



# Use of Probiotics in Preterm Infants

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Probiotic products in the United States are available for use in the general category of dietary supplements, bypassing the rigor of the US Food and Drug Administration (FDA) approval process in safety, efficacy, and manufacturing standards. As a result, currently available probiotics lack FDA-approved drug labeling and cannot be marketed to treat or prevent disease in preterm infants, including necrotizing enterocolitis and late-onset sepsis. Despite lack of availability of a pharmaceutical-grade product, the number of preterm infants receiving probiotics in the United States and Canada is steadily increasing. According to recent reports from large collaborative databases in the United States, approximately 10% of extremely low gestational age neonates receive a probiotic preparation during their stay in the NICU, with wide variation in practice among units. In sum, more than 10 000 preterm infants have been enrolled in randomized clinical trials of probiotic supplementation worldwide. Methodologic differences among study protocols included different strains and combinations of therapy, masking of trials, and a priori definitions of the primary outcome measure. Large meta-analyses of these trials have demonstrated the efficacy of multiple-strain probiotics in reducing necrotizing enterocolitis and all-cause mortality, whereas the efficacy of single-strain probiotic preparations is less certain. In the absence of an appropriate medical-grade product in the United States, dietary supplement-grade probiotics, some of which have been the subject of recent recalls for contamination, are being prescribed. Given the lack of FDA-regulated pharmaceutical-grade products in the United States, conflicting data on safety and efficacy, and potential for harm in a highly vulnerable population, current evidence does not support the routine, universal administration of probiotics to preterm infants, particularly those with a birth weight of <1000 g.

## INTRODUCTION

There is a rapidly growing body of literature related to the developing intestinal microbiome and the use of probiotics and prebiotics in the maintenance of health and in the prevention and treatment of a number of disease states. In preterm infants, probiotics have been evaluated in

## abstract

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a number of randomized clinical trials for the prevention of severe necrotizing enterocolitis (NEC), late-onset sepsis, and all-cause mortality.<sup>1</sup> Despite significant differences in the combination of probiotic preparations used in these trials and the lack of availability of a pharmaceutical-grade probiotic product in the United States, the number of preterm infants receiving probiotics is steadily increasing. According to recent reports from large collaborative databases in the United States, approximately 10% of extremely low gestational age neonates receive some type of probiotic during their stay in the NICU, with wide variation in practice among units.<sup>2</sup> Although some infant formulas for term infants available in the United States now contain probiotics, formulas for preterm infants do not.

The purpose of this clinical report is to (1) highlight differences among commercially available probiotic preparations and the current (lack of) regulatory standards in the United States; (2) outline potential risks associated with the use of probiotics, supporting a cautionary approach with their routine use in preterm infants; (3) review the current evidence evaluating the use of probiotics in both prevention and treatment of NEC, late-onset sepsis, and mortality; and (4) highlight the need for pharmaceutical-grade probiotics that have been rigorously evaluated for safety and efficacy.

### **INTESTINAL MICROBIOME OF THE PRETERM INFANT**

Over the past decade, the role of the intestinal microbiome as a marker of health and disease in preterm infants has been increasingly recognized. Differences in the intestinal microbiota among infants born at term and those born preterm have been demonstrated, with fewer bacterial species, less diversity, and increased proportions of potentially pathogenic strains in preterm infants.

In addition, a number of factors are known to alter the microbiota in preterm infants, including mode of delivery, exposure to antibiotics, use of histamine antagonists, and diet (especially human milk, promoting prevalence of *Bifidobacterium* species).<sup>3,4</sup> Numerous studies have described intestinal dysbiosis preceding the onset of NEC in preterm infants, most commonly characterized by increased *Proteobacteria* and decreased relative abundancies of *Firmicutes* and *Bacteroidetes* species.<sup>5</sup> Proposed benefits of probiotics include preventing intestinal dysbiosis and assisting in metabolism of dietary nutrients, leading to byproducts essential for intestinal health. For example, *Bifidobacterium longum* subspecies *infantis* consumes human milk oligosaccharides, promoting a healthy intestinal microbiota.<sup>6</sup>

