Letter to the Editor

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Neonatal sepsis associated with Lactobacillus supplementation

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To the Editor,

In the last few years, there has been an increasing interest in administering probiotics to preterm infants. Many studies, including randomized controlled trials, have demonstrated a role for probiotics in preventing or reducing the risk of major complications related to prematurity (e.g. necrotizing enterocolitis, late-onset sepsis), the overall neonatal mortality rate and the length of hospital stay [1–3]. Authors have consequently suggested that probiotics should be offered routinely to all high-risk preterm-born neonates [4, 5].

This clinical practice was introduced at our neonatal intensive care unit (NICU) in 2017. Since then, we have routinely administered oral probiotics (*Lactobacillus rhamnosus* GG 3×10^9 cfu/day– Dicoflor®) to all sepsis-free preterm newborns starting minimal enteral feeding.

In the first months after introducing this probiotic supplementation, we reported three cases of *L. rhamnosus* sepsis – one in a female supplemented with oral probiotics and two in males hospitalized in the same room, but not given any probiotic supplements.

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The first case of sepsis was an extremely low-birth-weight (ELBW) Caucasian female born at 25+6 weeks through emergency cesarean section due to suspected placental detachment. Her birth weight was 770 g. At 48 h of life, she started minimal enteral feeding with human milk from a donor. As of the third day of life, she was given enteral supplementation with oral drops of *L. rhamnosus* GG 3×10^9 cfu/day through the orogastric tube. Blood culture and serum C-reactive protein (CRP) assay on the first day of life were negative. She had a peripherally inserted central catheter (PICC). At 18 days of life, she developed abdominal distension, and laboratory tests revealed high CRP levels (34 mg/L). Enteral feeding and probiotic administration were discontinued, and broad-spectrum antibiotic therapy was begun with vancomycin and ceftazidime. Peripheral vein blood culture was positive for *L. rhamnosus*. The antibiogram showed susceptibility to ampicillin and resistance to vancomycin and ceftazidime, so ampicillin was started and the previous antibiotic therapy was discontinued. A second blood culture and PICC culture confirmed the presence of Lactobacillus species (*L. rhamnosus*). The patient recovered completely, and the antibiotic therapy was stopped after 17 days, when her CRP level was normal and microbiological tests were negative. She reached full enteral feeding on day 21. The patient was discharged at 121 days of life.

In the same room, two other premature boys developed abdominal distension, feeding intolerance and high CRP levels, and blood cultures were positive for *L. rhamnosus*. They both had a PICC as a risk factor. They were both treated with ampicillin and their clinical condition improved. They were discharged at 133 and 127 days of life.

The Lactobacillus isolates from the first and second blood cultures of the three newborns were identified using matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry (VITEKMS, bioMérieux, Marcy L'Etoile, France) as *L. rhamnosus*, suggesting a correlation with the probiotic preparation administered to the girl. When random amplification of polymorphic

DNA (RAPD) was used to compare the Lactobacillus isolates from the three patients with the probiotic strain (*L. rhamnosus* GG), the isolates from all three patients exhibited an identical RAPD profile to that of the probiotic strain *L. rhamnosus* GG (ATCC 53103).

It seems useful to share our experience of using probiotics at our NICU to highlight potential problems of its administration in everyday practice. Prematurity is associated with immunodeficiency, gastrointestinal and feeding problems, the need for a central venous catheter, prolonged antibiotic therapy, and higher risk of necrotizing enterocolitis. Very preterm infants are colonized with fewer probiotic microorganisms and more potential pathogens than term-born newborns [6]. All these are risk factors for the development of side effects of probiotics. The cases reported in this study are similar to others previously described [7], and confirm that both supplemented and non-supplemented infants are at high risk of probiotic-related systemic infections in NICUs [7]. Our isolation of *L. rhamnosus* in the PICC and bloodstream, which was being administered daily via the enteral tube, might point to contamination from the environment or healthcare personnel.

First of all, we need more information on the safety profile of probiotics, their dosage and use in ELBW infants, and how healthcare personnel should manage probiotics and body fluids in open-space NICUs. There is still limited data available on the optimal choice of probiotic organisms for safe administration in ELBW and high-risk infants [8, 9]. Studying possible probiotic overgrowth, and the pathogenic mechanisms that might lead to colonization and blood positivity could be one way to avoid side effects. A personalized approach, considering microbiota development and intestinal permeability, or looking for possible metabolomic markers of overgrowth, could help us to choose the most appropriate probiotic management case by case.

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References

1. Sun J, Marwah G, Westgarth M, Buys N, Ellwood D, Gray PH. Effects of probiotics on necrotizing enterocolitis, sepsis, intraventricular hemorrhage, mortality, length of hospital stay, and weight gain in very preterm infants: a meta-analysis. Adv Nutr 2017;8:749–63.
2. AlFaleh K, Anabrees J. Probiotics for prevention of necrotizing enterocolitis in preterm infants. Cochrane Database Syst Rev 2014;4:CD005496.
3. Dermyshi E, Wang Y, Yan C, Hong W, Qiu G, Gong X, et al. The "Golden Age" of probiotics: a systematic review and meta-analysis of randomized and observational studies in preterm infants. Neonatology 2017;112:9–23.
4. Manzoni P, Mostert M, Leonessa ML, Priolo C, Farina D, Monetti C, et al. Oral supplementation with Lactobacillus casei subspecies rhamnosus prevents enteric colonization by Candida species in preterm neonates: a randomized study. Clin Infect Dis 2006;42:1735–42.
5. Shane AL, Deshpande GC, Merenstein D. Improved neonatal outcomes with probiotics. JAMA Pediatr 2013;167:885–6.
6. Itani T, Ayoub Moubareck C, Melki I, Rousseau C, Mangin I, Butel MJ, et al. Preterm infants with necrotizing enterocolitis demonstrate an unbalanced gut microbiota. Acta Paediatr 2018;107:40–4.
7. Dani C, Coviello C, Corsini I, Arena F, Antonelli A, Rossolini GM. Lactobacillus sepsis and probiotic therapy in newborns: two new cases and literature review. Am J Perinatol Rep 2016;6:e25–9.
8. Pell LG, Loutet MG, Roth DE, Sherman PM. Arguments against routine administration of probiotics for NEC prevention. Curr Opin Pediatr 2019;31:195–201.
9. Kane AF, Bhatia A, Denning PW, Shane AL, Patel RM. Routine supplementation of Lactobacillus rhamnosus GG and risk of necrotizing enterocolitis in very low birth weight infants. J Pediatr 2018;195:73–9.