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Systematic Review

The clinical role of probiotic and prebiotic supplementations in preterm infants

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Abstract

Background: For over two decades we have been trying to study and demonstrate the role of the gut microbiota in the onset of cardiovascular, autoimmune, infectious and neurobiological diseases and more generally the clinical efficacy.

Aims: To study the clinical efficacy of the integrative use of prebiotics and probiotics in the prenatal population.

Materials and methods: All clinical trials and randomized controlled trials were selected through January 6, 2023, for a useful total of 32 studies and a cohort of more than 37,000 infants, of which just under half are term infants in the control groups.

Results: In the neonatal literature, studies on the clinical use of prebiotics and probiotics focus on specific topics of investigation, starting from the intestinal microbial composition and then extending the object of analysis to the effects of antibiotics on the microbiota, to the biochemical integration of these products, the use of breast milk or artificial or donor milk, the alleged claim to intervene on pathological processes arising from opportunistic infections of the respiratory tract, and also in relation to autoimmune, gastrointestinal and dermatological pathologies, up to food intolerances.

Conclusions: Significant evidence emerges in the literature that supports the therapeutic use for clinical purposes of prebiotics and probiotics even in neonatology; however, most of the published studies have structural and functional criticalities that often invalidate the research design and therefore the outcome obtained and published, risking to affect negatively the significance eventually detected. Further studies are needed that can confirm and expand scientific knowledge in this particular area.

Background and aims

For over twenty years we have been trying to study and demonstrate the role of the intestinal microbiota in the onset of cardiovascular, autoimmune, infectious and neurobiological diseases, and more generally the clinical efficacy of the integrative use of prebiotics and probiotics in human nutrition in order to reduce the onset of symptoms or prevent the pathological course. Therefore, there is a clinical need to answer these questions with greater certainty, in order to clarify the exact dynamics of the use of prebiotics and probiotics and their therapeutic interactions with allegedly related disorders, particularly in the neonatal setting on preterm infants (born before 36 weeks and with a birth weight less than 1500 grams) where the hypothesis of use for preventive and curative purposes appears to be not only a speculative suggestion.

Materials and methods

We searched on Pubmed until January 30, 2023, clinical trials and randomized controlled trials using in combination the keywords "gut microbiota", "preterm infants", "prebiotic" and "probiotic", selecting 219 useful results. To these were also added 8 reviews related to the last two years, in order to have a greater and complete overview of the topic, ultimately selecting

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a total of 40 research and studies, for a total population of over 37,000 infants, of which slightly less than half are represented by term infants in the control groups. Simple reviews, opinion contributions, or publications in popular volumes were excluded because they were not relevant or redundant for the purposes of this work, and 7 types of research of the final total because they did not present results or statistical samples but only protocol and research proposals [1-3], did not specifically address the relationship between the gut microbiota and preterm infants [4], the data were contradictory, unreliable, or otherwise, the research design had functional shortcomings [5], or the study sample was not directly preterm infants [6,7].

The search not was limited to English-language papers. No limit on the year of publication was set. We limited the search by applying the age filter "newborns" and used the following search terms and rationale: "preterm infants microbiota," "gastrointestinal microbiome AND necrotizing enterocolitis or NEC", "breastfeeding and enteral nutrition AND necrotizing enterocolitis OR NEC", "microbiota AND growth retardation", "gut microbiota AND weight gain", "gut microbiota AND growth", "gut microbiota AND extrauterine growth restriction", "microbiota of preterm infants AND late-onset sepsis OR LOS", "microbiota OR microbiome OR bacteria OR antibiotics OR gut AND lung OR airway OR BPD OR bronchopulmonary dysplasia" and "gut-lung axis" (Figure 1).

