ISSN (electrónico): 1699-5198 - ISSN (papel): 0212-1611 - CODEN NUHOEQ S.V.R. 318

Nutrición Hospitalaria

Revisión

Evidence on the benefits of probiotics for preterm infants

Evidencia sobre los beneficios del uso de probióticos en niños prematuros

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Abstract

This article reviews the evidence for the use of different strains of probiotics in the prevention of prevalent pathologies in premature neonates.

A systematic review was conducted of the use of probiotics in neonates with less than 37 weeks of gestational age, based on a search for systematic reviews and observational and experimental studies performed during the period from January 2014 to February 2021. For this purpose, the PubMed, MEDLINE and Cochrane Library databases were consulted. The aim of this article was to review the existing data on the relationship between the administration of probiotics (with different strains and doses) and the risk of necrotising enterocolitis, mortality, late sepsis and other disease parameters in premature infants.

The literature search obtained 240 articles, of which we selected 16, representing a total sample of over 200,000 premature infants. Analysis of the data obtained reveals statistical evidence that the combined administration of probiotics (especially of *Lactobacillus* and *Bifidobacterium* strains) reduces the incidence of grade II or higher necrotising enterocolitis, all-cause mortality, late sepsis, length of hospital stay and time until complete enteral nutrition is achieved. However, no benefits were apparent with respect to alleviating bronchopulmonary dysplasia, retinopathy of prematurity or intraventricular haemorrhage.

Further research is needed to determine the most appropriate strains, doses and treatment duration for preterm infants to achieve the health benefits identified.

Keywords:

Probiotics. Premature infants. Low birth weight infants. Morbidity. Necrotising enterocolitis.

Received: 18/06/2021 • Accepted: 05/08/2021

Acknowledgements: this study has been funded by Instituto de Salud Carlos III (ISCIII) through the project PI22/00661: "Analysis of the functional connectivity of the brain, its morphometry and psychomotor development of premature babies of school age: Relationship with the early nutritional contribution received", and co-funded by the European Union.

Conflict of interests: the authors declare no conflict of interest.

Artificial intelligence: the authors declare not to have used artificial intelligence (AI) or any AI-assisted technologies in the elaboration of the article.

Campos-Martínez AM, Fernández-Marín CE, Ruiz-López A, Cubero-Millán I, Uberos J. Evidence on the benefits of probiotics for preterm infants. Nutr Hosp 2024;41(4):889-896
DOI: http://dx.doi.org/10.20960/nh.03743

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Resumen

En este artículo se revisa la evidencia del uso de las diferentes cepas de probióticos en la prevención de diversas patologías prevalentes en recién nacidos prematuros.

Se ha realizado una revisión sistemática sobre el uso de probióticos en recién nacidos de menos de 37 semanas de edad gestacional, realizando una búsqueda de revisiones sistemáticas, estudios observacionales y experimentales desde enero de 2014 hasta febrero de 2021. Para ello se han utlizado motores de búsqueda como PubMed, MEDLINE y la biblioteca Cochrane. El objetivo de este artículo fue revisar los datos existentes sobre la relación entre la administración de probióticos (con diferentes cepas y dosis) y el riesgo de enterocolitis necrotizante, mortalidad, sepsis tardía, y otros parámetros de enfermedad en prematuros.

En la búsqueda se obtuvieron 240 artículos, de los que seleccionamos 16, obteniendo más de 200.000 recién nacidos prematuros como muestra. En esta revisión se muestra con evidencia estadística, que la administración combinada de probióticos (espcialmente cepas de *Lactobacillus* y *Bifidobacterium*) reducen la incidencia de NEC en grado II o mayor, mortalidad por todas las causas, sepsis tardía, días de estancia hospitalaria y tiempo en lograr nutrición enteral completa. No se han podido evidenciar beneficios en cuanto a la displasia broncopulmonar, retinopatía de la prematuridad y hemorragia intraventricular.

Se precisan nuevos estudios para conocer las cepas, dosis y tiempo de tratamiento más adecuados en neonatos prematuros para lograr beneficios en salud.

Palabras clave:

Probióticos. Prematuros. Neonatos muy bajo peso. Morbilidad. Enterocolitis necrotizante.

