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Probiotic Supplementation as Standard of Care in Early Preterm Infants and Rates of Necrotizing Enterocolitis: A Retrospective Cohort Study

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Keywords: Preterm infant; Necrotizing enterocolitis (NEC); Probiotic; Microbiome; Dysbiosis.

Abbreviations: AAP: American academy of pediatrics; BW: Birth weight; CMH: Children's mercy hospital; DOL: Day of life; GA: Gestational age; HM: Human milk; IND: Investigational new drug; NMA: Network meta-analysis; NEC: Necrotizing enterocolitis; NICU: Neonatal intensive care unit; NMA: Network meta-analysis; NPO: nil per os / nothing by mouth; PMA: Post-menstrual age; RCT: Randomized controlled trial; SGA: small-for-gestational age; TLR4: Toll-like receptor 4; TPN: Total parenteral nutrition.

Abstract

Objective: Intestinal dysbiosis is believed to be a contributing factor in the development of Necrotizing Enterocolitis (NEC), a severe gastrointestinal disease that disproportionally affects preterm infants. Routine probiotic administration of bacterial strains associated with gastrointestinal health have been shown to reverse gut dysbiosis and decrease NEC, infection, and death. Our objective was to determine the effect of implementing as standard of care the provision of a multi-strain probiotic supplement containing *Bifidobacterium lactis* (BB-12®), *Bifidobacterium infantis* (BB-02®), and *Streptococcus thermophilus* (TH-4®) on NEC in preterm infants.

Methods: Preterm infants born <32 weeks gestational age (n=78) were provided the probiotic supplement above until 33 weeks post-menstrual age. The comparison group (n=215) was a mix of historical patients, who would have been eligible for the study, and contemporary patients, who did not receive probiotic due to intermittent product unavailability. Those in the probiotic group were routinely monitored for evidence of probiotic sepsis.

Results: Infants who received the probiotic supplement had an 8% incidence of NEC (Bell Stage 2 and 3) compared to 13% in the comparison group, a 38% reduction (p=0.208, Cohen's d=0.30). Although the study was not powered to detect a reduction in NEC, and the result did not reach statistical significance, probiotic supplementation may have a clinically significant effect of reducing NEC. There were no cases of probiotic sepsis.

Conclusion: A multi-strain probiotic provided as standard of care appeared to reduce NEC in preterm, critically ill infants treated in our NICU without finding safety concern.

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Introduction

The microbiome of term, vaginally delivered, human milk-fed infants is considered optimal because they have the lowest rates of morbidity and mortality, including Necrotizing Enterocolitis (NEC) [1]. Their microbiome is characterized by a predominance of commensal bacteria – *Bifidobacterium* and *Lactobacillus* [2,3]. Alterations in the microbiome (dysbiosis) in preterm infants in commonly accepted to be a contributing factor to the development of NEC [1,3,4]. Dysbiosis is characterized by less strain diversity, more facultative anaerobes (e.g., *Enterococcus*, *proteobacteria*), which are potentially pathogenic, and a decrease in commensal anaerobes (e.g., *Bifidobacterium*) [2,3,5]. Dysbiosis has been shown to upregulate Toll-Like Receptor 4 (TLR4) [5,6]. TLR4 activation induces epithelial injury and apoptosis, compromising intestinal barrier integrity [6]. Accordingly, strategies to mitigate NEC include efforts to modify the gut microbiome with commensal bacteria using probiotics.

A recent Randomized Controlled Trial (RCT) found that probiotic supplementation reduced gut dysbiosis in preterm infants by increasing beta diversity (p=0.004) and increasing relative abundances of commensal bacteria (*Bifidobacterium* and *Lactobaccillus*) [7]. Probiotics containing commensal anerobes (i.e., *Bifidobacterium*) have been found effacious in reducing infant mortality and morbidity, including reduction in NEC, in preterm infants [3,4,8,9]. In two RCTs, a three-strain combination containing *Bifidobacterium lactis* (BB-12®), *Bifidobacterium infantis* (BB-02®), and *Streptococcus Thermophilius* (TH-4®) resulted in statistically significant reductions in NEC (16.4% to 4%, p=0.03 [10] and 4.4% to 2%, p=0.03) [11]. This probiotic combination was recommended for prevention or reduction of NEC by two expert groups (the American Gastroenterological Association and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition) [12-14]. Most recently, in late 2025, a quality improvement initative found that this exact strain combintion reduced NEC by more than 80% in preterm infants < 32 weeks Gestational Age (GA) [15].