Results

In the neonatal literature, studies on the intestinal microbiota focus on specific topics of investigation, starting from its composition and then extending the object of analysis to the effects of antibiotics on the microbiota, to the biochemical integration of prebiotics, probiotics and postbiotics, the use of breast milk or artificial or donor milk, up to the alleged claim to intervene on pathological processes arising from opportunistic infections of the respiratory tract, or even in relation to autoimmune, allergological, endocrinological, gastrointestinal and dermatological pathologies.

In a preterm infant, during the first 60 days of life, there is an intestinal microbial composition in which first *Staphylococcus*, then *Enterococcus* (which are able to delay the subsequent stages of development of the microbiota) and *Enterobacter* predominate, and then stabilize with *Bifidobacterium*, as happens in infants born at term, fed with breast milk and free of clinical complications [8]. The predominance of *Bifidobacterium* is correlated in several studies to the good health of the infant [9] or at least to the improvement of the clinical picture and an increase in weight [10], mainly as a result of the decrease of *Enterobacter* and *Clostridium* colonies [11]. The abundance of *Candida*-like *Saccharomycetes* is often present in the microbiota

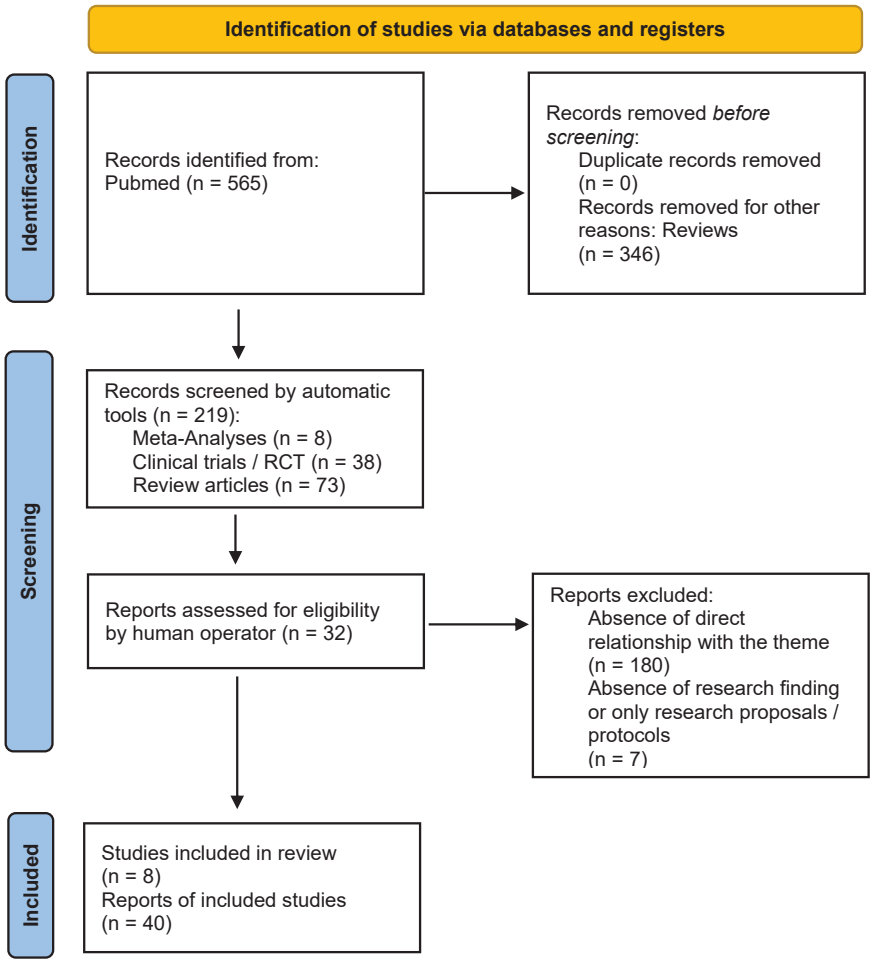

Figure 1: PRISMA flow diagram template for systematic reviews. Matthew J Page et al. BMJ 2021;372:bmj.n71.

