Original Paper

Neonatology
formerly Biology of the Neonate

Neonatology 2010;97:93–99
DOI: 10.1159/000235684

Received: September 4, 2008
Accepted after revision: January 1, 2009
Published online: August 25, 2009

# Probiotics Reduce the Risk of Necrotizing Enterocolitis in Preterm Infants: A Meta-Analysis

Khalid AlFaleh[a] Jasim Anabrees[b] Dirk Bassler[c]

[a]Division of Neonatology, Department of Pediatrics, King Khalid University Hospital and College of Medicine, King Saud University, and [b]Neonatal Intensive Care Unit, King Fahad Medical City, Riyadh, Saudi Arabia; [c]Department of Neonatology, University Children's Hospital, Tübingen, Germany

**Key Words**
Probiotics · Necrotizing enterocolitis · Systematic review · Preterm infants · Meta-analysis

**Abstract**
***Background:*** Necrotizing enterocolitis (NEC) is the most common serious acquired disease of the gastrointestinal tract in preterm infants. Probiotic bacteria are live microbial supplements that colonize the gastrointestinal tract and potentially provide benefit to the host. ***Objective:*** To compare the efficacy and safety of prophylactic enteral probiotics administration versus placebo or no treatment in the prevention of severe NEC and other morbidities in preterm infants. ***Methods:*** A meta-analysis was performed in accordance with the Cochrane Neonatal Review Group methods. Preterm infants <37 weeks' gestational age and/or <2,500 g birth weight were included. Literature searches were made of MEDLINE, EMBASE, Cochrane Library Controlled Trials Register (CENTRAL), and abstracts of annual meetings of the Society for Pediatric Research and the European Society of Pediatric Research. ***Results:*** Nine eligible trials randomizing 1,425 infants were included. Included trials were highly variable with regard to enrollment criteria, baseline risk of NEC in the control groups, timing, dose, formulation of the probiotics, and feeding regimens. In a meta-analysis, enteral probiotics supplementation significantly reduced the incidence of severe NEC [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 [weighted mean difference –1.9 (95% CI –4.6, 0.77)]. The statistical test of heterogeneity for NEC, mortality and sepsis was insignificant. Data regarding extremely low birth weight infants (ELBW) could not be extrapolated. The included trials reported no systemic infection with the probiotics supplemental organism. ***Conclusion:*** Enteral supplementation of probiotics reduces the risk of severe NEC and mortality in preterm infants. A large randomized controlled trial is required to investigate the benefit and safety profile of probiotics supplementation in ELBW infants.



## Introduction

Necrotizing enterocolitis (NEC) is characterized by bowel wall necrosis of various length and depth [1]. 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 (VLBW) infants [2].

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com


1661–7800/10/0972–0093$26.00/0

Accessible online at:
www.karger.com/neo

Dr. K. AlFaleh
Division of Neonatology, Department of Pediatrics
King Khalid University Hospital and College of Medicine, King Saud University
PO Box 7805, Riyadh 11472 (Saudi Arabia)
Tel. +966 5 5603 1222, Fax +966 1467 1709, E-Mail kmfaleh@hotmail.com

NEC is the most common serious acquired disease of the gastrointestinal tract in preterm infants [3]. The incidence of NEC varies among countries and neonatal centers. It has been reported to affect up to 10% of VLBW [2]. VLBW infants with NEC have a mortality rate of up to 20% [4, 5]. Approximately 27–63% of affected infants require surgical intervention [3]. Bowel perforation occurs in one third of the affected infants [1]. Strictures, primarily in the colon, occur in more than one third of affected infants [6]. An increased rate of total parenteral nutrition (TPN)-related complications and extended hospitalization have been reported [7]. 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 [8].

The pathogenesis of NEC remains poorly understood. NEC most likely represents a complex interaction of factors causing mucosal injury [9]. 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 [10, 11]. Bacterial colonization is necessary for the development of NEC [12, 13]. 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 [14, 15].

