Probiotic Supplementation for Preterm Neonates – What Lies Ahead?

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Necrotizing enterocolitis (NEC) continues to be a potentially disastrous illness in preterm very-low-birthweight (VLBW) neonates with significant mortality and morbidity including long-term neurodevelopmental impairment, especially in extremely preterm (<28 weeks’ gestation) neonates requiring surgical intervention for the illness. Probiotics may prevent NEC by maturing the intestinal host defenses including the gut mucosal barrier, promoting colonization of the gut with beneficial microbes, inhibiting colonization by pathogens, and modulating the immune system to the advantage of the host. Systematic reviews of randomized controlled trials (RCTs) indicate that prophylactic probiotic supplementation significantly reduces the risk of ≥stage NEC without adverse effects in preterm VLBW neonates. The acceptance of probiotic supplementation for preterm VLBW neonates is on the rise. A review of what lies ahead in this field is thus important.

Optimizing the benefits and minimizing the risks of probiotic supplementation in extremely preterm and preterm growth-restricted neonates is important considering their higher risk of NEC and suboptimal enteral nutrition. The mechanisms that may explain such issues in preterm neonates with intrauterine growth restriction (IUGR) following fetal umbilical artery absent/reversed end diastolic flow (AREDF) include fetal hypoxia, redistribution of the gastrointestinal blood flow to spare the brain the adverse circulatory effects of AREDF, structural and functional changes in the intestine, and altered gut colonization. Fetal gut injury increases intestinal vulnerability to ileus, abnormal colonization, and bacterial invasion in the postnatal period. The postprandial rise in superior mesenteric artery flow is compromised in preterm IUGR neonates. Deficits in the bioavailability of butyrate could adversely affect the proliferation of colonocytes and the maintenance of colonic homeostasis. IUGR impairs mucus barrier development and is associated with long-term alterations of mucin expression. Considering the significance of gut flora in IUGR, studies specifically addressing the effects
of probiotic supplementation in preterm growth-restricted neonates are required. Advancing the knowledge in other areas is equally important. The recently reported benefits of multistrain over single-strain probiotics, and of early (within 24–48 h) versus late (>48 h after birth) commencement of probiotic supplementation in optimizing gut colonization need to be confirmed. Evaluating the consumption of specific human milk oligosaccharides by different probiotic strains will help in developing optimal pre- and probiotic combinations. Research assessing the effects of killed/inactivated versus live probiotic agents is also important considering the potential benefits with regard to probiotic sepsis, development of antibiotic resistance, and need for maintaining a cold chain.

Probiotic prophylaxis outside the rigid framework of RCTs is expected to provide data on real-life benefits, and importantly, the uncommon/rare adverse effects of probiotics in preterm neonates. As with any intervention, it is expected that the real life benefits of probiotic supplementation may not be as dramatic as reported in clinical trials. It is important to appreciate that probiotics will not be a panacea for NEC, which is known to present at different postnatal ages with different triggers, and different modes of presentation. Strategies such as maximizing exposure to antenatal glucocorticoids, early feeding with maternal/donor breast milk, and aggressive approach for prevention and treatment of late-onset sepsis without misuse of antibiotics are therefore important if a ‘zero tolerance’ to NEC is required. Focusing on nutritional benefits of probiotics should also be a priority. Cooperation between various stakeholders, including the regulatory authorities and the industry, is urgently required to address the issue of quality control, and decide how probiotics should be classified to improve access to safe and effective probiotic products.