both studies [typical RR 0.17 (95% CI 0.02, 1.37). Although the trend favors the probiotics group with regard to NEC-related mortality, one can not make a strong conclusion due to the small number of events reported in the trials.

Sepsis (Outcome 01.03):
Five studies reported on sepsis (Bin-Nun 2005; Dani 2002; Millar 1993; Costalos 2003; Lin 2005; Manzoni 2006). There was no significant difference among both groups in the rate of culture proven sepsis [typical RR 0.93 (95% CI 0.73, 1.19).

Days on total parenteral nutrition (Outcome 01.04):
Two studies reported this outcome. No statistical difference was found in either of the studies. Dani 2002 reported a mean of 12.8 (13.9) days in the probiotics group, and a mean of 14.7(18.7) days in the control group [WMD -1.9 (-4.6, 0.77)]. Lin 2005 reported a mean of 14.7(5.7) days in the probiotics group and 13.9 (5.0) days in the control group [WMD 0.80 (-0.3, 1.9)]. Due to the significant test of heterogeneity, these results were not pooled.

Hospitalization days (Outcome 01.05):
Three studies reported this outcome. Over all there were no statistical differences among groups with regard to length of hospital stay. Reuman 1986 reported a mean (SD) of 59.4 (56.4) days, 38.7 (30.6), Millar 1993 reported A median (range) of 50 (23 - 136), 42.8 (19 - 114), and Lin 2005 reported a mean (SD) of 46.7 (27.1), 46.5 (26.10) total hospitalization days for both probiotics and controls respectively. Due to the significant test of heterogeneity, these results were not pooled.

Weight gain (Outcome 01.06):
Three studies (Reuman 1986; Millar 1993; Costalos 2003) reported weight gain results. No significant statistical difference in weight gain among study groups was observed. Due to the use of different scales i.e. g/week, g/day and g/kg/day, these results were not pooled.

The composite of death or severe NEC or sepsis (Outcome 01.07):
Only one study reported this outcome (Lin 2005). Probiotics significantly reduced the incidence of this composite [typical RR 0.54 (95% CI 0.37, 0.79)].

Systemic infection with the supplemented organism
None of the included studies reported a systemic infection caused by the supplemented probiotics organisms.

Neurodevelopmental impairment
No data were reported.

A subgroup analysis to demonstrate the effect of probiotics administration in ELBW infants was not performed since data pertains to this high risk group could not be extracted from the included studies.

DISCUSSION

Our review examined the evidence of probiotics efficacy in premature infants in eight randomized controlled trials. Only two studies enrolled large number of infants and reported adequate allocation concealment and blinding of intervention (Dani 2002; Lin 2005). All included trials evaluated probiotics use in premature infants. However, included trials were highly variable with regard to enrollment criteria (i.e. birth weight and gestational age), baseline risk of NEC in the control groups, timing, dose, formulation of the probiotics used and feeding regimens.

Enteral administration of probiotics significantly decreased the incidence of severe stage II-III NEC. The direction of this effect is consistent and homogenous among included studies. The benefit of enteral probiotics use in reducing the incidence of NEC in the highest risk population (Extreme Low Birth Weight infants <1000 g at birth) could not be evaluated in a sub-group analysis.

One recent trial of sufficient power (Lin 2005) showed a benefit of probiotics on prevention of sepsis. However, this effect did not reach statistical significance in our pooled estimate of all trials reporting this outcome.

Although five studies reported death as an outcome, only two (Lin 2005, Dani 2002) were of high quality. This review demonstrated a significant reduction in mortality in the probiotics group. Only two studies addressed NEC-related deaths and these events were rare (Bin-Nun 2005; Dani 2002). Therefore, this outcome was not sufficiently evaluated. This review showed no significant effect of probiotics on the number of days on TPN, hospitalization days, weight gain or apnoea.

There are case reports of systemic infections caused by probiotics organisms in the biomedical literature. The included studies showed no evidence of such an adverse effect. The use of probiotics was described as safe and well tolerated in the trials included. Although the data thus far is reassuring, the number of infants included in this review could not reliably assess this outcome.