Based on the available evidence in 2021, we chose to implement this same three-strain combination of bacteria as standard of care at Children's Mercy Hospital in Kansas City, Missouri. Providing treatment as standard of care is a way to shorten the time between new evidence and its implementation, thereby ensuring benefit sooner. Nevertheless, it is important to continue adding to the available evidence, including continuing evaluation of safety. Here we describe the effect of providing this three-strain probiotic as standard of care on the development of NEC in preterm infants admitted to our Neonatal Intensive Care Unit (NICU), and our evaluation of safety.

Methods

Study design

This was a nonrandomized cohort study with both prospective and retrospective aspects. Before starting this project, we completed a systematic literature review and an institutional probiotic product market analysis. We matched scientific evidence to market availability and evaluated product quality by the manufacturer. We implemented routine probiotic supplementation as a new standard of care in May 2021, a process comparable to a Quality Improvement (QI) project, but that included assessments for probiotic sepsis and periodic review of outcomes, comparable to a prospective clinical trial. We stopped probiotics in October 2023 when the product was removed from the market in response to a letter from the US FDA [16]. Before implementation, Children's Mercy Hospital Division of Neonatology, a level IV NICU in Kansas City, Missouri, approved this as a QI project, and later, the Children's Mercy Institutional Review Board (IRB) and the University of Kansas Medical Center IRB (Study00003376) approved this retrospective study for analysis of outcomes.

Under the new standard of care for routine probiotic supplementation, probiotics were administered to preterm infants born ≤33wks Gestational Age (GA) and tolerating ≥6ml of enteral feeding (human milk or formula) on or after Day of Life (DOL) 3. There were no restrictions on birth weight or medical diagnoses. This policy underwent approval by hospital leadership and the hospital Pharmacy and Therapeutics (P&T) committee. The P&T committee review was required, because we elected to have the probiotic supplement prepared in the pharmacy to ensure standardized preparation and administration and minimize the risk of cross-colonization. Parental consent prior to administration was not required since the intervention was a new standard of care. The probiotic was given until patients reached 33 wks Postmenstrual Age (PMA) or hospital discharge.

Every 6 months, one of the authors (LP) recorded probiotic product recipients and their incidence of sepsis (aerobic culture positive, anerobic culture positive, and culture negative), NEC (Bell Stage 2 and 3), and compliance metrics. Her findings were reported to and reviewed by the Neonatology division. These reports and review ensured ongoing oversight for any signal the product was unsafe, analogous to a Data Safety Monitoring Board for an RCT.

Study inclusion criteria for both the probiotic and comparison group were gestational age <32 wks, tolerance of ≥6 mL enteral feeding on or after DOL 3, and admission to our NICU by ≤DOL 7. Infants excluded from this study were ≥32 wks Gestational Age (GA), unable to tolerate at least 6 mL enteral feeding or admitted to our NICU after DOL 7.

The comparison group was a combination of historical patients (January 2017–April 2021), patients who were admitted following initiation of the new standard of care who would have been eligible for probiotic but did not receive it due to a temporary product backorder (October 2022 through January 2023), and patients meeting eligibility criteria after the probiotic product was removed from the market but before this retrospective analysis was conducted (November 2023–February 2024).

