Probiotic Research Update January 2025

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Welcome to a New Year. This Update for Clinicians is sponsored by Biofloratech Ltd, manufacturer of Labinic Probiotic Drops for babies. Labinic is:

- A triple strain preparation (L. acidophilus, B. bifidum & B. infantis)
- Highly concentrated in MCT oil (allows small administration volumes)
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- Excellent value

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Controversies in the use of Neonatal Probiotics – A Commentary on Safety and Efficacy

Safety and Efficacy of Probiotics for Preterm Infants. Soll R and Edwards EM. Pediatrics 2025; e2024069450. 10.1542/peds.2024-069450

There is a strong biological plausibility, based on animal and human studies, that modification of the microbiome in the gut, particularly in the preterm gut, could help the baby's fight against some very serious outcomes. Probiotics are not a treatment, and babies on probiotics can still suffer serious illnesses. The most recent Cochrane Review (2023) includes 11,156 babies in 60 trials, with meta-analysis showing a RR of 0.54 for NEC and 0.77 for mortality. In the US the early adoption of probiotics was slow and recent FDA announcements have severely curtailed probiotic use to the dismay of many clinicians and campaign groups.

** DISCLAIMER: This brief review was produced for Biofloratech Ltd who manufacture, and supply, Labinic Drops, a multispecies liquid probiotic food supplement. This review is written in technical language and is only intended for professional use. The content is not intended to advertise nor to describe any health claim for Labinic Drops, and all words including "probiotic" are used purely in their scientific WHO-approved forms. The purpose of the review is to stimulate discussion, debate and formulate research questions for the future. www.biofloratech.com

The authors point out that there are plenty of treatments given to babies which have less evidence of benefit and higher adverse side-effects too. So why are there still barriers to implementation in the USA? FDA states that biological agents must be safe, pure and potent.

In an accompanying article (summarised below) a Canadian Network study evaluated the use of probiotics. Most centres used a multistrain product, since meta-analytics suggest that multistrain products are superior in their desirable effects to single-strain one. In this study, mortality was reduced as was NEC. Probiotic sepsis was rare (0.14% of babies <34 weeks and 4% of babies with BW <1000g).

The answer, as always, is a call for more research. As more and more tiny babies survive, the fact that NEC rates are not increasing may be a small comfort, but nor are they going down.

Full text link to review here

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Effectiveness and risks of probiotics in Preterm Infants

Alshaikh BN, Ting J, Lee S, Lemyre B, Wong J, Afifi J, Beltempo M, Shah PS; Canadian Neonatal Network Investigators. Effectiveness and Risks of Probiotics in Preterm Infants. Pediatrics. 2025 Feb 12;155(3):e2024069102. doi: 10.1542/peds.2024-069102

This publication described the results of a retrospective cohort study (between 2016 and 2023) which included babies less than 34 weeks gestation at birth and with a birth weight of less than 1000g (planned subgroup). There were over 32,600 babies born before 34 weeks. 57.3% with a median GA of 29 weeks received a multistrain probiotic. Overall there was a reduction in mortality (aOR 0.62) but no reduction in NEC or sepsis.

In the subgroup of babies with BW <1000g, probiotic administration led to reduction in mortality (aOR 0.58) but not NEC or sepsis. The confidence interval for NEC was 0.74-1.01 and for LOS was 0.86-1.05, so whilst non-significant there was a good safety signal. Probiotic sepsis occurred in 4% of the babies <1000g and 1.4% of the whole recruited population. In total probiotic sepsis was a possible cause of death in 2 babies. 41-45% of babies with probiotic sepsis had NEC or SIP a week before or after the sepsis episode. The use of probiotics increased during the period, from 31% to 67% of all babies.

Overall the findings are in line with meta-analyses. The episodes of probiotic sepsis were described in detail, presumably as a response to the current FDA concerns, and are quite reassuring. The importance of good microbiology support are emphasised.

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Overall the NNT to prevent one additional death is 82 (70-103) for babies <34 weeks, and for babies born <1000g the NNT is 15 (13-18), although as a retrospective observational study these numbers may be inaccurate.

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Impact of the early life gut microbiome on later health in children and adults

Nunez H, Nieto PA, Mars RA, Ghavami M, Sew Hoy C, Sukhum K. Early life gut microbiome and its impact on childhood health and chronic conditions. Gut Microbes. 2025 Dec;17(1):2463567

This article gave an interesting overview of the importance of establishing a healthy early gut microbiome. We know that the gut is mainly colonised with Bifidobacteria in healthy breastfed term babies, and we also know that mode of delivery, gestation, maternal medications and diet, antibiotic exposure (direct/indirect) and maternal microbiome all have influence on the establishment of the gut microbiome. Longer term health conditions, such as asthma, atopy, diabetes and obesity are associated with an early dysbiosis. The importance therefore of maximising the opportunity to develop a healthy microbiome is key.

