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Review Article

# The Effect of Probiotics on the Prevention of Necrotizing Enterocolitis (NEC) in Low Birth Weight (LBW) and Very Low Birth Weight (VLBW) Infants

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## ABSTRACT

***Background:*** Necrotizing enterocolitis (NEC) is a life-threatening disease for premature and very low birth weight infants (VLBW).Traditional therapeutic methods such as administration of antibiotics and antacids and cessation of breastfeeding can exacerbate changes in the intestinal microbiota. The mechanisms of action are believed to involve modulation of the gut microbiome, enhancement of the gut barrier function, and immunomodulation**.** To review the current evidence regarding the use of probiotics for the prevention of NEC in low birth weight (LBW) and VLBW infants.

***Methods:*** A literature search was conducted across major databases (MEDLINE, Embase, Cochrane Library), supplemented by hand-searching of relevant articles and review of reference lists. The search encompassed randomized controlled trials (RCTs), meta-analyses, and review articles published up to 2024. This review included studies that investigated the effect of probiotic supplementation on NEC incidence and related outcomes in LBW and VLBW infants. Excluded studies were those of poor methodological quality or that did not report relevant outcomes.

***Results:*** In this study, a large number of studies on the effect of probiotics on the prevention of NEC in premature and low birth weight infants were found, which showed beneficial effects of probiotics. And probiotics have reduced the Incidence of NEC, Severity of NEC, Mortality. However, these studies were quite heterogeneous in terms of methodology and type of probiotic used. Adverse events associated with probiotic use were generally infrequent and mild, primarily involving transient diarrhea or vomiting. No significant increase in serious adverse events was reported in any of the included studies.

***Conclusion:*** Probiotic supplementation appears to be a beneficial intervention for preventing NEC in LBW and VLBW infants but yet The decision to use probiotics should be individualized, considering the infant's risk factors, probiotic availability, and parental preferences.

***Keywords:*** Low birth weight, Necrotizing enterocolitis, Probiotics, Very low birth weight

## Introduction

Necrotizing enterocolitis (NEC) is a devastating inflammatory bowel disease primarily affecting preterm infants, particularly those with low birth weight (LBW, <2500g) and very low birth weight (VLBW, <1500g) (1). Characterized by intestinal ischemia, inflammation, and necrosis, NEC leads to significant morbidity, including sepsis, short bowel syndrome, and neurodevelopmental impairment, and remains a leading cause of mortality in this vulnerable population (2,3). Despite advancements in neonatal care, the incidence of NEC remains a concern, underscoring

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the need for effective preventive strategies.

The pathogenesis of NEC is multifactorial, involving interactions between prematurity, intestinal dysbiosis, formula feeding, and an exaggerated inflammatory response (4). Premature infants have an immature gut microbiome, characterized by reduced bacterial diversity and colonization by potentially pathogenic organisms, increasing their susceptibility to NEC (5,6). An imbalance in the gut microbiota disrupts the normal protective mechanisms of the intestine, including the epithelial barrier function and immune regulation (6). Other risk factors include rapid enteral feeding advancement, formula feeding, and exposure to antibiotics (8, 9).

Probiotics, defined as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host have emerged as a promising strategy for NEC prevention (10, 11). The rationale for probiotic use is based on their ability to modulate the gut microbiome, enhance the intestinal barrier, and modulate the immune system in preterm infants. Probiotics can compete with pathogenic bacteria for colonization, promote the growth of beneficial bacteria, and produce antimicrobial substances (12). Furthermore, probiotics can strengthen the intestinal barrier by stimulating mucus production, increasing tight junction protein expression, and reducing intestinal permeability (13). They can also modulate the immune response by reducing pro-inflammatory cytokine production and promoting immune tolerance (14).

Numerous clinical trials and meta-analyses have evaluated the efficacy of probiotics in preventing NEC in preterm infants (15-17).

However, variability exists in the probiotic strains used, dosages administered, and study populations included. While several meta-analyses have demonstrated a significant reduction in NEC incidence and mortality with probiotic supplementation, questions remain regarding the optimal probiotic regimen and the long-term effects of probiotic use. Further, the effectiveness of different probiotic strains in preventing NEC may vary.

This descriptive review aims to provide a comprehensive overview of the current evidence regarding the effectiveness and safety of probiotics for NEC prevention in LBW and VLBW infants. The review will summarize key findings from clinical trials and meta-analyses, discuss the potential mechanisms of action of probiotics, and highlight the current recommendations and future directions for probiotic use in neonatal care.

## Methods

A comprehensive literature search was conducted across multiple electronic databases, including PubMed, Embase, the Cochrane Library, and Web of Science. The search strategy utilized a combination of keywords and Medical Subject Headings (MeSH) terms related to probiotics, necrotizing enterocolitis (NEC), low birth weight (LBW), very low birth weight (VLBW), preterm infants, and randomized controlled trials (RCTs). The search was limited to studies published in English to 2024. Studies were included if they met the following criteria: (1) involved LBW or VLBW infants; (2) investigated the effect of probiotic supplementation on the incidence of NEC; (3) reported on relevant outcomes, including NEC incidence, severity, mortality, and adverse events; (4) were RCTs, cohort studies, or meta-analyses. Studies were excluded if they lacked sufficient data on NEC incidence or were not published in English. Data were extracted from the included studies using a standardized data extraction form. A qualitative synthesis of the included studies was performed. The findings were summarized narratively.

