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Review Article

Efficacy and safety of probiotics in preterm infants

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Abstract. Probiotics are live microbial feed supplements that beneficially affect the recipient by improving intestinal balance. In an updated systematic review, nineteen trials randomizing more than 2800 infants were included. In a meta-analysis of trial data, enteral probiotic supplementation significantly reduced the incidence of severe necrotizing enterocolitis (typical RR 0.35, 95% CI 0.24 to 0.52) and mortality (typical RR 0.55, 95% CI 0.40 to 0.74). There was no evidence of significant reduction of nosocomial sepsis (typical RR 0.89, 95% CI 0.77 to 1.03). The included trials reported no systemic infection with - supplemented probiotics. Recent data in addition to a report by the European Society for Pediatric Gastroenterology (ESPGAN) concluded probiotics could be generally considered safe.

Keywords: Probiotics, preterm, NEC, neonatal sepsis

1. Introduction

Probiotics are live microbial feed supplements that beneficially affect the host by improving intestinal balance [1]. Metchnikoff and Tissier were the first investigators to make scientific suggestions about the use of probiotics [2, 3]. Members of the genera Lactobacillus and Bifidobacterium are the most commonly used species, but not exclusively, as probiotic microorganisms and a growing number of probiotic foods are available to the consumer [4]. Probiotics are associated with a number of positive health benefits. Over the past two decades there has been a significant increase in the scientific literature addressing the efficacy of probiotic supplementation in the preterm infants. This review summarizes the available evidence on the benefits of probiotics and potential safety issues about their use in preterm babies.

2. Efficacy of probiotics

2.1. Necrotizing enterocolitis

Necrotizing Enterocolitis (NEC) is the most common, serious acquired disease of the gastrointestinal tract in preterm infants [5]. It is characterized by bowel wall necrosis of various length and depth. Bowel perforation occurs in one third of the affected infants [6]. Although 5 to 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

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(infants with birth weight <1500 g) [7]. 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 [8]. 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) [7].

The pathogenesis of NEC remains incompletely understood. NEC most likely represents a complex interaction of factors causing mucosal injury [9]. It is speculated that NEC occurs when two of the following three pathologic events occur coincidently; 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].

VLBW infants with NEC have a mortality rate up to 20% [16, 17]. Approximately 27 to 63% of affected infants require surgical intervention [5]. Strictures occur primarily in the colon in more than one third of affected infants [18]. Increased rate of total parenteral nutrition (TPN) related complications and extended hospitalization have been reported [19]. 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 [20].

Probiotic bacteria colonize the gastrointestinal tract and potentially provide benefit to the host [21]. 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 [21].

Potential mechanisms by which probiotics may protect high risk infants from developing NEC and/or sepsis include increased barrier to migrating bacteria and their products across the mucosa [22, 23], competitive exclusion of potential pathogens [24], modification of host response to microbial products [25], augmentation of Immunoglobulin A (IgA) mucosal responses, enhancement of enteral nutrition that inhibits the growth of pathogens, and up-regulation of immune responses [26].

The evidence of the efficacy and safety of probiotic supplementation in preterm infants was recently updated. Nineteen randomized trials enrolling more than 2800 preterm infants were included in the analysis of the studies were quite variable in the enrollment criteria, probiotic strain, baseline risk of NEC in the control group and trial quality (Table 1). The enteral administration of probiotics reduced the incidence of severe NEC (stage II-III in Bell's classification) with a relative risk of 0.35, (95% CI 0.24 to 0.52) and a number needed to treat (NNT) of 20 (Fig. 1).

Most of the included trials enrolled preterm infants less than 1500 g at birth; however, specific efficacy data on most vulnerable infants (ELBW) was reported in only one study with no statistical difference. However due to lack of power, a firm conclusion could not be made.

2.2. Neonatal sepsis

Nosocomial infections are also frequent complications 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 [28]. Late onset sepsis is associated with an increased risk of death, neonatal morbidity and prolonged hospitalization [29, 30].

Pooled data shows a trend toward a benefit in the reduction of late onset sepsis (RR 0.89, 95% CI 0.77 to 1.03); however, this did not reach statistical significance (Fig. 2).

2.3. Mortality

The administration of probiotics resulted in an improved mortality rate (RR 0.55, 95% CI 0.40 to 0.74) with a trend toward a benefit in NEC-related mortality (RR 0.41, 95% CI 0.15 to 1.10) (Fig. 3).