This review utilized a very thorough and comprehensive search strategy; all attempts were made to minimize the potential of a publication bias. Only randomized or quasi-randomized controlled trials were included. To minimize the reviewer bias, all steps of this review were conducted independently by two review authors. The validity of our review's results is potentially compromised by the following: most of the included trials (except two) were of small sample size and inadequate information was reported to assess quality; included trials utilized different preparations and dosing regimens of the intervention under study; data on the highest risk population (ELBW infants) could not be retrieved.

The principal investigators of included trials are being contacted to get additional unreported information and, if further data becomes available, it will be incorporated in to update of this review.

AUTHORS' CONCLUSIONS

Implications for practice

Enteral supplementation of probiotics reduced the risk of severe NEC and mortality in preterm infants. This analysis supports a change in practice in premature infants > 1000 g at birth. Data regarding outcome of ELBW infants could not be extracted from the available studies; therefore, a reliable estimate of the safety and efficacy of administration of probiotic supplements cannot be made in this high risk group.

Implications for research

A large randomized controlled trial is required to investigate the potential benefits and safety profile of probiotics supplementation in the prevention of severe stage II-III NEC, mortality and sepsis in ELBW infants. More studies are also required to address the mechanism of action of probiotics supplementation in reduction of important intermediate neonatal outcomes.

POTENTIAL CONFLICT OF INTEREST

None

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TABLES

Characteristics of included studies

Study	Bin-Nun 2005
Methods	Single centre randomized study Method of generating randomization sequence: not described Blinding of randomization: not described Blinding of intervention: yes Blinding of outcome measurement: yes Completeness of follow-up: not specified
Participants	145 infants less than 1500 g at birth Demographic data: Probiotics Group N=72, Gestational age (weeks) 29.2(2.6), birth weight 1152 (262) Placebo Group N=73, Gestational age (weeks) 29.3 (4.3), birth weight 1111 (278)
Interventions	Probiotics group (N=72) received mixture of Lactobacillus bifidus, streptococcus thermophillus, and bifidobactrium infantis added to 3 ml of expressed breast milk or premature formula enteral feeds. Control group (N=73) received 3 ml of expressed milk or premature formula with no supplements added.
Outcomes	Stage 2 or 3 NEC. Mortality NEC or mortality Sepsis Days to full feeds Days till TPN stopped
Notes	Israel Period of study: Sept 2001-Sept 2004 Published: Journal of Pediatrics 2005 Source of Funding: ABC Dophilus
Allocation concealment	B – Unclear

Study	Costalos 2003
Methods	Single center randomized double blind study Method of generating randomization sequence: cards in sealed envelopes Allocation concealment: possibly adequate Blinding of intervention: Yes Blinding of outcome measurement: not described Complete Follow-up: Yes
Participants	87 infants, gestational age 28-32 weeks Exclusion criteria: Major anomalies, receiving antibiotics or anti -fungals, receiving breast milk Demographic data: Probiotics Group N=51, Gestational age (weeks) 31.1(2.5), birth weight 1651 (470) Placebo Group N=36, Gestational age (weeks) 31.8 (2.7), birth weight 1644 (348)

Characteristics of included studies (*Continued*)

Interventions	Probiotics group (N=51) received preterm formula containing approximately 15 nmol/dl polyamines with added Saccharomyces boulardii 50mg/kg every 12 hours during the first week of life when enteral feed are tolerated for 30 days. Placebo group (N=36) received same formula with maltodextrins
Outcomes	NEC Weight gain Abdominal distension Vomiting Gastric retention Stool characteristics Sepsis
Notes	Greece Period of study: not specified Published: 2003 Source of Funding: Unclear
Allocation concealment	B – Unclear

Study	**Dani 2002**
Methods	Multicenter randomized double blind study (12 centers) Method of generating randomization sequence: not described Allocation concealment: clearly adequate Blinding of Intervention: Yes Blinding of outcome measurement: Yes Complete Follow-up: Yes
Participants	585 infants, < 33 weeks gestation or <1500g birth weight enrolled. Exclusion criteria: congenital malformation and death within two weeks of birth Demographic data: Probiotics Group N=295, gestational age (weeks) 30.8(2.4), birth weight 1325 (361) Placebo Group N=290, gestational age (weeks) 30.7 (2.3), birth weight 1345 (384)
Interventions	Probiotics group (N=295) received standard milk with Lactobacillus GG (Dicoflor®, Dicofarm, Rome, Italy) with an added dose of 6×109 colony forming units (cfu) once a day until discharge, starting with first feed. Placebo group (N=290) received standard milk with placebo which was an indistinguishable dried powder of maltodextrins.
Outcomes	Severe NEC Incidence of PDA Duration of parenteral nutrition Urinary tract infection Bacterial sepsis (culture proven) Stage 2 and 3 NEC single course of antibiotics treatment NEC related mortality
Notes	Italy Period of study: not specified in paper Published: 2002 Source of Funding: not specified in paper

