Potential Benefits of Probiotics for Preterm Infants: A Review

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Abstract: Preterm infants are particularly susceptible to abnormal colonization and are therefore prone to systemic infections due to increased intestinal permeability to potentially pathogens. Abnormal pattern of colonization in pre-term infants may contribute to the pathogenesis of neonatal Necrotizing Enterocolitis (NEC), an acquired gastrointestinal (GI) disease associated with significant morbidity and mortality. Introduction of foods containing probiotic cultures may be advantageous as probiotics prevented gut colonization by abnormal flora. Endeavour has been made to explore the mechanism of gut colonization, suitability of breast milk for preterm infants, effect of administration of probiotics to preterm infants and its safety concerns. Human milk is also suitable for the management of premature infants but fortified breast milk may be a preferred choice and not the pooled pasteurized breast milk. Based upon Randomized Controlled Trials administration of probiotic in preterm infants with a birth weight >1000 g could be recommended due to significantly reduction in incidence of NEC and no systemic infections or serious adverse events was reported. Administration of probiotics in preterm neonates is recommended but further research is emerging for its routine application. Probiotic supplementation in preterm neonates exhibited good safety profile and did not show any side effects and can be recommended for preterm infants but not for extremely low birth weight (ELBW) infants [1, 2].

Keywords: Probiotics, Preterm infants, Breast milk, Gut colonization.

INTRODUCTION

Human breast milk is the best preferred choice for infant nutrition [3] owing to its inherent therapeutic and nutritional features [4, 5] and breastfeeding during the first 6 months of life for both normal and premature infants have been recommended [6, 7]. NEC is a medical condition primarily seen in premature infants where portion of bowel undergoes necrosis (tissue death). Premature infants could be categorized into three groups on the basis of birth weight as ELBW (< 1000 g), very low birth weight (< 1500 g) and low birth weight (< 2500 g). Premature infants are at greater risk than full-term infants due to delayed and abnormal pattern of gut colonization [8, 9, 10] which may predispose them to NEC [11, 12] and increase the risk of bacterial translocation [13]. No colonization by probiotic strains was detected in infants who weighed ≤1000 g, presumably because of more frequent suspensions of enteral feeding, more courses of antibiotic treatment, or both [14]. Based upon current evidence *L. reuteri* DSM 17938 is not recommended for infant feeding as it failed prevent NEC [15].

Human milk is also suitable for the management of premature infants (AAP, 1997) but fortified breast milk may be a preferred choice [16] and not the pooled pasteurized breast milk [17]. Recently, clinical studies proposed inclusion of certain immuno-regulatory substances such as nucleotides, prebiotics or probiotics to the nutrition of infants to enhance the bifidogenic effect on the gut flora, thereby reducing the number of latent invasive bacteria [18, 19]. Under these circumstances various specially developed cultured milk products can be recommended for feeding both normal and sick infants [20] and health promising results due to probiotic supplementation in low birth weight infants are reported [21, 22]. Probiotics are living microorganisms in foodstuffs which when ingested at certain levels provide equilibrium of the intestinal flora thus exhibiting a positive effect of consumer's health [23]. A double-blind, randomized controlled trial revealed that probiotic supplementation was efficacious in full-term infants with critical illness and induced a significantly reduced rate of nosocomial pneumonia (18% vs. 36%) and multiple organ dysfunction syndrome (6% vs. 16%) compared with the placebo group [24]. In the present article an endeavor has been made to enlighten suitability of probiotic supplementation for preterm infants in absence of human milk.

COLONIZATION OF GUT FLORA OF PREMATURE INFANTS

Human GI tract is sterile immediately after birth and is colonized by vaginal and faecal flora of mothers during birth [25, 26]. Microbes have also been detected in amniotic fluid and placenta from mothers and in the umbilical cord blood of healthy neonates [27] suggesting their contribution towards the initial colonization of the neonatal gut. Intestinal microbiota of mother during pregnancy is important as mother-fetal interactions influence the infant's health later in life.