The probiotic supplement was a multi-strain product consisting of *Bifidobacterium lactis* (BB-12®), *Bifidobacterium infantis* (BB-02®), and *Streptococcus thermophilus* (TH-4®) (Abbott Nutrition, Columbus, OH). As mentioned in the introduction, it was chosen because it was shown to have favorable outcomes in prior studies and was recommended by more than one expert group. Also, its manufacturer had a robust quality monitoring system, along with a potency and purity guarantee maintained through the end of its shelf life. The probiotic was packaged in a single use sachet (0.5 gm) guaranteed to contain one billion Colony Forming Units (CFU) when stored as directed. The product was prepared per manufacturer instructions and administered once a day, with a feeding (Human Milk (HM) or formula) at a gravity rate.

We continued probiotic supplementation through October 2023, at which time the FDA issued a warning letter to health care professionals indicating that probiotics used to prevent or

treat disease were required to be administered only under an approved Investigational New Drug (IND) protocol [16] and the company ceased production.

Data collection

NEC diagnosis was collected from the electronic medical record. Clinicians used Bell's modified staging criteria for NEC diagnosis [17], and we include both NEC Stage 2 and 3 as our primary outcome. Birth and all other patient demographic and feeding data were collected from the medical record. For patients in the probiotic group, we collected the number of days the probiotic was received and the results of the evaluation for probiotic sepsis. For patients who developed NEC, we recorded NEC stage, age NEC occurred, transfusion history, days on Total Parenteral Nutrition (TPN), and the occurrence of bloody stools.

Statistical analysis

Statistical analysis was completed using SAS, Version 8.3 Update 7. Statistical significance was defined as a p-value ≤0.05. Differences between group means of the continuous variables were assessed using t-tests, and differences between group proportions of the categorical variables were assessed using chi-square tests. Cohen's d was calculated for effect size.

Results

A total of 293 infants were included in this study - 78 infants in the probiotic group and 215 infants in the comparison group, who did not receive probiotic supplementation. Table 1 summarizes the birth characteristics of the groups.

Table 2 summarizes the nutritionally relevant events during hospitalization, including the primary outcome of NEC. Except for use of mixed feedings (formula and human milk) (p=0.002) and intake of fortified human milk (p=0.016), there were no statistically significant differences between the groups in any nutritionally relevant events during hospitalization. For the primary outcome of NEC, there was a relative reduction of 38%, from an incidence of 13% to 8% in the probiotic group with a small effect size (p=0.208, Cohen's *d*=0.30). There were no cases of probiotic sepsis.

Table 1: Birth characteristics.

Birth Characteristics	Probiotic (n=78)	No Probiotic (n=215)
Gestational Age (wks), mean ± SD	26.7±2	27.3±2.1
Birth Weight (grams), mean ± SD	916±300	1031±360
Small-for-gestational age	14%	9%
Male	49%	62%
Maternal Age (years), mean ± SD	27.8±6.1	28.1±5.9
Black race	27%	26%
Caesarean section birth	77%	71%

Discussion

We found a 38% relative reduction in risk of NEC after implementing the provision of a multi-strain probiotic supplement containing *Bifidobacterium lactis* (BB-12®), *Bifidobacterium infantis* (BB-02®), and *Streptococcus Thermophilus* (TH-4®) as standard of care in very low birth weight, preterm infants. Although this was not statistically significant, the reduction in NEC was clinically relevant and safe based on the absence of sepsis from the probiotic. We were unable to include more than 78 infants in the probiotic group, because the probiotic was discontinued following an FDA requirement for an IND [16].

Table 2: Nutritionally relevant events during hospitalization.

Event	Probiotic (n=78)	No Probiotic (n=215)	p-value
DOL enteral feeding started, mean ± SD	3.7±3.5	4.2±3.2	0.201
Total TPN days 1, mean ± SD	22.1±14.3	25.8±18.1	0.073
Modified TPN days 2	20.5±11.3	22.6±14.4	0.182
Feed Type			
Infant Formula Only	1%	4%	0.226
Mixed Feeding (HM + Formula)	3%	16%	0.002*
Unfortified Human Milk (MOM/DHM)	18%	16%	0.735
Fortified Human Milk (MOM/DHM)	78%	63%	0.016*
Achieved ≥ 80ml/day within study period	83%	77%	0.23
Days probiotic received, mean ± SD	22±11.3	N/A	----
Bloody Stools 3	15%	17%	0.711
SIP	6%	10%	0.372
Death (any cause)	8%	4%	0.159
Probiotic Sepsis	0%	N/A	-----
NEC	8%	13%	0.208

DHM=Donor human milk; DOL: Day of life; HM: Human milk; MOM: Mother's own milk; NEC: Necrotizing enterocolitis; SIP: Spontaneous intestinal perforation; TPN: Total parenteral nutrition

*Statistically significant, p≤0.05

[1]Total number of TPN days received during birth hospitalization.