2.4. Time to full enteral feeds

Probiotic administration shortened time to full feeds by approximately 4 days with a weighted mean difference of −3.96 (95% CI −4.45 to −3.48).

3. Safety of probiotics

Recently, the safety of probiotics in VLBW infants has been extensively reviewed. Although probiotics

Table 1
Characteristics of randomized controlled trials** addressing the efficacy of administered probiotics in preterm infants

The study	Al-Hosni 2012	Bin-Nun 2005	Braga 2011	Costalos 2003	Dani 2002	Kitajima 1997	Li 2004	Lin 2005	Manzoni 2006
SC or MC	MC	SC	SC	SC	MC	SC	SC	SC	SC
Method of generating randomization	Not described	Not described	A	A	Not described	Not described	Unclear	A	A
Allocation concealment	Not specified	Not specified	A	A	A	Not described	Not described	A	Unclear
Blinding of intervention	Y	Masked	Y	Masked	Masked	Unclear	Unclear	Unclear	Unclear
Blinding of outcome measurement	Y	Not specified	Y	Blinded	Blinded	Unclear	Unclear	Blinded	Blinded
Complete follow-up	Y	Not specified	Y	Y	Y	No	Unclear	Y	Y

	Mahatsch 2010	Millar 1993	Reuman 1986	Lin 2008	Manzoni 2009	Mohan 2006	Rougé 2009	Samanta 2009	Sari 2010	Stratiki 2007
SC or MC	SC	SC	SC	MC	MC	SC	Two centers	SC	SC	SC
Method of generating randomization	A	Not described	IA*	A	A	A	A	CT	A	CT
Allocation concealment	A	Not described	IA	A	A	Not described	Possibly adequate	CT	CT	CT
Blinding of intervention	Y	Masked	Masked	Y	Y	Y	Y	CT	CT	CT
Blinding of outcome measurement	Y	Unclear	Blinded	Y	Y	Unclear	Y	CT	Y	Y
Complete follow-up	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

A, Adequate. IA, inadequate. Y, Yes. CT, Can't tell. SC, Single Center. MC, Multi Center. *Random number charts and the last digit of patient's chart number; the next matched infant is assigned to the opposite group. **reference 27.

have been described as safe and well tolerated based on the current literature [27], there have been some concerns that this conclusion requires additional exploration. Unfortunately, data addressing the safety of probiotics are still scarce.

There is a theoretical risk of bacteremia secondary to specific 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 [31]. Several microorganisms in probiotics have been isolated from patients with endocarditis, bacteremia or local infections [32–35], and infections with Lactobacillus species in infants and children have been reported [36–41]. However, none of the reported trials explicitly indicate the use of specific culture techniques to detect sepsis caused by individual probiotic organisms.

Subsequently published guidelines for the Evaluation of probiotics further emphasize the need to fully evaluate the safety of probiotics, in particular the risk of infection in subjects with compromised immunity and subjects at risk for endocarditis [4].

The French Agency for Food Safety (AFFSA) reviewed the safety of probiotics in infants. The agency recommended for safety reasons that probiotics should not be given to immunocompromised or preterm infants [42].

The Scientific Committee on Food of the European Commission also commented on the use of probiotic bacteria in food products for infants. It recommended that infant formulas with probiotic microorganisms