Characteristics of included studies (*Continued*)

Allocation concealment	A – Adequate

Study	**Kitajima 1997**
Methods	Single center randomized study Method of generating randomization sequence: not described Allocation concealment: Not described Blinding of Intervention: Not described Blinding of outcome measurement: not described Complete Follow-up: No (6 patients dropped)
Participants	91 infants, birth weight <1500 g enrolled. Exclusion criteria: major anomalies, severe asphyxia, severe IUGR Demographic data: Probiotics Group N=45, gestational age (weeks) 28.3(2.3), birth weight 1026 (24) Placebo Group N=46, gestational age (weeks) 28.2 (2.1), birth weight 1026 (205)
Interventions	Probiotics group (N=45) received 1 ml supplement of Bifidobacterium breve with distilled water 0.5×109 of live B. breve within the 1st 24 hrs of life once per day for 28 days Control group (N=46) received distilled water
Outcomes	Colonization rate Mean aspired air volume Vomiting times/week Apnoea times/week Weight gain
Notes	Japan Period of study: May 1990-April 1991 Published: 1997 Source of Funding: Unclear
Allocation concealment	B – Unclear

Study	**Li 2004**
Methods	Single center randomized study Method of generating randomization sequence: unclear Allocation concealment: Not described Blinding of Intervention: not described Blinding of outcome measurement: not described Complete Follow-up: unclear
Participants	30 infants, of low birth weight. Exclusion criteria: Major anomalies, chromosomal anomalies, intrauterine infection Demographic data: Probiotics Group A N=10, gestational age (weeks) 33.8(2.9), birth weight 1523 (490) Probiotics Group B N=10, gestational age (weeks) 33.8(3.2), birth weight 1354 (280) Control (C) Group N=10, gestational age (weeks) 32.4 (3.1), birth weight 1480 (237)

Characteristics of included studies (*Continued*)

Interventions	Probiotics group (N=10) received through gastric tube Bifidobacterium breve twice a day with feeds till discharge. Group A within several hours of birth, while group B after the 1st 24 hrs. Control group (N=10) received no supplement
Outcomes	Colonization rate NEC Sepsis
Notes	Japan Period of study: Jan 2000- Aug 2002 Published: 2004 Source of Funding: Morinaja Milk industry and Meiji Dairies
Allocation concealment	B – Unclear

Study	**Lin 2005**
Methods	Single centre randomized study Method of generating randomization sequence: random-number table sequence. Allocation concealment: clearly adequate Blinding of intervention: Yes, only investigators and breast milk team were unblinded. Blinding of Outcome measurement: Yes Completeness of follow up: Yes
Participants	367 infants less than 1500 g at birth, survived beyond 7 days of life, and started on enteral feed were enrolled Demographic data: Probiotics Group N=180, gestational age (weeks) 28.5(2.5), birth weight 1104 (242) Placebo Group N=187, gestational age (weeks) 28.2 (2.5), birth weight 1071 (243)
Interventions	Probiotics group (N=180) received Infloran® (L acidophilus and B infantis) obtained from the American Type Culture Collection in 1973, 125 mg/kg/dose twice daily with breast milk until discharge. All enrolled infants received maternal or banked breast milk. Control group (N=187) received breast milk without any addition (no placebo).
Outcomes	Death Stage 2 or 3 NEC Sepsis (culture proven) Composite outcomes of death+ NEC, sepsis+ NEC, death+ NEC+ Sepsis Duration of parenteral nutrition Hospitalization days
Notes	Taiwan Period of study: July 1999- December 2003 Published: 2005 Source of Funding: supported by research department of China medical university hospital.
Allocation concealment	A – Adequate