Probiotic bacteria are live microbial supplements that colonize the gastrointestinal tract and potentially provide benefit to the host. 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 [16]. Potential mechanisms by which probiotics may protect high-risk infants from developing NEC and/or sepsis include an increased barrier to bacterial migration along with their products across the mucosa [17, 18], competitive exclusion of potential pathogens [19], modification of host response to microbial products [20], augmentation of IgA mucosal responses, enhancement of enteral nutrition that inhibit the growth of pathogens, and upregulation of immune responses [21]. There is a theoretical risk of bacteremia secondary to enterally administered probiotic strains, though few data support this concern. Bacillus species administered as probiotics were reported to be associated with invasive disease in target populations [22]. In this meta-analysis we evaluate the efficacy and safety of probiotic supplementation in preterm infants.

## Methods

*Search Strategy*

The standard search strategy for the Cochrane Neonatal Review Group (CNRG) was used. Randomized and quasi-randomized controlled trials that compared enteral probiotics to placebo or no treatment in preterm 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 restriction was applied.

Other databases were searched including: EMBASE (1980 to December 2006), Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 3, 2006). In addition, we manually searched the abstract books from the Society of Pediatric Research (SPR) and the European Society of Pediatric Research (ESPR) from 1998 to 2006. Additional citations were sought using references in articles retrieved from searches. Content experts were contacted to identify unpublished and ongoing studies.

*Data Extraction*

Retrieved articles were assessed for eligibility, and data on patients, intervention, control, outcomes and methodological quality were abstracted independently by two authors. Discrepancies were resolved by discussion and consensus. Where data were incomplete, the primary investigator of the primary study was contacted for further information and clarification.

*Methodological Quality of the Studies*

Standard methods of the Cochrane Collaboration and the Neonatal Review Group were used to assess the methodological quality 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. The methodological details of the studies were extracted from the published data and by contacting the primary author.

*Statistical 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 using 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 extremely low birth weight (ELBW) infants was planned a priori. A sensitivity analysis was carried out to assess the effect of methodological quality on results of the meta-analysis. Heterogeneity was defined as a significant test of heterogeneity ($p < 0.1$) and/or differences in the treatment effects across studies. Tests for between-study heterogeneity (including the $I^2$ test) were performed.

## Results

An initial electronic search yielded 191 potentially relevant citations. After reading abstracts, 12 articles were identified as potentially relevant citations. Review of full-

