HHS Public Access

Author manuscript

Semin Perinatol. Author manuscript; available in PMC 2024 February 01.

Published in final edited form as:

Semin Perinatol. 2023 February ; 47(1): 151689. doi:10.1016/j.semperi.2022.151689.

Probiotics for Prevention of Necrotizing Enterocolitis: Where do we stand?

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Abstract

In this review, we provide a historical perspective on probiotic use in preterm infants. We review recent data on the treatment effects of probiotics on necrotizing enterocolitis, sepsis, and mortality. We highlight guidance statements from professional societies and organizations, discussing key points within the context of the currently available evidence from both randomized trials and cohort studies. Finally, we summarize experiences from several North American centers that have reported on the routine use of probiotics, including our center. Our goal is to highlight some of the considerations and complexities surrounding routine probiotics use in preterm infants.

Introduction

Probiotics are live microorganisms, that, when consumed in the appropriate amount, confer health benefits to the host[1]. Probiotic supplementation in preterm infants has been extensively studied for its use in the prevention of necrotizing enterocolitis (NEC), a devastating gastrointestinal disease that primarily affects preterm infants, causing significant morbidity and mortality[2]. In pre-clinical models of NEC, probiotic supplementation reduced the risk of developing NEC-like injury by close to 50%[3]. Through *in vitro* and *in vivo* studies, we have learned that probiotics can improve the health of the immature intestine through several mechanisms, including enhancement of the intestinal barrier, production of short-chain fatty acids such as butyrate, competition with pathologic bacteria, down-regulation of pro-inflammatory genes, upregulation of cytoprotective genes and regulation of cellular immunity[4].

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Disclosure:
The authors report no conflicts of interest.

History of Probiotic Use in Preterm Infants

One of the initial reports of routine probiotic administration to preterm infants was in 1999[5]. Dr. Angela Hoyos reported that daily administration of *Lactobacillus acidophilus* (*L. acidophilus*) and *Bifidobacterium infantis* (*B. infantis*) to all infants admitted to a neonatal intensive care unit (NICU) lead to a significant reduction in NEC and NEC-associated mortality[5]. Since that time over 10,000 preterm infants have been randomized in trials to assess the effects of probiotics administration in preterm infants[6]. There is significant methodological heterogeneity between each trial, with regards to the population studies and product used. Even with this heterogeneity, pooled risk ratios favor the use of probiotics for the prevention of NEC, mortality, and late-onset sepsis[4]. Additionally, effect estimates for probiotic administration on the risk of NEC demonstrate low statistical heterogeneity (I^2 <20%). Despite the breadth of pre-clinical and clinical evidence supporting the use of probiotics for the prevention of NEC in preterm infants, the routine administration of probiotics to preterm infants continues to be controversial. Two important factors that mitigate routine use are the lack of an FDA-approved pharmaceutical-grade probiotic in the United States and concerns for risks of probiotic-associated sepsis[7]. Some of these concerns are highlighted in statements from professional societies, that we discuss in detail below.

Statements from Professional Societies

Several professional societies have published statements and guidance on the use of probiotics in preterm infants. In 2019, the Canadian Pediatric Society (CPS) published a statement in which they recommended using caution when considering the use of probiotics in preterm infants. CPS encouraged the promotion of breastfeeding and stated that probiotic administration may be considered in preterm infants who are at risk for NEC and have a birthweight greater than 1 kilogram (kg)[8]. In 2020, the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) published consensus-based guidance for the use of probiotics in preterm infants. In this report, ESPGHAN recommended that if probiotics are used, the product should be manufactured according to current good manufacturing practices, hospital laboratories should be able to detect probiotic bacteremia and clinicians should be prepared to share the potential risks and benefits of probiotics with the parents of preterm infants[9]. The panel also conditionally recommended the use of *Lactobacillus rhamnosus GG* (LGG) with a dose of 1×10^9 colony forming units (CFUs) to 6×10^9 CFUs or a combination of *B infantis*, *Bifidobacterium lactis (B. lactis)* and *Streptococcus thermophilus (S. thermophilus)* with a dose of $3–3.5 \times 10^8$ CFUs for each strain (low certainty of evidence)[9]. Additionally, the panel highlighted the lack of evidence for optimal initiation and length of treatment[9].