Study	**Manzoni 2006**
Methods	Single centre randomized study Method of generating randomization sequence: computer generated randomization Allocation concealment: Unclear Blinding of intervention: can't tell Blinding of Outcome measurement: can't tell

Characteristics of included studies (*Continued*)

	Completeness of follow up: Yes
Participants	80 infants less than 1500 g at birth, survived beyond 3 days of life, and started on human or donor milk enteral feed were enrolled Demographic data: Probiotics Group N=39, gestational age (weeks) 29.6 (5), birth weight 1212 (290) Placebo Group N=41, gestational age (weeks) 41(4), birth weight 1174 (340)
Interventions	Probiotics group (N=39) received LGG [Diclofor 60;Dicofarm spa]; single dose (1/2 packet of Diclofor 60) daily mixed with human or donor milk till end of the sixth week or discharge. Control group (N=41) received human or donor milk without any addition (no placebo).
Outcomes	Fungal colonization rates Stage 2 or 4 NEC Death Sepsis (culture proven) Time to full feeds
Notes	Italy Period of study: 12 months Published: 2006 Sources of support: non reported
Allocation concealment	B – Unclear

Study	**Millar 1993**
Methods	Single center randomized blinded study Method of generating randomization sequence: not described Allocation concealment: Not described Blinding of Intervention: Yes Blinding of outcome measurement: Unclear Complete Follow-up: Yes
Participants	20 infants, < 33 weeks gestation enrolled. Demographic data: Probiotics Group N=10, gestational age (weeks) 30.5(26-33), birth weight 1445 (800-2560) Placebo Group N=10, gestational age (weeks) 30.0 (24-33), birth weight 1500 (830-2150)
Interventions	Probiotics group (N=10) received milk feeds with Lactobacillus GG 108 (cfu) twice a day for 14 days, starting with first feed. Placebo group (N=10) received un-supplemented milk
Outcomes	Weight gain Sepsis clinical or lab proven Antibiotics treatment Oxygen and ventilatory requirements Hospital stay Perineal candidal infection Duration of hospital stay
Notes	UK Period of study: Sept 1991-Jan 1992 Published: 1993 Source of Funding: Wessex Medical Trust
Allocation concealment	B – Unclear

Study	Reuman 1986
Methods	Randomized double blind study Method of generating randomization sequence: random number charts and the last digit of patient's chart number, the next matched infants is assigned to the opposite group Allocation concealment: clearly inadequate Blinding of Intervention: Yes Blinding of outcome measurement: Yes Complete Follow-up: Yes
Participants	45 infants, <2000 gm at birth weight who survived beyond first 24 hrs and are younger than 72 hrs Demographic data: Probiotics Group n=15, gestational age (weeks) 30.6(2.7), birth weight 1366 (302) Placebo Group n=15, gestational age (weeks) 30.5 (2.8), birth weight 1377 (344) Untreated group n=15, gestational age(weeks) 30.7(2.9), birth weight 1329(337)
Interventions	Probiotics group received at least 1 ml of formula containing lactobacillus. 5×1010 organisms/ml preparation diluted 100 times in infants formula. Placebo group received 1 ml of formula with no added lactobacillus Both groups started within 72 hrs of birth The untreated group received nothing per mouth for 2 weeks
Outcomes	Death Colonization rates Hospitalization duration Daily weight gain Hospital acquired infection
Notes	US Period of study: not specified in paper Published: 1986 Source of Funding: not specified in paper
Allocation concealment	C – Inadequate

Characteristics of excluded studies

Study	Reason for exclusion
Agarwal 2003	No clinical outcomes were presented
Stansbridge 1993	No clinical outcomes were presented, physiological outcomes were addressed

ANALYSES

Comparison 01. Probiotics vs. control

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Severe Necrotising Enterocolitis (stage II-III)	5	1264	Relative Risk (Fixed) 95% CI	0.32 [0.17, 0.60]
02 Mortality			Relative Risk (Fixed) 95% CI	Subtotals only
03 Sepsis	6	1284	Relative Risk (Fixed) 95% CI	0.93 [0.73, 1.19]
04 Parenteral nutrition duration (days)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only

05 Hospitalization days			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
06 Weight gain			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
07 Death or severe NEC or sepsis	1	367	Relative Risk (Fixed) 95% CI	0.54 [0.37, 0.79]

