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Bifidobacterium longum subsp *infantis* (EVC001) is associated with reduced incidence of necrotizing enterocolitis stage ≥2 and bloody stools in premature babies

Kristin Sohn [1,2]✉, Victoria Palacios [3] and Reese Clark[4]

OBJECTIVE: To utilize an evidence-based probiotic protocol to achieve a 50% reduction in necrotizing enterocolitis (NEC) ≥ stage 2 and bloody stools.

STUDY DESIGN: From January 2022 through September 2023, daily enteral *Bifidobacterium longum* ssp. *infantis* EVC001 (*B. infantis* EVC001) was administered to babies ≤ 33 6/7 weeks gestation until 36 weeks post menstrual age. Feeding tolerance and complications were compared to babies admitted during the prior two-year period. Fisher's Exact test was used to analyze proportional data and *t* test was used for continuous variables.

RESULTS: A total of 265 babies received EVC001, and a total of 277 babies formed the pre-probiotic cohort. Probiotic use was associated with decreased NEC ≥ stage 2 ($p = 0.0058$), reduced bloody stools ($p < 0.0001$), decreased time to full enteral feeds ($p < 0.0001$), and decreased total parenteral nutrition (TPN) days ($p < 0.0001$).

CONCLUSION: Administration of *B. infantis* EVC001 was associated with a decrease in NEC, a decrease in bloody stools, and improvement in feeding tolerance in premature babies.

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INTRODUCTION

The premature gut microbiome exhibits delayed colonization and decreased biodiversity when compared to full term infants, and premature babies are at high risk for dysbiosis due to multiple factors, including cesarean section, prolonged hospitalization, poor nutrition, and perinatal antibiotics. The composition of the gut microbiota can play a role in gut mucosal inflammation. Dysbiosis is associated with chronic, life-long diseases, including diabetes, inflammatory bowel disease, and cancer [1]. More immediately, dysbiosis, particularly the loss of protective *B. infantis*, is associated with distal colon inflammation and hematochezia [2] and is known to precede the development of necrotizing enterocolitis (NEC), with a relative increased abundance of Proteobacteria and a decreased abundance of Firmicutes and Bacteroidetes prior to disease onset [3–5].

NEC is a devastating gastrointestinal disease with high mortality and life-long complications. The spectrum of severity of NEC is clinically staged using Modified Bell Staging Criteria, which ranges from mild intestinal disturbance (stage 1 A) to clinical illness with the presence of pneumatosis intestinalis on abdominal radiograph (stage 2) to fulminant intestinal necrosis with pneumoperitoneum (stage 3B) [6]. Mortality for NEC ≥ stage 2 is 23.5%, while mortality of surgical NEC is 34.5% [7]. For survivors, complications include poor growth and gastrointestinal problems, such as strictures, adhesions, cholestasis, short bowel syndrome, intestinal failure, and feeding difficulties [8]. Furthermore, the inflammatory cascade that begins in the gut also affects brain development through the gut-brain axis [9], leading to high risk for neurodevelopmental impairment [10–12]. Among survivors, neurodevelopmental disability is between 24.8 and 61.1% [6]. Most survivors report long-term complications that impact their physical and mental health, their social experiences, and their overall quality of life [13].

Probiotics are foods or supplements that contain live microorganisms intended to maintain or improve health. The dysbiosis in premature babies offers a unique time point to affect life-long health with the use of probiotics. Human milk oligosaccharides (HMOs), the third largest component of human milk, are only digestible with the help of glycosidases possessed by specific bacteria, and *Bifidobacterium longum* ssp. *infantis* EVC001 (*B. infantis* EVC001) specifically, has the unique ability to consume HMO as its sole carbon source [14]. As *B. infantis* consumes HMOs, it secretes indole-3-lactic acid (ILA) as a by-product of catabolism, and this molecule acts as an anti-inflammatory protective metabolite in the preterm gut [15, 16]. Probiotics containing *B.infantis* offer gastrointestinal protection from illness and disease due to the organism's anti-inflammatory properties and ability to decrease intestinal permeability [17]. It has been shown that probiotics containing *B. infantis* may be more beneficial for preterm infants than probiotics not containing *B. infantis* [18].