The authors describe nicely the critical functions that a healthy microbiome has, which include the metabolism of human milk oligosacharides, and the immune functions that HMOs and their metabolites are involved in. The strain B. infantis is an avid metaboliser of HMOs and B. bifidum is a moderate metaboliser. Probiotic microbes produce SCFAs which are critically involved in maintaining gut health. Combinations of Bifidobacteria and Lactobacillus are important in reducing the carriage of pathogenic and antibiotic resistant bacteria. The balance of the immune regulation of the gut, including between Th1 and Th2/Th17 to dampen inflammatory responses is described. The impact of delivery, antibiotics and diet is critical to developing and maintaining a healthy gut microbiome and the evidence is presented to support this. Finally the risks for longer term important health conditions are presented.

Overall this is an excellent overview, demonstrating that a focus on gut health particularly in the early years should be a critical component of child health programmes, the aim being to reduce the risks of important and chronic health outcomes

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The benefits of breastfeeding to babies and their mothers

Ener Cagri Dinleyici; Breastfeeding and Health Benefits for the Mother-Infant Dyad: A Perspective on Human Milk Microbiota. *Ann Nutr Metab* 2025

This review article describes in detail the numerous (and many already known) benefits of breastfeeding to babies and mothers, but also the wider societal benefits such as reducing antibiotic resistance and the overall costs of healthcare through better health. The evidence is clear that important diseases such as necrotising enterocolitis and late-onset sepsis in preterms, and later health issues such as diabetes, allergies, cardiovascular disease, cancers, neurodevelopmental delay, obesity and child mortality can all potentially be reduced through breastfeeding. In addition, benefits to mothers including reductions in risks for breast cancer, postnatal mental health problems and cardiovascular health are described.

There is an interesting section on the human milk microbiome which should be of particular interest to readers of this newsletter. As we know, it was not until about 20 years ago that breast milk was considered to be sterile, until the description of lactic acid bacteria in breast milk and the subsequent evidence that breast milk contains over 800 bacterial species, but with some genera more prevalent than others. The differences between colostrum and more mature breast milk is now clear, with higher proportions of Bifidobacteria and Lactobacillus present in colostrum compared to mature milk. In fact the human milk microbiome is a diverse mixture of bacteria, viruses and fungi, and we have previously described in this newsletter the fascinating mechanism of how the gut virome protects children from viral infections, and evidence emerged that breast milk can inhibit SARS-Cov-2 and support passive immunity to a wide range of other viruses. The particular importance of bifidobacteria on the immune system and its development is highlighted, in relation to the metabolism of HMOs.

Overall this is an excellent and relevant review article, and once again the importance of Lactobacilli and Bifidobacteria in the healthy human gut are emphasised.

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Stress can affect the Human Milk microbiome

Hannah G. Juncker, Rasmus R. Jakobsen, Eva F.G. Naninck, Mark Davids, Hilde Herrema, Johannes B. van Goudoever, Susanne R. de Rooij, Aniko Korosi. Maternal stress in the early postpartum period is associated with alterations in human milk microbiome composition. Brain, Behavior, and Immunity, Volume 124, 2025, Pages 74-84

Having reviewed the substantial benefits of breast milk in the previous article, this paper shows that as health professionals we also need to be aware of the fragility of the ecosystem. This was a

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prospective cohort study from Holland, with subjects divided into two groups of mothers who were diagnosed using questionnaires and cortisol levels to be High Stress (HS n=30) or control (n=86). Breast milk analysis showed substantial variation in the microbiome using 16S analysis, and bacterial β-diversity was also measured. There were strong and significant differences in β-diversity between the groups. Additionally maternal educational level, BMI and stress scores influenced β-diversity, as did having a male infant. No association with cortisol levels were noted between the groups.

The authors speculate that a pro-inflammatory state, which may be present in stress, can lead to higher levels of Acineter bacteria, although the clinical consequences of this are unclear due to conflicting literature. Likewise differences in levels of Gemella and Veillonella bacteria were noted to be reduced in the HS group, which have been linked to risks for diabetes and atopic disease respectively. Corynebacteria and Klebsiella spp were increased in the HS group, which have been linked to neonatal infections and necrotising enterocolitis.

The impact of mental health as well as physical health on breast milk composition is a fascinating addition to the literature, and should enable us to develop strategies to optimise the health advantages of breast milk. After all, if we are to support and promote breast feeding, we should also support the optimisation of the breast milk being given to the baby.

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Maternal salivary cortisol and the human milk microbiome

Deflorin, Nadia PhD; Ehlert, Ulrike PhD; Amiel Castro, Rita T. PhD. Associations of Maternal Salivary Cortisol and Psychological Symptoms With Human Milk's Microbiome Composition. Biopsychosocial Science and Medicine 87(1):p 33-45, January 2025

Another recent prospective study, from Switzerland, of the impact of maternal stress on the human milk microbiome showed that perinatal anxiety (measured using validated questionnaires) was associated with alterations in the bacterial composition. In a study population of 100 mothers, positive correlation with maternal cortisol was noted with some specific bacterial strains (Stenotrophomonas, Kocuria, G. hemolysans and S. mitis). However no association between material anxiety and cortisol was found, and there was no association between cortisol levels and bacterial diversity. There are some limitations to the study, such as the single time point for cortisol and for milk sampling which limited the ability to look at trends. The authors also note that the study was carried out during the COVID pandemic, which imposed restrictions and changes in lifestyle which were not normal.