COVER SHEET

Title	Probiotics for prevention of necrotizing enterocolitis in preterm infants
Authors	AlFaleh K, Bassler D
Contribution of author(s)	KA developed the protocol. Both review authors assessed trials for eligibility, quality and extracted the data independently. KA wrote the manuscript with revisions made by DB.
Issue protocol first published	2005/4
Review first published	2008/1
Date of most recent amendment	14 November 2007
Date of most recent SUBSTANTIVE amendment	31 August 2007
What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
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DOI	10.1002/14651858.CD005496.pub2
Cochrane Library number	CD005496
Editorial group	Cochrane Neonatal Group
Editorial group code	HM-NEONATAL

Analysis 01.01. Comparison 01 Probiotics vs. control, Outcome 01 Severe Necrotising Enterocolitis (stage II-III)

Review: Probiotics for prevention of necrotizing enterocolitis in preterm infants

Comparison: 01 Probiotics vs. control

Outcome: 01 Severe Necrotising Enterocolitis (stage II-III)

Study	Probiotics n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bin-Nun 2005	1/72	10/73		26.3	0.10 [0.01, 0.77]
Costalos 2003	5/51	6/36		18.6	0.59 [0.19, 1.78]
Dani 2002	4/295	8/290		21.4	0.49 [0.15, 1.61]
Lin 2005	2/180	10/187		26.0	0.21 [0.05, 0.94]
Manzoni 2006	1/39	3/41		7.7	0.35 [0.04, 3.23]
Total (95% CI)	637	627		100.0	0.32 [0.17, 0.60]

Total events: 13 (Probiotics), 37 (Control)

Test for heterogeneity chi-square=3.20 df=4 p=0.53 I^2 =0.0%

Test for overall effect z=3.53 p=0.0004

Analysis 01.02. Comparison 01 Probiotics vs. control, Outcome 02 Mortality

Review: Probiotics for prevention of necrotizing enterocolitis in preterm infants

Comparison: 01 Probiotics vs. control

Outcome: 02 Mortality

Study	Probiotics n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 All cause neonatal mortality					
Bin-Nun 2005	3/72	8/73		20.4	0.38 [0.11, 1.38]
Dani 2002	0/295	2/290		6.5	0.20 [0.01, 4.08]
Lin 2005	7/180	20/187		50.4	0.36 [0.16, 0.84]
Manzoni 2006	5/39	6/41		15.0	0.88 [0.29, 2.64]
Reuman 1986	1/15	3/15		7.7	0.33 [0.04, 2.85]
Subtotal (95% CI)	601	606		100.0	0.43 [0.25, 0.75]

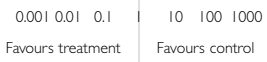
Total events: 16 (Probiotics), 39 (Control)

Test for heterogeneity chi-square=2.10 df=4 p=0.72 I^2 =0.0%

(*Continued . . .*)

(... *Continued*)

Study	Probiotics n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Test for overall effect z=2.99 p=0.003					
02 NEC realted mortality					
Bin-Nun 2005	0/72	3/73		58.0	0.14 [0.01, 2.75]
Dani 2002	0/295	2/290		42.0	0.20 [0.01, 4.08]
Subtotal (95% CI)	367	363		100.0	0.17 [0.02, 1.37]
Total events: 0 (Probiotics), 5 (Control)					
Test for heterogeneity chi-square=0.02 df=1 p=0.89 I^2 =0.0%					
Test for overall effect z=1.66 p=0.1					



Analysis 01.03. Comparison 01 Probiotics vs. control, Outcome 03 Sepsis

Review: Probiotics for prevention of necrotizing enterocolitis in preterm infants