### **PROBIOTIC PREPARATIONS**

An expert panel convened by the International Scientific Association for Probiotics and Prebiotics defined probiotics as “live microorganisms that, when administered in adequate amounts, confer a health benefit to the host.”<sup>7</sup> In contrast, a prebiotic is a nutrient (oligosaccharides, for example) that can modify the gut microbiota. Importantly, this consensus panel proposed benchmark standards, recognizing differences in regulatory approaches for probiotics in different countries. Such differences have significant implications for interpretation of studies of probiotic supplementation and for recommendations for clinical use of probiotics in the NICU, including but not limited to the number of colony-forming units (CFUs) in the product, claims of benefit that are not strain specific, and the intent to support a healthy gut microbiota versus to prevent disease. Unlike products used as dietary supplements, probiotics labeled with the intent to treat are

required to meet higher regulatory standards. Indeed, the International Scientific Association for Probiotics and Prebiotics expert panel noted distinctive criteria for a “probiotic drug” with a specific indication for treatment or prevention of disease to require a defined strain(s) of live microbe, proof of delivery of viable probiotic at efficacious dose at end of shelf-life, and a risk/benefit assessment to justify use based on appropriate trials to meet regulatory standards for drugs.<sup>8</sup> It is important to note that none of the probiotic trials published to date in preterm infants for the prevention of NEC meet these criteria or level of evidence. In the United States, probiotic products are typically manufactured as a dietary supplement. If a probiotic is going to be marketed as a drug for treatment of a disease or disorder, it has to meet stricter requirements, including proof of safety and efficacy for its intended use through clinical trials and approval by the US Food and Drug Administration before it can be sold.<sup>9,10</sup>

Probiotic preparations may include a single bacterial strain or a combination of multiple strains. In addition to the particular bacterial species on the probiotic product label, the preparations are highly variable in terms of the number of viable microorganisms both at the time of manufacturing and after shelf storage.

Studies evaluating the efficacy of oral probiotics for the prevention of NEC have included single bacterial strains and mixtures of probiotics, often including *Lactobacillus*, *Bifidobacterium*, and/or *Saccharomyces* species. Despite the observation that infants receiving human milk are colonized with *Bifidobacterium breve* and *Bifidobacterium infantis*,<sup>6</sup> not all probiotic preparations contain these bacteria. It is also important to note that the duration of colonization of the gastrointestinal tract after

administration of products containing *Bifidobacterium* organisms is discontinued may only persist for a few months.<sup>11</sup> In a recent study, 16 different commercially available probiotic products were evaluated to determine if the bacteria species listed on the label matched that obtained by culture and polymerase chain reaction in the laboratory. Disturbingly, only 1 of the 16 products containing *Bifidobacterium* organisms matched the label exactly, and there was substantial variability in the composition of probiotics by lot and pill. One of the products tested did not contain any of the species listed.<sup>12</sup>

## SAFETY

The potential infectious risk associated with probiotic supplementation may be related to the risk of sepsis associated with the bacterial strain in the probiotic product that colonizes the infant or from contamination of the product with a pathogen during the manufacturing process.

Although there have been a few cases of probiotic-associated sepsis reported in neonates receiving *Lactobacillus rhamnosus GG*,<sup>13</sup> a meta-analysis including more than 5000 infants in randomized trials reported no systemic infection with the supplemental probiotic organism.<sup>14</sup> Although the risk appears to be low, the potential of bacterial cross-colonization among infants within a unit is also a potential risk.<sup>15</sup> In the Probiotics in Very Preterm Infants (PiPS) trial, *B breve* was identified as a cross contaminant in 37% of infants randomly assigned to the placebo control group.<sup>16</sup> However, it may be difficult to distinguish the change in the infant from the change in the resident flora of the NICU.

There have been several recent recalls of dietary supplement-grade probiotics for contamination, including with *Salmonella*, *Rhizopus*,

and *Penicillium* species.

Gastrointestinal mucormycosis has been reported in a preterm infant receiving contaminated ABC Dophilus Powder.<sup>17</sup>

The Agency for Healthcare Research and Quality recently issued a report on the safety of probiotics to reduce risk and prevent or treat disease including 622 studies. Unfortunately, one-third of the studies reported only nonspecific safety statements (such as “well-tolerated”), and the authors noted that adverse events were not well documented in the majority of studies. The conclusions of this report were as follows: “There is a lack of assessment and systematic reporting of adverse events in probiotic intervention studies, and interventions are poorly documented. The available evidence in [randomized controlled trials] does not indicate an increased risk; however, rare adverse events are difficult to assess, and despite the substantial number of publications, the current literature is not well equipped to answer questions on the safety of probiotic interventions with confidence.”<sup>18</sup> Other systematic reviews have similarly reported inadequate reporting of adverse and serious adverse events in studies evaluating probiotics in high-risk patients.<sup>19,20</sup>