INTRODUCTION

Probiotics were first described in the 1960s, but perhaps the definitive expression was offered in 2014, when the World Health Organisation defined probiotics as "live microorganisms which when administered in adequate amounts confer a health benefit on the host" (1).

After childbirth, the maternal flora predominates over environmental flora, playing an essential role in the development of the infant's systemic and mucosal immunity. Bacteria promoting oxidative metabolism, such as *Enterobacteriaceae, Streptococci* and *Staphylococci*, are the first to proliferate in the gut.

It is widely accepted that breast milk should be the first feeding option for neonates, infants and, of course, premature infants. Breast milk is a complete food, from the nutritional, immunological and microbiological standpoint, and is a source of commensal or probiotic bacteria for the newborn's intestine. Probiotic supplementation is considered a promising alternative means of simulating the microbiological characteristics of breast milk and thus achieving its associated beneficial effects. However, this belief must be based on solid scientific evidence of specific beneficial effects, obtained in properly designed clinical studies, in which the appropriate strain, dose and administration route are selected for the therapeutic goals addressed (2).

According to several recent studies, the composition of the neonate's gut microbiota may be affected by gestational age and birth weight. Any alteration in this respect is an important risk factor for the development of necrotising enterocolitis (NEC), sepsis and increased mortality. Studies have also considered whether the appropriate supply of probiotics to premature infants reduces hospital stay and the time required to achieve complete enteral nutrition.

The aim of the present study is to compile evidence on the use of probiotics in preterm infants, and the impact on NEC, mortality, sepsis, and time to achieve complete enteral nutrition.

METHODS

This systematic review was performed via a search of websites presenting data on relevant clinical practice: the Cochrane Library, PubMed and MEDLINE databases. In PubMed, the MeSH terms used were "Infant, Premature"(Mesh) AND ("Infant, Very Low Birth Weight"(Mesh) OR "Infant, Premature/classification"(Mesh) OR "Infant, Premature/growth and development"(Mesh) OR "Infant, Premature/mortality"(Mesh) AND 2014(PDAT): 2021(PDAT) AND (English(lang) OR Spanish(lang)) AND (Clinical Trial(ptyp) OR Meta-Analysis (ptyp) OR Practice Guideline (ptyp) OR Randomized Controlled Trial (ptyp) OR Review (ptyp)) AND "Infant"(Mesh) AND "Probiotics"(Mesh).

Ethics committee approval was not required for this study.

The following selection criteria were applied: a) premature infants with less than 37 weeks' gestational age or less than 2500 g birth weight; b) studies published during the period 2014 to 2021; c) studies focused on diagnosis or treatment; and d) comparison between intervention groups, with placebo or negative control.

The exclusion criteria were: a) articles in which there were no interventions with probiotics; b) articles in languages other than Spanish or English; c) studies dealing exclusively with animals; d) articles that presented insufficient data; and e) articles that did not differentiate between premature infants and other age groups.

The probiotics identified in this review were various strains of *Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Bacillus* and others, used either in combination or in monotherapy, and compared with the administration of a placebo. The flow chart for the source selection process is shown in figure 1.

RESULTS

The literature search initially yielded 240 articles. After discarding duplicates and excluding unrelated articles (according to the document title and abstract), 25 papers remained, for which the full texts were obtained. Following application of the inclusion/exclusion criteria described, nine of these papers were excluded, leaving sixteen for the final analysis (Fig. 1).

The main results presented in these papers concerned the relation between the consumption of probiotics and the incidence of NEC, late sepsis, mortality, length of hospital stay and the time required to achieve complete enteral nutrition. The details of each study are summarised in table I.