Comparison: 01 Probiotics vs. control

Outcome: 03 Sepsis

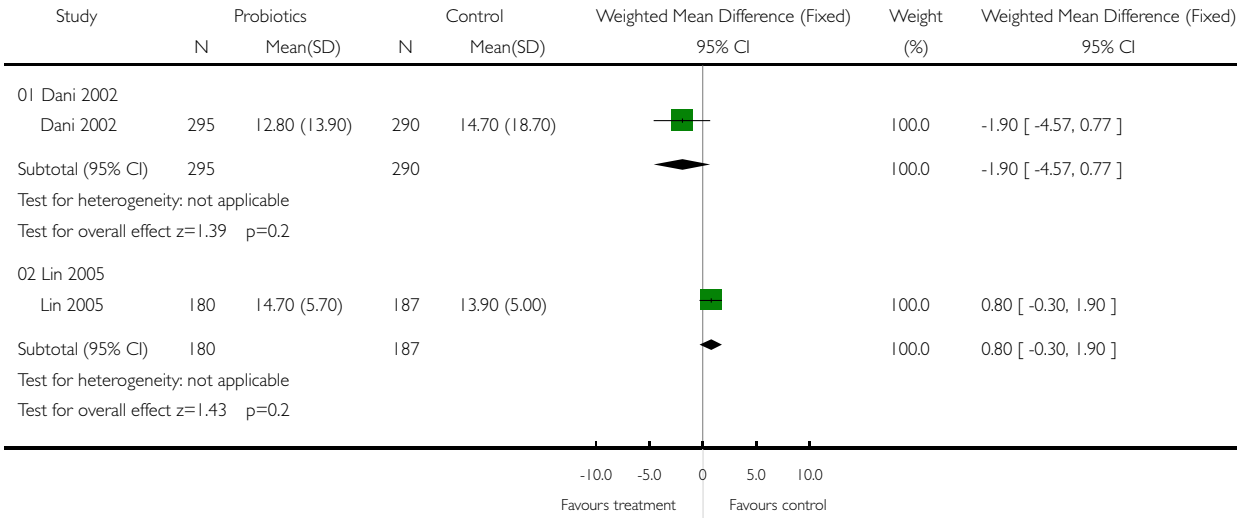
Study	Probiotics n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Culture proven sepsis					
Bin-Nun 2005	31/72	24/73		24.8	1.31 [0.86, 2.00]
Costalos 2003	3/51	3/36		3.7	0.71 [0.15, 3.30]
Dani 2002	14/295	12/290		12.6	1.15 [0.54, 2.44]
Lin 2005	22/180	36/187		36.7	0.63 [0.39, 1.04]
Manzoni 2006	19/39	22/41		22.3	0.91 [0.59, 1.40]
× Millar 1993	0/10	0/10		0.0	Not estimable
Total (95% CI)	647	637		100.0	0.93 [0.73, 1.19]
Total events: 89 (Probiotics), 97 (Control)					
Test for heterogeneity chi-square=5.30 df=4 p=0.26 I^2 =24.5%					
Test for overall effect z=0.58 p=0.6					

Analysis 01.04. Comparison 01 Probiotics vs. control, Outcome 04 Parenteral nutrition duration (days)

Review: Probiotics for prevention of necrotizing enterocolitis in preterm infants

Comparison: 01 Probiotics vs. control

Outcome: 04 Parenteral nutrition duration (days)