## CURRENT EVIDENCE

### Probiotics for the Prevention of NEC

Several recent meta-analyses have evaluated the effects of probiotics to prevent NEC (Bell stage 2 or 3), late-onset sepsis, and death in preterm infants (typically very low birth weight infants). In the past 5 years, there have been numerous published systematic reviews.<sup>21,22</sup> Despite great heterogeneity among studies, the cumulative pooled risk ratio (RR) for NEC (including more than 10 000 infants) is strongly in favor of treatment with probiotics for the prevention of NEC.<sup>22</sup>

Three of the earliest randomized trials of probiotics in preterm infants suggesting benefit were conducted outside the United States. Bin-Nun et al<sup>23</sup> (Israel) evaluated the mixture of *B infantis*, *Streptococcus thermophilus*, and *Bifidobacteria bifidus*; Dani et al<sup>24</sup> (Italy) evaluated *L rhamnosus GG*; and Lin et al<sup>25</sup> (Taiwan) evaluated *Lactobacillus acidophilus* and *B infantis*. In each of these early studies, researchers found a reduction in the incidence of NEC in infants who were randomly assigned to receive probiotics when compared with those in the control group. These 3 studies and those that have followed have had wide heterogeneity of subjects and interventions and are also limited by the small number of infants with a birth weight less than 1000 g, the population at highest risk for NEC.

The studies are hindered by methodologic differences among study protocols, including different strains and combinations of therapy, masking of trials, and having an a priori definition of the primary outcome measure. It is not clear whether it is appropriate to pool data from trials by using different strains of probiotics, leading many investigators to urge caution in interpretation of meta-analyses of probiotics for the prevention of morbidity in preterm infants.<sup>26</sup>

The PiPS trial, conducted in the United Kingdom, was a large, multicenter, randomized controlled trial of *B breve* supplementation in 1315 very preterm infants. In contrast to some of the earlier trials conducted in low-resource settings, in the PiPS trial, researchers found no difference in the primary outcomes of NEC (RR, 0.93; 95% confidence interval [CI], 0.68–1.27), sepsis (RR, 0.97; 95% CI, 0.73–1.29), or death (RR, 0.93; 95% CI, 0.67–1.30) before hospital discharge.<sup>16</sup>

The ProPrams trial, conducted in 10 perinatal centers in Australia and New Zealand, evaluated the effect of

a probiotic combination (*B infantis*, *Streptococcus thermophiles*, and *Bifidobacterium lactis*) in 1099 very low birth weight (<1500 g) infants with high exposure to human milk. Although no difference in the primary outcome of late-onset sepsis was found in this trial, the incidence of NEC (Bell stage 2 or greater) was reduced (2.0% vs 4.4%) in infants randomly assigned to receive the probiotic combination (RR, 0.46; 95% CI, 0.23–0.93). However, in a prespecified subgroup analysis of infants born at <28 weeks' gestational age and with a birth weight of <1000 g, there was no difference in the rate of NEC.<sup>27</sup>

### Not All Probiotics Are Equal: Single Versus Multiple Strain

Multiple-strain probiotics were associated with a significant reduction in NEC (pooled odds ratio, 0.36; 95% CI, 0.24–0.53) and mortality (pooled odds ratio, 0.58; 95% CI, 0.43–0.79), whereas interventions using single-strain probiotic (usually *Lactobacillus*) had only a borderline effect in reducing NEC and no effect on mortality.<sup>28</sup> The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recently published a strain-specific systematic review of the efficacy of probiotics for prevention of NEC, highlighting important differences among various bacterial strains.<sup>29</sup>

### Probiotics for the Prevention of Culture-Proven Sepsis in Preterm Infants

In a 2014 Cochrane review that included 19 randomized or quasi-randomized trials of probiotic supplementation in 5338 preterm infants, there was no evidence of significant reduction of nosocomial sepsis (RR, 0.91; 95% CI, 0.80–1.03).<sup>14</sup>

