REVIEW

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Probiotics for the Prevention of Sepsis in Preterm Infants: A Comprehensive Review of Recent Evidence

Preterm Bebeklerde Sepsisin Önlenmesinde Probiyotiklerin Rolü: Güncel Kanıtlara Dayalı Kapsamlı Bir Derleme

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Abstract

Preterm infants are highly susceptible to late-onset sepsis due to immaturity of their immune system and imbalances in gut microbiota. In recent years, probiotics have emerged as a promising strategy to reduce the incidence of necrotizing enterocolitis (NEC) and sepsis in this vulnerable group. This review synthesizes findings from randomized controlled trials and meta-analyses published between 2020 and 2025, focusing on the effects of probiotic supplementation on NEC, sepsis, and overall mortality. Studies were identified through systematic searches of PubMed, Cochrane, and Scopus databases. The analysis also considers the most commonly studied strains, dosing regimens, timing of administration, safety data, and current clinical recommendations. Across the literature, probiotic use is consistently associated with a marked reduction in NEC, and some evidence indicates modest reductions in mortality. However, the impact on sepsis prevention varies considerably depending on strain combinations, trial design, and clinical context. While cases of probiotic-related sepsis are rare, ensuring product safety and quality control remains essential. When appropriate strains are used under careful clinical oversight, probiotics represent a valuable adjunctive strategy in the care of preterm infants, particularly for NEC prevention.

Keywords: Gut microbiota, necrotizing enterocolitis, neonate, preterm infants, probiotics, sepsis

Öz

Prematüre bebekler, immün sistemlerinin henüz olgunlaşmamış olması ve bağırsak mikrobiyotasındaki dengesizlik nedeniyle geç başlangıçlı sepsis ve nekrotizan enterokolit (NEC) açısından yüksek risk altındadır. Son yıllarda probiyotikler, bu komplikasyonların önlenmesinde destekleyici bir yaklaşım olarak dikkat çekmektedir. Bu derlemede, 2020-2025 yılları arasında yayımlanan randomize kontrollü çalışmalar ve meta-analizler incelenerek, probiyotik desteğinin NEC, sepsis ve mortalite üzerindeki etkileri değerlendirilmiştir. Literatür taraması PubMed, Cochrane ve Scopus veri tabanları kullanılarak sistematik olarak yapılmıştır. Derlemede ayrıca en sık kullanılan suşlar, doz rejimleri, uygulama zamanı, güvenlik verileri ve uluslararası kılavuz önerileri ele alınmıştır. Bulgular, özellikle çoklu suş içeren preparatların NEC insidansını anlamlı düzeyde azalttığını ve mortalite oranlarında da sınırlı da olsa olumlu etkiler sağlayabildiğini göstermektedir. Sepsisi önleyici etkiler ise çalışmalara göre değişkenlik göstermekte; kullanılan suşlara, çalışmanın kalitesine ve klinik koşullara bağlı olarak farklılık arz etmektedir. Probiyotik kaynaklı sepsis olguları oldukça nadir bildirilmiş olsa da, kullanılan ürünlerin kalite kontrolü ve güvenilirliği kritik önemdedir. Uygun suşlar dikkatli bir klinik gözetim altında kullanıldığında, probiyotikler özellikle NEC'nin önlenmesinde değerli bir destekleyici yaklaşım olarak öne çıkmaktadır.

Anahtar kelimeler: Mikrobiyota, nekrotizan enterokolit, preterm bebek, probiyotik, sepsis, yenidoğan

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Introduction

Preterm infants, especially those born before 32 weeks of gestation, are highly vulnerable to severe infections due to their immature immune systems and the frequent need for invasive medical interventions (1). Late-onset sepsis (LOS), typically diagnosed after the third day of life, remains a major threat to both survival and clinical stability in this population (2). Necrotizing enterocolitis (NEC), another life-threatening complication, often precedes or coexists with LOS and is characterized by systemic inflammation and intestinal injury (3). Disruptions in the gut microbiota of preterm neonates, characterized by insufficient colonization by beneficial microbes and overgrowth of pathogens, play a central role in the development of both NEC and LOS (4).