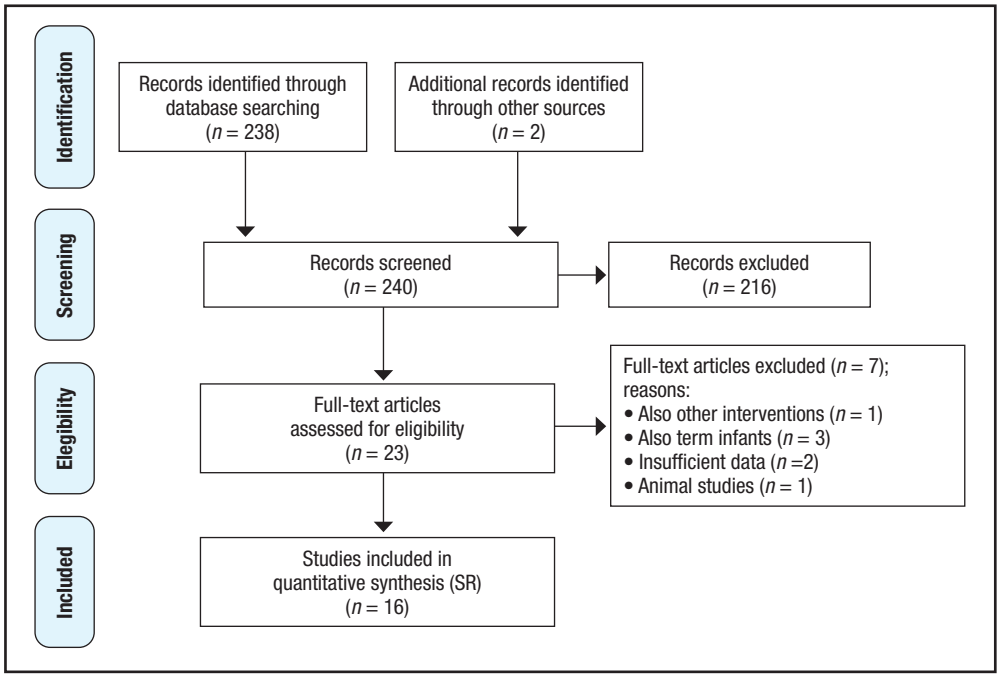

Figure 1.

Flow diagram (PRISMA) of the studies selected for analysis.

The meta-analyses reported by Chris et al. in 2018 (3) and Chi et al. in 2020 (4) described 96 studies and analysed the following variables: mortality, NEC, late sepsis and time to achieve complete enteral nutrition. Chris et al. (3) analysed 51 studies. In four of these (representing a total study population of 830 premature infants), mortality decreased following the use of different strains of *Bifidobacterium, Lactobacillus* and *S. thermophilus*, with a relative risk (RR) of 0.17. The presence of grade II or higher NEC was reduced, with a RR that was significantly lower for seven treatments in which different strains of *Lactobacillus* and *Bifidobacterium* were combined. The RR for late sepsis was significantly lower with the *Lactobacillus* + *Bifidobacterium* combination, compared to placebo treatment. Similarly, the time required to achieve complete enteral nutrition was reduced when the following probiotics were supplied: *L. reuteri*; the combination of *B. bifidum*, *B. infantis*, *B. longum* and *L. acidophilus*; and the combination of *B. longum* and *L. rhamnosus GG*.

In 2020, Chi et al. (4) conducted a meta-analysis of 45 trials conducted between 2002 and 2018, with a total population composed of 12,320 premature infants with less than 37 weeks' gestational age or less than 2500 g birth weight. The administration of *Bifidobacterium* and *Lactobacillus* reduced mortality rates (RR 0.56) and NEC (RR 0.47) compared to the placebo treatment.

The reviews by Bi et al. (5) and Jin et al. (6) both evaluated the impact on NEC in preterm infants given probiotics. The first of these reviews analysed 34 studies with a total population of 9,161 patients and reported that the risks of NEC (OR 0.38, 95 % CI 0.27-0.54), gastro-intestinal sepsis (OR 0.82, 95 % CI 0.69-0.98) and mortality (OR 0.54, 95 % CI: 0.42-0.71) were all significantly reduced after the administration of a combination of probiotics, especially those with *Lactobacillus* and/or *Bifidobacterium*, versus placebo treatment. Furthermore, there was a significant decrease in mortality in the preterm infants who received a combination of probiotics, compared to placebo treatment (OR 0.49, 95 % CI 0.32-0.69). In the second of these reviews, Jin et al. (6) examined various experimental studies, with a total population of 10,520 infants, and observed great variability in terms of the probiotic strains, doses and administration times described. These authors concluded that the combination of *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* Bb-12/B94 was effective in reducing NEC. Despite clinical heterogeneity, the conclusion of this cumulative meta-analysis was that probiotic treatment decreased the incidence of NEC (RR 0.53; 95 % CI 0.42-0.66). However, one of the trials in this review, focused on premature infants with less than 28 weeks gestational age, concluded that the routine use of "Infloran®" was associated with an increase in grade II or higher NEC (13.3 % vs 5.9 %, $p = 0.010$).