### CURRENT PRACTICE GUIDELINES

The American Academy of Pediatrics, Canadian Pediatric Society, and ESPGHAN have all issued statements

advocating for caution with regard to routine use of probiotics in preterm infants. In 2010, an American Academy of Pediatrics clinical report cautioned that “the combinations of probiotics most convincing for NEC prevention are not available in the United States... not all probiotics have been studied; therefore, all probiotics cannot be generally recommended.”<sup>30</sup> In 2019, the Canadian Pediatric Society reaffirmed the lack of safety and efficacy data for infants with a birth weight of <1000 g as follows: “Probiotics may help to prevent NEC. Administering live microorganisms to preterm newborns should be approached with caution. Along with breastfeeding promotion, probiotics can be considered for the prevention of NEC in preterm infants >1 kg who are at risk for NEC. There is currently no data for infants weighing <1000 g.”<sup>31</sup> The ESPGHAN recently published consensus-based guidance for the potential use of probiotics in preterm infants.<sup>32</sup> With regard to the safety of administration of probiotics to preterm infants, the panel stipulated that local laboratories should have the ability to detect probiotic bacteremia, that only products manufactured according to current good manufacturing practices should be used, and that the potential risks and benefits are provided to parents of preterm infants. The panel conditionally recommended use of *L rhamnosus GG* (dose from  $1 \times 10^9$  CFUs to  $6 \times 10^9$  CFUs) or a combination of *B infantis*, *B lactis*, and *S thermophilus* (dose of 3.0 to  $3.5 \times 10^8$  CFUs of each strain) for the reduction of stage 2 or 3 NEC but noted low certainty of evidence. In addition, the panel recommended against the use of certain probiotic preparations on the basis of safety concerns and uncertainty of evidence. Finally, the panel noted the lack of evidence related to the optimal start and length of treatment. Most recently, the American Gastroenterological Association published recommendations using the Grading of Recommendations Assessment, Development and

Evaluation approach.<sup>33</sup> Similar to the ESPGHAN, the American Gastroenterological Association made a conditional recommendation for use of a certain probiotic strain or strain combination for the prevention of NEC in preterm infants but did not address the lack of a pharmaceutical-grade product for this population.

### PROS AND CONS OF ADMINISTRATION OF CURRENTLY AVAILABLE PROBIOTIC PRODUCTS

NEC remains a devastating disease in preterm infants, with high mortality and morbidity.<sup>34</sup> Given the number of publications in favor of using probiotics for the prevention of NEC, it is not at all surprising that the use of probiotics is increasing, even with the inherent limitations of dietary supplement-grade products that are currently available in the United States. A recent series of articles has eloquently outlined the pros and cons of routine usage of currently available probiotic products,<sup>35,36</sup> and other groups have also urged caution before implementation of routine use of probiotics.<sup>37</sup>

Some of the products currently available in the United States include Culturelle (*L rhamnosus GG*), Similac Probiotic Tri-Blend (*B infantis*, *S thermophilus*, and *B lactis*), and Evivo (*B infantis*). Each of these preparations are categorized as dietary supplements and are not labeled with the number of CFUs for the probiotic strain(s).

### LONG-TERM CONSIDERATIONS

The long-term implications of giving probiotics to preterm infants and how administration of microorganisms may permanently alter the microbiome is currently unknown. Jacobs et al<sup>38</sup> found comparable rates of survival without major neurodevelopmental impairment among subjects enrolled in the ProPrems trial. Although reassuring that administration of the probiotic preparation was not associated with adverse neurodevelopmental

outcomes, future studies are needed to more rigorously assess the effects of probiotics on longer-term outcomes.

## ONGOING CLINICAL TRIALS

Although many trials involving probiotics use of a dietary supplement-grade product, a phase Ib study evaluating the safety and tolerability of 2 doses of a pharmaceutical-grade probiotic (STP206; NCT01954017) in preterm infants was recently completed. In addition, a phase III randomized clinical trial to evaluate the safety and efficacy of *Lactobacillus reuteri* (IBP-9414; NCT03978000) to prevent NEC in preterm infants is currently ongoing. Proponents for routine administration of probiotics for NEC prevention agree that future research should compare high-quality probiotic products (both purity and viability of microbes) and doses.<sup>36</sup>

## SUMMARY

- In studies supporting the use of probiotics to decrease the risk of NEC and late-onset infection, researchers have used multiple different products in diverse settings and in diverse preterm target populations. The most recent modern trials have not demonstrated a reduction in NEC in infants at the highest risk for this morbidity. A pharmaceutical-grade probiotic product is not currently available in the United States. Long-term safety remains unknown. For

these reasons, current evidence does not support the routine, universal administration of probiotics to preterm infants, particularly those with a birth weight of <1000 g.

- Centers making the decision to administer probiotics to select preterm infants should discuss the potential risks and benefits of this therapy with parents and should strongly consider a formalized informed consent process. Such centers should develop local guidelines addressing probiotic use and conduct surveillance to assess local impacts because the introduction of probiotics has been shown to alter the center's flora and potentially affect all infants cared for in the center.
- Clinicians must be aware of the lack of regulatory standards for commercially available probiotic preparations manufactured as dietary supplements and the potential for contamination with pathogenic species.
- Centers choosing to administer probiotics should carefully document outcomes, adverse events, and safety.