Probiotics, defined as live microorganisms that confer health benefits when administered in adequate amounts, have been proposed as a preventive strategy in this context. They may help restore microbial balance, strengthen the intestinal barrier, and modulate immune responses. Numerous randomized controlled trials and meta-analyses have investigated the role of probiotics in reducing the incidence of NEC, sepsis, and mortality in preterm neonates.

This review brings together current evidence on the use of probiotics in preterm infants, with a focus on clinical outcomes, safety data, commonly studied strains, dosing strategies, and recommendations from key health authorities.

Methods

We conducted a structured literature search using three major biomedical databases: PubMed, Scopus, and the Cochrane Library. The search covered publications from January 2020 to March 2025 and focused on the following search terms: Probiotics, preterm, sepsis, NEC, and neonates. The selection process prioritized randomized controlled trials, systematic reviews, and meta-analyses that assessed the effects of probiotics on clinical outcomes in preterm infants. Studies were included based on their relevance to the topic, methodological quality, and reporting of key outcomes such as NEC, LOS, mortality, and adverse events. The findings were synthesized narratively to provide a comprehensive overview of current evidence.

Efficacy of Probiotics on Sepsis Prevention

Evidence regarding the efficacy of probiotics in reducing LOS in preterm infants remains inconclusive. A 2023 Cochrane meta-analysis update encompassing more than 11,000 infants confirmed that probiotics significantly reduced the incidence of NEC and may reduce mortality, whereas their effect on LOS was minimal or uncertain (5).

Conversely, a Bayesian network meta-analysis by Thomas et al. (6), analyzing 29 trials, reported that a specific combination of four probiotic strains (*B. longum, B. bifidum, B. infantis*, and *L. acidophilus*) significantly lowered sepsis incidence. Nevertheless, the overall certainty of the evidence was limited because of heterogeneity in trial design and regional variation (6). Another comprehensive network meta-analysis published in JAMA Pediatrics in 2023, which included more than 25,000 preterm infants from 106 RCTs, concluded that combinations of probiotics and lactoferrin were more effective in reducing sepsis rates than probiotics alone (7).

Recent large-scale reviews underscore that while the benefit of NEC reduction is well established, sepsis outcomes are highly variable and appear to depend on the specific strain used, dosage, and patient population. For instance, Deshpande et al. (8), in a review of over 70,000 infants, observed significant reductions in NEC and mortality but reported inconsistent findings regarding LOS.

Probiotic Effects on NEC and Mortality

The most consistent finding in the literature is a significant reduction in NEC incidence following probiotic administration. Meta-analyses have shown that probiotic use can reduce NEC (Bell stage ≥II) by approximately 40 to 60 percent, especially when multi-strain formulations are employed (5,7). This protective effect is largely attributed to improved intestinal barrier function and suppression of pathogenic bacteria.

Since NEC is a known precursor to secondary sepsis and mortality, preventing NEC may indirectly reduce sepsis-related deaths. Some studies have reported reductions of 25-30 percent in all-cause neonatal mortality with probiotic use (7,8). However, the extent to which these mortality benefits are directly linked to sepsis prevention remains unclear.

Probiotic Strains, Doses and Administration

The most widely studied probiotic strains in preterm infants include *Lactobacillus rhamnosus* GG, *L. reuteri*, *Bifidobacterium breve, B. longum*, and *B. lactis*. Multi-strain preparations tend to offer broader benefits than single-strain formulations. Effective regimens generally contain between 10^8 and 10^9 colony-forming units per strain per

day. Administration typically begins within the first few days of life and continues until 34-36 weeks' postmenstrual age (6,8,9).

The 2020 ESPGHAN position paper identified two probiotic approaches with the strongest supporting evidence. These include *L. rhamnosus* GG alone and a combination of *B. infantis* Bb-02, *B. lactis* Bb-12, and *Streptococcus thermophilus* TH-4 (10). Updated guidance emphasizes the importance of preparation quality, dose standardization, and rigorous monitoring to ensure safety and efficacy.