In January 2022, after completing a quality review and careful review of the literature, an evidence-based probiotic protocol was implemented to augment our existing standardized human

[1]Department of Pediatrics, University of Nevada School of Medicine, Reno, NV, USA. [2]Pediatrix Neonatology of Nevada, Reno, NV, USA. [3]University of Nevada School of Medicine, Reno, NV, USA. [4]Pediatrix Center for Research and Education, Sunrise, FL, USA. ✉email: kristin.sohn@pediatrix.com

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milk-based feeding protocol. Our goal was to determine if our change in care would reduce feeding intolerance and achieve a 50% reduction in bloody stools and NEC ≥ stage 2 within two years of protocol implementation. By including hematochezia as a primary outcome, this study sought to add to the scarcity of published literature regarding the effects of probiotic use on hematochezia.

METHODS

This was a single-center prospective cohort study of probiotic use in preterm babies at Renown Children's Hospital NICU, a 49-bed level III. Pediatric cardiologists are readily available, but as there are no local pediatric cardiothoracic surgery services, most patients with significant congenital heart disease are referred prenatally or transferred shortly after birth. Renown has a formal affiliation with the University of Nevada, Reno School of Medicine, approved by the Nevada System of Higher Education Board of Regents, which facilitates the integration of clinical services, medical education and research.

Ethics approval and consent to participate

The study was approved by the University of Nevada, Reno Institutional Review Board (IRB), ID 1777112-3, and the Pediatrix Clinical Research Department, ID 770695214. A waiver of informed consent was approved by the IRB, as probiotics were adopted as standard of care in our unit; however, written parental consent for probiotics was obtained from all participants to facilitate risk and benefit discussion with families. No parents declined probiotic treatment. The study was performed in accordance with the Declaration of Helsinki and in accordance with relevant guidelines and regulations.

Intervention

B. infantis was chosen due to its dominance in the microbiome of healthy breastfed babies [19]. EVC001 (Infinant Health, Davis, California, USA) was chosen for both its possession of the complete gene cluster for H5 ABC-type transporter, which binds to core HMO structures and completely metabolizes them [20], and the company's high quality manufacturing process, cold chain distribution practices, safety testing, ensured CFUs, and availability of ready-to-use single-dose vials, which decreases risk of contamination. Previous studies have demonstrated that EVC001 is safe, well tolerated, and efficient at colonizing the preterm gut [21–24].

In January 2022, our NICU implemented a new treatment plan to promote intestinal health. Enteral EVC001 was administered at a dose of 0.5 mL [8 billion Colony Forming Units (CFUs) of *Bifidobacterium longum* subspecies *infantis* suspended in 0.47 mL medium chain triglyceride oil] per day with the first or second feed of day shift. EVC001 was ordered to start when enteral feeds were initiated and was continued until babies were 36 weeks post menstrual age (last dose at 35 6/7 weeks). EVC001 was held during any period of NPO (nil per os). A sample size of 228 was calculated for an 80% power to achieve a 50% reduction in bloody stools with a p value of 0.05.

The study was originally planned, approved, and funded for two years, ending December 2023; however, due to an abundance of caution, probiotic administration was discontinued on September 29, 2023, after the U.S. Food and Drug Administration (FDA) issued a warning regarding possible risks of probiotic use in premature babies. There were no adverse events related to probiotic use in our unit during the period of probiotic implementation.

Study populations

All patients admitted to the NICU were screened for the inclusion criteria of gestational age ≤ 33 and 6/7 weeks. Exclusion criteria were the presence of a lethal medical condition or a congenital gastrointestinal anomaly. Data was collected from electronic medical record review and cross-referenced with Pediatrix Clinical Data Warehouse, retrospectively for the pre-implementation control cohort and in real-time for the probiotic cohort.

The control cohort consisted of 253 babies born from January 2020 through December 2021. Both cohorts received a human milk-based diet, consisting of either maternal breast milk or donor human milk. A standardized feeding protocol was consistent between the two cohorts. Trophic human milk feedings were started at 20 ml/kg/d at the discretion of the attending neonatologist, and advanced by 20 ml/kg each day, except for days on which feeds were fortified, to a goal of 150–160 mL/kg/d. Babies <1250 g at birth received five days of trophic feeds before advancement and received fortification with Prolacta Human Milk Fortifier. Prolacta +6 was added when babies were not achieving optimal z-score growth on full enteral feeds of Prolacta +4. Babies ≥1250 g received fortification with Enfamil liquid Human Milk Fortifier. Donor Human Milk and Prolacta Human Milk Fortifier were weaned to bovine milk-based fortifier and/or formula over a three-day period, starting at either 34 weeks corrected gestation age (CGA) or 5 days of life, whichever occurred later. Full enteral feeds were achieved when supplemental intravenous nutrition was discontinued, between 130-140 ml/kg/d of feeding volumes.