In 2020, the American Gastroenterological Association published recommendations on the use of specific probiotics in preterm infants for the prevention of NEC[10]. Specifically, they recommended using a combination of Lactobacillus species and Bifidobacterium species such as *L rhamnosus* ATCC 53103 and *B infants*; or *L casei* and *B breve*; or *L rhamnosus*, *L acidophilus*, *L casei*, *B infants*, *B bifidum* and *B longum;* or *L acidophilus* and *B infants*; or *L acidophilus* and *B bifidum;* or *L rhamnosus* ATCC 53103 and *B longum Reuter* ATCC

BAA-999; or *L acidophilus*, *B bifidum*, *B lactis* and *B longum;* or *B lactis* or *L reuteri* or *L rhamnosus*[10]. This recommendation was based on moderate/high-level evidence[10].

In 2021, the American Academy of Pediatrics (AAP) Committee on Fetus and Newborn published a statement on the use of probiotics in preterm infants. In this statement, the AAP did not recommend universal administration of probiotics to preterm infants, especially those with a birth weight of less than 1 kg. This statement was based on several concerns including the lack of an FDA-approved pharmaceutical-grade product in the United States, the potential risk for harm in this population (e.g. sepsis), and conflicting evidence on efficacy and safety[7]. Four key points in the statement included:

1. Emphasis on the uncertainty of evidence and recommendations against universal use in preterm infants.
2. Clinicians should discuss the risks and benefits with parents and develop local guidelines.
3. The potential for contamination should be recognized and mitigated.
4. Centers should monitor outcomes.

In August of 2021, the NEC Society released a Statement on Probiotics (https://necsociety.org/probiotics/). The statement advised that “probiotics can be considered as a strategy to help reduce the risks of NEC and death in very low birth weight infants (VLWBs).” Consistent with the AAP, the statement also emphasized the importance of informing families about the risk and benefits of probiotics and the collection of data to track and understand the effect of probiotics for centers adopting use. Additionally, the NEC Society provides resources for clinicians, such as a probiotic information sheet for parents.

Evidence from RCT and observational studies

In the section below, we place the aforementioned guidance statements within the context of available data.

Randomized Trials

Since 2002, over 56 RCTs which include over 10,000 preterm infants have been conducted to assess the effect of routine probiotics administration in preterm infants[16]. Bin-Nun et al conducted an RCT in Israel, with 145 preterm infants, in which the mixture of *B infantis*, *S thermophilus,* and *B bifidus* lead to a reduction in the incidence of NEC[11]. Dani et al conducted an RCT in Italy which included 585 preterm infants in which supplementation with LGG resulted in a reduction in the incidence of NEC[12]. Additionally, an RCT with 367 preterm infants in Taiwan evaluated *L acidophilus* and *B infantis* supplementation in preterm infants and found a reduction in NEC[13]. The PiPS trial was a large RCT of *Bifidobacterium breve* supplementation in very preterm infants which was conducted in the United Kingdom. There were 1315 preterm infants randomized. This trial found no difference in outcomes of NEC (RR 0.93; 95% CI, 0.68–1.27), sepsis (RR 0.97; 95% CI, 0.73–1.29) or mortality (RR 0.93; 95% CI, 0.67–1.3) before hospital discharge[14]. It is important to note that in every study site in this trial (24 hospitals), there were patients randomized to the control

group who became colonized by the probiotic being studied. By 2 weeks of life, 20% of patients in the control group were colonized with *B breve,* and by 36 weeks post-menstrual age (PMA), 49% had been colonized. This contamination may have diminished the results toward the null. The ProPrems trial was a large RCT conducted in Australia and New Zealand which included 1099 very low birth weight infants who had significant exposure to a human milk diet. In this RCT, supplementation with *B infantis*, *S thermophiles,* and *B lactis* was evaluated. This trial found no difference in late-onset sepsis with probiotic supplementation but did find that the incidence of NEC decreased by over half (RR 0.46; 95% CI, 0.23–0.93) among infants randomized to receive probiotics, compared to placebo. However, in a prespecified subgroup analysis, among infants who were born before 28 weeks gestation with a birth weight of less than 1 kg, estimates suggested less efficacy of probiotic supplementation on the rate of NEC[15]. While there is significant heterogeneity between these trials, several systematic reviews, and meta-analyses that have evaluated these RCTs have found that probiotic supplementation favors the prevention of NEC in preterm infants[4,16–19]. For instance, one systematic review reported that the cumulative pooled risk ratio for NEC, strongly favors probiotic administration for the prevention of NEC (RR 0.54; 95% CI, 0.45–0.65), mortality (RR 0.76; 95% CI, 0.65–0.89) and invasive infection (RR 0.89; 95% CI, 0.82–0.97)[16] (Figure 1).