Safety and Probiotic-associated Sepsis

Overall, probiotics appear to be well tolerated in preterm infants. Randomized trials and observational studies report similar rates of adverse events between probiotic and control groups. A 2022 comprehensive review documented only 32 cases of probiotic-associated sepsis, mostly involving species of Bifidobacterium or *Lactobacillus*; the majority of affected infants recovered fully after antibiotic therapy (11).

Despite the low incidence, safety concerns persist. The United States Food and Drug Administration has issued advisories cautioning against the routine use of probiotics in preterm neonates due to risks associated with contamination and variable product quality (12). A fatal case of fungal sepsis linked to a contaminated product has heightened awareness of the need for pharmaceutical-grade formulations and stringent manufacturing standards.

Clinical Guidelines and Global Practices

Clinical recommendations regarding probiotic use in preterm infants vary across regions. The American Academy of Pediatrics does not support routine probiotic use due to unresolved safety concerns, particularly in extremely low birth weight infants (13). In contrast, ESPGHAN and the World Health Organization conditionally recommend selected probiotic strains for preterm infants fed with human milk, provided that high-quality products are used (10,14).

In some countries, including the United Kingdom and Canada, national neonatal networks have integrated routine probiotic supplementation into NICU protocols based on favorable risk-benefit profiles.

As concerns persist about live microbial supplementation, attention is shifting toward non-viable alternatives such as paraprobiotics. These inactivated microbial preparations maintain immunomodulatory properties while minimizing the risk of systemic infection. Emerging evidence from preclinical studies suggests that paraprobiotics may strengthen gut barrier integrity and reduce inflammation in models of NEC and colitis. For example, Batista et al. (15) demonstrated that paraprobiotics derived from *Lactobacillus delbrueckii* CIDCA 133 alleviated 5-FU-induced intestinal inflammation in neonatal mice. Sundram et al. (16) and Li et al. (17) provided further support for the protective potential of heat-inactivated *Lactiplantibacillus plantarum* strains against microbial dysbiosis and gut injury. However, clinical trials in preterm infants are currently limited, and further investigation is warranted.

A recent large-scale cohort study conducted in Canadian NICUs reported that probiotic use in preterm infants was associated with a significant reduction in mortality but not with a significant decrease in the incidence of NEC or LOS (18).

According to the 2025 guidelines of the Turkish National Neonatology Association, the routine use of probiotics is not recommended in enteral feeding protocols for preterm infants. However, if the unit chooses to administer probiotics and has the necessary conditions in place, specific strains with proven safety and efficacy may be considered for infants born before 32 weeks' gestation and weighing between 1.000 and 1.500 grams. In these cases, clinicians are advised to inform families about potential benefits and risks and to obtain informed consent. Routine use in infants with a birth weight below 1.000 grams is not currently recommended (19).

Conclusion

Probiotic supplementation in preterm infants consistently reduces the incidence of NEC and may contribute to a modest decrease in overall mortality. However, its direct impact on sepsis prevention remains unclear. While some combinations, especially those that include lactoferrin, show promise, inconsistencies in study findings and heterogeneity in probiotic formulations limit the ability to draw broad conclusions. Although cases of probiotic-associated sepsis are rare, careful monitoring and strict quality control are essential. Future research should focus on defining optimal strains, dosages, and duration of therapy and ensuring pharmaceutical-grade production. As evidence continues to accumulate, probiotics hold promise as a supportive intervention in neonatal care, provided their use is guided by high-quality data and individualized clinical judgment.

Footnotes

Authorship Contributions

Concept: E.C., Ş.H., Y.K., C.Y., Design: E.C., Ş.H., Y.K., C.Y., Data Collection or Processing: Y.K., C.Y., Analysis or Interpretation: E.C., Ş.H., Literature Search: Y.K., C.Y., Writing: E.C., Ş.H., Y.K., C.Y.

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