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Research Progress on Probiotics and the Development of Gut Microbiota and Immune System in Newborns

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Abstract: ***The neonatal period is a critical window for gut microbiota colonization and immune development. This article systematically reviews the research progress of probiotics in regulating gut microbiota, immune modulation, disease prevention, and safety in newborns. Full-term and preterm infants show different responses to probiotics, with the latter exhibiting more severe dysbiosis; probiotics can increase beneficial bacteria and reduce pathogenic bacteria. Metabolomics reveals that the metabolic function mediated by short-chain fatty acids (acetate, lactate) produced by probiotics is more critical than simple colonization in preventing late-onset sepsis. High-level clinical evidence indicates that probiotics significantly reduce the risk of necrotizing enterocolitis (pooled RR = 0.51) and all-cause mortality (pooled RR = 0.72) in preterm infants, with multi-strain formulations showing better efficacy; a consistent protective effect is also observed against late-onset sepsis. Early supplementation with infant-type bifidobacteria in full-term infants reduces the risk of eczema (RR = 0.78). Probiotic-associated invasive infections are rare, and the benefit/risk ratio is favorable under strict quality control.***

Keywords: Probiotics, Neonates, Gut microbiota, Necrotizing enterocolitis, Short-chain fatty acids**.**

1. Introduction

The neonatal period is a critical window for gut microbiota colonization and immune system development, with long-term implications for health outcomes. Dysbiosis of the gut microbiota in early life has been closely linked to the pathogenesis of various diseases, including allergic diseases, asthma, obesity, and necrotizing enterocolitis (NEC) [1]. The International Scientific Association for Probiotics and Prebiotics defines probiotics as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" [2]. However, the clinical application of probiotics in neonates is still evolving, and their specific mechanisms of action, optimal strain selection, and dosing regimens remain a central focus of academic research.

In recent years, with the application of multi-omics technologies such as metagenomics and metabolomics, as well as the publication of numerous high-quality randomized controlled trials and meta-analyses, significant breakthroughs have been achieved in the field of probiotic research in neonates. The clinical value of specific strains, represented by infant-type bifidobacteria (ITB), has been validated in full-term infants. Umbrella meta-analyses and network meta-analyses in preterm infants have provided the highest level of evidence to date for the prevention of necrotizing enterocolitis (NEC) and late-onset sepsis (LOS) [3-6]. Furthermore, advances in metabolomics have opened new perspectives for understanding the protective mechanisms of probiotics [7].

This article systematically reviews the recent research advances in this field from four aspects: the modulatory effects of probiotics on the neonatal gut microbiota, immunomodulatory mechanisms, evidence for clinical application, and safety, aiming to provide a reference for the clinical use of probiotics in neonates and future research directions.

2. Probiotic Modulation of the Neonatal Gut Microbiota

2.1 Differences in Microbiota Modulation Between Full-term and Preterm Infants

The establishment of the neonatal gut microbiota is influenced by multiple factors, including mode of delivery, feeding method, antibiotic exposure, and hospital environment. Probiotic supplementation has been shown to modulate the composition and function of the gut microbiota during the perinatal period and infancy, increasing the abundance of beneficial bacteria such as Bifidobacterium and Lactobacillus while reducing levels of potentially pathogenic bacteria [8]. However, significant differences exist in the characteristics of microbiota modulation between full-term and preterm infants, which are closely associated with their distinct baseline microbiota status.

Full-term infants typically have a relatively mature intestinal microecological environment, with good gut microbiota diversity and stability. Supplementation with infant-type "Bifidobacteria" helps further enrich the abundance of the "Bifidobacterium" genus and maintain gut microbiota homeostasis, thereby exerting health benefits such as preventing eczema and respiratory infections [9].

In contrast, very preterm infants often exhibit significant gut dysbiosis due to factors such as prolonged exposure to the hospital environment, early antibiotic treatment, and delayed enteral nutrition. This dysbiosis is primarily characterized by overgrowth of opportunistic pathogens such as "Enterobacteriaceae" and a marked reduction in beneficial bacteria like "Bifidobacteria". A systematic review by Vievermanns et al. comprehensively evaluated the effects of probiotic supplementation on the gut microbiota in very preterm infants. Including 29 studies, the review found that in

the majority of studies, the beta diversity (differences in microbiota composition between groups) of the probiotic supplementation group differed significantly from that of the control group. Probiotic supplementation increased the relative abundance of the supplemented strains while reducing the relative abundance of potential pathogens such as "Clostridium", "Streptococcus", "Klebsiella", and "Escherichia" [10]. The combined use of probiotics and prebiotics (synbiotics) can also accelerate the establishment of a "Bifidobacterium"-dominated gut microbiota and mitigate microbiota dysbiosis in preterm infants [11]. This gut microbiota-modulating effect is considered a potential mechanistic basis for the ability of probiotics to reduce the risks of NEC, sepsis, and mortality in preterm infants [12, 13].

