Probiotic Research Update July 2024

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What effects do antibiotics have when given at, or soon after, birth, on the gut microbiome?

Ainonen S, Tejesvi MV, Mahmud MR *et al*. Antibiotics at birth and later antibiotic courses: effects on gut microbiota. Pediatric Research (2022) 91:154–162.

This was an update on the single-centre prospective cohort study from Finland including 100 babies delivering vaginally which we reviewed in the previous newsletter. This is the first important thing, as pretty much all babies delivered by Caesarean section are exposed to antibiotics. In this cohort, 27 babies had no exposure, 27 had intrapartum prophylaxis (IAP) 2-24hrs before birth, 24 had postnatal (PN) antibiotics within 24 hrs of birth, and 22 had both IAP and PN exposure. In this centre, all babies given PN antibiotics routinely received probiotic (of only 1 x 10^8 daily)

The authors had previously demonstrated that perinatal exposure led to changes in the microbiome which persisted for 6 months, and in this work they followed the same cohort to 1 year of age, recording any further courses of antibiotics received (which occurred in 28 babies). However they only received samples from 100 of the original cohort of 150 babies.

Interestingly the results show that the impact of perinatal antibiotics was more persistent than the impact of later oral antibiotics, and there was an (adverse) dose effect in those who received both IAP and PN antibiotics. The use in PN babies of the single strain Lactobacillus probiotic did not lead to a persisting difference in Lactobacilli at 1 year. Perinatal antibiotics led to increased Proteobacteria such as *E.coli* in the gut at 1 year, abundance of which is a known risk for urinary tract infection and other important conditions including obesity.

Overall there is a persistent impact of perinatal antibiotics on the composition of the infant microbiome, which may be linked to the risk for future health conditions such as urinary tract infection, obesity and Crohn's disease, for examples.

Full text link to review here

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Intrapartum antibiotics and their effect on longer term growth, atopy and fungal infections.

Hutton EK, Simioni .C, Thabane L. *et al.* Associations of intrapartum antibiotics and growth, atopy, gastrointestinal and sleep outcomes at one year of age. *Pediatr Res* 94, 1026–1034 (2023)

This is another prospective study which evaluated the association between intrapartum antibiotic exposure, and subsquent body mass and height, as well as reported atopy and fungal infections. Babies who were not given peripartum antibiotics were less likely to have atopic disease (p=0.007) and fungal infections (p=0.046), and were more likely to show increased fat mass at 5 months of age (p=0.03).

This growing body of evidence supports the concept that protection of the neonatal and infant healthy microbiome is of paramount importance.

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Giving probiotics to babies may reduce their need for hospital admission in the first 2 years

Srinivasjois R, Gebremedhin A, Silva D *et al*. Probiotic Supplementation in the Neonatal Age Group and the Risk of Hospitalisation in the First Two Years: A Data Linkage Study from Western Australia. Nutrients. 2024 Jun 30;16(13):2094

This was a retrospective study which included preterm babies <32+6 weeks across 2 different epochs where single strain probiotic supplements were introduced in the second. A total of 1238 babies in Epoch 1 and 1422 in Epoch 2 were included. There was a small degree of reduced hospitalisation of any cause in Epoch 2 allowing for confounding factors (RR 0.92 (0.87-0.98)). There was a similar effect in hospitalisations for respiratory problems, but no significant difference for gut-infection hospital admissions. In addition, there were no differences in babies born <28 weeks in the two Epochs.

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Further to the FDA warning on probiotic use – ESPGHAN and EFCNI respond

van den Akker CHP, Embleton ND, Lapillonne A *et al*. Reevaluating the FDA's warning against the use of probiotics in preterm neonates: A societal statement by ESPGHAN and EFCNI. J Pediatr Gastroenterol Nutr. 2024 Jun;78(6):1403-1408.

Inevitably, the "de-introduction" of probiotics from neonatal use in the USA continues to drive debate, further study and concerns about how the risks and benefits are being considered. This paper from the Special Interest Group at the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), co-authored with representatives from the European Foundation for the Care of Newborn Infants (EFCNI), provides a view from the scientific and the patient advocacy perspectives.