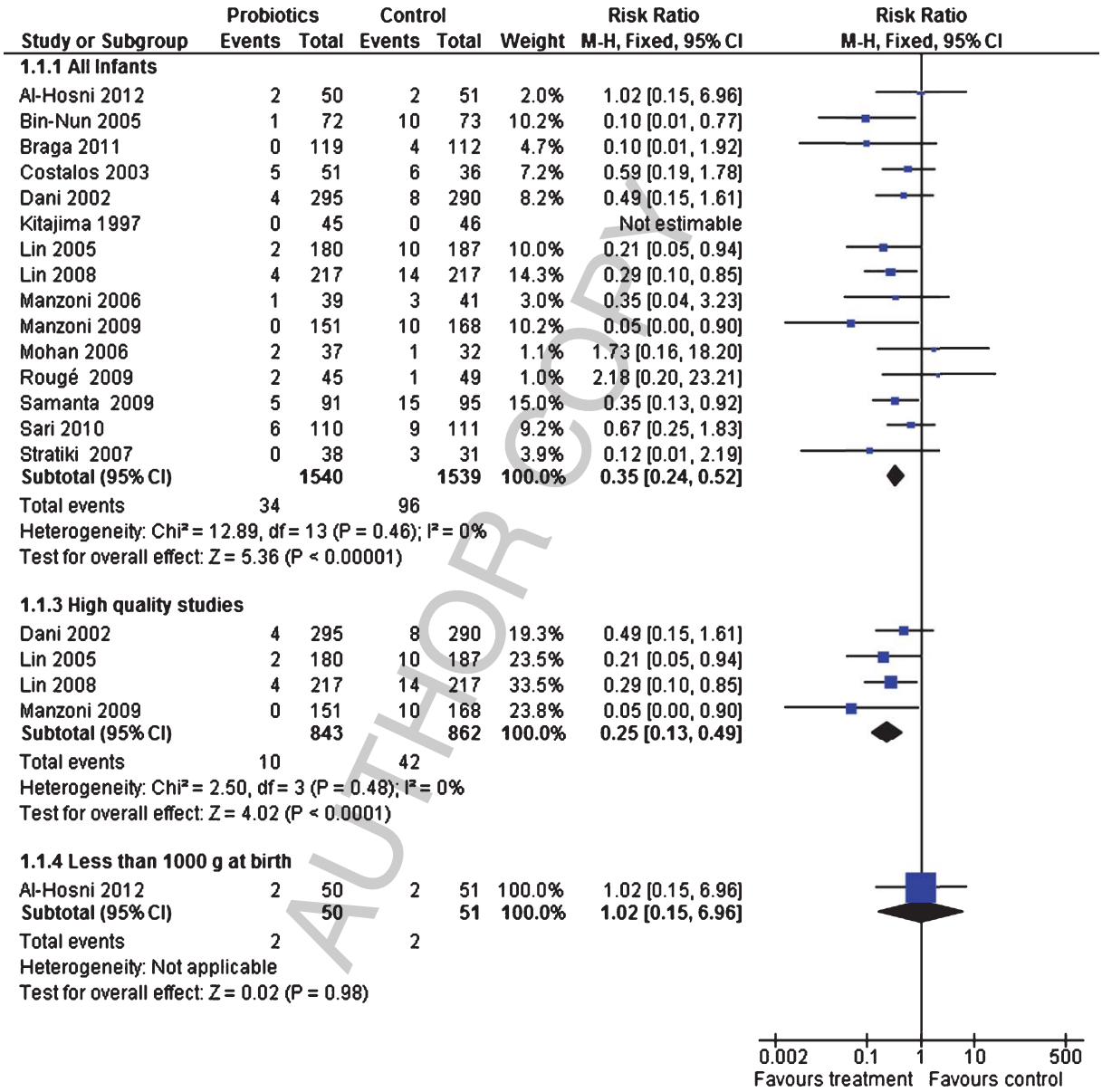

Fig. 1. Forest plot of a meta-analysis of the efficacy of probiotics in the prevention of severe NEC in preterm infants.

should be marketed only if their benefit and safety have been evaluated according to the principles outlined by the same Committee [43].

Almost all patients presenting with probiotic microorganism sepsis in these studies have had underlying conditions predisposing them to infection, e.g. structural heart defects in case of endocarditis, or indwelling catheters in case of sepsis. In most cases of infection, the organism appears to have originated from the patient's own microflora. In a limited number of cases, the organism was thought to be related to the consumption of a commercial probiotic product containing *L. rhamnosus* [32, 34, 36–39, 40, 41, 44], Saccharomyces [45], and Bacillus [46, 47, 31]. In these patients too, serious underlying conditions were common. Cases of infection with Bifidobacterium during supplementation have not been reported. A report from Finland indicated that the increased use of Lactobacillus GG in food has not resulted in an increased incidence of