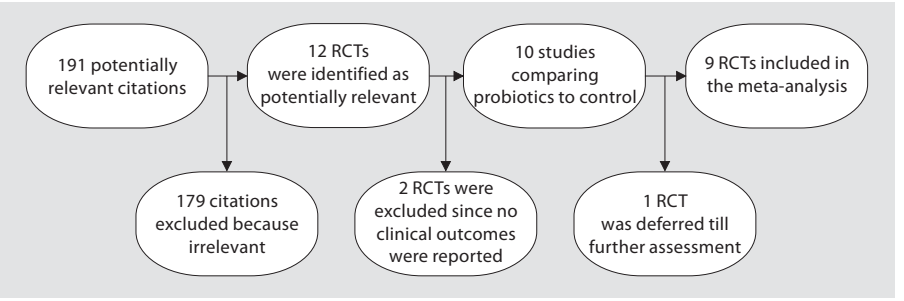


**Fig. 1.** Selection process details.

**Table 1.** Clinical details of included studies

| Reference (first author) | Participants | | Probiotics group |
|---|---|---|---|
| | n | characteristics | |
| Bin-Nun, 2005 [26] | 145 | <1,500 g at birth | Mixture of *Lactobacillus bifidus*, *Streptococcus thermophillus*, and *Bifidobactrium infantis* |
| Costalos, 2003 [27] | 87 | 28–32 weeks' gestation | *Saccharomyces boulardii* |
| Dani, 2002 [28] | 585 | <33 weeks' gestation or <1,500 g at birth | *Lactobacillus* GG (Dicoflor®, Dicofarm SpA, Rome, Italy) |
| Kitajima, 1997 [29] | 91 | <1,500 g at birth | *Bifidobacterium breve* |
| Li, 2004 [30] | 30 | low birth weight | *Bifidobacterium breve* |
| Lin, 2005 [31] | 367 | <1,500 g at birth | Infloran® (*L. acidophilus* and *B. infantis*) |
| Manzoni, 2006 [32] | 80 | <1,500 g at birth | LGG (Diclofor 60®; Dicofarm SpA) |
| Millar, 1993 [33] | 20 | <33 weeks' gestation | *Lactobacillus* GG108 |
| Reuman, 1986 [34] | 45 | <2,000 g at birth | *Lactobacillus* |

text articles identified ten studies comparing probiotic administration to control treatment. Two studies [23, 24] were excluded since no clinical outcomes were reported. A decision regarding the inclusion of one study [25] was deferred till further assessment. This study included infants between 25 and 42 weeks' gestation. Attempts were made to contact the author in order to extract data relevant to preterm infants alone (fig. 1).

Nine eligible trials [26–34] randomizing 1,425 infants were included. Included trials were highly variable with regard to enrollment criteria, baseline risk of NEC in the control groups, timing, dose, formulation of the probiotics, and feeding regimens. Details of included studies are presented in table 1.

Only two studies enrolled large number of infants and reported adequate allocation concealment and blinding of intervention [28, 31]. The methodological quality of the studies is summarized in table 2.

In a meta-analysis of trial data, enteral probiotics supplementation significantly reduced the incidence of severe NEC [typical RR 0.32 (95% CI 0.17, 0.60)] (fig. 2) and total mortality [typical RR 0.43 (95% CI 0.25, 0.75)] with the number needed to treat of 25 for both outcomes. Although five studies reported death as an outcome, only two [28, 31] were of high methodological quality. Two studies addressed NEC-related deaths but events were rare [26, 28].

There was no evidence of significant reduction of nosocomial sepsis [typical RR 0.93 (95% CI 0.73, 1.19)] or days on TPN [weighted mean difference (WMD) –1.9 (95% CI –4.6, 0.77)]. The included trials reported no systemic infection with the probiotics supplemental organism. No data were reported in any of the trials regarding neurodevelopmental impairment. Details of results are presented in table 3.

A subgroup analysis to demonstrate the effect of probiotics administration in ELBW infants was not performed since data pertaining to this high-risk group could not be extracted from the included studies. The statistical test of heterogeneity for NEC, mortality and sepsis was insignificant.