Baldasarre et al. (7) conducted an extensive literature search concerning the management of intestinal dysbiosis with probiotics, and the resulting impact on NEC. The results obtained indicate that the use of probiotics (*Lactobacillus* + *Bifidobacerium*) reduces the incidence of NEC in premature infants with less than 34 weeks' gestational age or less than 1500 g birth weight, and also reduces the time to achieve complete enteral nutrition, as well as the incidence of late sepsis.

Another study, by Robertson et al. (8), examined the results obtained for a sample of 982 infants during a ten-year period (five before the routine use of probiotics in preterm infants, and five after their introduction), for NEC, late sepsis and mortality. The rate of NEC fell from 7.5 % (35/469 neonates) in the first period to 3.1 % (16/513 neonates) in the second (HR = 0.44, 95 % CI 0.23 to 0.85, $p = 0.014$), regardless of any other covariates, including breastfeeding. Similar, the rate of late sepsis

decreased from 22.6 % to 11.5 % ($p < 0.0001$). With the introduction of routine probiotic administration, mortality (all causes) also fell, from 14.3 % to 9.2 %. Finally, the NEC-reducing effect was most pronounced during the two weeks of postnatal life.

In 2018, Underwood et al. (9) reviewed nine meta-analyses of controlled trials, from which they concluded that the use of probiotics reduced the incidence of NEC and mortality, but had no beneficial effect in preventing intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD) or retinopathy of prematurity (ROP). They also reported that in a subgroup of 4,683 extremely low birth weight neonates (< 1000 g), the administration of probiotics produced a significant reduction in NEC, mortality and late sepsis (HR for NEC 0.48, death 0.59, late sepsis 0.83). Similar findings were reported by Xiong et al. (10), who reviewed 98 articles in this context and observed a moderate decrease in the incidence of NEC (stage II or greater) and mortality after the administration of a combination of probiotics.

Bi et al. (11) analysed 34 studies with a total population of 9,161 patients. These authors found that different strains of *Lactobacilli, Bifidobacteria, Bacillus, Saccharomyces* and a combination of probiotics significantly reduced the incidence of NEC after the administration of probiotics, compared to placebo treatment (from 6.23 % to 3.54 %) (RR = 0.58, 95 % CI 0.48-0.69, $p < 0.05$).

For the probiotic combination group, the incidence of NEC (2.48 %) was approximately 40 % that of the placebo group (6.33 %) (RR = 0.40). *Lactobacilli* and *Bifidobacteria*, administered separately, also reduced the incidence of NEC compared to the placebo. In addition, the risk of sepsis was significantly reduced (probiotics group 15.59 %; placebo group 17.95 %), as was mortality (5.23 % and 7.41 %, respectively) (RR = 0.72, 95 % CI 0.61 to 0.85).

A meta-analysis by Sun et al. (12) of studies of preterm infants with less than 1500 g birth weight or less than 32 weeks' gestational age reported that infants given probiotics achieved a 37 % reduction in NEC, 37 % in late sepsis and 20 % in mortality, as well as 3.8 days' reduction in the length of hospital stay. These authors also reported that probiotics were more effective when taken with breast milk, when they were consumed for at least six weeks, when a dose of less than 10^9 CFU was administered, and when multiple strains were administered.

In 2020, Morgan et al. (13) reviewed 63 clinical trials of probiotic supplementation versus placebo treatment, finding that the combination of one or more strains of *Lactobacillus* spp. and *Bifidobacterium* spp. reduced all-cause mortality (OR 0.56, 95 % CI 0.39 to 0.80). Combinations of one or more strains of *Lactobacillus* spp. and one or more strains of *Bifidobacterium* spp., *Bifidobacterium animalis* subspecies *lactis*, *Lactobacillus reuteri* or *Lactobacillus rhamnosus* significantly reduced severe NEC. It was also observed that combinations of *Lactobacillus* spp. and *Bifidobacterium* spp and *Saccharomyces boulardii* reduced the number of days required to achieve full enteral nutrition (mean reduction: 3.30 days). The review found moderate or high-quality evidence that, compared to placebo, a single strain of B. *animalis* subspecies *lactis* or *L. reuteri* significantly reduced the length of hospital stay (mean reductions: 13 days, 95 % CI, 22.7 to 3.3 days; and: 7.9 days, 95 % CI 11.6 to 4.2 days, respectively).