2.2 Metabolite-mediated Mechanisms of Microbiota-host Interaction

Traditional views hold that the health benefits of probiotics mainly depend on colonization and competitive exclusion of pathogens. However, recent metabolomics-based studies have provided new perspectives for understanding the mechanisms of action of probiotics. A study published in "Cell Reports" analyzed the effects of a multi-strain probiotic (containing "Bifidobacterium longum" subsp. "longum" and "Lactobacillus acidophilus") on the gut microbiome and metabolome of very low birth weight (VLBW) infants. A total of 175 VLBW infants (70 of whom developed late-onset sepsis, LOS) were included. The results showed that probiotic intervention not only facilitated the colonization of beneficial bacteria and reduced the abundance of hospital-acquired opportunistic pathogens such as "Klebsiella", but more importantly, revealed that in preterm infants who subsequently developed LOS, the intestinal levels of key fermentation products—acetate and lactate—were significantly lower before the onset of infectious symptoms compared to matched controls without LOS (acetate: P_{adj}=0.0049; lactate: P_{adj}=0.048) [7].

Bifidobacteria can metabolize human milk oligosaccharides in breast milk to produce short-chain fatty acids (mainly acetate) and lactate. These metabolites exert protective effects through multiple pathways, including enhancing intestinal epithelial barrier function and regulating local and systemic immune responses [14]. As key signaling molecules between the gut microbiota and the host immune system, short-chain fatty acids play a central role in maintaining intestinal barrier integrity and regulating immune cell functions [15]. In the neonatal population, dynamic changes in short-chain fatty acid levels are directly involved in T-cell development and functional regulation, and are closely associated with the prevention of inflammatory diseases [16].

Based on these findings, the metabolic function (i.e., acid-producing capacity) of probiotics may be more critical than simple gut colonization in preventing late-onset sepsis (LOS). This discovery challenges the traditional colonization-oriented thinking and shifts the focus of probiotic research from a microbiota composition-centered perspective to a metabolic function-centered perspective, offering new insights for future precision interventions.

2.3 Immunomodulatory Mechanisms

The gut microbiota plays a central role in the development and maturation of the neonatal immune system. The normal colonization process of the microbiota is essential for the development of gut-associated lymphoid tissue, the differentiation of regulatory T cells, and the establishment of a balanced Th1/Th2 immune response. A review by Mogoș et al. points out that the gut microbiota in early life plays a key role in immune system development and maturation, and that dysbiosis can alter the host's resistance to pathogens, promoting atopic diseases, food sensitization, and infectious diseases such as necrotizing enterocolitis (NEC) [1].

Probiotics exert immunomodulatory effects through multiple pathways. On the one hand, probiotics reduce the adhesion and colonization of pathogenic bacteria on the intestinal mucosa through competitive exclusion, thereby lowering the risk of excessive inflammatory responses activated by pathogen-associated molecular patterns [17]. On the other hand, metabolites produced by probiotics (especially short-chain fatty acids) can act as signaling molecules that directly act on intestinal epithelial cells and lamina propria immune cells, regulating cytokine production and immune cell recruitment [18]. Metabolites of infant-type bifidobacteria can modulate the intestinal mucosal immune barrier and reduce the transdermal/transmucosal exposure to allergens and the subsequent Th2-biased immune deviation, which explains why this strain significantly reduces the risk of eczema. A meta-analysis of 25 studies showed that early supplementation with ITB probiotics in healthy full-term infants significantly reduced the risk of eczema (*RR*=0.78, 95% CI 0.68–0.90), and the risk of respiratory tract infections also showed a decreasing trend (*RR*=0.74, 95% CI 0.54–1.00) [19].

3. Clinical Application of Probiotics in the Prevention of Neonatal Diseases

The most evidence-supported application of probiotics in neonatal disease prevention is for the prevention of necrotizing enterocolitis (NEC) and late-onset sepsis (LOS) in preterm infants. In recent years, a growing body of evidence has also focused on their potential in preventing allergic diseases in full-term infants.

3.1 Prevention of Necrotizing Enterocolitis (NEC)

NEC is one of the most serious intestinal complications in preterm infants, associated with high mortality and the risk of adverse long-term neurodevelopmental outcomes. In recent years, multiple high-level meta-analyses have provided solid clinical evidence for the prevention of NEC in preterm infants with probiotics.