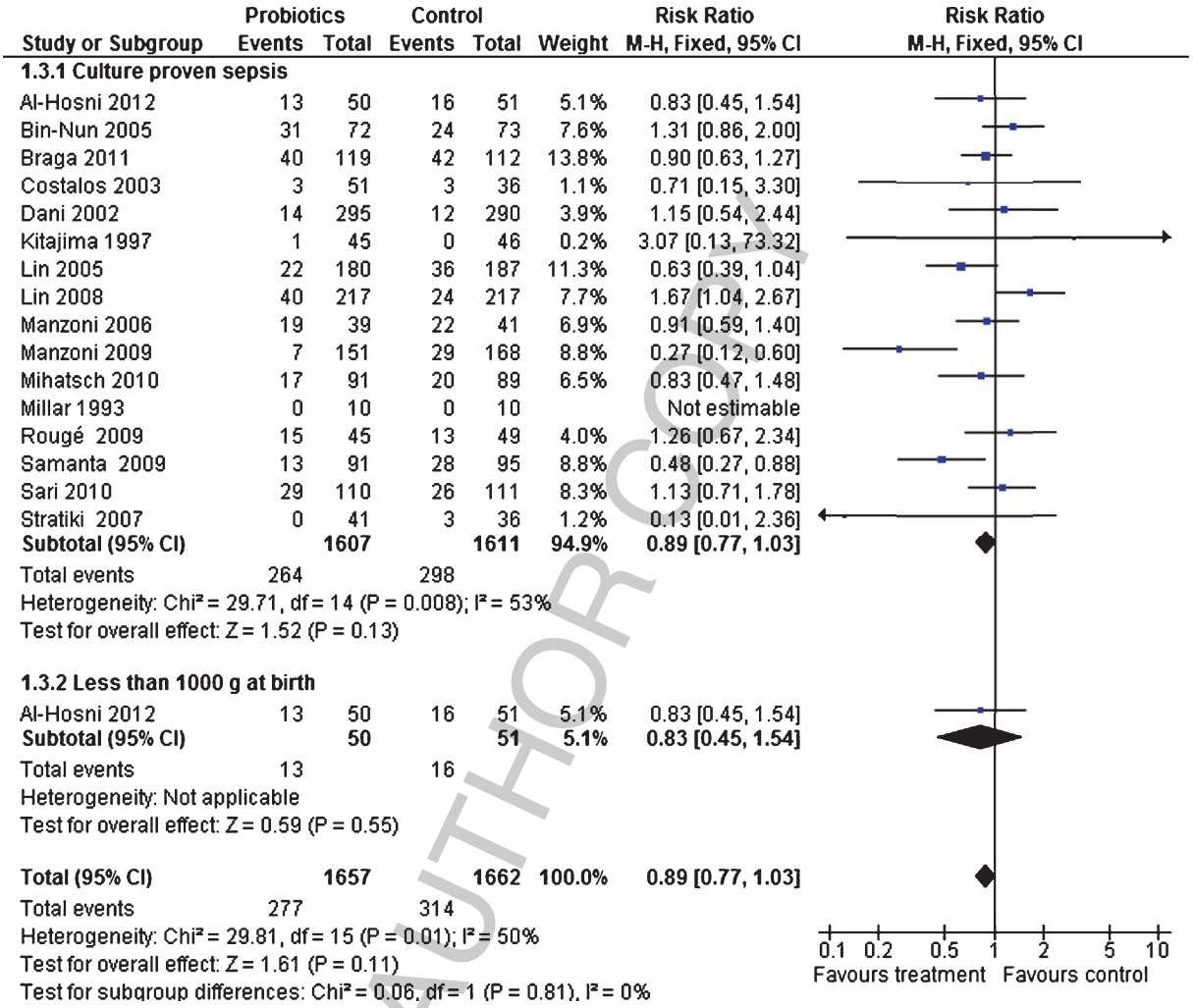

Fig. 2. Forest plot of a meta-analysis of the efficacy of probiotics in the prevention of sepsis in preterm infants.

Lactobacillus bacteremia or in the proportion of Lactobacillus bacteremia among all cases of bacteremia [48].

Bacteremia associated with enterally administered probiotics was not reported in all trials enrolling preterm infants.

Several evaluations of the published literature have concluded that the risk of infection with probiotic lactobacilli or bifidobacteria is similar to that of infection with commensal strains, and that consumption of such products is a negligible risk to consumers, including immunocompromised hosts [49]. In a recent retrospective study of two Italian neonatal units, no isolation of Lactobacillus species was reported in more than 5000 surveillance and clinical cultures. The authors' chart review did not reveal any major adverse effects or intolerance attributable to probiotics despite the administration of more than 17,000 doses of Lactobacillus [50].

Other side effects in which probiotics could theoretically play a role include deleterious metabolic activity, excessive immune stimulation, and gene transfer [51]. However, the available data from preclinical and clinical evaluations do not provide any indication that such adverse effects would occur with probiotic strains currently in use. ESPGAN concluded that probiotics so far used in clinical trials could be generally considered as safe. However, surveillance for possible side effects, such as infection in high-risk groups, is lacking and is needed [52].