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Emerging knowledge of the important of a healthy neonatal gut microbiome – more than just reducing the risk of NEC

Yang Ru , Shi Zeyao , Li Yuan , Huang Xi , Li Yingxin , Li Xia , Chen Qiong , Hu Yanling , Li Xiaowen. Research focus and emerging trends of the gut microbiome and infant: a bibliometric analysis from 2004 to 2024. Frontiers in Microbiology. VOL. 15. 2024.

There has been a rapid advance in our knowledge of the importance of a healthy gut, from the earliest postnatal days, in the development of immune and general health, which can have life-long impacts. Over the years of producing these newsletters on behalf of Biofloratech Ltd, the role of probiotics as a tool to promote and influence gut health has become established, and other articles in this edition have shown that the composition of the human milk microbiome is an area for consideration as well. The colonisation of the newborn infant gut, at any gestation, depends on a huge array of competing factors, and our duty as clinicians (and scientists) is to promote healthy, safe and practical ways to optimise the natural benefits of human milk and the promotion of healthy microbiomes in different systems (breast milk, maternal and infant).

This article is a huge review of the bibliometrics of the published evidence on the infant gut microbiome. The authors have demonstrated where most research is being published from (the USA, Italy and China being the top 3) with the University of California and Harvard being the top 2 most productive institutions.

The most published areas concern effects on the immune system, necrotising enterocolitis, HMOs and Caesarean section.

It is now well described that probiotics can influence the gut microbiome in preterm babies, and that maturation driven by Bifidobacteria in particular leads to potential benefits. The impact on necrotising enterocolitis is described, as well as the potential reduction in risk from Group B streptococcus as a result of, for example, the known anti-GBS actions of Lactobacilli.

The article also describes published effects of probiotics that are outside the neonatal period. These include the reduction in asthma risk associated with B. infantis probiotics, the reductions in eczema and atopic dermatitis associated with administration of mixtures of Lactobacillus and Bifidobacterium.

Overall this is an interesting overview of nearly 10,000 publications over the past 20 years.

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Does length of hospital stay postpartum affect the infant gut microbiome?

Bashar S, Tun HM, Ting JY, Hicks M, Mandhane PJ, Moraes TJ, Simons E, Turvey SE, Subbarao P, Scott JA, Kozyrskyj AL. Impact of postpartum hospital length of stay on infant gut microbiota: a comprehensive analysis of vaginal and caesarean birth. J Hosp Infect. 2025 Feb;156:50-60 This

There are competing pressures in maternity systems everywhere. The need to minimise length of stay (LOS) in hospital to maintain bed and staff availability competes with the need for peripartum safety, which has led in many systems to increasing rates of caesarean sections, after which mothers and babies cannot be discharged as quickly as a vaginal birth. Concerns exist around the risks of healthcare acquired infections (HAIs) from prolongation of hospitalisation.

This study from Canada looked at 1313 babies from the CHILD cohort study, defining a prolonged stay in hospital as 2 or more days for vaginal delivery, and 3 or more days for caesaean section birth. 64% of babies born vaginally and 75% of babies delivered by CS met the criteria. Gut microbiota were analysed using 16S RNA sequencing at 3-4 and 12 months of age. 44% of vaginally delivered babies were breastfeeding at 3 months, compared to 28% of those born by CS, and in those babies who were breastfed there was an impact on their gut microbiome. Very few babies received exogenous probiotics.

There was significant influence on gut β-diversity from LOS which persisted in the 12 month samples, regardless of delivery mode. In vaginally-born babies with no maternal antibotics (IAP), increased LOS led to more Enterococci, Citrobacter and C. difficile present in early and later infancy. There were reductions in Bifidobacteria in babies born by CS with prolonged LOS, who also showed greater abundance of Enterobacteria, again persisting to late infancy (at least, as no further samples were taken).

This study shows that there is a significant, under-appreciated and undesirable effect of prolonged LOS on the infant gut microbiome, creating a dysbiosis of pathogenic bacteria that persist at least for a year. Further studies are needed, underlining the message that interest in the neonatal microbiome needs to extend beyond preterm infants and needs to be considered as having prolonged and important effects on developing infants.

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This technical newsletter for Health Professionals was commissioned by Biofloratech Ltd who manufacture Labinic® Drops, a liquid multi-strain probiotic containing Lactobacillus acidophilus, Bifidobacterium infantis and Bifidobacterium bifidum in a total daily recommended dose of 2

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billion cfu/day. Labinic is manufactured to stringent high-quality control standards in a cGMP and cGPP compliant, licenced manufacturing pharmacy.

Labinic has an excellent safety profile and is widely used in NHS (UK) and in neonatal units overseas.

We are pleased to see further evidence of its use emerging in clinical papers and we confirm that we have had no influence over any publications describing use of Labinic.

Thank you for reading this update, we hope you found it interesting. Please feel free to share with healthcare and other professional colleagues. **All disclaimers are fully applied .**

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