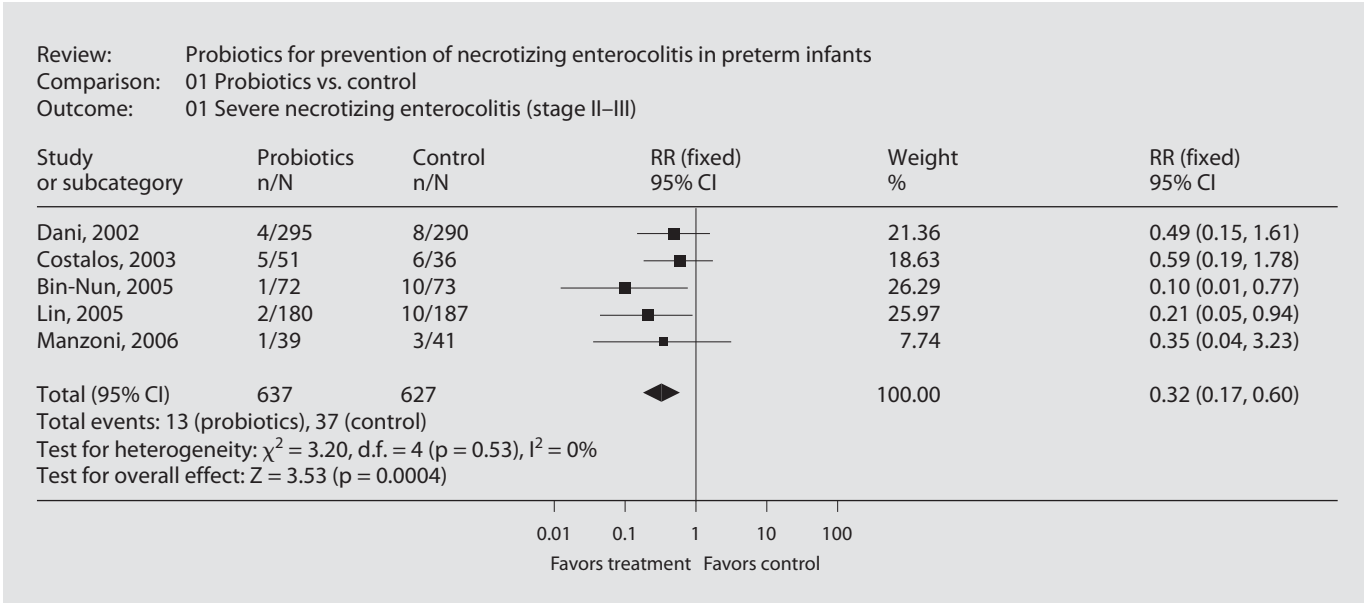


**Fig. 2.** Probiotics for prevention of NEC in preterm infants. Probiotics vs. controls. Severe necrotizing enterocolitis (stage II–III) outcome.

**Table 2.** Methodological quality of included trials

| | Bin-Nun 2005 [26] | Costalos 2003 [27] | Dani 2002 [28] | Kitajima 1997 [29] | Li 2004 [30] | Lin 2005 [31] | Manzoni 2006 [32] | Millar 1993 [33] | Reuman 1986 [34] |
|---|---|---|---|---|---|---|---|---|---|
| Single center or multicenter | single center | single center | multi-center | single center | single center | single center | single center | single center | single center |
| Method of generating randomization | not described | adequate | not described | not described | unclear | adequate | adequate | not described | inadequate[1] |
| Allocation concealment | not specified | adequate | adequate | not described | not described | adequate | unclear | not described | inadequate |
| Blinding of intervention | masked | masked | masked | unclear | unclear | unclear | unclear | masked | masked |
| Blinding of outcome measurement | not specified | blinded | blinded | unclear | unclear | blinded | blinded | unclear | blinded |
| Complete follow-up | not specified[2] | yes | yes | no[3] | unclear | yes | yes | yes | yes |

[1] Random number charts and the last digit of patient's chart number, the next matched infant is assigned to the opposite group.
[2] 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 trial results.
[3] Six infants excluded for various reasons.