They review some of the positive safety aspects of probiotics – evidence from meta-analysis of over 55,000 babies demonstrating high levels of safety, and that lives potentially saved from the devastating consequences of NEC likely to considerably outnumber the one case identified by the FDA, without full details yet available, where a baby sadly died from sepsis after receiving a strain of *B. infantis* (EVC001). 400 babies a year die from NEC in the USA, and if the use of probiotics, especially the multistrain preparations containing Lactobacillus and Bifidobacteria which appear to offer the greatest effects according to the meta-analyses, can reduce deaths by up to 50%, then the risk-benefit evaluation does not appear to be correct.

The authors also point out that other bodies, such as the American Gastroenterological Association (AGA), the World Health Organization (WHO) and the American Academy of Pediatrics (AAP) all advocated positively for the use of probiotics in premature infants. Whilst the AAP raised concerns about the lack of evidence for effect in babies <1000g, who have the greatest risks of NEC and death, the authors say this does not imply that probiotics should not be used in this group – just that greater caution should be exercised.

Parental rights appear to have been ignored by the FDA, and it is important that parents are also allowed to review the evidence, consider the risk-benefit position, and discuss their views with their baby's clinical team.

From our perspective, the death of any baby is a tragedy, but a potentially avoidable death needs to be evaluated to see what preventive strategies are in place. Bifidobacteria and Lactobacilli do not produce LPS endotoxins (like Gram negative bacteria do), they do not produce exotoxins (like GBS does) and therefore, in reported cases of probiotic sepsis, the babies do not die and the probiotic bacteria can be killed with a wide range of normally used antibiotics.

Labinic is a very high quality multistrain probiotic, designed to deliver both efficacy and good value-per-baby, and therefore scores strongly on both health economic as well as NEC,

mortality, sepsis and pathogen colonisation reduction, as well as improved feed tolerance. We hope that the clinicians and the FDA can come to an agreement based on science and evidence. Biofloratech Ltd has not funded any of the members of the Special Interest Group at ESPGHAN or ESPNIC.

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Promising therapies derived from the microbiome – for NEC?

Cifuentes MP, Chapman JA, Stewart CJ Current Research in Microbial Sciences 2024 ; (6) :

This review article looked at the potential therapeutic effects of Short Chain Fatty Acids (SCFAs) such as butyric, acetic and propionic acids, although there are many more. SCFAs are produced by the intestinal microbiome from metabolism of HMOs and other carbohydrates, especially in the proximal colon. They are a class of carboxylic acids, which have been previously shown to have anti-inflammatory activity (such as decreasing IL-6, IL-8 and TNFα), as well as preserving the intestinal barrier for example. However, in very high (supplemented) concentrations, they may also be harmful.

The primary nutritional source of HMOs in babies is breast milk, and many bacteria especially various strains of Bifidobacteria and Lactobacilli (Firmicutes phylum), produce SCFAs, and some work symbiotically together or use products from their own metabolism to generate further metabolites.

It is also evident that babies who are developing NEC show alterations in their SCFA profiles, and there is interest in using this effect for early diagnostic purposes for gut health, but no clear evidence is yet available for a clinically useful tool. As mentioned above, administration of exogenous SCFA can be harmful, particularly in the immature and/or sick gut, leading to mucosal injury. Perhaps restoring physiological levels should be the aim, either directly or indirectly (through use of probiotics for example).

It is likely that this work will lead to potentially valuable diagnostic tools (or at least tools which raise suspicion of a high-risk gut for NEC), and the question will be whether that then leads to a change in outcomes. It may also lead to the development of “replacement” therapies at doses shown to have a positive clinical effect.

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What impact has the FDA had on probiotic use in the USA?