[2]TPN days during hospitalization but stopping day count at time of NEC (if applicable) to assess if TPN is a predictor of NEC.

[3]Anytime during birth hospitalization

There is an estimated 17-year lag between initial research findings and implementation [18]. After two randomized clinical trials using the same probiotic demonstrated a reduction in NEC [10,11], we chose to provide the probiotic as standard of care instead of conducting another RCT to ensure more infants received the benefit of probiotics. We believe our careful consideration of safety in the pre-implementation and implementation stages contributed to the absence of probiotic sepsis in our study. Evidence for safety is important because one reason probiotic use in preterm infants was slowed and eventually halted nationally was because there was insufficient evidence of their safety in small preterm infants [16,19]. Our process for ensuring safety (preparation in the pharmacy, 6-month data monitoring reports, and ensuring sepsis monitoring captured probiotic bacteremia) provides a model for future studies. Our finding of safety with probiotic supplementation is consistent with two separate meta-analyses published in 2025 [5,20].

The three-strain probiotic we used was found in two RCTs to result in a statistically signficiant reduction in NEC [10,11]. Both prior studies included preterm infants who had demographics similar to our cohort, i.e., birth weight <1500gm, gestational age <32 weeks, ~70% born by cesearan section, and with similar proportions for sex and race [10,11]. Like our cohort, >90% of the infants studied by Jacobs et al [11] were fed human milk, however, both their control group and probiotic group had lower NEC rates than in our cohort (4.4% and 2%, respectively). In contrast, only ~45% of the control group in Bin-Nun et al [10] received human milk. Compared to our findings, their control group had a higher incidence of NEC (16.4%) and their probiotic

group a lower incidence (4%). In a recent quality improvement study, this probiotic reduced NEC by 80%, and following FDA market removal, NEC incidence rebounded from 0.6% to 3.8% (p=0.045) [15].

Within six months of beginning probiotics as standard of care, a Network Meta-Analysis (NMA) concluded that a probiotic containing the commensal anerobe *Lactobacillus*, either in combination with *Bifidobacterium* or a prebiotic, is likely the most effective, but that other strain mixtures, including our three-strain combination, were efficacious [21]. Among these, they cited positive results found in the two RCTs that used the supplement we chose to provide as standard of care [10,11]. The meta-analysis reassured us of our decision to use probiotics as standard of care.

In the same 6-month period, a report by the American Academy of Pediatrics (AAP) cautioned use of probiotics in preterm infants to mitigate disease (i.e., NEC) given the lack of a pharmaceutical grade product, conflicting efficacy data, and the potential risk of probiotic sepsis [19]. The AAP clinical report especially cautioned on probiotic supplementation in extremely low birth weight infants (birth weight <1000 gm) citing limited data for this population in the early 2000s, when much of the research was conducted. Following a review of these reports and discussion, we chose to proceed with probiotics as standard of care without a minimum birth weight requirement.

Most of our cohort were fed fortified human milk, either unpasteurized Mother's Own Milk (MOM) or pasteurized Donor Human Milk (DHM), and only 1% of the probiotic group and 4% of the comparison group did not receive any human milk. Human milk compared to infant formula has consistently been shown to be protective against NEC [1,3,22-26], however, NEC still occurs in infants fed exclusively human milk [22,24,27]. One accepted mechanism for human milk protection is its provision of commensal bacteria [2,22], the mechanism addressed by probiotics. On the other hand, bioactive nutrients in human milk also play important roles in intestinal physiology and influence the incidence of NEC [28]. Because the amounts of nutrients in human milk are influenced by maternal nutrient intake, this could contribute to the variability in NEC incidence among human milk-fed infants. Although 95% of our cohort received some human milk, our NEC rate was higher than reported in several other studies of human milk-fed preterm infants [11,24].