Covariables

Variables analyzed as potential predictors, confounders, or modifiers included gestational age at birth, birth weight, sex, small for gestational age (SGA) status, mode of delivery, maternal antibiotics (defined as ≥1 dose prior to delivery), maternal betamethasone (defined as ≥1 dose prior to delivery), days of antibiotics in the immediate post-natal period, and hemodynamically significant congenital heart disease, defined as moderate to large cardiac shunts with increased pulmonary flow or ductal dependent lesions.

Outcomes

Primary outcomes were bloody stools at any time during NICU hospitalization and NEC ≥ stage 2. Bloody stools were diagnosed visually with confirmatory hemoccult testing if diagnosis was uncertain. The diagnosis of NEC was determined using the modified Bell staging criteria [6, 25, 26]. Initial diagnosis was made by the on-service attending neonatologist, and the diagnosis was confirmed by a radiologist and one additional neonatologist. Cases of spontaneous intestinal perforation, defined as gastrointestinal perforation without signs of NEC, were excluded. Secondary outcomes included NPO days, total parenteral nutrition (TPN) days, days to achieve full enteral nutrition, late antibiotic days (after initial infectious screen period), late onset sepsis, urinary tract infections (UTI), tracheitis, meningitis, length of hospital stay, and CGA at discharge.

Statistical analysis

Data was initially analyzed by descriptive statistics. Subsequent comparison of outcome measures was analyzed with Microsoft Excel (Version 16.82, 2024) using the Fisher's Exact test for proportional data and two-sided student t test for continuous variables. Two-sided p values < 0.05 were considered statistically significant. Cohorts were divided into subgroups based on gestational age.

RESULTS

Figure 1 shows the patient flowchart. Of 937 babies admitted to the NICU and screened for eligibility during the probiotic implementation period, 265 babies met the inclusion criteria of being <34 weeks gestational age at birth. Data collection and analysis was completed in 250 babies. Of the seven babies transferred out of our facility, all received EVC001, but they were not included in data analysis due to incomplete data availability for primary and secondary outcomes. Reasons for transfer included post-hemorrhagic hydrocephalus (3), PDA coil treatment (3), and insurance coverage (1); none of the babies transferred had documented bloody stools, NEC, *Bifidobacterium* positive blood cultures, or other infections prior to transfer. Of the 7 deaths in the probiotic cohort, 3 received at least one dose of EVC001. Deaths were due to neurological or respiratory complications of prematurity (pulmonary hemorrhage, $n = 1$; respiratory failure, $n = 3$; severe intraventricular hemorrhage, $n = 3$). None of the deaths in the probiotic cohort were due to NEC or sepsis.

EVC001 was started at a mean day of life 1.9 (range 0–19; delays were due to prolonged NPO status). The mean duration of EVC001 was 30 days (range 3–73), with 7586 total EVC001 days completed during the study.

There were no significant differences in baseline characteristics between the two cohorts (Table 1). The mean gestational age at