Wala SJ, Ragan MV, Pryor E, Canvasser J, Diefenbach KA, Besner GE. Contemporary use of prophylactic probiotics in NICUs in the United States: a survey update. J Perinatol. 2024 May;44(5):739-744

A survey in 2015 showed that probiotics were given to VLBW infants in 14% of US NICUs (up from 5.2% in 2013), and this had nearly doubled (to 29.1%) in 2023. The main reason for administration was to reduce the risk of NEC, but also respondents indicated that they used probiotics to reduce sepsis risks and to improve feed tolerance. A secondary survey of 60 NICUs conducted after the FDA intervention showed that only 3% continued to give probiotics.

The FDA intervention occurred in September 2023, highlighting the death of a single baby given Evivo®, a single strain preparation of B. infantis. As a result of communication with the manufacturer, as well as other manufacturers, Evivo and others were withdrawn from the market.

It is estimated that the cost to develop an FDA-approved product (between 2009 and 2018) was $985 million, and any infant product would first have to be tested in adults. This prohibitive expense means that very few, if any, probiotic manufacturers are in a position to develop such a product, and if they do the cost of the probiotic will be extremely high to enable cost recovery. It appears that a relatively safe and cheap intervention has been taken away from neonatologists and parents. At least one of the authors (JC) is a well-known campaigner for a world without NEC through her leadership of the NEC Society and her personal experience of losing her son from complications of NEC.

Given this position, in the US litigious medical system, it would appear that the only compromise could be a (difficult to administer) medico-legal waiver / no fault arrangement, to enable Hospitals to trust their clinicians to work with parents for the best interests of their patients.

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Is there a shared bacteriome between mothers and their babies?

Vélez-Ixta JM, Juárez-Castelán CJ, Ramírez-Sánchez D, *et al.* J. Nutrients. 2024 Jun 22;16(13):1990

The entero-mammary pathway (gut-breast axis) is a specialized system where dendritic cells move bacteria to the newborn intestine via the mammary gland. Certain bacterial strains are selected to start the colonisation of the newborn gut. It is also evident that the pathway can

also transfer key metabolites, such as SCFAs, which are present during pregnancy as potential markers for maternal disease such as pre-eclampsia.

This study set out to investigate common probiotic profiles between maternal and neonatal gut flora and breast milk. They found a strong suggestion for vertical transmission, and that human milk supports a newborn gut environment rich in Streptococcus, Lactobacillus and Bifidobacterium.

It is interesting that Lactobacillus is one of the significant bacteria found. Lactobacillus are known to have anti-inflammatory effects and this "real world" analysis of healthy babies adds to the knowledge of what we should be aiming to consider as a healthy microbiome in the newborn.

The authors also presented evidence that some maternal dietary metabolites are present in the infant stool (for example from coffee, onions, pulses, oranges, alcohol and milk), and many of them have important metabolic effects.

This study demonstrates vital interactions between mother's diet, breast milk and the infant gut in the first 4 months. It may one day be possible to make recommendations about maternal diet and probiotic use which would benefit the baby due to this clear evidence for vertical transmission.

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Evidence on the benefits of probiotics for preterm infants.

Campos Martinez AM, Fernández Marín CE, Ruiz López A, *et al*. J.Nutr Hosp. 2024 Jun 19

This systematic review from Spain looked at the available evidence for the benefits of probiotic use in preterm babies. They included 16 papers, in which hundreds of studies had been meta-analysed.

The findings of the individual papers, and the overall systematic review published here, are astonishing consistent.

The combination of Lactobacillus and Bifidobacteria remained the most effective probiotics when the outcomes were the reduction of NEC, reduction of death and reduction of sepsis. The authors confirm that, whilst breast milk confers protection for preterm babies against NEC and sepsis, this effect is augmented by providing combination (multistrain) probiotic supplements. They state that "the use of lactobacillus and bifidobacteria does not cause

concern, because these strains normally reside in the GIT of healthy infants" (and see comment on Lactobacillus in previous paper in this bulletin).

Full text link here (download PDF)

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This update 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 billion cfu/day. Labinic is manufactured to stringent high-quality control standards in a GMP manufacturing licenced pharmacy.

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

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 its use.

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 fully applied.

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