At the level of umbrella meta-analysis, Zhou et al. (2025) conducted a systematic re-analysis of previously published meta-analyses, including 35 eligible meta-analyses covering 26 single-strain interventions and 32 multi-strain interventions. The results showed that probiotics significantly reduced the risk of NEC in preterm infants (pooled *RR*=0.51, 95% *CI* 0.46–0.55, $P < 0.001$; pooled *OR*=0.59, 95% *CI* 0.48–0.72, $P < 0.001$) and all-cause mortality (pooled *RR*=0.72, 95% *CI* 0.68–0.76, $P < 0.001$; pooled *OR*=0.77, 95% *CI* 0.70–0.84, $P < 0.001$), suggesting that probiotics should be considered an

effective preventive strategy for NEC in preterm and very preterm infants, with multi-strain formulations showing greater efficacy [3].

At the level of strain/comparison, the network meta-analysis by Dai et al. systematically evaluated 51 randomized controlled trials (including 11,661 preterm infants) to compare the effects of different probiotic strains and combinations on NEC, mortality, and other clinical outcomes. For the first time, this study comprehensively ranked different probiotic regimens using network meta-analysis and found that the combination of Bifidobacterium, Lactobacillus, and Enterococcus was the most effective in reducing the incidence of NEC and mortality. Regarding the effects of individual probiotics or combinations on specific outcomes, Lactobacillus alone (RR=0.59, 95% CI 0.29–0.98), the combination of Bifidobacterium + Lactobacillus (RR=0.47, 95% CI 0.20–0.87), and the combination of Bifidobacterium + Lactobacillus + Streptococcus (RR=0.17, 95% CI 0.00–0.84) all significantly reduced all-cause mortality. Furthermore, Lactobacillus alone effectively shortened the length of hospital stay (mean difference –4.23 days, 95% CI –7.6 to –0.81) and the time to achieve full enteral feeding (mean difference –2.15 days, 95% CI –3.70 to –0.64), indicating its clinical value in promoting feeding tolerance [4].

At the specific strain level, the meta-analysis by Abdullahi et al. focused on the preventive effects of *Bifidobacterium breve* BBG-001, including 9 studies with a total of 7,180 preterm infants. The results showed that BBG-001 significantly reduced the risk of NEC stage ≥ II (*OR*=0.66, 95% *CI* 0.47–0.94, *P*=0.02), all-cause mortality (*OR*=0.74, 95% *CI* 0.62–0.89, *P*=0.001), and the incidence of sepsis (*OR*=0.71, 95% *CI* 0.53–0.93, *P*=0.01). This strain also reduced the incidence of periventricular leukomalacia (*OR*=0.61, 95% *CI* 0.47–0.78, *P* < 0.0001) and intraventricular hemorrhage (*OR*=0.48, 95% *CI* 0.33–0.69, *P* < 0.0001), suggesting that the protective effects of probiotics may not be limited to the intestine but may also exert neuroprotective effects by reducing systemic inflammation [5]. This study is one of the few that links NEC prevention with long-term neuroprotective outcomes, providing a new endpoint indicator for comprehensive evaluation of probiotics.

3.2 Prevention of Late-Onset Sepsis (LOS)

LOS refers to sepsis occurring after 72 hours of birth and is one of the major causes of death in preterm infants. The meta-analysis by Maulida et al. included 31 studies with 8,040 preterm infants and systematically evaluated the preventive effect of probiotics on LOS. The results showed that probiotics significantly reduced the incidence of LOS (pooled *RR*=0.83, 95% *CI* 0.72–0.95). Subgroup analysis indicated that multi-strain formulations had a better preventive effect than single strains (*RR*=0.76, 95% *CI* 0.72–0.95); the low-dose regimen (defined in this analysis as $\leq 10^9$ CFU/d) was also more effective than the high-dose regimen (*RR*=0.72, 95% *CI* 0.56–0.91). These findings suggest that optimized strain combinations and appropriate dosing regimens are particularly critical in the prevention of LOS. In addition, probiotic supplementation was associated with a shortened hospital stay and a trend toward reduced mortality (not statistically significant) [6].

The meta-analysis by Abdullahi et al. also confirmed that BBG-001 was effective in preventing sepsis (*OR*=0.71, 95% *CI* 0.53–0.93, *P*=0.01) and reduced the risk of infection-related mortality (*OR*=0.80, 95% *CI* 0.65–0.99, *P*=0.04) [6]. However, it should be noted that the network meta-analysis by Dai et al. did not find a significant effect of probiotics on sepsis risk (4). This discrepancy may reflect heterogeneity among studies in terms of sepsis definitions, etiological spectra, and probiotic strains selected, suggesting that the preventive effect on sepsis may be strain-specific, and that the overall effect of mixed strains may mask the true effect of effective strains.

Taken together, these high-level evidence consistently demonstrate that probiotics can effectively reduce the incidence and mortality of NEC in preterm infants, and also show a consistent protective effect against LOS, although the magnitude of the effect may vary depending on the strain and dosing regimen.