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of the preterm infant and therefore could be a contributing cause of the condition [12]. What consistently emerges is that the intestinal microbiota tends to change, favoring dysbiotic processes in the hypothesis of intrapartum exposure, antibiotic use, premature birth, duration, and type of breastfeeding [9]. Research has then attentively addressed the need to improve the identification of the viable microbiota in order to increase the accuracy of clinical inferences made regarding the impact of the preterm gut microbiota on health and disease; this study validates the use of Propidium Monoazide (PMA), a DNA chelating agent that is excluded from an intact bacterial membrane, to reduce the bias associated with 16S rRNA gene analysis of clinical stool samples. Indeed, the meta-analysis showed a significant reduction in bacterial diversity in 68.8% of PMA-treated samples, as well as a significantly reduced overall abundance of rare taxa. Importantly, the overall abundances of genera associated with protection and propensity for necrotizing enterocolitis and sepsis such as *Bifidobacterium*, *Clostridium* and *Staphylococcus sp.* were significantly different after PMA treatment [10].

But it is the lack of breast milk intake, in particular, that appears to be related to several circumstances that promote gut dysbiosis: a) preterm infants who receive breast milk develop a gut microbiota very similar to that of infants born at term who are equally breastfed [8], with a predominance of *Bifidobacterium* and *Bacteroides* and a consequent 60% reduction in food intolerances, significant weight gain and greater gut microbial biodiversity, even compared with donor milk that has a greater presence of *Staphylococcus* [13,14]; b) in both preterm and term infants, evidence emerges of a deficiency of metabolites present in breast milk, such as fucose and β-hydroxybutyrate, which predisposes to the metabolic syndrome and food allergies [15,16]; breast milk, when administered to the adult, precisely because it is rich in oligosaccharides (HMOs) capable of significantly shaping the intestinal microbiota by selectively stimulating the growth of specific bacteria (with immune and gastrointestinal benefits), produces substantial increases in the abundance of *Actinobacteria* and *Bifidobacterium*, and a reduction in *Firmicutes* and *Proteobacteria* [17], and therefore also in the preterm infant has the same positive efficacy [18].

Other studies on the intestinal microbial composition have been done starting from dietary supplementation of different mixtures (other than breast milk); compared to standard nutritional therapy: a) addition of a High Polyunsaturated Fatty Acid (HF-PUFA) blend of fish oil and safflower oil resulted in increased bacterial biodiversity and lower abundance of *Streptococcus*, *Clostridium*, and many pathogenic genera within the *Enterobacteriaceae* family, positively correlating with normal metabolic processes of amino acids, carbohydrates, fatty acids and secondary bile acid synthesis [19]; b) the integration of bovine lactoferrin, a glycoprotein with recognized antibacterial, antiviral, anti-inflammatory and protective faculties of the gastrointestinal system [20], to the diet of the preterm infant, does not alter the intestinal flora, neither on its composition nor on its function, thus excluding that it can generate dysbiosis as it happens with the administration of antibiotics [16], since as for the term newborn it is able to increase *Citrobacter* and reduce *Enterobacterium* (and in particular *Klebsiella*) and *Firmicutes* (in particular *Staphylococcus*), responsible for many neonatal infections [21]; c) dietary supplementation of bee honey for medical purposes produces a modification of the intestinal microbiota by increasing Bifidobacterium and Lactobacillus, resulting in increased body weight, improved clinical picture and growth values, although it does not impact on the inflammatory profile detectable by the presence of CD4 and CD8 cytokines [22]; d) the mixture of fermented milk and supplemented with probiotic strains of *Bifidobacterium breve C50* and *Streptococcus thermophilus o65* does not impact on *bifidus* but significantly decreases the values of fecal calprotectic, actually intervening on intestinal inflammatory states [23]; e) Galacto-Oligosaccharide/Polydextrose (GOS/PDX) mixture positively impacted on respiratory infections and atopic dermatitis [24], as *Bifidobacterium* have a protective role in respiratory infections while *Clostridium* in atopic dermatitis [25]; f) breast milk is the best option to avoid or reduce the risk of necrotizing enterocolitis but in its absence bovine colostrum is the best option even compared to artificial and human donor milk, as it stimulates intestinal immunity and digestive functions more, although causing transient increased thyroxine [26].

