JPPT | Commentary

Utilization of a High Potency Probiotic Product for Prevention of Necrotizing Enterocolitis in Preterm Infants at a Level IV NICU

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ABSTRACT Necrotizing enterocolitis (NEC) is a serious gastrointestinal disease that can be seen in premature infants with high risk for morbidity and mortality. There is currently no US Food and Drug Administration (FDA) medication approved for the prevention of NEC. Despite great heterogeneity among available studies, large meta-analyses of clinical trials have demonstrated the efficacy of multiple-strain probiotics in reducing NEC and all-cause mortality. In 2020, Medical City Dallas's Level IV neonatal intensive care unit (NICU) implemented a probiotic protocol for NEC prevention. As a result, a reduction in NEC was observed, with no occurrence of probiotic-related sepsis.

ABBREVIATIONS CFU, colony-forming unit; cGMP, current good manufacturing practice; ELBW, extremely low birth weight; ESPGHAN, European Society for Paediatric Gastroenterology Hepatology and Nutrition; FDA, US Food and Drug Administration; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; RCT, randomized controlled trial; RPS, routine probiotic supplementation; VLBW, very low birth weight

KEYWORDS *Bifidobacterium*; *Lactobacillus*; necrotizing enterocolitis; premature infant; probiotic; *Streptococcus thermophilus*; Visbiome

J Pediatr Pharmacol Ther 2023;28(5):473–475

DOI: 10.5863/1551-6776-28.5.473

Background

Necrotizing enterocolitis (NEC) is a serious gastrointestinal disease that can be seen in premature infants, particularly those with very low birth weight (VLBW, <1500 grams) or extremely low birth weight (ELBW, <1000 grams). Necrotizing enterocolitis has been associated with high mortality (15%–30%, or up to 45%–100% in ELBW infants), and long-term neurodevelopmental disabilities.[1–3] Premature infants make up 70% of NEC cases nationwide.[4] The high incidence of NEC is due to intestinal immaturity, increased intestinal permeability, and an immature immune system that occurs due to prematurity.[5] Numerous studies have shown that intestinal dysbiosis precedes the onset of NEC in preterm infants due to the lack of diversity in their bacterial colonies, the reduced amount of bacterial species present within their intestinal tract, and the higher proportion of potentially pathogenic strains.[6] The modified Bell's staging criteria classified NEC into 3 stages based on the degree of severity: stage 1 (suspected), stage 2 (definite), and stage 3 (advanced).[7] To prevent microbiota dysbiosis, more than 10,000 preterm infants had participated in randomized controlled trials (RCTs) focused on probiotic usage worldwide, suggesting that probiotics could potentially reduce the incidence of NEC, sepsis, and mortality.[4,5,8]

Probiotics are defined as live microorganisms that can produce a beneficial effect on a host when taken in adequate amounts.[9] These benefits include improvements to the host's microbiota, adjustments in their inflammatory and immunological responses, and improvements to their intestinal barrier.[9] Probiotics can be beneficial in working against the predisposing factors of NEC in preterm infants. However, probiotics are considered dietary supplements in the United States and are therefore not subjected to the US Food and Drug Administration (FDA)'s approval process.

Based on a growing body of evidence, in 2020, the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) published a strain-specific systematic review to provide guidance on the selection of probiotics in preterm infants for NEC.[5] The ESPGHAN position paper conditionally recommended the use of multi-strain probiotics with strains that have proven effectiveness in NEC, mortality reduction, and an established safety profile in a large number of VLBW infants.[5,10] Van Den Akker et al[5] also recommended a combination of *Bifidobacterium infantis*, *B lactis*, and *Streptococcus thermophilus* to reduce NEC stage 2 or greater. This recommendation was based on the ProPrems trial conducted in 10 perinatal centers in Australia and New Zealand. Jacobs et al[11] evaluated the

effect of probiotic combination (*B infantis*, *B lactis*, and *S thermophilus*) in 1099 VLBW infants and concluded that the incidence of NEC stage 2 or greater was reduced in the infant group assigned to receive the probiotic combination. In addition, ESPGHAN provided a dose ranging from 1 to 6 billion colony-forming units (CFUs) per day but did not clearly indicate an optimal starting dose or length of treatment. All recommendations had very low to moderate certainty of evidence due to the availability of current research.[5] They also noted the importance of using probiotics manufactured using the current good manufacturing practice (cGMP) to reduce the chances of probiotic bacteremia due to product contamination. In contrast to ESPGHAN, the American Academy of Pediatrics did not support the routine use of probiotics in ELBW preterm infants due to the lack of FDA-regulated pharmaceutical grade products, conflicting data on safety, and the potential harm of probiotics. Despite significant heterogeneity among studies, large meta-analyses of clinical trials have demonstrated the efficacy of multiple-strain probiotics in reducing NEC and all-cause mortality.[6,12] In addition, Deshmukh and Patole[2] recently attempted to provide real life data by conducting a systematic review of 30 non-RCTs from 18 countries for the implementation of routine probiotic supplementation (RPS) in preterm infants (<37 weeks of gestation). The meta-analysis concluded that RPS was associated with significantly reduced NEC stage 2 or greater, length of stay, all-cause mortality in preterm infants, and NEC stage 2 or greater in ELBW infants. Hence, many neonatal units have adopted probiotics as a standard prophylaxis for preterm infants.