In 2017, Aceti et al. (14) analysed the relationship between type of diet (breast milk or artificial milk) and probiotic supplementation, evaluating data from 5,868 neonates. Regardless of the type of diet, fewer cases of late sepsis were observed in the probiotic group (13.6 %) than in the placebo group (17.24 %) (RR 0.79). Moreover, the breastfed neonates who received one of the probiotic combinations showed fewer cases of late sepsis. In this review, the following probiotics were considered: *Lactobacillus rhamnosus, Lactobacillus reuteri, Lactobacillus sporogenes*.

Also, in 2017, Dermyshi et al. (15) reviewed 30 clinical trials and 14 observational studies and concluded that the administration of probiotics in premature infants reduced rates of NEC (grade II or higher) and all-cause mortality. In addition, the risk of sepsis fell by 12 % in the experimental studies and by 19 % reduction in the observational studies. By probiotic groups, the following results were obtained: *Lactobacillus GG* and *Bifidobacterium lactis* significantly reduced the incidence of severe NEC stage II-III; however, neither *L. reuteri, B. breve* nor *Saccharomyces boulardii* alone achieved a significant reduction in severe NEC. Subgroup analysis showed that combinations of two or more strains of probiotics were most beneficial in reducing the risk of NEC.

In 2020, Sharif presented a systematic review (16) of the use of probiotics to prevent NEC in very low birth weight preterm infants. This review examined 56 trials with a total population of over 10,000 infants. The most widely used probiotics were combinations of *Bifidobacterium* spp., *Lactobacillus* spp., *Saccharomyces* spp. and *Streptococcus* spp. The administration of probiotics reduced the risk of NEC, although at least 33 patients had to be treated for this beneficial effect to become apparent (NNTB 33, 95 % CI 25 to 50). On the other hand, this analysis concluded that probiotics may have little or no effect on severe neurodevelopmental impairment.

In 2018, in a related study, Grev et al. (17) conducted a review of probiotic supplementation for mothers aimed at preventing morbidity and mortality in preterm infants. The studies included in this review considered populations of pregnant women who received probiotics supplements from 36 weeks of gestation, or earlier, until delivery. The probiotics examined belonged to the *Lactobacillus*, *Bifidobacterium* and *Saccharomyces* genera. No significant differences were observed in the incidence of NEC or mortality, but in this case the quality of the scientific evidence generated was very low.

In 2017, our research group published a quasi-experimental study (18) on the use of probiotics in premature infants with less than 32 weeks of gestational age. The study aim was to determine whether routine supplementation with probiotics -*L. rhamnosus* GG (LGG) or *L. acidophilus* + *B. bifidum*- was associated with a reduced risk of severe NEC, in preterm infants with less than 32 weeks' gestation. The results obtained showed that routine supplementation with LGG or *L. acidophillus* + *B. bifidum* was associated with a reduced risk of severe NEC, late-onset sepsis and mortality in preterm infants with less than 32 weeks' gestation.