**Table 3.** Outcome results of included trials

| Outcome | Studies[1] | | Probiotics | Control | RR/WMD | RD | NNT |
|---|---|---|---|---|---|---|---|
| Severe NEC (stage II–III) | 5 | | 13/637 | 36/627 | RR 0.32 [0.17, 0.60] | –0.04 (95% CI –0.06, –0.02) | 25 |
| Mortality | 5 | | 16/601 | 39/606 | RR 0.43 [0.25, 0.75] | –0.04 (95% CI –0.06, –0.01) | 25 |
| NEC-related mortality | 2 | | 0/367 | 5/363 | RR 0.17 [0.02, 1.37] | | |
| Sepsis | 5 | | 89/647 | 97/637 | RR 0.93 [0.73, 1.19] | | |
| TPN, days | 2 | Dani, 2002 [28] | 12.8 (13.9) | 14.7 (18.7) | WMD –1.9 (–4.6, 0.77) | | |
| | | Lin, 2005 [31] | 14.7 (5.7) | 13.9 (5.0) | WMD 0.80 (–0.3, 1.9) | | |
| Hospitalization, days | 3 | Reuman, 1986 [34] | 59.4 (56.4) | 38.7 (30.6) | WMD 20.70 [–11.77, 53.17] | | |
| | | Millar, 1993 [33] | 50 (23–136) | 42.8 (19–114) | | | |
| | | Lin, 2005 [31] | 46.7 (27.1) | 46.5 (26.10) | WMD 0.20 [–5.25, 5.65] | | |
| Weight gain | 3 | Costalos, 2003 [27] | 163.00 (17.70) | 155.80 (16.50) | WMD 7.20 [–0.06, 14.46] | | |
| | | Reuman, 1986 [34] | 16.00 (5.00) | 15.00 (7.00) | WMD 1.00 [–3.35, 5.35] | | |
| | | Millar, 1993 [33] | 21.50 (9.20) | 22.00 (7.90) | WMD –0.50 [–8.02, 7.02] | | |
| Death or severe NEC or sepsis | 1 | | 31/180 | 60/187 | 0.54 [0.37, 0.79] | | |
| Systemic infection with the supplemented organism | | no data were reported | | | | | |
| Neurodevelopmental impairment | | no data were reported | | | | | |

[1]Number of studies or first author is indicated.

NEC = Necrotizing enterocolitis; TPN = total parenteral nutrition; RR = relative risk; RD = risk difference; WMD = weighted mean difference; NNT = number needed to treat.

## Discussion

Our review examined the efficacy of probiotics in preterm infants in nine randomized controlled trials. 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.

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 [29, 30], competitive exclusion of potential pathogens [31], modification of host response to microbial products [32], augmentation of IgA mucosal responses, enhancement of enteral nutrition that inhibits the growth of pathogens, and upregulation of immune responses [33]. There is a theoretical risk of bacteremia secondary to enterally administered probiotic strains, though few data support this concern. Bacillus species administered as probiotics were reported to be associated with invasive disease in target populations [34].

There are case reports of systemic infections caused by probiotic organisms in the biomedical literature. The studies included in our review reported no such events. The use of probiotics was described as safe and well tolerated in the primary studies.

A commentary by ESPGHAN Committee on Nutrition concluded that only a limited number of controlled trials have studied health outcomes following enteral administration of probiotic organisms in preterm infants, and additional studies are needed. Based on the available data, the authors conclude that probiotics so far used in clinical trials can be generally considered as safe. However, surveillance for possible side effects, such as infection in high-risk groups, is lacking and is needed [35].

Recently, two systematic reviews were published [36, 37]. Our review included three additional trials [24, 27, 28]. We excluded the trial by Mohan et al. [38] during our primary screening process since it enrolled both term and preterm infants. Both reviews had similar results with regard to NEC, mortality and sepsis. Deshpande et al. [36] were able to demonstrate a shorter time to full feed by 3 days in the probiotics group.

Our review utilized a 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 review authors. The validity of our review's results might be compromised by the following: most of the included trials (except two) were of small sample size with inadequate data reported to assess quality; included trials utilized different preparations and dosing regimens of the intervention under study, and data on the highest risk population (ELBW infants) could not be retrieved. Therefore, the benefit of enteral probiotics administration in reducing the incidence of NEC in the highest risk population (ELBW infants) could not be evaluated in a subgroup analysis.

In summary, enteral supplementation of probiotics reduces the risk of severe NEC and mortality in preterm infants. A large randomized controlled trial is required to investigate the benefit and safety profile of probiotics supplementation in ELBW infants.