Other profiles studied in research concern the use of antibiotics in premature infants and their interaction with the intestinal microbiota. It has been shown that a single course of antibiotics has a limited effect on the microbial composition [27] but if prolonged or repeated negatively impacts by promoting the increase of pathogenic bacterial strains (as in the case of *Proteobacter* type *E. coli* and *Helicobacter pylori*) and therefore dysbiotic processes that increase the onset of gastrointestinal, infectious and immune complications, in some cases even fatal as necrotizing enterocolitis and sepsis [28,29].

In fact, some probiotics used in neonatology would appear to positively affect specific morbid conditions, just as necrotizing enterocolitis and sepsis. Research on a sample of more than 10,000 preterm infants, who participated in randomized controlled trials of probiotics worldwide, suggests that probiotics in general could reduce the rates of necrotizing enterocolitis, sepsis and mortality, without however indicating specific techniques about the related bacterial strain to be used, the correct dosage and time of administration. Questions remain about the guarantee of the product used, the certification of the strain used for the absence of antibiotic-resistant genes, and the possible risk of probiotic sepsis [30]. Another study analyzed data from 15,712 preterm infants, and compared with a placebo, a combination of 1 or more Lactobacillus species (spp) and one or more *Bifidobacterium spp* was the only intervention with moderate or high-quality evidence of reducing all-cause mortality. Interventions with moderate or high-quality evidence of efficacy compared with placebo included combinations of: a) one or more *Lactobacillus spp* and one or more *Bifidobacterium spp*, *Bifidobacterium animalis subspecies lactis*, *Lactobacillus reuteri* or *Lactobacillus rhamnosus* is able to significantly reduce severe necrotizing enterocolitis [31], whereas administration of *Bifidobacterium breve* has been shown to be futile [29]; b) one or more *Lactobacillus spp* and one or more *Bifidobacterium spp* and *Saccharomyces boulardii*, which

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can reduce the number of days to reach full nutrition [31]; c) the monospecific product *B animalis subsp lactis* or *L reuteri*, which can significantly reduce the duration of hospitalization [31]; d) combined probiotic supplementation of *Bifidobacterium longum subsp. infantis BB-02*, *Streptococcus thermophilus TH-4* and *Bifidobacterium animalis subsp. lactis BB-12* reduces the presence of *Enterococcus* favoring a 54% case-controlled reduction of necrotizing enterocolitis [32]; e) combined probiotic supplementation of *Bifidobacterium* is able to alleviate dysbiosis (both in single and multiple administration) [33] and reduce the consequences of late sepsis [34]; the mixture of prebiotics and probiotics based on galacto-oligosaccharides and polydextrose 1:1 and *Lactobacillus rhamnosus GG* can alleviate symptoms of agitation and crying in the preterm infant resulting from gastrointestinal disorders such as colic [35] and also positively impact respiratory rhinovirus infections [25].

However, there are studies that have completely opposite results, albeit with extremely small and non-significant population samples, which support the little or total uselessness in the use of prebiotics and probiotics, both in terms of incidence of the pathogenic microbial amount and in terms of weight gain or length of hospital stay [36,37]; studies that are then disproved or otherwise challenged by meta-analysis with large and representative samples: a recent study, in fact, which included 12,320 participants, supports the importance of the association of *Bifidobacterium* and *Lactobacillus* in therapeutic use, to reinforce the beneficial effects and decrease mortality rates [38]. Observational studies then demonstrating reduced rates of infection, necrotizing enterocolitis and mortality in preterm infants fed breast milk, compared to formula, prompted attempts to achieve similar effects with the right choice of food and food additives; the use then of prebiotic oligosaccharides found reduced infection but not mortality, as enteral L-glutamine reduced infection rates and enteral L-arginine reduced the morbid condition [39,40] (Table 1).