Table I. Characteristics of the studies included in the systematic review

Authors. Study design and number of articles analysed	Characteristics of patients	Sample size	Intervention	Results
Chris et al. (2018) (3) NMA (51)	37 GA < 2500 g	*n:* 11231	*Bacillus Bifidobacterium Enterococcus Lactobacillus Saccharomyces, Streptococcus*	Some strains or combinations of probiotics are effective in reducing mortality and morbidity due to NEC. No recommended dose or duration of treatment established
Chi et al. (2021) (4) NMA (45)	< 37 GA < 2500 g	*n:* 13230 (intervention*n:* 6577; placebo: 5743)	*Lactobacillus, Prebiotic + Bifidobacterium*	Used alone, probiotics are of limited effectiveness. Mortality is reduced with the Bifidobacterium + prebiotic combination. Morbidity from NEC is lower in the Lactobacillus + prebiotic association. In all cases, the probiotic results are better than those of placebo treatment
Bi et al. (2019) (5) NMA (34)	< 37 GA < 2500 g	*n:* 9161	*Lactobacillus, Bifidobacterium, Bacillus, Saccharomyces, Lactobacillus + Bifidobacterium*	The combination of probiotics + Bifidobacterium presents advantages when used in premature infants. Further research is needed before other probiotics can be recommended, as no reduction in the incidence of NEC, sepsis or mortality was observed
Jin et al. (2019) (4) SR (23)	< 37 GA < 2500 g	*n:* 10520	*Lactobacillus + Bifidobacterium*	The use of probiotics reduced the incidence of NEC, although further studies to determine the quality of probiotic preparations, their safety, optimal dose and treatment duration are needed before routine use can be recommended. It cannot be concluded that the use of a single probiotic is less useful than that of a combination. The incidence of NEC was higher in preterm infants < 27 weeks' GA who received Infloran
Baldassarre et al. (2019) (7) NMA	< 34 GA or < 1500 g	*n:* not stated	*Lactobacillus + Bifidobacterium*	The incidence of NEC was lower in the patients who received probiotics, as was the time to achieve complete enteral nutrition, the length of hospital stay and all-cause mortality. No differences were found in the risk of developing ROP, in the appearance of IVH or in the alleviation of BPD
Robertson et al. (2020) (8) SR	< 36 GA + < 1500 g	*n:* 982	*Lactobacillus + Bifidobacterium*	The incidence of NEC and late sepsis was reduced with the administration of *Lactobacillus* and *Bifidobacterium*
Underwood (2018) (9) MA (23)	< 37 GA < 28 GA < 1000 g	*n:* 85596 *n:* 4683	*Lactobacillus + Bifidobacterium*	The use of probiotics reduced the risk of NEC, and of all causes of mortality. There were no changes in the incidence of ROP, HIV or BPD. However, no predetermined dosage can be recommended. In preterm infants <28 weeks' GA and <1000 g birth weight, NEC, late sepsis and mortality were all lower in the group that received probiotics
Xiong et al. (2019) (10) SR (98)	< 37 GA < 2500 g	*n:* unknown	*Lactobacillus, Bifidobacterium* and/or *Saccharomyces*	The combined use of probiotics reduced the risk of grade II or higher NEC, and all causes of neonatal mortality

(Continues on next page)

Table I (cont.). Characteristics of the studies included in the systematic review

Authors. Study design and number of articles analysed	Characteristics of patients	Sample size	Intervention	Results
Bi et al. (2019) (11) MA (34)	< 37 GA < 2500 g	*n:* 9161 (intervention*n:* 4648; control: 4523	*Lactobacillus + Bifidobacterium*	In premature infants, the combined administration of probiotics reduced the risk of NEC, sepsis of the intestinal tract and mortality, compared to the use of probiotics alone or placebo. The exact dose of probiotics and duration of treatment cannot be concluded
Sun et al. (2017) (12) MA (32)	< 32 GA or < 1500 g	*n:* 8604	*Lactobacillus, Bifidobacterium, Enterococcus, Streptococcus*	The combined administration of low-dose probiotics (< 10^9 CFU) in preterm infants reduces the incidence of NEC, sepsis, mortality and length of hospital stay, if administered for < 6 weeks. No effects on weight gain or IVH were observed
Morgan et al. (2020) (13) MA (63)	< 37 GA < 2500 g	*n:* 15712	*Lactobacillus + Bifidobacterium. Bacillus + Enterococcus. Bifidocbacterium + Streptoccus* isolate	The combined administration of *Lactobacillus + Bifidobacterium* reduces the incidence of NEC and all causes of mortality. The combined administration of *Lactobacillus + Bifidobacterium + S. boulardii* reduces the number of days to complete enteral nutrition, compared to other combinations and placebo
Aceti et al. (2017) (14) MA (37)	< 37 GA	*n:* 5868 (intervention*n:* 2934; control: 2934)		The combined administration of probiotics with breast milk reduced the incidence of late sepsis in preterm infants. No specific treatment duration or dose could be established
Dermyshi et al. (2017) (15) MA (44)	< 34 GA < 1500 g	*n:* 26855	*Lactobacillus + Bifidobacterium*	The combined administration of incidence of NEC and all causes of mortality. No effects on late onset sepsis
Sharif et al. (2020) (16) MA (56)	< 32 GA < 1500 g	*n:* 10812	*Lactobacillus, Bifidocacterium, Saccharomyces, Streptococcus*	Probiotics in very low brith weight infants can reduce the risk oz NEC, sepsis and detah. No effects on neurodevelopment
Grev et al. (2018) (17) MA (12)	< 37 GA	*n:* 1204	*Lactobacillus, Bifidobacterium, Saccharomyces*	The administration of probiotics to mothers of premature infants appears to reduce the time to achieve enteral nutrition, but does not reduce the risk of NEC, surgery for NEC or mortalityin premature infants
Uberos et al. (2017) (18) CT	< 32 GA < 1500 g	*n:* 261	*Lactobacillus + Bifidobacterium (Bivos* or *Infloran)*	The administration of probiotics in premature infants between 27-32 w GA decreases the incidence of NEC, late sepsis and mortality. In patients under 27 w GA, more studies are requiered for its routine recommendation