Medical City Dallas is an 899-bed, acute care hospital, including a full-service children's hospital with a 108-bed Level IV neonatal intensive care unit (NICU) and Level IV Maternal Designation. Our Level IV NICU provides the highest level of care for infants of all gestational ages who are critically ill and/or have complex conditions. The multidisciplinary team works closely with VLBW and ELBW infants, the population with the highest risk of developing NEC. Medical City Dallas's NICU was actively searching for a multi-strain liquid probiotic product manufactured using cGMP to avoid powder usage and to reduce the risk of contamination. After thoroughly reviewing multiple products, their corresponding evidence, and the available dosage forms, Visbiome (ExeGi Pharma LLC) was selected as the probiotic of choice to be added to the NEC reduction process improvement plan. Visbiome contains multiple bacterial strains that align with those recommended by ESPGHAN and meets cGMP requirements.[5,8,13] Education on Visbiome was subsequently provided to all medical, nursing, and pharmacy staff prior to protocol implementation.

Visbiome has been subjected to over 70 published clinical studies totaling 5000 adults and pediatric patients, making it a widely studied probiotic.[9] Visbiome contains 8 strains of live, lyophilized, probiotic bacteria (*Lactobacillus paracasei, L plantarum, L acidophilus, L helveticus*, *B lactis, B longum, B breve,* and *S thermophilus*) called the De Simone Formulation, which is the same formulation found in VSL #3 before January 31, 2016. The De Simone Formulation has been shown to reduce days of hospitalization in infants and aid in managing microbial imbalances associated with irritable bowel syndrome, ulcerative colitis, antibiotic-associated diarrhea, pouchitis, and hepatic encephalopathy.[9,14] The probiotic strains in Visbiome are non-pathogenic, non-toxigenic, and generally recognized as safe food ingredients. Visbiome comes in 4 different formulations, but our Level IV NICU has focused particularly on the infant drops formulation, which contains 50 billion CFUs per 5-mL bottle, for its ease of administration with feeding along with its potential low risk of contamination. Sinha et al[14] conducted a randomized, double-blind, placebo-controlled trial to compare RPS using the De Simone Formulation to placebo in 1340 low birth weight infants. The trial results showed that the RPS group had a reduction in neonatal sepsis incidence by 21% after 30 days of use, with a significant reduction found in the subgroup of infants between 1500 and 2000 grams. Survival analysis showed a 15-day delay in the onset of sepsis in the intervention arm, and this disease-free window during the first 28-day period was extremely crucial for neonatal survival.[14]

Our Current Practice and Experience

Medical City Dallas's NICU has been administering Visbiome infant drops for infants who are <1500 grams and/or less than 34 weeks' gestation since 2020. Premature infants receive 2 billion CFUs, or 0.2 mL, with feeding every day until 36 weeks' gestation or discharge, whichever occurs first. There is an average of 350 premature infants who are less than 34 weeks' gestation seen per year. We have noticed a remarkable decrease in NEC incidence within our NICU after implementing Visbiome to our feeding protocol. Prior to the practice change in 2020, our rates were as high as 10%, but now we are consistently seeing rates as low as 0.8% in the recent years of 2020 and 2021. In addition, no cases of probiotic-related bacteremia or fungemia sepsis occurred post-protocol implementation.

Conclusion

The inclusion of a high potency probiotic product with beneficial bacterial strains in combination with a standardized feeding protocol has reduced NEC incidence in preterm infants at a Level IV NICU. Future well-designed and carefully conducted RCTs are warranted to assess the effectiveness of probiotic utilization for NEC prevention. Long-term implications from neurodevelopment, safety, and microbiome alteration perspective will need to be addressed in future research.

Article Information

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Disclosure. The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

Disclaimer. This research was supported in whole by HCA Healthcare and/or an HCA Healthcare affiliated entity. The views expressed in this publication represent those of the authors and did not necessarily represent the official views of HCA Healthcare or any of its affiliated entities.

Acknowledgments. The authors thank Rebecca Gaffney and Anthony B. Nguyen at Medical City Dallas Hospital for their assistance with the implementation of the Visbiome infant drops.

Submitted. November 2, 2022

Accepted. December 6, 2022

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