Table 1: Cohort studies. Legend: p (preterm), ft (full-term), pc (preterm-clinic), pp (preterm-placebo), ftc (full-term clinic), ftp (full-term placebo), an (adult).

Author (Year)	Objectives	n	Key Results and Conclusions
Podlesny D, et al. (2021)	Strain inheritance and neonatal gut microbiota development.	625(p)	Infants delivered vaginally shared more strains with their mothers than infants delivered by cesarean section, but strain sharing was reduced if mothers received antibiotic treatment. Regardless of the type of delivery, older infants shared strains with their mothers and fathers. The most important fecal commensal bacteria were among both frequently transferred (eg, Bacteroides and Sutterella) and newly acquired taxa (eg, Blautia, Faecalibacterium, and Ruminococcus).
Yap PSX, et al. [15]	Neonatal Intensive Care Unit (NICU) exposures exert a sustained influence on the progression of gut microbiota and metabolome in the first year of life.	19(p) + 20(ft)	Those who are not fed breast milk have a deficiency of certain metabolites such as fucose and β-hydroxybutyrate, which predisposes them to metabolic syndrome.
Kim CS, et al. [27]	Effect of antibiotic use within first 48h of life on the preterm infant microbiome.	22(p)	A single course of antibiotics has a limited effect on microbial composition.
Chi C, et al. [38]	Effects of probiotics in preterm infants.	45(p)	A combination of Lactobacillus, Bifidobacterium, and Streptococcus thermophilus reduces episodes of Necronizing Enterocolitis (NEC) and late sepsis
Ai J et al. (2021)	Antibiotics exposure and childhood attention-deficit/ hyperactivity disorder.	Meta	Plonged maternal intake of antibiotics during pregnancy may be associated with an increased risk of ADHD in offspring, but there is no conclusive evidence to support this conclusion.
Bührer C, et al. [39]	Nutritional interventions to reduce rates of infection, necrotizing enterocolitis, and mortality in very preterm infants.	Meta	Selenium, inulin, GOS/FOS prebiotics, and enteral L-glutamine are associated with reduced infection rates. Zinc, L-arginine, donor milk, and multiple strains of probiotics are associated with lower rates of NEC. Inulin, zinc, and multiple-strain probiotics are associated with reduced all-cause mortality.
Upadhyay RP, et al. (2020)	Effect of prebiotic and probiotic supplementation on neurodevelopment in preterm very low birth weight infants.	Meta	Limited evidence to support the utility of prebiotics and probiotics that do not demonstrate a difference in neurodevelopmental outcomes.
Venter C, et al. (2020)	Dietary factors during pregnancy and atopic outcomes in childhood: A systematic review from the European Academy of Allergy and Clinical Immunology.	17(pc) + 78(pp)	Vitamin D and Omega-3 are Beneficial effects for the prevention of asthma, allergies, and risk modulation of skin and gastrointestinal outcomes.
Campione E, et al. [20]	Lactoferrin is a protective natural barrier of respiratory and intestinal mucosa against coronavirus infection and inflammation.	13(p)	Bovine lactoferrin is protective properties for the gastrointestinal system. It has antibacterial, antiviral, and anti-inflammatory.
van den Akker CHP, et al. [30]	Probiotics and preterm infants.	39(p)	Combination of Lactobacillus, Bifidobacterium, and Streptococcus thermophilus Reduces episodes of Necronizing Enterocolitis (NEC) and late sepsis.
Morgan RL, et al. [31]	Probiotics reduce mortality and morbidity in preterm, low-birth-weight infants.	Meta	Combination of Lactobacillus, Bifidobacterium, and Streptococcus thermophilus reduces episodes of Necronizing Enterocolitis (NEC).
Ford SL, et al. [14]	Improved feeding tolerance and growth are linked to increased gut microbial community diversity in very-low-birth-weight infants fed their mother's own milk compared with donor breast milk.	43(pc) + 74(pt)	Predominance of Bifidobacterium and Bacteroides with a 60% reduction in food intolerances, significant weight gain, and greater intestinal microbial biodiversity, even compared to donor milk which has a greater presence of Staphylococcus.