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Transfer of maternal features to the newborn and intestinal microbiota of normal-weight pregnant women to be more populated with *Bifidobacterium* and *Bacteroides* and less with Staphylococcus, Enterobacteriaceae, and *Escherichia coli* in contrast to overweight pregnant women were noted [28] . Higher incidence of *E. coli* in feaces of women with excessive weight gain with respect to those with normal weight gain was also reported by them. The most important determinants of the gut microbiotic composition in infants were the mode of delivery, type of infant feeding, gestational age, infant hospitalization, and antibiotic use by the infant. The newborn gut microflora foster integrity of the immune system protecting from infections with enteric pathogens, produce vitamins, and encourage mucosal maturation [29, 30].

Dominance of bifidobacteria and other lactic acid bacteria in breast-fed infants but a more diverse microbial population comprising of bifidobacteria, *Bacteroides*, Clostridia and streptococci, staphylococci, streptococci and *Enterobacteriaceae* in formula-fed infants have been reported [31, 32]. Preterm infants are particularly susceptible to abnormal colonization. Diversity in gut flora of preterm infants and term infants [8, 33] and delayed bifidobacteria colonization [8] coupled with higher prevalence of *Clostridium difficile* [34] in preterm infants may be attributable to the use of parenteral nutrition and antibiotic therapy for extended periods [8]. Gut colonization in breast-fed preterm infants was characterized by high initial numbers of enterobacteria and streptococci, while bifidobacteria appeared on 11 day and became predominant on 19 day, in contrast to full-term infants who were colonized at 4 days of age [8].

Various factors such as the immature intestinal function, frequent use of broad-spectrum antibiotics, delay in initiating enteral feeding, infection control procedures and sterilization of milk limit the exposure of preterm infants to normal commensal microorganisms [14] and are therefore prone to systemic infections due to increased intestinal permeability to potentially pathogens [35]. Low-birth-weight premature infants delivered by caesarian section are more prone to microbial infections due to late initiation of breast feeding, no colonization as resulted from ingestion during vaginal birth [36] and antibiotic therapy [34]. Antibiotic administration results in suppression of all anaerobic bacteria except clostridia and increased numbers of *Klebsiella*, *Enterobacter*, *Citrobacter* and *Pseudomonas* and Lactobacilli and bifidobacteria are generally absent in the intestine of antibiotic-treated infants [37, 38]. Fecal flora of a pre-term infant's intestine constituted of less than 20 different bacterial strains [36], whereas these of healthy adults had more than 400 types [39]. Stool specimens of extremely low birth-weight (<1000 g) infants were predominated with *Enterococcus faecalis, Escherichia coli, Staphylococcus epidermidis, Enterobacter cloacae, Klebsiella pneumoniae*, *Staphylococcus haemolyticus*, however *Lactobacillus* and bifidobacteria spp. could be identified in only one stool specimens [36].

Premature newborns in the intensive care acquire colonizing bacteria from the intensive care microenvironment rather than their mother [9] and harbor a bacterial flora composed of predominant aerobes such as *Staphylococcus aureus*, *Klebsiella* and enterococci, whereas the predominant anaerobes include Clostridia [36]. All preterm infants attain more similar genetic profiles in fecal samples after four weeks, indicating that all preterm infants had a similar bacterial composition, regardless of birth weight, feeding regime, and antibiotic therapy [9].

Various pathways for early patterns of microbial colonization are enumerated below [40].

- enhancement of the mucosal protective barrier
- modification of systemic immune response
- competitive exclusion of less desirable microbe
- protein and carbohydrate degradation
- vitamin and butyrate production
- mucosal differentiation

Preterm infants have immature physiological systems due to an underdeveloped GI resulting in translocation of potentially pathogenic bacteria from the intestinal lumen causing systemic infections [41, 42]. Factors influencing the onset of infections in preterm infants are depicted below [43].