Observational Studies

In addition to RCTs, it is important to evaluate observational studies. This is because treatments demonstrating efficacy in an RCT may not show effectiveness when implemented in a routine clinical setting. A systematic review and meta-analysis of 30 good quality non-randomized studies which included over 77,000 infants in 18 different countries found that probiotic supplementation reduced the risk of NEC (OR 0.6; 95% CI, 0.5–0.73)[20]. There may also be differences in outcomes based on the type of probiotic used---whether it is a single strain or multiple strain[21].

Routine Use of Probiotics

Variability in Probiotic Use within Large Cohorts Around the World

There is substantial variability in the use of probiotics in NICUs worldwide. A survey from 2016 estimates that approximately 14% of NICUs in the United States use probiotics[6]. While a report from a large collaborative database estimates that 10% of extremely preterm infants in the United States receive probiotics during their NICU admission[6]. In Canada, 21% of infants with gestational age less than 29 weeks receive probiotics[22]. In the United Kingdom, 12% of NICUs use probiotics[23], while 68% of NICUS in Germany[24] and 100% of NICUs in New Zealand report the use of probiotics[25]. These data may not reflect current practice.

Experiences of Selected Centers

Below are four examples of protocols and experiences of implementing probiotic supplementation from NICUs in North America, which are provided as examples of protocols used and associated results.

1. Sunnybrook Health Sciences Centre NICU in Toronto, Ontario, Canada, is a tertiary level, 42-bed unit which cares for approximately 300 very low birth weight infants each year. Between 2003–2014, the rate of NEC among VLBW infants was about 5%. This NICU began the administration of *Lactobacillus reuteri* DSM 17938 suspension (BioGaia, Ferring, Stockholm, Sweden) to infants <33 weeks' gestation. Patients received probiotic supplementation from the first day of life or the first day of admission (for outborn patients). In addition, these infants were fed an exclusive human milk diet with either maternal breastmilk or donor breastmilk and a feeding protocol was used to advance enteral feeds. NEC rates decreased from 4.4% to 1.7%. There was no reduction in mortality and no adverse events occurred[26]. Adherence to guidelines was tracked and was ~100%.

2. Oregon Health & Science University NICU in Oregon, Washington, United States, a level-IV NICU. The unit began supplementation with *B infants* EVC001 (Evivo; Evolve BioSystem) to infants with a birthweight <1500 grams after their third day of life. Infants received 8 billion CFU of *B infantis* suspended in 0.5 ml of medium-chain triglyceride oil daily via a gastric tube before morning feed. From June 2018 to July 2019 probiotic supplementation was started at feeding volumes of 80–100 ml/kg/day and in August 2019 the protocol was revised, and probiotic supplementation was started on the second day of trophic feeding. *B infantis* was given daily until 34 weeks post menstrual age or for a minimum of 2 weeks, whichever was longer. In addition, these infants received a human milk diet and their feedings were advanced based on an established feeding protocol.[27] The probiotic product was produced in a dedicated facility as a Food for Special Dietary Use under US FDA guidelines. Pathogen testing and heavy metal analysis were performed by an independent third-party laboratory. The strain identity of each lot was confirmed by whole genome sequencing and a shelf-life testing program ensured the product contained 8 billion CFU per dose at the end of shelf life[27]. The incidence of NEC decreased from 11% to 2.7%, comparing pre- and post-probiotic supplementation periods. Additionally, NEC-related mortality decreased from 2.7% to 0%. These authors also found a similar reduction in NEC incidence and risk for ELBW infants[27].