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Blakstad EW, et al. [11]	Enhanced nutrient supply and intestinal microbiota development in very low birth weight infants.	45(p)	Relative Bifidobacterium abundance tended to increase more in MVP controls compared to the intervention group. The abundance of pathogens was not increased in the intervention group. Higher relative Bifidobacterium abundance was associated with improved weight gain. Nutrition may affect richness, diversity, and microbiota composition; there was no increase in the relative abundance of pathogens among infants receiving an enhanced nutrient supply. Favorable microbiota development was associated with improved weight gain.
Korpela K, et al. [8]	Intestinal microbiota development and gestational age in preterm neonates.	45(p)	The premature infant receiving breast milk develops a gut microbiota that is very similar to that of infants born at term who are equally breastfed. Microbiota development proceeded in four phases indicated by the dominance of Staphylococcus, Enterococcus, Enterobacter, and finally Bifidobacterium. The Enterococcus phase was only observed among extremely premature infants and appeared to delay the microbiota succession. The results indicate that hospitalized preterm infants receiving breast milk may develop a normal microbiota resembling that of term infants.
Plummer EL, et al. [32]	Gut microbiota of preterm infants supplemented with probiotics.	68(p)	Combination of Lactobacillus, Bifidobacterium, and Streptococcus thermophilus reduces episodes of Necronizing Enterocolitis (NEC).
Ranucci G, et al. [25]	Galacto-Oligosaccharide/ Polidextrose Enriched Formula Protects against Respiratory Infections in Infants at High Risk of Atopy.	201(pc) + 199(pp)	Galacto-Oligosaccharide/Polydextrose (GOS/PDX) is a positive impact on respiratory infections and atopic dermatitis, as Bifidobacterium has a protective role in respiratory infections while Clostridium in atopic dermatitis. Relieve symptoms of agitation and crying in the preterm infant resulting from gastrointestinal disorders such as colic.
Young GR, et al. [10]	Reducing viability bias in the analysis of gut microbiota in preterm infants at risk of NEC and sepsis.	16(p)	Meta-analysis highlighted a significant reduction in bacterial diversity in 68.8% of PMA-treated samples as well as significantly reduced overall rare taxa abundance. Importantly, overall abundances of genera associated with protection from and propensity to NEC and sepsis such as Bifidobacterium; Clostridium, and Staphylococcus sp. Were significantly different following PMA treatment. These results suggest that non-viable cell exclusion by PMA treatment reduces bias in gut microbiota analysis from which clinical inferences regarding patient susceptibility to NEC and sepsis are made.
Forsgren M, et al. [9]	Direct and indirect effects of preterm birth on the development of the gut microbiota.	43(p) + 75(ft)	Differences in the presence of specific species were detected at the age of six months, although the microbiota alterations were most prominent following delivery. As well as prematurity, the mode of birth, intrapartum and neonatal antibiotic exposure, and the duration of breastfeeding had an additional impact on gut microbiota development. The gut microbiota composition was significantly different between late preterm and full-term infants at least six months after birth. Antibiotic exposure was common in late preterm infants and modulated gut colonization, but preterm birth also affected gut microbiota development independently.
Russell JT, et al. [28]	Antibiotics and the developing intestinal microbiome, metabolome, and inflammatory environment.	91(p)	Prolonged antibiotic therapies are able to increase Citrobacter and reduce Enterobacterium (and particularly Klebsiella) and Firmicutes (particularly Staphylococcus), which are responsible for many neonatal infections.
Millar M, et al. [29]	The microbiome of preterms.	24(p)	Prolonged antibiotic therapy negatively impacts by promoting the increase of pathogenic bacterial strains (as in the case of Proteobacter type E. coli and Helicobacter pylori) and therefore dysbiotic processes that increase the occurrence of gastrointestinal, infectious, and immune complications, in some cases even fatal such as necrotizing enterocolitis and sepsis. Combination of Lactobacillus, Bifidobacterium, and Streptococcus thermophilus reduces episodes of Necronizing Enterocolitis (NEC).
Berkhout DJC, et al. [33]	Detection of sepsis in preterm infants by fecal volatile organic compounds analysis.	36(p)	A combination of Lactobacillus, Bifidobacterium, and Streptococcus thermophilus reduces episodes of late sepsis.
Qiao LX, et al. [16]	Effect of early administration of probiotics on gut microflora and feeding in preterm infants.	30(p) + 30(ft)	Those who are not fed breast milk have a deficiency of certain metabolites such as fucose and β-hydroxybutyrate, which predisposes them to food allergies.
Aceti A, et al. (2017)	Probiotics prevent late-onset sepsis in human milk-fed, very low birth weight preterm infants.	Meta	Breast milk and probiotic supplementation reduce the risk of necrotizing enterocolitis and sepsis.
Younge N, et al. [19]	Enteral high fat-polyunsaturated fatty acid blend alters the pathogen composition of the Intestinal microbiome in premature infants with an enterostomy.	16(pc) + 16(pp)	Blend of Highly Polyunsaturated Fatty Acids (HF-PUFA) from fish oil and safflower oil: increased bacterial biodiversity and decreased abundance of Streptococcus, Clostridium, and Enterobacteriaceae, positively correlating with normal metabolic processes
Aly H, et al. [22]	Medically graded honey supplementation formula to preterm infants as a prebiotic.	40(p)	Bee honey increased Bifidobacterium and Lactobacillus, with increased body weight, and improved clinical picture and growth values, although not impacting CD4 and CD8 cytokines.