3.3 Prevention of Allergic Diseases and Common Infections in Full-Term Infants

In addition to preterm infants, the application of probiotics in full-term infants has also gained new evidence from recent studies. A systematic review and meta-analysis published by Szajewska in 2025 systematically evaluated the clinical effects of early supplementation with infant-type Bifidobacterium (ITB) probiotics in healthy full-term infants, including 25 studies. The analysis showed that early ITB probiotic application was associated with a significant reduction in the risk of eczema (*RR*=0.78, 95% *CI* 0.68–0.90) and a borderline association with a reduced risk of respiratory tract infections (*RR*=0.74, 95% *CI* 0.54–1.00) [19]. Other routinely reported outcomes, such as antibiotic use, diarrhea, wheezing bronchitis, and food allergy, also showed trends toward preventive effects, but these did not reach statistical significance.

This study suggests that probiotics have value in preventing common diseases in healthy full-term infants, but there are limitations such as high heterogeneity, lack of long-term follow-up, and lack of standardized outcome measures. Future high-quality randomized controlled trials with larger sample sizes and standardized outcome measures are needed to clarify the short-term and long-term effects.

4. Safety of Probiotics

With the widespread use of probiotics in the neonatal intensive care unit (NICU), their safety has attracted increasing attention. In 2023, the U.S. Food and Drug Administration (FDA) issued a warning about a specific probiotic product following a case of probiotic-associated infection, pushing this issue to the forefront of clinical regulation. The review by Younge and Patel systematically discussed the epidemiology and pathophysiology of probiotic-associated invasive infections in preterm infants, noting that based on current reports, invasive infection is a rare but known risk of probiotic supplementation [20]. Among neonates, extremely preterm infants, those with central venous catheters, and those with impaired intestinal barrier function are at the highest risk for probiotic-associated

infections [21-23]. In current large-scale randomized controlled trials and cohort studies, the overall incidence of invasive infections resulting from routine prophylactic probiotic supplementation in preterm infants is very low; probiotic-associated bacteremia/sepsis is a rare event, and attributable deaths are extremely rare [24]. In contrast, the reductions in the risks of necrotizing enterocolitis (NEC), late-onset sepsis (LOS), and mortality are substantial, particularly in preterm infants at high risk for NEC and LOS [25, 26]. Therefore, under the premise of quality-controlled formulations and adequate monitoring, prophylactic probiotic use shows a clearly favorable benefit/risk ratio [27].

Current evidence indicates that, under the conditions of strict quality control, appropriate strain selection, and standardized procedures, probiotics significantly reduce NEC and mortality in many preterm infants. However, greater caution is warranted in high-risk populations such as extremely preterm infants, those with central venous catheters, or those with severe intestinal diseases [28]. The core elements of safety assurance include establishing an independent product quality testing system, strictly screening indications and high-risk contraindications, using specific strains and dosages that have been proven effective and safe in high-quality clinical trials, and continuously monitoring probiotic-associated infections.

The 2025 Chinese edition of the *Expert Consensus on Clinical Application of Microecological Modulator*s and the *Evidence-Based Guideline for Clinical Application of Probiotics in Pediatrics (2023)* provide a guiding framework for the scientific use of probiotics in newborns. High-quality clinical trials and meta-analyses conducted in China have also provided important evidence. For example, a meta-analysis published in the *Chinese Journal of Contemporary Pediatrics* confirmed that probiotics reduce the risk of clinical late-onset sepsis (LOS) in very low birth weight infants [29].

5. Conclusion

Current evidence has fully confirmed the clinical value of probiotics in regulating the neonatal gut microbiota and reducing the risks of necrotizing enterocolitis (NEC) and late-onset sepsis (LOS) in preterm infants. The field is now shifting from focusing on “which strain is supplemented” to focusing on “what metabolic functions probiotics exert” – particularly their ability to produce short-chain fatty acids (e.g., acetate, lactate). Future research faces the following challenges: mechanistic studies need to go beyond the traditional perspective of colonization and deeply explore the metabolic regulatory network centered on short-chain fatty acids; individualized intervention strategies urgently need to be established, leveraging multi-omics technologies to achieve precise matching of strain combinations; safety regulatory systems need to be strengthened, with independent product quality testing and adverse event monitoring networks established for extremely high-risk populations such as extremely preterm infants and those with central venous catheters, while promoting globally unified probiotic product approval standards [30, 31]; and long-term outcome evaluation should be extended from intestinal complications to neurodevelopment, with large-scale, long-term, multicenter cohort studies to clarify the causal effects of probiotics on cognitive and behavioral outcomes [32-34].

Future research should focus on: elucidating metabolism-driven protective mechanisms; conducting adaptive RCTs based on individual baseline microbiota; establishing globally recognized quality and safety guidelines for probiotics; and taking neurodevelopment as a secondary endpoint. This will enable a shift from “broad-spectrum supplementation” to “precision intervention”, providing safer and more effective probiotic strategies for newborns, especially high-risk populations.

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