- origin of infections before birth
- intrauterine (prenatal) onset of infections
- poor development of splanchnic organs of the newborn
- immature GI tract
- origin of infections because of NICU (Neonatal intensive care unit) environment
- invasive NICU care including mechanical ventilation

- misuse of intravenous antibiotics at the NICU
- total parenteral nutrition using indwelling lines
- origin of infections related to the GI tract
- early/late onset of enteral feeding?
- amount of nutrition (minimal enteral nutrition)
- relation to the origin of NEC
- postnatal malnutrition particularly in infants, 26 weeks
- effects on infections by specific food components
- effects of amino acids, nucleotides, pre- and probiotics

The ability of non pathogenic intestinal microflora, such as lactic acid bacteria, to associate with and bind to the intestinal brush border tissue is thought to be an important attribute that prevents harmful pathogens from accessing the GI mucosa [44]. Abnormal pattern of colonization in pre-term infants may contribute to the pathogenesis of neonatal NEC, an acquired GI disease associated with significant morbidity and mortality. [11, 12] and increase the risk of bacterial translocation [13]. Initially, ischaemic injury to the immature gastrointestinal tract (GIT) was thought to be the basic cause of NEC, later other involved factors such as issues related to the introduction and advancement of enteric feeding, alterations in the normal bacterial colonization of the GIT, bacterial translocation and activation of the cytokine cascade, decreased epidermal growth factor, increased platelet activating factor and mucosal damage from free radical production were reported [45].

BREAST MILK FOR PREMATURE INFANTS

Breastfeeding confers advantages on both mothers and babies, including health, immunological, developmental, psychological, social, economic and environmental benefits [46]. Human milk is suitable for the management of premature infants [47] due to certain benefits such as improvements in host defense, digestion and absorption of nutrients, neurodevelopment, GI function as well as psychological effects on the mother [48]. Trophic feeds, defined as minimal volumes of milk feeds (10–15 mL/kg/day) should be started within 24 h of life [49]. Premature infants must be offered more human milk to lower the incidence of NEC and shorter duration of hospitalization [16, 50]. Mother's own milk should be the first choice for feeding preterm infants but in case of insufficient production, donor human milk should be preferred [51] over a preterm formula for retaining the protective effects of mother's milk [50]**.** One of the studies revealed donor breast milk to be equally efficacious as mother's own milk towards protection against NEC [52], however, meta-analysis of published data indicated poor growth in infants receiving donor milk compared to those receiving preterm formula [50, 53, 54]. Protective effect of donor milk for NEC is not conclusive. Optimizing of the banking procedure and application of breast milk fortifiers are suggested to overcome the losses of biological components due to storage and pasteurization of donor milk [51]. In case of unavailability of maternal or donor milk, formula milk should be introduced within 24-48 h [49].

Concentrations of protein, sodium and zinc decline in human milk with the continuation of lactation, but the nutrient needs of VLBW infants remain high [55] and therefore exclusive feeding of premature infants with unfortified human milk may be associated with poor rates of growth and nutritional deficits during and beyond the period of hospitalization [56, 57] and must be supplemented with necessary nutrients to optimize it for feeding premature infants [58, 59]. Introduction of reformulated iron-fortified powdered human milk fortifier and powdered commercially available human milk fortifier were reported to be safe and lower incidence for NEC and sepsis encountered in VLBW infants than those fed with human milk [60]. Premature human milk has strong antimicrobial activity against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Candida albicans* and addition of the milk fortifier Eoprotein does not change this effect, however the antimicrobial activity reduced with the addition of iron [61]. It was suggest that despite a slower early growth rate, human milk fed low birth weight infants have development at least comparable to that of infants fed nutrient-enriched formula [62].

PROBIOTICS FOR PREMATURE INFANTS

Probiotic bacteria are reported not only to compete and suppress 'unhealthy fermentation' in human intestine but also to exhibit a number of beneficial health effects [63] either directly or indirectly through modulation of the endogenous ecosystem or immune system [64], competitive interactions, direct antagonism of pathogens, and production of antimicrobial factors [65]. Recommended probiotic cultures for preterm infants are enlisted in Table **1**.