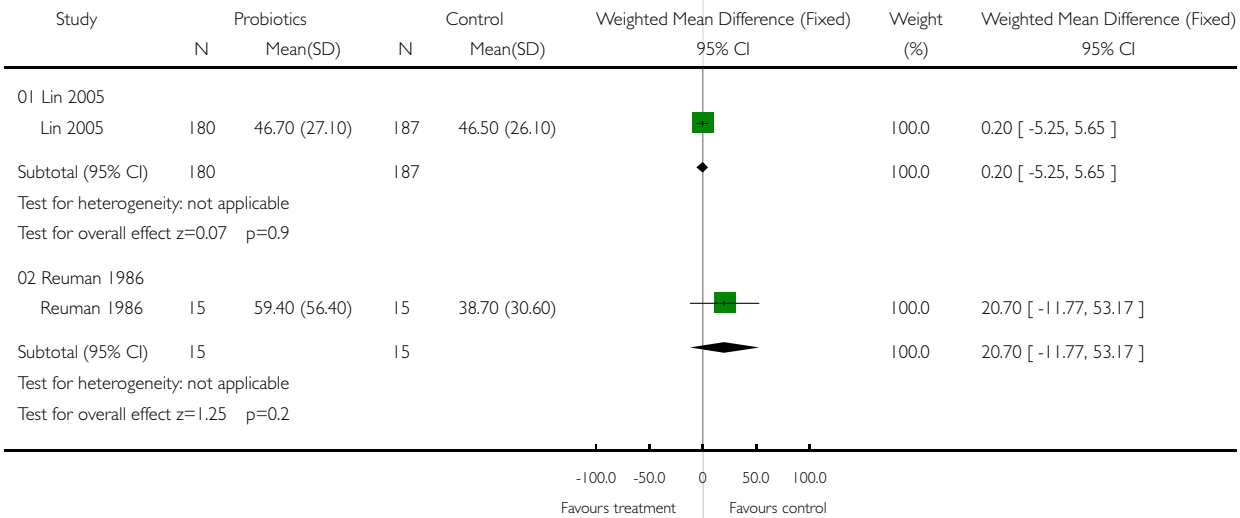


Analysis 01.05. Comparison 01 Probiotics vs. control, Outcome 05 Hospitalization days

Review: Probiotics for prevention of necrotizing enterocolitis in preterm infants

Comparison: 01 Probiotics vs. control

Outcome: 05 Hospitalization days

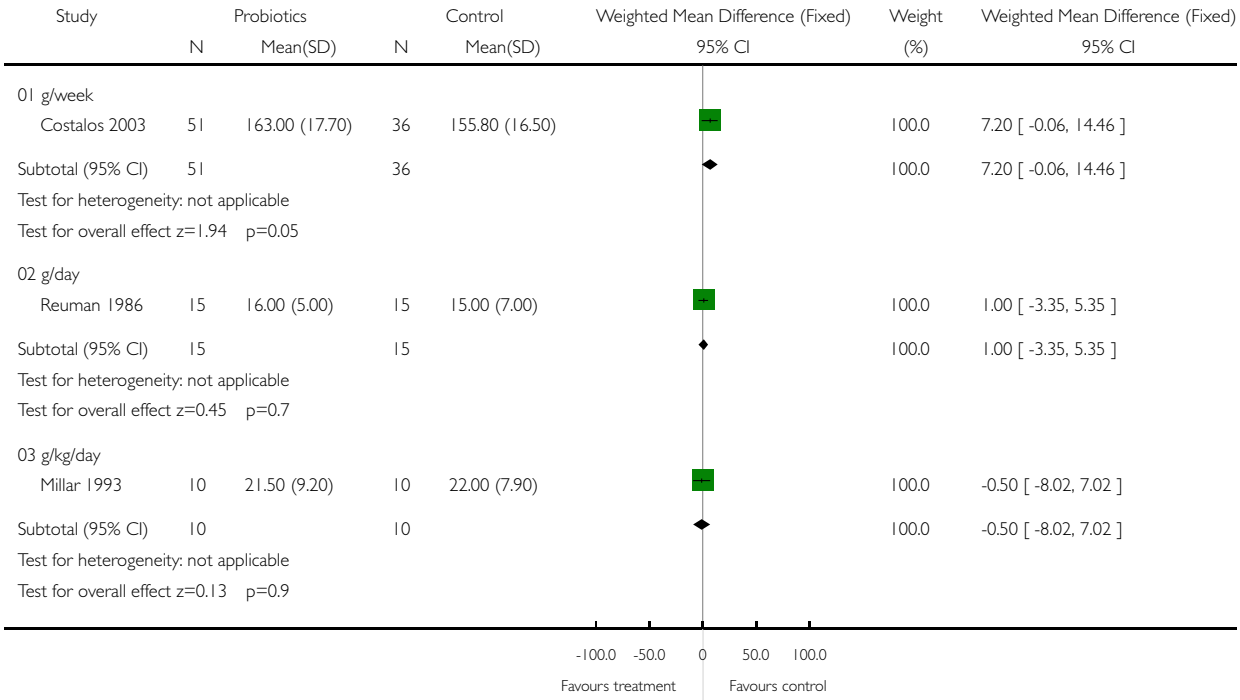


Analysis 01.06. Comparison 01 Probiotics vs. control, Outcome 06 Weight gain

Review: Probiotics for prevention of necrotizing enterocolitis in preterm infants

Comparison: 01 Probiotics vs. control

Outcome: 06 Weight gain



Analysis 01.07. Comparison 01 Probiotics vs. control, Outcome 07 Death or severe NEC or sepsis

Review: Probiotics for prevention of necrotizing enterocolitis in preterm infants

Comparison: 01 Probiotics vs. control

Outcome: 07 Death or severe NEC or sepsis