## References


1 Kafetzis DA, Skevaki C, Costalos C: Neonatal necrotizing enterocolitis: an overview. Curr Opin Infect Dis 2003;16:349–355.
2 Kosloske AM: Epidemiology of necrotizing enterocolitis. Acta Paediatr Suppl 1994;396: 2–7.
3 Lee JS, Polin RA: Treatment and prevention of necrotizing enterocolitis. Semin Neonatol 2003;8:449–459.
4 Caplan MS, Jilling T: New concepts in necrotizing enterocolitis. Curr Opin Pediatr 2001; 13:111–115.
5 Holman RC, Stoll BJ, Clarke MJ, Glass RI: The epidemiology of necrotizing enterocolitis infant mortality in the United States. Am J Public Health 1997;87:2026–2031.
6 Ricketts RR: Surgical treatment of necrotizing enterocolitis and the short bowel syndrome. Clin Perinatol 1994;21:365–387.
7 Bisquera JA, Cooper TR, Berseth CL: Impact of necrotizing enterocolitis on length of stay and hospital charges in very low birth weight infants. Pediatrics 2002;109:423–428.
8 Stoll BJ, Hansen NI, Adams-Chapman I, Fanaroff AA, Hintz SR, Vohr B, Higgins RD: Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. JAMA 2004; 292:2357–2365.
9 Neu J: Necrotizing enterocolitis: the search for a unifying pathogenic theory leading to prevention. Pediatr Clin North Am 1996;43: 409–432.
10 Kosloske AM: Pathogenesis and prevention of necrotizing enterocolitis: a hypothesis based on personal observation and a review of the literature. Pediatrics 1984;74:1086–1092.
11 La Gamma EF, Browne LE: Feeding practices for infants weighing less than 1,500 g at birth and the pathogenesis of necrotizing enterocolitis. Clin Perinatol 1994;21:271–306.
12 Kosloske AM: A unifying hypothesis for pathogenesis and prevention of necrotizing enterocolitis. J Pediatr 1990;117:S68–S74.
13 Musemeche CA, Kosloske AM, Bartow SA, Umland ET: Comparative effects of ischemia, bacteria, and substrate on the pathogenesis of intestinal necrosis. J Pediatr Surg 1986;21:536–538.
14 Goldmann DA, Leclair J, Macone A: Bacterial colonization of neonates admitted to an intensive care environment. J Pediatr 1978; 93:288–293.
15 Gewolb IH, Schwalbe RS, Taciak VL, Harrison TS, Panigrahi P: Stool microflora in extremely low birth weight infants. Arch Dis Child Fetal Neonatal Ed 1999;80:F167–F173.
16 Millar M, Wilks M, Costeloe K: Probiotics for preterm infants? Arch Dis Child Fetal Neonatal Ed 2003;88:F354–F358.
17 Orrhage K, Nord CE: Factors controlling the bacterial colonization of the intestine in breastfed infants. Acta Paediatr Suppl 1999; 88:47–57.
18 Mattar AF, Drongowski RA, Coran AG, Harmon CM: Effect of probiotics on enterocyte bacterial translocation in vitro. Pediatr Surg Int 2001;17:265–268.
19 Reid G, Howard J, Gan BS: Can bacterial interference prevent infection? Trends Microbiol 2001;9:424–428.
20 Duffy LC: Interactions mediating bacterial translocation in the immature intestine. J Nutr 2000;130:432S–436S.
21 Link-Amster H, Rochat F, Saudan KY, Mignot O, Aeschlimann JM: Modulation of a specific humoral immune response and changes in intestinal flora mediated through fermented milk intake. FEMS Immunol Med Microbiol 1994;10:55–63.
22 Richard V, Van der Auwera AP, Snoeck R, Daneau D, Meunier F: Nosocomial bacteremia caused by *Bacillus* species. Eur J Clin Microbiol Infect Dis 1988;7:783–785.
23 Stansbridge EM, Walker V, Hall MA, Smith SL, Millar MR, Bacon C, Chen S: Effects of feeding premature infants with *Lactobacillus* GG on gut fermentation. Arch Dis Child 1993;69:488–492.
24 Agarwal R, Sharma N, Chaudhry R, Deorari A, Paul VK, Gewolb IH, Panigrahi P: Effects of oral *Lactobacillus* GG on enteric microflora in low-birth-weight neonates. J Pediatr Gastroenterol Nutr 2003;36:397–402.
25 Uhlemann M, Heine W, Mohr C, Plath C, Pap S: Effects of oral administration of bifidobacteria on intestinal microflora in premature and newborn infants newborn infants. Z Geburtshilfe Neonatol 1999;203: 213–217.
26 Bin-Nun A, Bromiker R, Wilschanski M, Kaplan M, Rudensky B, Caplan M, Hammerman C: Oral probiotics prevent necrotizing enterocolitis in very low birth weight neonates. J Pediatr 2005;147:192–196.
27 Costalos C, Skouteri V, Gounaris A, Sevastiadou S, Triandafilidou A, Ekonomidou C, et al: Enteral feeding of preterm infants with *Saccharomyces boulardii*. Early Hum Dev 2003;74:89–96.
28 Dani C, Biadaioli R, Bertini G, Martelli E, Rubaltelli F: Probiotics feeding in prevention of urinary tract infection, bacterial sepsis and necrotizing enterocolitis in preterm infants. A prospective double-blind study. Biol Neonate 2002;82:103–108.
29 Kitajima H, Sumida Y, Tanaka R, Yuki, Takayama H, Fujimura M: Early administration of *Bifidobacterium breve* to preterm infants: randomised controlled trial. Arch Dis Child Fetal Neonatal Ed 1997;76:F101–F107.
30 Li Y, Shimizu T, Hosaka A, Kaneko N, Ohtsuka Y, Yamashiro Y: Effects of *Bifidobacterium breve* supplementation on intestinal flora of low birth weight infants. Pediatr Int 2004;46:509–505.
31 Lin HC, Su BH, Chen AC, Lin TW, Tsai CH, Yeh TF, Oh W: Oral probiotics reduce the incidence and severity of necrotizing enterocolitis in very low birth weight infants. Pediatrics 2005;115:1–4.