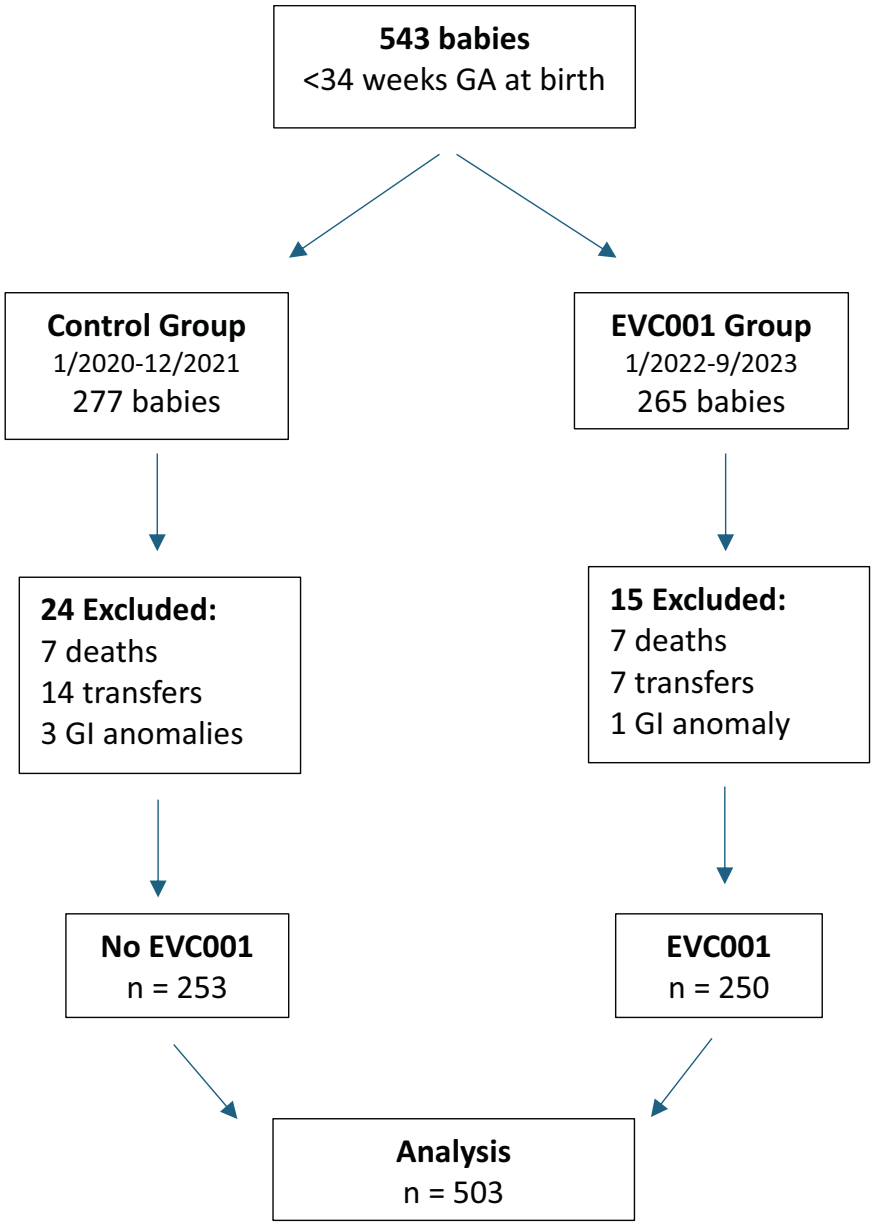

Fig. 1 Flow diagram of babies included in analysis. The number of patients admitted during each cohort period with a gestational age less than 34 weeks and the reasons for exclusion in final analysis. GA gestational age. GI gastrointestinal.

birth was 31 weeks in the control cohort and 31.1 weeks in the probiotic cohort. The mean birthweight was 1579 g in the control cohort and 1568 g in the probiotic cohort. Most babies in both cohorts were male, born via cesarean section, and received antenatal steroids. Hemodynamically significant congenital heart disease consisted of moderate to large patent ductus arteriosus with signs of myocardial dysfunction on echocardiogram and 1 baby with pink Tetralogy of Fallot in each cohort.

Babies who required gastrostomy tubes (GTs) for discharge due to poor PO feeds were excluded from two outcomes, length of hospital stay and CGA at discharge, but they were included in the analysis of all other outcomes for both cohorts. There were 11/253 (4%) babies in the pre-implementation cohort and 16/250 (6%) babies in the post-implementation cohort who required GTs.

Regarding primary outcomes (Table 2), there was a significant reduction in incidence of visually bloody stools in the probiotic group, a decrease from 19 to 4.8% ($p < 0.0001$). Incidence of NEC stage ≥2 was also significantly decreased in the probiotic cohort, from 4.7 to 0.4% ($p = 0.0058$; relative risk (RR) 0.084, 95% CI = 0.011 to 0.064). The relative risk reduction (RRR) was 94.6% and the number needed to treat (NNT) based on this outcome was 23 (95% CI = 14.1 to 62.7). The incidence of NEC in very low birth weight (<1500 g) babies was also significantly decreased in the probiotic cohort, from 7.7 to 0.9% ($p = 0.012$, RR 0.12, RRR 88, NNT 15, 95% CI = 8.3 to 66.0). Of the 12 NEC cases in the control cohort, one resulted in death due to NEC. The singular case of stage 2 NEC in the probiotic cohort was a 657 g 25-week male who received prolonged antibiotics due to thrombus in the setting of methicillin-susceptible *Staphylococcus aureus* sepsis and did not receive EVC001 until day of life 19 due to clinical instability, hypotension, and prolonged NPO. He was treated with bowel rest and antibiotics and survived to discharge.