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Juhl SM, [26]	Necrotizing enterocolitis – classification and two initial steps towards prevention.	20(pc) + 20(pp)	Breast milk is the best option to avoid or reduce the risk of necrotizing enterocolitis, but in its absence, bovine colostrum is the best option even compared to formula and human donor milk, although it causes transient hypertyrosinaemia in 50% of cases.
Elison E, et al. [17]	Oral supplementation of healthy adults with 2'-O-fucosyllactose and lacto-N-neotetraose is well tolerated and shifts the intestinal microbiota.	100(a)	Breast milk, being rich in oligosaccharides (HMOs), can significantly shape the gut microbiota by selectively stimulating the growth of bacteria that promote the abundance of Actinobacteria and Bifidobacterium.
West CE, et al. (2015)	Gut microbiome and innate immune response patterns in IgE-associated eczema.	20(p)	Reduced relative abundance of potentially immunomodulatory gut bacteria (Ruminococcaceae) is associated with exaggerated inflammatory cytokine responses to TLR-ligands and subsequent development of IgE-associated eczema. Mothers whose children developed IgE-associated eczema had lower α-diversity of Bacteroidetes, although this was not seen later in their children, whereas, at 1 year, α-diversity of Actinobacteria was lower in children with IgE-associated eczema than in controls
Underwood MA, et al. [18]	Human milk oligosaccharides in premature infants: absorption, excretion, and influence on the intestinal microbiota.	14(p)	Breast milk, being rich in oligosaccharides (HMOs), can significantly shape the gut microbiota by selectively stimulating the growth of bacteria that promote the reduction of Firmicutes and Proteobacteria.
Luoto R, et al. [24]	Prebiotic and probiotic supplementation prevents rhinovirus infections in preterm infants.	26(pc) + 21(pp)	Galacto-Oligosaccharide/Polydextrose (GOS/PDX) is a positive impact on respiratory infections and atopic dermatitis.
Pärtty A, et al. [35]	Effects of early prebiotic and probiotic supplementation on the development of gut microbiota and fussing and crying in preterm infants.	94(p)	Galacto-oligosaccharides and polydextrose 1:1 and Lactobacillus rhamnosus relieve symptoms of influence respiratory rhinovirus infections.
Chrzanowska-Liszewska D, et al. [23]	The effect of Lactobacillus rhamnosus GG supplemented enteral feeding on the macrobiotic flora of preterm infants-double.	46(p)	Fermented milk with probiotics (Bifidobacterium breve and Streptococcus thermophilus) does not impact bifidus but significantly decreases fecal call protective values, effectively intervening in intestinal inflammatory states.
Mohan R, et al. [12]	Effects of Bifidobacterium lactis Bb12 supplementation on intestinal microbiota of preterm infants.	83(pc) + 69(pp)	The gastrointestinal microbiota of preterm infants in a neonatal intensive care unit differs from that of term infants. In particular, colonization of preterm infants by bifidobacterial is delayed. Infants supplemented with Bb12 also had lower vital counts of Enterobacteriaceae and Clostridium spp. Than infants in the placebo group. B. lactis Bb12 supplementation did not reduce colonization by antibiotic-resistant organisms in the study population; however, probiotic supplementation increased the cell counts of bifidobacterial and reduced the cell counts of Enterobacteriaceae and Clostridia spp.