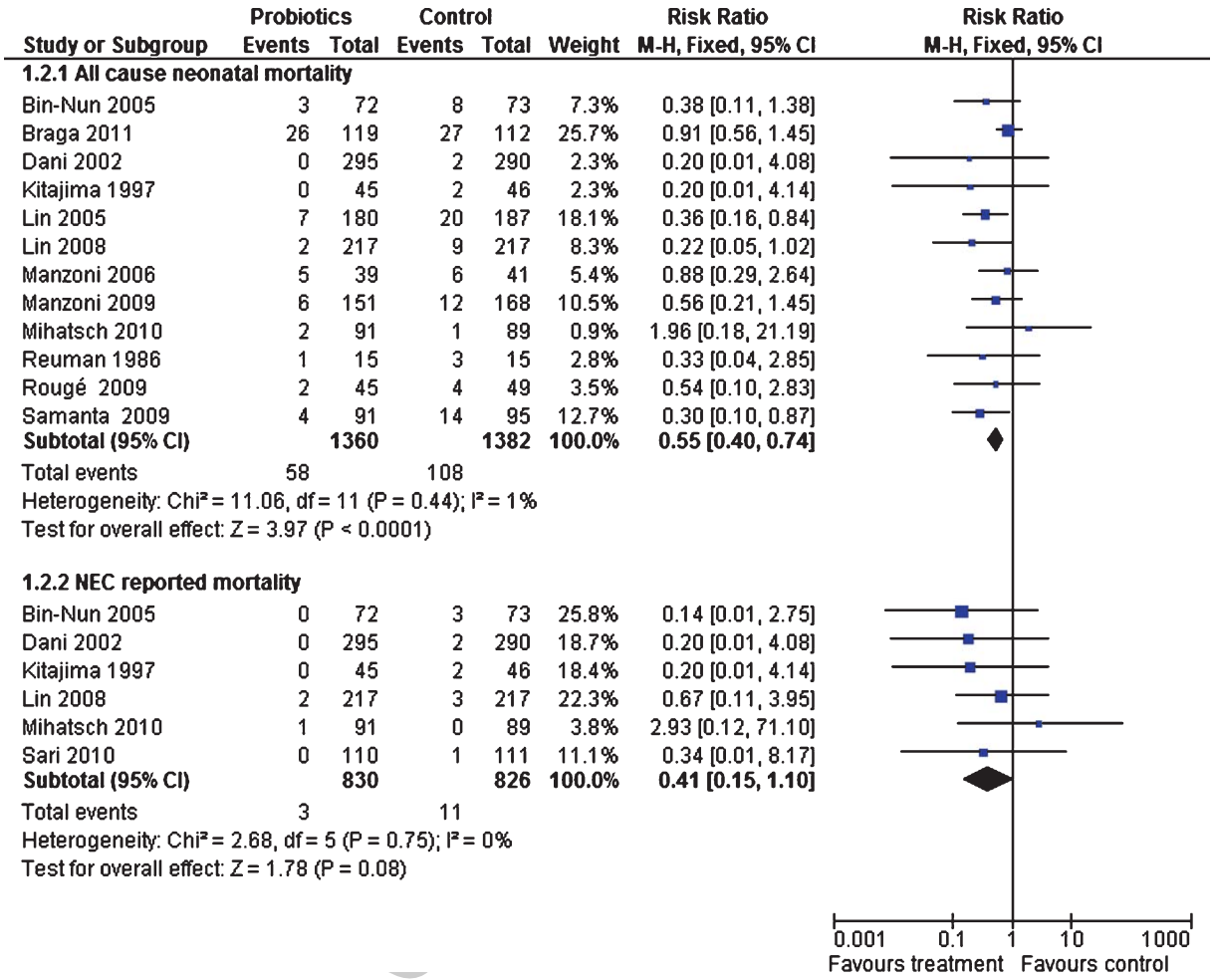

Fig. 3. Forest plot of a meta-analysis of the efficacy of probiotics in the prevention of mortality in preterm infants.

4. Current controversy

The most important question that needs to be addressed; Is it time to change practice and adopt the use of probiotics as a standard of care in preterm infants?

This issue has been widely discussed among experts and has resulted in two schools of thought. The first suggests waiting until further precise data of efficacy and safety in ELBW infants are available in addition to the determination of the most effective preparation and dose to be utilized [53].