Regarding secondary outcomes (Table 2), there was a statistically significance decrease in day of life to achieve full enteral feeds, with a mean of 16.2 days in the control cohort and 12.7 days in probiotic cohort ($p < 0.0001$). In direct correlation,

Table 1. Characteristics of babies in both cohorts.

Characteristics	Control cohort ($n = 253$)	Probiotic cohort ($n = 250$)	p value
Gestational age at birth, weeks, mean (IQR[a])	30.95 (29.0–33.0)	31.14 (29.6–33.1)	0.39
Birth weight, grams, mean (IQR[a])	1579 (1199–2002)	1,568 (1233–1862)	0.80
Male sex, %	58.5	58.0	0.91
SGA, %	7.5	9.6	0.26
<1250g BW, %	26.5	27.2	0.86
Antenatal steroids, %	87.4	82.4	0.12
Antenatal antibiotics, %	45.8	40.0	0.19
Cesarean delivery, %	66.8	68.0	0.77
Admission antibiotic days[b], mean	1.53	1.32	0.08
Hemodynamically significant congenital heart disease[c], %	8.7	10.4	0.52

[a]IQR = interquartile range, Q1–Q3.
[b]Days of antibiotics in immediate post-natal period.
[c]Moderate to large cardiac shunts with increased pulmonary flow or ductal dependent lesions.

Table 2. Primary and secondary outcomes of babies in the two cohorts.

	Control cohort ($n = 253$)	Probiotic cohort ($n = 250$)	p value
Primary outcomes			
Bloody stools	45 (17.8%)	12 (4.8%)	<0.0001
NEC ≥ stage 2	12 (4.7%)	1 (0.4%)	0.003
Secondary outcomes			
DOL to full enteral feeds	16.2	12.7	<0.0001
Customized TPN days	14.1	9.8	<0.0001
NPO days[a]	1.2	0.8	0.27
Late antibiotic days	2.2	1.3	0.09
Late onset sepsis	8 (3.2%)	9 (3.6%)	0.37
UTIs	7 (2.8)	7 (2.8)	0.42
Tracheitis	11 (4.3%)	5 (2%)	0.14
Meningitis	3 (1.2%)	0	0.25
Duration of hospital stay, mean days	48.3	47.1	0.59
CGA at discharge, mean weeks	38.13	38.16	0.9

[a]NPO days after initiation of enteral feeds.

there was also a statistically significant decrease in mean TPN days in the probiotic cohort, from 14.1 days to 12.7 days ($p < 0.0001$). Unexpectedly, there was a statistical significance in the day of life enteral feeds were started, with a mean of 1.3 days in the control cohort and 0.9 days in the probiotic cohort ($p = 0.0008$). There was no statistically significant difference in mortality, NPO days, late antibiotic days, late onset sepsis, UTI, tracheitis, or meningitis.

Subgroup analyses showed consistent results (Table 3), with decreases in bloody stools, day of life to full enteral feeds, and TPN days amongst all subgroups. These decreases reached statistical significance in all but the smallest gestational subgroup (24-26 weeks). Babies born at 31 weeks completed gestation (control $n = 31$; probiotic $n = 38$) had a statistically significant decrease in mean duration of hospital stay, from 49 days to 41 days ($p = 0.03$) and CGA at discharge from 38.5 weeks to 37.4 weeks ($p = 0.03$).

There were no cases of confirmed probiotic sepsis; however, one patient had a positive peripheral blood culture for *Bifidobacterium longum*, which may have represented probiotic bacteremia. The patient was a 28-week baby who had a negative blood culture on admission and received 2 doses of EVC001 before being made NPO on day of life 3 due to decreased perfusion and metabolic acidosis. The baby then received 36 h of empiric broad-spectrum antibiotic coverage, and the blood culture grew *B. longum* on culture day 5. Antibiotics were not restarted, and a repeat blood culture remained negative for *B. longum*. While the symptoms were clinically attributed to a large PDA, symptoms resolved with indomethacin, and the positive blood culture was thought to be a contaminant, it is important to note this positive blood culture could have represented true probiotic bacteremia.