32 Manzoni P, Mostert M, Leonessa ML, Priolo C, Farina D, Monetti C, Latino MA, Gomirato G: Oral supplementation with *Lactobacillus casei* subspecies *rhamnosus* prevents enteric colonization by *Candida* species in preterm neonates: a randomized study. Clin Infect Dis 2006;15:1735–1742.
33 Millar MR, Bacon C, Smith SL, Walker V, Hall MA: Enteral feeding of preterm infants with *Lactobacillus* GG. Arch Dis Child 1993; 69:483–487.
34 Reuman PD, Duckworth DH, Smith KL, Kagan R, Bucciarelli RL, Ayoub EM: Lack of effect of *Lactobacillus* on gastrointestinal bacterial colonization in preterm infants. Pediatr Infect Dis 1986;5:663–668.
35 Agostoni C, Axelsson I, Braegger C: Probiotic Bacteria in Dietetic Products for Infants: A Commentary by the ESPGHAN Committee on Nutrition. J Pediatr Gastroenterol Nutr 2004;38:365–374.
36 Deshpande G, Rao S, Patole S: Probiotics for prevention of necrotising enterocolitis in preterm neonates with very low birth weight: a systematic review of randomised controlled trials. Lancet 2007;369:1614–1620.
37 Barclay AR, Stenson B, Simpon JH, et al: Probiotics for necrotizing enterocolitis: a systematic review. J Pediatr Gastroenterol Nutr 2007;45:569–576.
38 Mohan R, Koebnick C, Schildt J, et al: Effects of *Bifidobacterium lactis* Bb12 supplementation on intestinal microbiota of preterm neonates: a double placebo-controlled, randomised study. J Clin Microbiol 2006;44: 4025–4031.