3. University of Utah Medical Center NICU, Salt Lake City, Utah, United States, a 52 bed, level III unit that admits approximately 185 preterm infants born less than 33 weeks gestation per year. Infants with a birthweight < 1500 grams or gestational ages between 24 $^{0/7}$ weeks and 33 $^{0/7}$ weeks, age ≥ 72 hours old and tolerating over 6 ml per day of human milk for 24 hours, received Ultimate Flora Baby Probiotic (Renew Life, Palm Harbor, Florida, USA) until a corrected gestational age of 36 $^{0/7}$ weeks. Infants with lethal anomalies or significant gastrointestinal anomalies did not receive probiotic supplementation. Ultimate Flora Baby Probiotic contains four Bifidobacteria species (*Bifidobacterium breve HA-129*, *Bifidobacterium bifidum HA-132*, *Bifidobacterium infants HA-117*, *Bifidobacterium longum HA-135)* and *Lactobacillus rhamnosus HA-111,* for a total of 4 billion CFU per gram[28]. As described, safety measures included preparation outside of patient care areas,

use of gloves when handling suspension, and nursing staff required to perform hand hygiene after probiotic administration. The microbiology lab within the hospital was able to culture Lactobacillus and Bifidobacterium species from pediatric blood culture specimens. The annual rate of NEC decreased from 7% to 2%. Among infants born < 30 weeks' gestation, the annual NEC rate decreased from 10% to 2%. There was no change in the rate of surgical NEC. There were no cases of probiotic sepsis. There was one case of *Lactobacillus paracasei* and *Candida lusitaniae* sepsis in a patient born at 26 $^{1/7}$ weeks' gestation who had received three doses of probiotic and had a bowel perforation, this infant survived to discharge.

4. Emory University Midtown Neonatal Intensive Care Unit, Atlanta, Georgia, United States, a level-III NICU with 48 beds. Implementation of probiotic supplementation began in 2014 with Culturelle (LGG) at a dose of 2.5–5 × 10^9 CFU per day. The use of LGG supplementation was not associated with a reduction in NEC and there were no episodes of Lactobacillus sepsis, as previously reported[29]. Following this initial effort, antimicrobial stewardship through the Vermont Oxford Network iNICQ was pursued and probiotic supplementation was changed to *Lactobacillus reuteri* (BioGaia, Ferring, Stockholm, Sweden), due to ease of administration. The target population was infants with a birthweight < 1500 grams and gestation age <34 weeks with no congenital gastrointestinal anomalies. Supplementation with *L reuteri* occurred once a day once an infant began enteral feedings. The neonatal pharmacist prepared a patient-specific oral syringe of *L reuteri* and delivered it to the NICU within a plastic bag. Nurses used gloves at all times and washed their hands before and after handling the syringe with probiotics. Nurses did not touch vascular access devices or administer intravenous medications during times of probiotic administration. Probiotic syringes were discarded immediately following administration and surfaces were cleaned with hospital-grade wipes. Routine blood cultures are able to detect Lactobacillus in the local microbiology lab. The incidence of NEC decreased from a baseline of 13.2% to 5.6%, with a special cause reduction (8 points below the prior mean). There were no cases of Lactobacillus-sepsis. A summary of the implementation of *L. reuteri* supplementation within the context of quality improvement efforts to prevent NEC is shown in Figure 2.

Potential for contamination

Quality of product

In the United States, probiotics are manufactured as dietary supplements. Thus, the product itself may have variations in the CFUs and/or in the actual strain of bacteria within each product. In one study, 16 different commercially available probiotic products were analyzed to assess whether the probiotic product matched the bacterial species listed on the label[30]. Using culture and polymerase chain reaction, the authors only found 1 out of 16 products matched their label[30]. This study also found significant variability in the composition of the product, with one product not containing any of the species listed[30]. An expert panel

convened by the International Scientific Association for Probiotics and Prebiotics expressed concern that when probiotics are used with the intent to treat or prevent disease, the products administered must meet a higher standard of regulation[7]. While probiotics, which are consumed with the purpose of supporting a healthy intestinal microbiome, can be regulated like dietary supplements, this panel recommended that probiotics given to treat or prevent disease should meet the following regulatory requirements: a defined strain of bacteria, proof that microbe can be delivered at an efficacious dose at the end of shelf-life and a risk/benefit assessment based on RCT to meet regulatory standards for drugs[7].