DISCUSSION

The implementation of a probiotic protocol in our NICU was associated with a 90% reduction in rates of NEC ≥Stage 2 in babies born ≤33 6/7 weeks. These results support the findings of many randomized control trials and metanalysis that have shown probiotics are associated with reduced NEC [27–30]. Although some studies suggest the superiority of multi-strain probiotics, others have suggested that *Bifidobacterium* alone offers a unique benefit to the premature gut [31] and probiotics containing *B. infantis* are more beneficial than probiotics without *B. infantis* to premature babies [15]. *B. infantis* EVC001 has been associated with significant reductions in the incidence of NEC in very low birth weight infants [20]. Our study adds to that existing research to support *B. infantis* EVC001 as a means to decrease NEC in premature infants.

Our probiotic protocol was also associated with improved feeding tolerance, as a cohort and across all gestational ages, evidenced by decreased bloody stools, fewer mean TPN days and fewer mean days to full enteral feeds. Some studies have found that probiotics are associated with decreased time to reach full enteral feeds [32, 33], while others have found no effect on TPN days [34].

Dysbiosis has been cited as a risk factor for bloody stools [35], but published data is limited regarding the association between probiotics and bloody stools in preterm babies.

Two studies have shown a trend toward decreased bloody stools with the use of probiotics, one using *Lactobacillus rhamnosus* in babies born at 24 to 31 weeks gestation [36] and

Table 3. Primary and secondary outcomes by gestational age subgroup analyses.

	24-26 weeks Control Probiotic $n = 24$ $n = 19$	27-29 weeks Control Probiotic $n = 52$ $n = 52$	30-31 weeks Control Probiotic $n = 50$ $n = 64$	32-33 weeks Control Probiotic $n = 126$ $n = 115$
Bloody stools	3 (12.5%) 3 (15.8%) *NS*	12 (23%) 2 (3.8%) $p = 0.003$	10 (20%) 2 (3.1%) $p = 0.003$	20 (15.8%) 4 (3.5%) $p = 0.001$
NEC ≥ stage 2	1 (4.2%) 1 (5.3%) *NS*	6 (11.5%) 0 p=0.01	1 (2.0%) 0 *NS*	3 (2.4%) 0 *NS*
DOL to full enteral feeds	28.1 23.0 *NS*	20.3 16.4 $p = 0.004$	17.1 12.6 $p = 0.0004$	12.0 9.4 $p = 0.0007$
Customized TPN days	24.0 23.0 *NS*	19.7 13.4 $p < 0.0001$	13.7 8.9 $p < 0.0001$	10.0 6.5 $p < 0.0001$
Duration of hospital stay, mean days	98.3 100.9 *NS*	70.9 70.0 *NS*	50.3 44.7 $p = 0.05$	31.8 31.9 *NS*
CGA at discharge, mean weeks	40.1 41.1 *NS*	38.9 38.7 *NS*	38.3 37.5 $p = 0.027$	37.5 37.7 *NS*

another using a multi-strain probiotic of *Bifidobacterium* and *Lactobacillus* in babies less than 29 weeks gestation [32]. This is the first study to evaluate bloody stools as a primary outcome after introduction of *B. infantis*. Prior to probiotic implementation, our NICU had a high baseline rate of bloody stools in babies < 34 weeks, which often prompted NEC evaluations, including bowel rest and broad-spectrum antibiotics. Due to this, our protocol inclusion criteria was broadened to include babies born at 32 and 33 weeks completed gestation.

Dysbiosis has been implicated as a cause of distal colon inflammation and resultant hematochezia, and a significant reduction of *Bifidobacterium* specifically has been linked to hematochezia in babies [2]. Although the exact mechanisms are not completely understood, *B. infantis* colonization has been shown to decrease enteric inflammation [37, 38], reduce colonic mucin degradation [39], and accelerate microbiome maturation, leading to improved metabolic and immune function and increased epithelial integrity [16, 40]. Overall, *Bifidobacterium* has been shown to assist in accelerating and maintaining the protective barrier function of the gastrointestinal tract.