The second is in favor of change in practice based on significant reduction in severe NEC and all cause mortality. This group believes that a delay in adopting effective treatment will have serious consequences [54].

We believe that based on the available evidence for probiotic use in the preterm infant, the number of included infants, and the narrow confidence interval, that a change in practice is warranted at this stage. Parents of preterm infants should be informed of the current evidence if placebo controlled trials are to continue [27].

5. Future questions

Further evaluation that addresses the optimum type of probiotic, the dosage, and the effect in ELBW is still needed. Currently there are a number ongoing randomized trials and one trial has been terminated recently for statistical reasons (http://clinicaltrials.gov) (Table 2). Although the ongoing trials may not answer

Table 2
Ongoing randomized controlled trials of the efficacy of probiotics in preterm infants

Study	Participants	Interventions	Outcomes
Costeloe (UKISRCTN05511098)	Before 31 completed weeks of gestation.	1,300 babies will be recruited over 30 months. *Bifidobacterium breve* strain BBG (B breve BBG). The placebo is corn starch alone.	Primary: Episodes of blood stream infection, NEC, Death before discharge Secondary: Many composite outcomes, Number of positive blood culture with an organism recognised as a skin commensal, Number of babies with episodes of blood stream infection with organisms other than skin commensals, Number of babies with isolates of organisms, babies with a positive culture of B breve BBG from any normally sterile site, days of antibiotics and/or anti-fungals per baby, babies colonised with the administered probiotic strain, Stool flora, Age at achieving full enteral nutrition, Change of weight, BPD, Hydrocephalus and/or intraparenchymal cysts, ROP, and Length of stay.
Lozano (Colombia NCT00727363)	BWT < 2000 g Stable < 48 hours of age	Enrolment 751 *Lactobacillus reuteri* DSM 17938 at a dose of 10^8 cfus in 5 drops of a commercially available oil suspension once per day until discharge. Placebo 5 drops of an available oil suspension	Primary: Deaths and episodes of nosocomial sepsis Secondary: Necrotizing enterocolitis This study has been terminated.
Tobin (Australia ACTRN12607000144415)	BWT < 1500 g and <32 weeks gestation	1,100 babies Probiotic combination (ABC Dophilus Infant Powder, contains 1×10^9 of total organisms, consisting of 3 bacterial strains (Bifidobacteriuminfantis, *Bifidobacterium bifidus*, *Streptococcus thermophilus*).	Primary: The incidence of late onset sepsis Secondary: The incidence of necrotizing enterocolitis, death, length of the primary admission, courses of antibiotics, time to full oral feeds, Growth, Atopic eczema, food allergies, and wheeze from term until 12 months corrected age.
Cooper (South Africa NCT00977912)	BWT 800–1500 g Tolerating enteral feeding within 48 hours	Enrolment 1000 Probiotic supplementation vs Supplement: Milk containing placebo	Primary: NEC onset Secondary: Antibiotic administration and stool microbiology
Moral (USA NCT01181791)	BWT 700–1500 g Survive >3 days	Enrolment 120 *Lactobacillus* reuteri vs Placebo	Primary: Time to reach full feeds, Days to reach full feeds from the day feeds were started Secondary: Intestinal colonization, PCR quantification of lactobacillus reuteri in the stools, Intestinal immunological response, Quantification immunological markers in the stools
Punnahitananda (Thailand NCT01340469)	Gestational age < 35 weeks, BWT < 1500 g Survived first 3 days of life	Enrolment 160 Probiotics vs Placebo	Primary: incidence of nosocomial infections 28 days or until discharge, Nosocomial infections. Secondary: incidence of NEC 28 days or until discharge, feeding tolerance, the volume of feeding on day 7,14,21, and 28 of study, time to full enteral feeding, time required to reach full feeding at 150 ml/kg/day.
Kusuda (Japan NCT01375309)	BWT < 1500 g	Enrolment 246 *Bifidobacterium bifidum* vs Placebo contains dextrin.	Primary: enteral feeding exceeded 100 ml/kg/day or date of death from any cause, Death or unsuccessful of establishing enteral feeding exceeded at 100 ml/kg/day before day 28 of age is considered failure to reach primary endpoint. Secondary: SD scores of BW and head circumference at discharge, NEC or sepsis, Intestinal flora

the remaining questions, these studies will report on as many infants as have been enrolled in the last published meta-analysis [27]. These trials will undoubtedly help refine our assessment of risks and benefits of probiotic administration.

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