Probiotics prevented gut colonization by Candida and conferred protection against sepis and abnormal

Table 1: Recommended Probiotic Cultures for Preterm Infants

Probiotic cultures	Birth weight	Reference
Lactobacillus rhamnosus GG *Bifidobacterium infantis*	501 to 1000 g	[66]
Lactobacillus bifidus, *Streptococcus thermophillus* *Bifidobactrium infantis*	<1500 g	[67]
Lactobacillus casei *Bifidobacterium breve*	750 - 1500 g	[68]
Saccharomyces boulardii	-	[69]
Lactobacillus GG	-	[70] [71]
Saccharomyces boulardii	-	[72]
Bifidobacterium breve	-	[73] [74]
Lactobacillus acidophilus *Bifidobactrium infantis*	<1500 g	[75]
Bifidobacterium bifidum *Lactobacillus acidophilus*	<1500 g	[22]
Lactobacillus casei	<1500 g	[76]
Lactobacillus rhamnosus GG	<1500 g	[77]
Bifidobacterium lactis Bb12	-	[78] [79]
Bifidobactrium infantis *Streptococcus thermophilus* *Bifidobactrium lactis*	-	[80]
Lactobacillus	-	[81]
Lactobacillus reuteri DSM 17938	-	[82]
Lactobacillus reuteri ATCC) 55730 *Lactobacillus rhamnosus ATCC 53103*	-	[83]
Lactobacillus rhamnosus GG *Bifidobactrium longum BB536*	-	[14]
Bifidobacteria infantis, *Bifidobacteria bifidum,* *Bifidobacteria longum,* *Lactobacillus acidophilus*	-	[84]
Lactobacillus sporogenes	-	[85]

neurological outcomes in preterm infants and greater efficacy of *L. reuteri* than *L. rhamnosus* [83] may be attributed to a lower colonization of *L. rhamnosus* in preterm infants with a birth weight <1500 g than in those with a birth weight between 1500 and 1999 g [86]. Administration of *Lactobacillus acidophilus* at a level of 10^8 cfu induced colonization of GIT with Lactobacillus in 37% preterm infants and improved feeding tolerance [87].

Reviewed literature provided evidence-based guidelines which indicated that Lactobacillus GG alone may not be effective but a probiotic combination comprising of *Lactobacillus* and at least one *Bifidobacterium* species at a daily dose level of 3×10^9 organisms must be initiated within first 7 days of life and to be continued for at least until 35 weeks corrected age or discharge in preterm neonates [67, 75]. Supplementation with *Bifidobacterium longum* BB536 and *Lactobacillus rhamnosus* GG may not

improve the GI tolerance to enteral feeding in very-low-birth weight infants but may improve GI tolerance in infants weighing >1000 g. [14]. Onset of bacterial resistance against antibiotics is suspected [40] but a reduction in the incidence of death or NEC in very low birth weight preterm infants was encountered due to administration of *Bifidobacterium* and *Lactobacillus* for 6 weeks [22].

Based upon Randomized Controlled Trials (RCT) administration of probiotic in preterm infants with a birth weight >1000 g could be recommended due to significantly reduction in incidence of NEC [21,88. 89] and no systemic infections or serious adverse events was reported. Recently systematic reviews of randomized, controlled trials indicated lower mortality and NEC in very low birth weight neonates [90]. Enteral feeding of premature infants with *Lactobacillus* sp. strain GG showed survival of the organism through the GIT but could not confer any detectable benefits [70]. Probiotic supplementation induced colonization of intestinal flora with *Bifidobacterium lactis* Bb12 [78] in preterm infants and resulted in beneficial effects on survival, infection rate, and incidence of NEC [75] and a recent double-blind, randomized, controlled clinical trial concluded that oral probiotic supplementation with *B. breve* and *L. casei* reduced the occurrence of NEC [68]. Probiotic supplementation comprising *Bifidobacterium infantis*, *Lactobacillus*, and *B. lactis* to preterm modulated the intestinal microflora and minimize enteral fungal colonization, reduced invasive fungal sepsis, earlier establishment of full enteral feeds, and reduced duration of hospital [91]. A joint FAO/WHO report stated that *B. lactis* is the only probiotic bacterium which has undergone FDA evaluation for use in infant formulas from birth and has been found equally safe for vulnerable populations, such as preterm infants, malnourished infants that can be commercialized for this application [92].