Regarding our case of potential probiotic bacteremia, premature babies are inherently at risk for bacterial translocation due to decreased epithelial integrity, altered microbiome, and compromised intestinal immunity [41]. It follows that probiotic bacteremia is an expected side effect and risk of probiotic therapy. Although probiotic sepsis is rare, there have been multiple case reports, the majority of which recovered with or without antibiotic treatment [42–44]. The low risk of probiotic sepsis must be compared to the relatively large reduction in NEC burden achieved by efficacious probiotic strains [45]. In contrast to the high pathogenicity and virulence of Proteobacteria, *Bifidobacterium* are slow growing, commensal, and beneficial organisms with low pathogenicity. They are early colonizers of the neonatal gut and act to strengthen the neonatal gut barrier, assist in maturation of the intestinal immune system, and promote anti-inflammatory immune responses [5, 16, 46, 47].

Although metanalyses have shown that probiotics decrease late onset sepsis [28, 48], this study did not find a decrease in late onset sepsis. A reduction in both meningitis (from 3 cases to 0) and tracheitis (from 11 cases to 5) was observed, but neither was of statistical significance. Metanalyses have also shown that probiotic use leads to a decreased duration of hospital stay for premature babies [10]. Although there was a significant decrease in hospital stay for babies born at 31 weeks completed gestation, there was not a significant decrease in duration of hospital stay for other gestational ages or in the probiotic cohort as a whole.

As a single-center prospective cohort study, there are inherent limitations to this study. Rates of NEC vary year to year; our rate has been consistently 4–6% over the last decade. Another potential confounding variable is changes in clinical practice over time. Our feeding protocol and use of human milk remained consistent over both cohort periods. The decision to initiate enteral feeds is up to the discretion of the neonatologist on service, and there was a reduction in the mean day of life that feedings were initiated from the control cohort to the probiotic cohort (from 1.3 to 0.9 days, $p = 0.0009$). Early human milk enteral feedings are thought to be protective against NEC by stimulating hormone secretion, mucosal cell signaling, and peristalsis [49], and although statistically different, both cohort means fall within the first 48 h after birth and can therefore be considered early feeding [50, 51].

We were fortunate to have strong nursing support for probiotic use in our NICU, and many bedside nurses reported that babies were less fussy and had improved stooling patterns and consistency during the probiotic implementation period. This also represents a potential source of information bias, as bedside nurses may have been less likely to categorize stools as bloody.

Our probiotic protocol was initially planned and funded for 24 months, but probiotic use was ceased on September 29, 2023, when the FDA issued a warning regarding the risk of invasive, potentially fatal disease caused by use of probiotics in preterm infants. *Bifidobacterium* species are traditionally considered ubiquitous nonpathogenic commensal organisms and have low MICs (<0.5 mg/L) to beta-lactam antibiotics [52], which makes them less pathogenic than the bloom of Proteobacteria that precedes NEC. As previously discussed, probiotic sepsis is a rare occurrence, and most cases result in recovery [41]. On the other hand, NEC is a leading cause of death in premature babies and is a devastating disease with high mortality, morbidity, and neurodevelopmental disability [53]. Additionally, surgical NEC has been shown to have the highest total cost of all complications of prematurity [54].

Two proven and widely accepted interventions to decrease the risk of NEC are utilizing human milk [55, 56] and a standardized feeding protocol [57]. Data from meta-analyses support probiotic utilization as an intervention to decrease the risk of NEC. In 2023, just prior to the FDA warning, approximately 39% of NICUs in the U.S were using probiotics [58]. At that time, the percentage was steadily increasing; however, since the FDA warning, many NICUs have reported cessation of probiotic use.

This study demonstrates the benefits that probiotics can confer to premature babies. Use of a *B. infantis* probiotic significantly decreased NEC ≥ stage 2, bloody stools, days to full enteral feeds, and TPN days. Our data supports continued research to determine optimal formulations and dosing of probiotics. The overwhelming amount of current evidence and our data demonstrate a positive

risk benefit ratio for the use of probiotics in preterm babies. The data supports finding a path to gain FDA approval for probiotics to be used in preterm babies to prevent intestinal dysbiosis, and thereby decrease the incidence of NEC, its profound short and long-term complications, and improve the quality of life for patients beyond their NICU stay.

DATA AVAILABILITY

Data is summarized in Tables 1, 2, 3, with full details omitted to protect patient privacy and identification. Detailed information is available upon request.

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AUTHOR CONTRIBUTIONS

KS designed study, acquired funding, curated, analyzed and interpreted data, wrote manuscript, and approved final version. VP drafted initial manuscript and approved final version. RC supervised study, analyzed data, edited manuscript, and approved final version.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Kristin Sohn.

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