

The Use of Probiotics in Premature Infants: They are Safe and Effective, Right?

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“When I began reading the paper by Alshaikh and colleagues, a large retrospective cohort study involving 33 neonatal intensive care units (NICUs) of the Canadian Neonatal Network (CNN) between January 1, 2016, and December 31, 2022, I became hopeful (1).”

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There has been extensive basic science and clinical research on the efficacy and safety of enteral supplementation with multi-strain and single-strain probiotics in premature infants to reduce necrotizing enterocolitis (NEC), yielding hopeful, mixed, and negative results (1).

The study focused on preterm infants born at less than 34 weeks' gestation and with a birth weight of less than 1000 g. Among the infants born at less than 34 weeks' gestation, there were 32667 eligible: 18793 (57.5%) received probiotics, and 13874 (42.5%) did not receive probiotics. (2) The primary outcomes were necrotizing enterocolitis (NEC), late onset sepsis (LOS), and mortality. Probiotic use was associated with decreased mortality rates, but no decrease in NEC or LOS was observed (2). Among the 7,401 infants born weighing less than 1000 grams, probiotics were also associated with reduced mortality, with no decrease in NEC or LOS rates (2).

There was evidence of probiotic sepsis in 27 (1.4/1000) infants born before 34 weeks' gestation and 20 born < 1000 g birthweight. Three infants with probiotic sepsis died, with probiotic sepsis deemed a possible cause in 2 cases (2). Among the 27 with probiotic sepsis only, 3 had both *Lactobacillus* and *Bifidobacterium*, isolated simultaneously. Eleven (41%) had NEC or spontaneous intestinal perforation 7 days before or after probiotic sepsis (2). There were 24 infants with probiotic sepsis in the extremely low

birthweight (ELBW) cohort. Twenty (4/1000) had probiotic sepsis without other isolated organisms. Three had *Lactobacillus* and *Bifidobacterium* isolated (2). Nine (45%) had NEC or spontaneous intestinal perforation 7 days before or after probiotic sepsis (2). Notably, probiotic sepsis occurred only in infants who received probiotics (2). Probiotic sepsis occurred only in infants who received multi-strain probiotics (2).

A Pareto optimal outcome is one in which no individual can be made better off without making someone else worse off. In this case, the use of probiotics in preterm infants aims to provide benefits, including a reduction in the risk of necrotizing enterocolitis (NEC). However, the occurrence of probiotic sepsis in 27 infants, including fatal cases, demonstrates a trade-off between potential benefits and significant risks.

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This outcome is not Pareto optimal because there exists a subset of infants who experience harm (probiotic sepsis and potential deaths) without an equivalent benefit that compensates for these losses. Specifically:

1. **Sepsis and Mortality** – The death of three infants, with probiotic sepsis possibly contributing to two of these deaths, indicates that at least some infants were made worse off without a clear alternative intervention that could mitigate this harm.
2. **Association with NEC and SIP** – The fact that 41% of those

with probiotic sepsis also had NEC or spontaneous intestinal perforation within a short timeframe suggests a possible unintended consequence of probiotic use in vulnerable infants.

3. **Unclear Risk-Benefit Balance** – While probiotics may reduce the risk of NEC in some cases, the presence of severe infections linked to probiotics suggests that the intervention does not benefit all infants equally and may harm some significantly.

For the outcome to be Pareto optimal, the use of probiotics would need to improve overall health without introducing risks that harm a subset of infants. Given the observed cases of probiotic sepsis and associated mortality, an alternative approach, such as better screening of candidates for probiotics, adjusting dosage, or using strains with lower infection risk, could potentially improve outcomes without worsening others, indicating that the current situation is not Pareto efficient.

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Despite the somewhat positive and promising results regarding the decrease in mortality in preterm infants born at <34 weeks' gestation and <1000 grams birth weight who received multi-strain probiotics, there was only a trend in the decrease in NEC and LOS in these infants in this large, well-organized study (2-4). In addition, the incidence of probiotic sepsis was rare in this study (2,3). The overall conclusion remains that, although there is some progress, further large clinical trials need to be done, and are being done, to prove the safety and efficacy in the reduction of mortality, NEC, and LOS in preterm infants born at < 34 weeks gestation or at < 1000 grams birthweight (1-4).

References:

1. Frost, B. L., & Caplan, M. S. (2013). Necrotizing enterocolitis: Pathophysiology, platelet-activating factor, and probiotics. *Seminars in Pediatric Surgery*, 22(2), 88-93. <https://doi.org/10.1053/j.sempedsurg.2013.01.005>.
2. Alshaikh BN, Ting J, Lee S, et al. Effectiveness

and risks of probiotics in preterm infants. *Pediatrics* 2025;155(3):e2024069102.

3. Soll RF, Edwards EM. Safety and efficacy of probiotic for preterm infants. *Pediatrics* 2025;155(3):e2024069450.
4. Poindexter B and AAP Committee of the Fetus and Newborn. Use of probiotics in preterm infants. Clinical Report. *Pediatrics* 2021;147(6): e2021051485.

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