Discussion and limitations

Beyond the easy enthusiasm, most of the published studies have structural and functional criticalities that often invalidate the research design and therefore the outcome obtained and published, risking to affect negatively the significance eventually detected. The main criticalities refer to the following circumstances: a) the population sample selected is too limited and therefore not representative, almost always below 100 units; b) the variables that can trigger the dysbiotic process are multiple and not all known, as well as the etiological causes underlying the onset or aggravation of a disease and therefore correlate the use of probiotic or a specific mixture is not always possible without considering the risk of bias or oversimplification of a given clinical problem; c) in few studies, the authors report anthropometric data of newborns, such as birth weight, gestational age and size of body districts, in full; d) in almost all studies there is a lack of publication of technical data about the related bacterial strain to be used, the correct dosage and time of administration, as well as safety data regarding the guarantee of the product used, the certification of the microbial strain about the absence of antibiotic-resistant genes and the possible risk of probiotic sepsis; e) the economic interests on the production of a specific integrative product, patented or to be patented, which in the best cases can favor the conditioning need of the investigators to confirm the scientific validity. This representative approach is more reinforced in the clinical setting, both for neonatal and pediatric as well as adult, precisely because of the increasing difficulty concerning the ability to objectively analyze the multifactorial landscape according to a holistic key.

Conclusion

Significant evidence emerges in the literature, that supports the therapeutic use for clinical purposes of prebiotics and probiotics even in neonatology, of specific bacterial strains of *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces boulardii* to reduce the risk of NEC, sepsis and systemic infections. In addition, the use of mixtures of High Polyunsaturated Fatty Acids (HF-PUFA) from fish oil and safflower oil, galacto-oligosaccharides and polydextrose 1 appear useful: 1, bovine lactoferrin, bee honey, fermented milk supplemented with probiotic strains, Galacto-Oligosaccharides/Polydextrose (GOS/PDX), and bovine colostrum to strengthen and support the immune system, as well as the use of Propidium Monoazide (PMA) as a DNA chelating agent to reduce the bias associated with 16S rRNA gene analysis of clinical stool samples. These data are consistent with results obtained with adult patients, confirming the importance of using prebiotics and probiotics, for clinical purposes, from pregnancy and birth.

It emerges, therefore, the need, in such a varied and contradictory landscape, to design a research project that takes into account first of all a significant and representative sample of the population, but above all that does not underestimate the critical issues mentioned above, in order to address with

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scientific method the proper and functional use of prebiotics and probiotics in neonatal and pediatric in general; therefore, further studies are needed that can confirm and expand scientific knowledge in this particular field.

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