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## ABBREVIATIONS

CFU: colony-forming unit  
CI: confidence interval  
ESPGHAN: European Society for Paediatric Gastroenterology, Hepatology and Nutrition  
NEC: necrotizing enterocolitis  
PIPS: Probiotics in Very Preterm Infants  
RR: risk ratio

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## REFERENCES

1. Dermyshe E, Wang Y, Yan C, et al. The “golden age” of probiotics: a systematic review and meta-analysis of randomized and observational studies in preterm infants. *Neonatology*. 2017;112(1):9–23
2. Viswanathan S, Lau C, Akbari H, Huyen C, Walsh MC. Survey and evidence based review of probiotics used in very low birth weight preterm infants within the United States. *J Perinatol*. 2016; 36(12):1106–1111
3. Neu J. The developing intestinal microbiome: probiotics and prebiotics. *World Rev Nutr Diet*. 2014;110:167–176
4. Lenfestey MW, Neu J. Probiotics in newborns and children. *Pediatr Clin North Am*. 2017;64(6):1271–1289
5. Pammi M, Cope J, Tarr PI, et al. Intestinal dysbiosis in preterm infants preceding necrotizing enterocolitis: a systematic review and meta-analysis. *Microbiome*. 2017;5(1):31

6. Underwood MA, German JB, Lebrilla CB, Mills DA. Bifidobacterium longum subspecies infantis: champion colonizer of the infant gut. *Pediatr Res*. 2015; 77(1–2):229–235
7. Hill C, Guarner F, Reid G, et al. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol*. 2014;11(8):506–514
8. National Institutes of Health, Office of Dietary Supplements. Frequently asked questions. Regulatory information. Available at: [https://ods.od.nih.gov/Health\\_Information/ODS\\_Frequently\\_Asked\\_Questions.aspx#Regulatory](https://ods.od.nih.gov/Health_Information/ODS_Frequently_Asked_Questions.aspx#Regulatory). Accessed October 13, 2020
9. Fenster K, Freiburg B, Hollard C, Wong C, Rønhave Laursen R, Ouwehand AC. The production and delivery of probiotics: a review of a practical approach. *Microorganisms*. 2019;7(3): 83
10. Drago L, Rodighiero V, Celeste T, Rovetto L, De Vecchi E. Microbiological evaluation of commercial probiotic products available in the USA in 2009. *J Chemother*. 2010;22(6):373–377
11. Frese SA, Hutton AA, Contreras LN, et al. Persistence of supplemented *Bifidobacterium longum* subsp. *infantis* EVC001 in breastfed infants. *mSphere*. 2017;2(6):e00501–e00517
12. Lewis ZT, Shani G, Masarweh CF, et al. Validating bifidobacterial species and subspecies identity in commercial probiotic products. *Pediatr Res*. 2016; 79(3):445–452
13. Dani C, Coviello C C, Corsini I I, Arena F, Antonelli A, Rossolini GM. Lactobacillus sepsis and probiotic therapy in newborns: two new cases and literature review. *AJP Rep*. 2016;6(1): e25–e29
14. AlFaleh K, Anabrees J. Probiotics for prevention of necrotizing enterocolitis in preterm infants. *Cochrane Database Syst Rev*. 2014;(4):CD005496
15. Hickey L, Garland SM, Jacobs SE, O'Donnell CPF, Tabrizi SN; ProPrems Study Group. Cross-colonization of infants with probiotic organisms in a neonatal unit. *J Hosp Infect*. 2014; 88(4):226–229
16. Costeloe K, Hardy P, Juszcak E, Wilks M, Millar MR; Probiotics in Preterm Infants Study Collaborative Group. Bifidobacterium breve BBG-001 in very preterm infants: a randomised controlled phase 3 trial. *Lancet*. 2016; 387(10019):649–660
17. Vallabhaneni S, Walker TA, Lockhart SR, et al.; Centers for Disease Control and Prevention (CDC). Notes from the field: fatal gastrointestinal mucormycosis in a premature infant associated with a contaminated dietary supplement—Connecticut, 2014. *MMWR Morb Mortal Wkly Rep*. 2015;64(6): 155–156
18. Hempel S, Newberry S, Ruelaz A, et al. Safety of probiotics used to reduce risk and prevent or treat disease. *Evid Rep Technol Assess (Full Rep)*. 2011;(200): 1–645
19. Abbasi J. Are probiotics money down the toilet? Or worse? *JAMA*. 2019;321(7): 633–635