## Results

The literature search yielded more than hundreds studies that met the inclusion criteria. Of these, RCTs, cohort studies, and meta-analyses, the probiotic strains most frequently investigated were Bifidobacterium infantis, Bifidobacterium longum, Lactobacillus rhamnosus, and Lactobacillus reuteri. Dosage and administration routes varied considerably across the studies.

Overall, a trend towards reduced NEC incidence was observed in infants receiving probiotic supplementation compared with controls (18).

Studies varied in their reporting of NEC severity. However, a trend towards reduced severe NEC was observed in some studies.

Several studies reported a lower mortality rate in infants receiving probiotics (19).

Adverse events associated with probiotic use were generally infrequent and mild, primarily involving transient diarrhea or vomiting. No significant increase in serious adverse events was reported in any of the included studies (17-19).

## Discussion

This descriptive review synthesizes the

existing literature on the effect of probiotic supplementation on the prevention of necrotizing enterocolitis (NEC) in low birth weight (LBW) and very low birth weight (VLBW) infants. The findings indicate a trend towards a reduction in NEC incidence and severity, as well as all-cause mortality, with the administration of probiotics to preterm infants (15-17). These benefits are likely mediated through modulation of the gut microbiome, enhancement of the intestinal barrier function, and immunomodulatory effects (7,13,14).

Mechanisms of Action: The protective effects of probiotics in NEC prevention are multifaceted. Probiotics promote the colonization of beneficial bacteria in the gut, which can outcompete pathogenic bacteria and restore microbial balance. By strengthening the intestinal barrier, probiotics reduce intestinal permeability and prevent the translocation of harmful bacteria and toxins into the bloodstream (13). Furthermore, probiotics can modulate the immune response, reducing the excessive inflammation that characterizes NEC (14). This modulation includes decreased production of pro-inflammatory cytokines and increased secretion of anti-inflammatory mediators, which contribute to gut homeostasis.

Our findings align with previous systematic reviews and meta-analyses on the topic. For example, a Cochrane review by AlFaleh and Anabrees concluded that probiotics significantly reduce the risk of NEC and mortality in preterm infants (15).

Similarly, meta-analyses by Sharif et al. and Aceti et al. reported similar benefits (16, 17) However, it is important to note that the specific probiotic strains, dosages, and administration protocols varied across these studies, which may influence the observed outcomes.

Bin-Nun et al conducted an RCT, with 145 preterm infants, in which the mixture of probiotics lead to a reduction in the incidence of NEC (20).

Dani et al conducted an RCT in Italy which included 585 preterm in which supplementation of probiotic resulted in a reduction in the incidence of NEC (21).

Also, an RCT with 367 preterm in Taiwan probiotic supplementation in preterm infants cause a reduction in NEC (22).

A systematic review of 30 good quality non-randomized studies which included over 77,000 infants in 18 different countries found that probiotics reduced the risk of NEC (23).

Although In pre-clinical models of NEC, probiotic supplementation reduced the risk of developing NEC-like injury by close to 50% (24).

among infants less than 28 weeks with a birth weight less than 1 kg, estimates suggested less efficacy of probiotic supplementation on the rate of NEC (25).

and despite the supporting data, the routine administration of probiotics to preterm infants continues to be controversial (26).

In 2020 recommendations of the American Gastroenterological Association published the use of specific probiotics in preterm infants for the prevention of NEC is effective (27).

In 2021, the American Academy of Pediatrics (AAP) published a statement that did not recommend universal administration of probiotics to preterm infants, especially those with a birth weight of less than 1 kg (26).

Despite the promising evidence, several inconsistencies and limitations exist in the literature. There is significant heterogeneity among the studies in terms of probiotic strains used, dosage regimens, and study populations. Some studies used single-strain probiotics, while others used multi-strain formulations. The optimal dosage and timing of administration remain unclear. Moreover, the definition of NEC and the diagnostic criteria used to vary across studies, which can affect the reported incidence rates.

Based on the current evidence, probiotic supplementation should be considered as part of a comprehensive strategy for NEC prevention in LBW and VLBW infants. However, it is crucial to select appropriate probiotic strains with proven efficacy and safety. Clinical decision-making should take into account the individual infant's risk factors, the availability of specific probiotic products, and the institution's experience with probiotic use. A standardized approach to probiotic administration, including consistent dosing and monitoring for adverse events, is recommended.

Future research should focus on addressing the existing gaps in knowledge. Well-designed randomized controlled trials (RCTs) are needed to evaluate the efficacy of specific probiotic strains and combinations in preventing NEC. These trials should adhere to rigorous methodological standards and include standardized definitions of NEC and other clinical outcomes. The long-term effects of probiotic supplementation on gut microbiome development, immune function, and neurodevelopmental outcomes should also be investigated. Furthermore, research is needed to

identify biomarkers that can predict which infants are most likely to benefit from probiotic therapy.

Limitations: This descriptive review provides a comprehensive overview of the current evidence on probiotics and NEC prevention. However, it is important to acknowledge several limitations. First, the review is descriptive in nature and does not involve a formal meta-analysis or quantitative synthesis of the data. Second, the review is limited by the heterogeneity of the included studies and the potential for publication bias. Third, the review does not address the economic aspects of probiotic use, such as cost-effectiveness.

## Conclusion

Probiotic supplementation shows promise as a strategy for preventing NEC in LBW and VLBW infants. However, further high-quality research is needed to optimize the selection of probiotic strains, dosages, and administration protocols.

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## Conflicts of interest

The authors declare that they have no conflict of interest regarding the publication of the current study.

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