Cases of contamination

There is concern for the risk of contamination of the probiotic product leading to serious infection in this vulnerable population. There have been several cases of probiotic-associated sepsis among infants receiving probiotics[12]. Thus, it is important for facilities that implement probiotic supplementation to develop guidelines to ensure safety measures[31] and for parents to be aware of these risks. When implementing probiotic supplementation, it is important to monitor the effects of this therapy. Centers should decide what parameters they would like to follow and implement a system to monitor these outcomes. We highlighted select safety measures among reports of probiotic use from 4 centers. If a unit chooses not to implement probiotic supplementation, then the following outcomes are still important to assess the incidence of NEC. Furthermore, there are many interventions that can help to decrease the rate of NEC such as promotion of breastfeeding, reduction of antibiotics when an infection is unlikely, elimination of acid-suppressing medications, and the use of a feeding protocol[31] (Figure 2), which should be pursued regardless of whether probiotic supplementation is implemented.

Conclusion

In conclusion, the use of probiotics to prevent NEC in preterm infants has been extensively studied. More clinical trials will likely not lead to a difference in pooled outcomes, given the large number of studies to date[32]. The decision of whether to implement probiotic supplementation is complex and will vary based on many factors such as a center's baseline NEC incidence and the status of other efforts to decrease the risk of NEC, such as the promotion of a human milk diet. While the lack of a pharmaceutical grade FDA regulated product is a valid concern, tens of thousands of infants have received probiotic products in trials and cohort studies with data demonstrating its beneficial effects and a reduction in the incidence of NEC, mortality, and late-onset sepsis. Thus, if a unit's NEC rate is particularly high, the benefit of initiating probiotic supplementation may outweigh the risks. Since the decision to pursue routine use of probiotics is a complex one, it is critical to involve multiple stakeholders, including the perspectives of families, as routine use is considered.

Acknowledgments

Supported in part by NIH K12 HD072245 to Maria Estefania Barbian.

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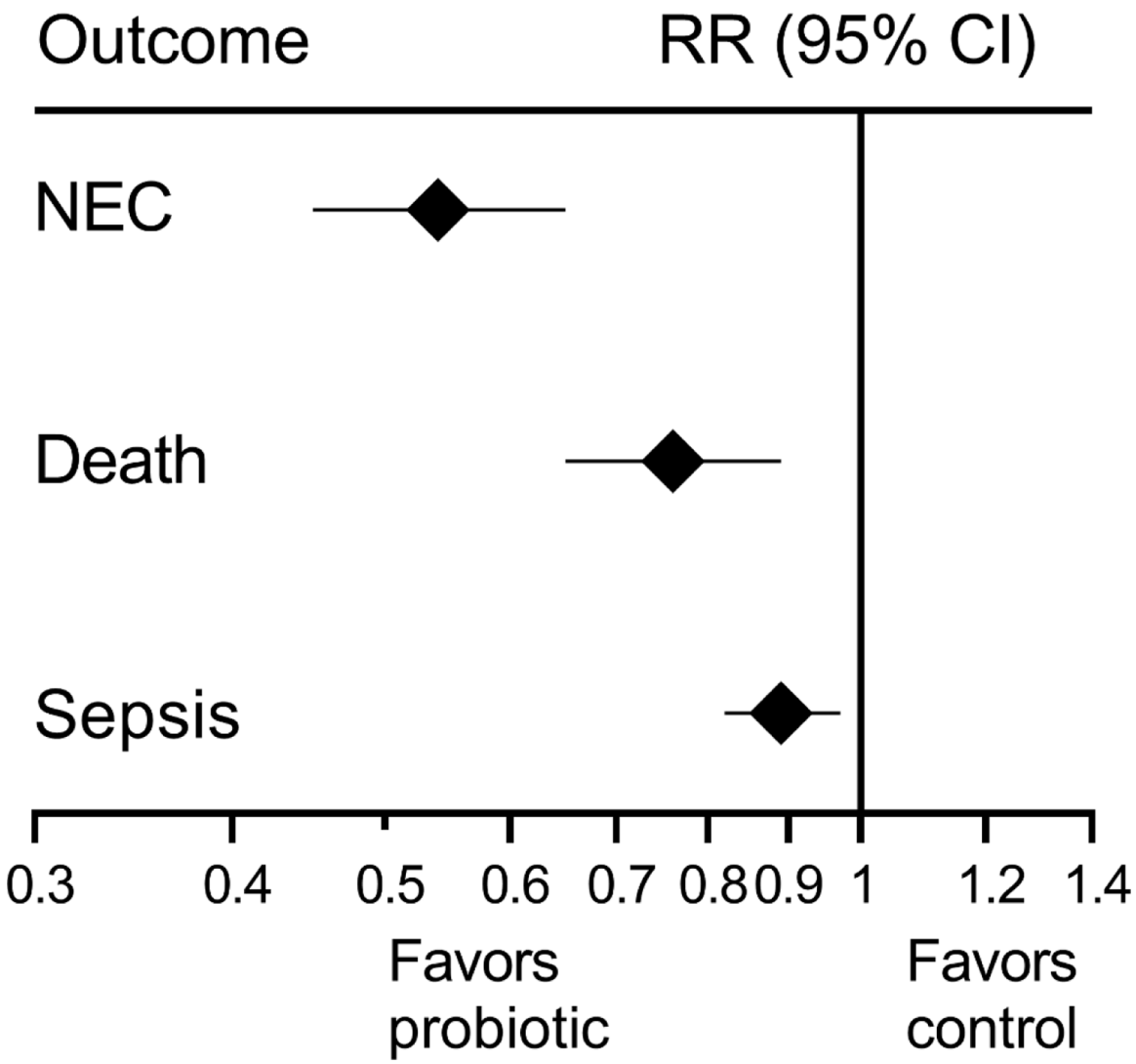

