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Editorial

# Probiotics and Prebiotics-Applications to Neonatal Intensive Care

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## Editorial

Advances in neonatal intensive care over the last 25 years have significantly improved the survival of preterm very low birth weight (VLBW: Birth weight <1500 g) infants. Necrotizing enterocolitis (NEC ≥ Stage II) is the commonest acquired gastrointestinal emergency in this population. NEC affects about 6 to 7% of preterm VLBW infants and carries significant mortality (~25%) and morbidity including recurrent sepsis, complications of prolonged parenteral nutrition, need for surgery, and survival with short bowel syndrome [1]. Mortality (45% to 100%) and the risk of long term Neurodevelopmental Impairment (NDI) is higher in extremely low birth weight (ELBW: Birth weight < 100 g) infants needing surgery for the illness. The economic burden of NEC is also significant considering the complications of ≥ Stage II NEC that prolong the hospital stay [1].

The acceptance of probiotic supplementation (PS) as a strategy to prevent definite (≥ Stage II) NEC in preterm infants is an important event in the history of neonatal intensive care [2-4]. Alfaleh et al have recently updated their systematic review of Randomised Controlled Trials (RCT) assessing effects of prophylactic PS in preterm VLBW neonates [4]. There was significant heterogeneity in clinical characteristics (e.g. birth weight and gestational age), baseline risk of NEC, probiotic protocol (probiotic strain/s, dose, duration), type of milk, and feeding regimens. Meta-analysis of data from 24 trials indicated that PS significantly reduced the risk of definite NEC (RR: 0.43, 95% CI: 0.33-0.56) and all cause mortality (RR: 0.65, 95% CI: 0.52 -0.81) without any adverse effects. There was no evidence of significant reduction in late onset sepsis (LOS: RR 0.91, 95% CI: 0.80 to 1.03) [4]. Results of the multicentre trial from Australia (Proprems) have confirmed what was reported in the earlier systematic reviews, i.e. probiotics reduce the risk of definite in preterm VLBW neonates but have no significant effect on LOS [5]. It also confirmed the findings from systematic reviews that probiotics can reduce the risk of NEC even when the baseline incidence of the condition is low (<6%) [5]. Results of the multicentre trial (PiPS; ISRCTN No: 05511098) from UK will add more knowledge to this field as the trial has adequate power to detect the desired effect on both definite NEC and all cause mortality. It is also the largest RCT evaluating PS with a single strain.

The acceptance of routine provision of PS in preterm VLBW neonates is on the rise [6-9]. Reporting population based data from routine use is important for optimal assessment of adverse effects of PS such as probiotic sepsis, antibiotic resistance, and altered long term immune responses. So far the evidence in this context is reassuring. Continued research to address the current gaps in knowledge (e.g. optimal strain/s, combinations, efficacy in ELBW infants) and overcoming the regulatory hurdles to improve access to probiotics is also important. It is accepted that the effects of probiotics are strain-specific, and that understanding the specific mechanisms/pathways of benefit of probiotics is important. However considering the cumulative evidence from RCTs, experimental studies and reports on routine PS it is not appropriate to delay offering PS to preterm infants if safe and clinically proven probiotic products are available.

Compared to probiotics, the progress in the field of supplementation of preterm infants with prebiotic Oligosaccharides (OS) has been slow. A recent updated systematic review of RCTs has assessed the effects of prebiotic OS supplementation in improving clinical outcomes such as NEC and sepsis in preterm (≤37 weeks) infants [10]. The review included 7 trials with 417 infants with 5 trials (n=345) reporting on NEC and another 3 (n=295) reporting on LOS. Meta-analysis revealed a pooled RR (95% CI) of 1.24 (0.56-2.72) for NEC, and 0.81 (0.57-1.15), p=0.23 for LOS. Three trials (n=295) reported no improvement in the time to enteral feeds after the intervention. Meta-analysis indicated a statistically significant difference in the growth of bifidobacteria in the OS group: Weighted mean difference 0.53 (95% CI: 0.33, 0.73) $x10^6$ colonies/g, $p < 0.00001$. A reduction in stool viscosity and pH was also observed. None of the trials reported any significant adverse effects [10]. The limited evidence from this systematic review supports the bifidogenic effect of prebiotic OS supplementation on the gut flora in preterm infants but whether this translates into clinically significant benefits is not clear. Large RCTs with clinically significant outcomes such as definite NEC and LOS are needed. Conducting placebo controlled trials of prebiotic OS in preterm infants could be difficult considering the increasing acceptance of PS in this population. Set ups where accessing probiotics is difficult will therefore be ideal for such trials. Head to head trials assessing the effects of probiotics versus synbiotics will be helpful knowing breast milk provides both probiotics and prebiotic OS together. So far the commercially available prebiotic OS are close to but not identical to the natural human milk OS. Advances in biotechnology may be able to overcome this limitation in future.

Overall, the field of probiotic and prebiotic supplementation for preterm infants has provided new opportunities as well as challenges for all involved in neonatal intensive care.




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