Protective effect of probiotics towards development of NEC and/or sepsis in high risk infants may be attributed to increased barrier for migration of bacteria and their products across the mucosa [93, 94], competitive exclusion of potential pathogens [95], modification of host response to microbial products [96], augmentation of IGA mucosal responses, enhancement of enteral nutrition that inhibit the growth of pathogens and up-regulation of immune responses [97]. Probiotics may play a role in preventing the onset of NEC [45, 98] however more large-scale, definitive studies [45] and understanding of the mechanisms of the microbiota-epithelium interactions through parallel infant and animal trials [99] are emerging. Inconsistent effect of probiotic administration on NEC sensitivity in preterm pigs (decreases and increases) but decreased NEC incidence in preterm infants indicate host defense factors appear more important than the nature of the gut microbiota [100]. Probiotics found efficacious in the prevention of NEC in certain populations of preterm infants but further research are required to explore appropriate treatment regimes, strain-specific effects on sub-selected populations and long term effects of probiotic administration [100]. Administration of probiotics in preterm neonates is recommended but further research are emerging for its routine application [101], countries such as Denmark have already issued guidelines for use of probiotics in preterm neonates [102].

SAFETY OF PROBIOTIC APPLICATIONS IN PRE-MATURE INFANTS

Administration of probiotics during the perinatal and early postnatal period [103] and lactation favour infant gut colonization due to transmission of beneficial microflora from mother to neonate through direct contact with maternal microbiota during birth and through the supply of breast-milk bacteria during lactation [103, 105].

Although probiotics have an excellent overall safety record but may not be appropriate for premature neonates and generalized statement for prophylactic properties of probiotics should not be given as it is strain specific [106]. Routine use of probiotics in the preterm infant could not be recommended due to many uncertainties such as the mechanisms of action of probiotics, health effects of employed probiotics, determination of reasons for the efficacy of probiotics, forms of microbial adaptations and ecological consequences [107]. Probiotics may differ in their efficacy to exhibit health benefits and all probiotics have been studied therefore general recommendations for all probiotics cannot be made [21]. Routine probiotic supplementation is justified for preterm infants except for ELBW [1, 2] and further investigations are required to assess the potential benefit and safety of probiotic supplementation for ELBW infants [21, 108]. Probiotic supplementation in preterm neonates exhibited good safety profile and did not show any side effects [91], however more randomized controlled trials to evaluate safety profile of probiotic supplementation for the prevention of NEC in ELBW infants [109] and as an additive treatment to prevent invasive fungal infections in preterm neonates [91] are emerging. Further, optimal

probiotic strain, duration of administration and host selectivity remain unclear due to heterogeneity of trial design and therefore repeated studies using a single design protocol to demonstrate reproducibility, safety and efficacy are suggested [110]. Reviews on clinical report on the use of probiotics indicated modestly effectiveness in treating acute viral gastroenteritis and preventing antibiotic-associated diarrhea but preliminary encouraging results for the treatment childhood *Helicobacter pylori* gastritis, irritable bowel syndrome, chronic ulcerative colitis and infantile colic in healthy children and require further confirmation [107].

CONCLUSION

Preterm infants are prone to systemic infections due to increased intestinal permeability to potentially pathogens resulting from immature intestinal function, frequent use of broad-spectrum antibiotics, delay in initiating enteral feeding, infection control procedures and sterilization of milk. Abnormal pattern of colonization in pre-term infants may contribute to the pathogenesis of neonatal NEC, an acquired GI disease associated with significant morbidity and mortality. Introduction of foods containing probiotic cultures may be advantageous as probiotics prevented gut colonization. Probiotic supplementation in preterm neonates exhibited good safety profile and did not show any side effects and can be recommended for preterm infants but not for ELBW infants.

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