Figure 1. Effects of Probiotics on NEC, Sepsis, and Mortality.
Data are from a meta-analysis of RCT by Sharif et al.[16]

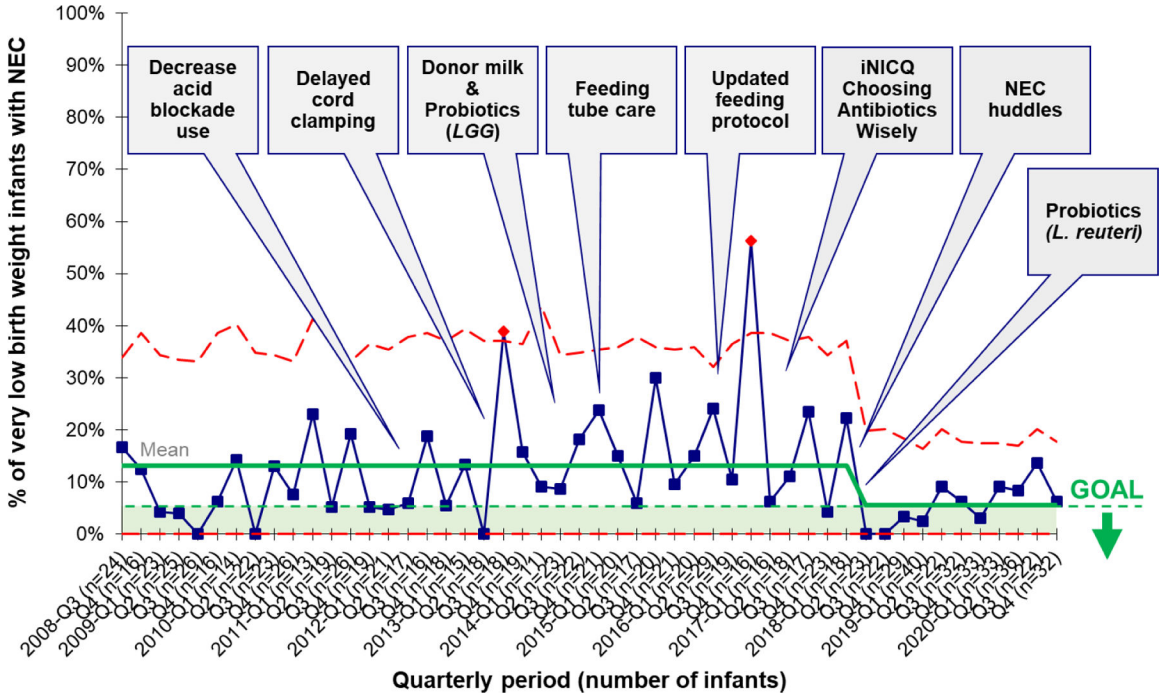

Figure 2. Probiotic supplementation as part of quality improvement efforts to reduce NEC.

Data from 1089 very low birth weight infants at Emory University Hospital Midtown from 2008 through 2020. The annotated statistical process control chart shows 3 sigma control limits (red dotted line) along with the mean incidence of NEC (solid green line), with individual data points (blue boxes) showing quarterly incidence. The goal denotes a target NEC incidence of < 5%. There was a reduction in the incidence of NEC from 13.2% to 5.6%, meeting special cause rules.