20. Bafeta A, Koh M, Riveros C, Ravaud P. Harms reporting in randomized controlled trials of interventions aimed at modifying microbiota: a systematic review. *Ann Intern Med*. 2018;169(4): 240–247
21. Sawh SC, Deshpande S, Jansen S, Reynaert CJ, Jones PM. Prevention of necrotizing enterocolitis with probiotics: a systematic review and meta-analysis. *PeerJ*. 2016;4:e2429
22. Patel RM, Underwood MA. Probiotics and necrotizing enterocolitis. *Semin Pediatr Surg*. 2018;27(1):39–46
23. Bin-Nun A, Bromiker R, Wilschanski M, et al. Oral probiotics prevent necrotizing enterocolitis in very low birth weight neonates. *J Pediatr*. 2005; 147(2):192–196
24. Dani C, Biadaioi R, Bertini G, Martelli E, Rubaltelli FF. Probiotics feeding in prevention of urinary tract infection, bacterial sepsis and necrotizing enterocolitis in preterm infants. A prospective double-blind study. *Biol Neonate*. 2002;82(2):103–108
25. Lin HC, Su BH, Chen AC, et al. Oral probiotics reduce the incidence and severity of necrotizing enterocolitis in very low birth weight infants. *Pediatrics*. 2005;115(1):1–4
26. Szajewska H, van Goudoever JB. To give or not to give probiotics to preterm infants. *Am J Clin Nutr*. 2014;100(6): 1411–1412
27. Jacobs SE, Tobin JM, Opie GF, et al.; ProPrems Study Group. Probiotic effects on late-onset sepsis in very preterm infants: a randomized controlled trial. *Pediatrics*. 2013;132(6): 1055–1062
28. Chang HY, Chen JH, Chang JH, Lin HC, Lin CY, Peng CC. Multiple strains probiotics appear to be the most effective probiotics in the prevention of necrotizing enterocolitis and mortality: an updated meta-analysis. *PLoS One*. 2017;12(2):e0171579
29. van den Akker CHP, van Goudoever JB, Szajewska H, et al.; ESPGHAN Working Group for Probiotics, Prebiotics & Committee on Nutrition. Probiotics for preterm infants: a strain-specific systematic review and network meta-analysis. *J Pediatr Gastroenterol Nutr*. 2018;67(1):103–122
30. Thomas DW, Greer FR; American Academy of Pediatrics Committee on Nutrition; American Academy of Pediatrics Section on Gastroenterology, Hepatology, and Nutrition. Probiotics and prebiotics in pediatrics. *Pediatrics*. 2010;126(6):1217–1231
31. Marchand V. Using probiotics in the paediatric population. *Paediatr Child Health*. 2012;17(10):575–576
32. van den Akker CHP, van Goudoever JB, Shamir R, et al. Probiotics and preterm infants: a position paper by the European Society for Paediatric Gastroenterology Hepatology and Nutrition Committee on Nutrition and the European Society for Paediatric Gastroenterology Hepatology and Nutrition Working Group for Probiotics and Prebiotics. *J Pediatr Gastroenterol Nutr*. 2020; 70(5):664–680
33. Su GL, Ko CW, Bercik P, et al. AGA clinical practice guidelines on the role of probiotics in the management of gastrointestinal disorders. *Gastroenterology*. 2020;159(2):697–705
34. Patel RM, Kandefer S, Walsh MC, et al.; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Causes and timing of death in

- extremely premature infants from 2000 through 2011. *N Engl J Med.* 2015; 372(4):331–340
35. Pell LG, Loutet MG, Roth DE, Sherman PM. Arguments against routine administration of probiotics for NEC prevention. *Curr Opin Pediatr.* 2019; 31(2):195–201
36. Underwood MA. Arguments for routine administration of probiotics for NEC prevention. *Curr Opin Pediatr.* 2019; 31(2):188–194
37. Garland SM, Jacobs SE, Tobin JM, Opie GF, Donath S; ProPrems study group. A cautionary note on instituting probiotics into routine clinical care for premature infants. *Pediatrics.* 2010;126(3):e741- NaN–e745
38. Jacobs SE, Hickey L, Donath S, et al.; ProPremsStudy Groups. Probiotics, prematurity and neurodevelopment: follow-up of a randomised trial. *BMJ Paediatr Open.* 2017;1(1):e000176

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