Infants in the probiotic group were somewhat smaller and of lower GA, which could have increased their risk of developing NEC, yet they had a lower incidence of NEC. The finding of a higher mean proportion of patients who received fortified human milk in the probiotic group is consistent with the somewhat higher proportion who achieved an enteral intake ≥ 80ml/kg in the first 28 days of life, because our feeding protocol indicated fortification when infants reached an intake of 80ml/kg. This finding, and the somewhat fewer days on TPN, could be a sign that infants receiving probiotics tolerated enteral feeding better and had their enteral feeding advanced somewhat faster than the comparison group. The window of time for the comparison group was chosen to ensure the same protocol for enteral feeding.

The minimum duration of probiotic exposure to confer protective effects is unknown. In our study, infants in the probiotic group who developed NEC did so after receiving probiotic for a mean of 22±11.3 days. Participants who received the same probiotic in previous studies developed NEC after receiving probiotic for ~16 days [11] and ~20 days [10]. From the published data, we also estimated that NEC occurred on average at ~31 weeks [11] and ~32.5 weeks [10] PMA in those studies compared to ~32.5 weeks in our cohort. The PMA of onset among the three studies is remarkably similar and within the cited mean window for the development of NEC [3].

Limitations

The group fed probiotics was limited in size due to the product being discontinued, which limited our ability to conclude with certainty that the probiotic used reduced NEC, however, we did find a clinically meaningful reduction in NEC. Another possible limitation is that we did not obtain data on antibiotic exposure during probiotic supplementation. Antibiotics alter the microbiome and may perpetuate dysbiosis [29] thereby influencing the capacity for probiotics to reduce NEC.

Conclusion

We used strict criteria to justify the use of probiotics as standard of care in our Level IV NICU. After the implementation of probiotics, we found a clinically relevant reduction in NEC (Bell's Stage 2 and 3) with a combination of *Bifidobacterium lactis* (BB-12®), *Bifidobacterium infantis* (BB-02®), and *Streptococcus thermophilus* (TH-4®). We found no concerns for safety in critically ill infants <32 weeks gestational age with careful clinical monitoring for probiotic sepsis, addressing the AAP concerns [19] about the need for evidence in this population.

Author declarations

Statement of ethics

This study was reviewed and approved by the Children's Mercy Hospital IRB and the University of Kansas Medical Center IRB, Study00003376. on November 5, 2024. This is an IRB-approved retrospective study, all patient information was de-identified and patient consent was not required. Patient data will not be shared with third parties.

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All authors collaborated on study design as part of LP's PhD project. LP conducted the research in collaboration with SEC, BG, DNC, LT, JMD, and non-author Clinician-Scientists at Children's Mercy Hospital. LP analyzed the data. LP wrote the first draft of the paper with the assistance of SEC. LP and SEC had primary responsibility for final content. All authors read, reviewed and approved the final manuscript. None of the authors have any interests, financial or otherwise, that could be perceived as influencing the submitted work. LBP became an employee of Abbott during her time as a PhD candidate; however, this work was completed outside her job responsibilities and was collaborated on with non-Abbott employees. LT is a consultant for Nutricia North America.

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Author contributions

All authors collaborated on study design as part of LP's PhD project. LP conducted the research in collaboration with SEC, BG, DNC, LT, JMD, and non-author Clinician-Scientists at Children's Mercy Hospital. LP analyzed the data. LP wrote the

first draft of the paper with the assistance of SEC. LP and SEC had primary responsibility for final content. All authors read, reviewed and approved the final manuscript.

Data availability

Data described in the manuscript, code book, and analytic code were available with permission to LP, however, they will not be made available because of protected health information that is not approved by Children's Mercy Hospital.

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