NMA: network meta-analysis. SR: systematic review. MA: meta-analysis. CT: clinical trial. GA: gestational age (weeks). NEC: necrotising enterocolitis. IVH: intraventricular haemorrhage. ROP: retinopathy of prematurity. BPD: bronchopulmonary dysplasia.

DISCUSSION

Current scientific evidence confirms the utility of different combinations of probiotics in the prevention of NEC and late neonatal sepsis in very low birth weight preterm infants. Achieving a good balance in intestinal microbiota can inhibit intestinal dysbiosis and regulate the immune response (19). The fact that preterm infants have a less developed immune system increases the risk of infections, NEC and morbidity-mortality (20).

Breast milk is the best nutrition for neonates, especially premature infants (21), protecting them against NEC and sepsis, and this effect is increased with probiotic supplementation. Very low-weight preterm infants may be immunologically more vulnerable, and so information regarding the efficacy, safety and possible side effects of the different strains used must be available before their routine use. However, the use of lactobacillus and bifidobacteria does not cause concern, because these strains normally reside in the gastrointestinal tract of healthy infants (2). Careful selection of the strain or strains used in probiotic supplementation will minimise the risk of side effects.

Evidence suggests that rates of NEC, late sepsis and mortality, and length of hospital stay and time required to achieve complete enteral nutrition all decrease with the use of probiotics. However, other variables such as IVH, ROP and BPD are not affected by this supplementation (7,9,12).

The meta-analysis by Chris et al., in 2018 (3), examined the use of different types of strains of *Bacillus, Bifidobacterium, Enterococcus, Lactobacillus, Saccharomyces* and *Streptococcus*, but was unable to establish the most suitable combinations or doses to reduce the incidence of NEC, mortality, length of hospital stay or time to achieve enteral nutrition. However, these authors did observe that the most commonly used probiotics were combinations of *Lactobacillus* and *Bifidobacterium*. Another meta-analysis, by Bi (5), concluded that although a combination of probiotics with *Bifidobacterium* seems to reduce the incidence of NEC, more studies are needed to determine which probiotic strain is ideal in preterm infants, as was also concluded by Jin (6). The use of *Lactobacillus* and *Bifidobacterium* during the first two weeks of postnatal life is a safe and inexpensive option, which also reduces the incidence of NEC (8). Studies have shown that 10^9 CFU seems to be a sufficient dose to achieve a beneficial effect (12), and that the combination of several strains of probiotics is the most effective means of reducing the risk of late sepsis and NEC (13,15-17).

The main limitation of the present study is the lack of detailed information regarding the analysis of each gestational age group, beyond the inclusion of premature infants with less than 37 weeks' gestational age or less than 2,500 g birth weight. Without more extensive data, it is hard to determine the real benefit obtained from the use of probiotics in extremely low-weight newborns.

Nevertheless, it can be concluded that the administration of probiotics is safe and effective in reducing the risk of NEC, late sepsis and mortality, as well as the length of hospital stay and the time required to achieve complete enteral nutrition in premature infants. Furthermore, combinations of several strains of probiotics seem to be more effective than the administration of single strains. Those most commonly used are *Lactobacillus* and *Bifidobacterium*. At present, there is no clear evidence as to which strains should most appropriately be administered, nor for how long or at what doses.

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