Background and Transparency: This update was commissioned by Biofloratech Ltd, who manufacture Labinic® drops, which contain *Lactobacillus acidophilus*, *Bifidobacterium infantis* and *Bifidobacterium bifidum.* Information intended for healthcare professionals.

****

The negative effects of antibiotics on the infant gut

Xu et al. Antibiotic exposure prevents acquisition of beneficial metabolic functions in the preterm infant gut microbiome. Microbiome (2022) 10:103.

It is well known that antibiotics cause abnormalities in the microbiome at all ages. This study looked at potential mechanisms for this and how they might be related to adverse outcomes in babies.

The paper:

Stool and skin samples were analysed from 68 babies born prematurely with a median birth weight of 1384g (smallest baby 648g) and median gestational age 30.5 weeks (lowest gestation 24 weeks). 87% had exposure to maternal antibiotics. 22 received postnatal antibiotics and 46 did not. Most babies (85%) received breast milk. Samples were collected at birth and at 3 weeks of age, to analyse the effects of antibiotics given after birth and to compare the development of the normal microbiome, babies with antibiotic exposure were compared with those without.

In the first samples, there was no significant difference in the more preterm compared to the more mature babies. Antibiotic treatment after birth reversed the normal maturation of the gut microbiome over the study period. Babies exposed to antibiotics had greater proportions of Gram negative bacteria (Sphingomonas and Acidovorax) and Candida.

The bacteria which produced short-chain fatty acids (SCFAs) such as butyrate and acetate were particularly affected with almost complete suppression of SCFAs in the antibiotic exposed babies.

Comment:

This study showed that even short-term exposure to antibiotics after birth caused significant derangement of the microbiome and metabolic pathways, regardless of gestational age. These pathways are increasingly believed to be important in the baby's defence against NEC and late onset sepsis.

++

** DISCLAIMER: This brief review was produced for Biofloratech Ltd who manufacture and supply Labinic Drops, a multispecies liquid bio-flora 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

Lactobacillus and Bifidobacteria are key to production of SCFA metabolites that are important for human health

O'Riordan KJ et al. Short chain fatty acids: Microbial metabolites for gut-brain axis signalling. Molecular and Cellular Endocrinology. 2022;546:111572

This detailed review paper from an academic centre in Cork, Ireland, provides a detailed overview of the interactions of the microbiome with the brain. The direct and indirect effects of short-chain fatty acids (SCFAs) are important, because the administration of probiotics (especially Lactobacillus and Bifidobacteria) can increase circulating concentrations of these metabolites.

SCFAs are one of the most highly studied bacterial metabolites. They are produced when bacteria ferment non-digestible oligosacchardies and dietary fibres, although there are other less important sources. The most common SCFAs are butyrate, acetate and prioprionate, all of which are carboxylic acids. SCFAs have been implicated in the regulation of many important physiological functions including sleep, blood-pressure, immunity, brain maturation and behaviour. SCFAs have specific receptors called Free Fatty Acid Receptors (FFARs) which are specific for different SCFAs and are widely expressed on white cells, the gut, blood vessels, kidneys and neurons.

SCFAs protect gut health through improving the intestial barrier and local immunity, but they also reduce neuroinflammation and may have effects on reducing obesity and some psychiatric disorders. This review describes some of the positive effects in children and adults, including in IBS and inflammatory bowel diseases too.

Research on the direct intracolonic administration of SCFAs can have beneficial effects in animal studies, but it is likely that a multi-metabolic environment is required for pathways to function optimally, and research in this area is still in its infancy.

++

More evidence of the harm caused by early-life antibiotics

Chen WY et al. Increased antibiotic exposure in early life is associated with adverse outcomes in very low birth weight infants. J Chin Med Assoc. 2022 June

This study was a retrospective cohort of 132 very low birthweight (VLBW) infants with primary outcome measures being NEC and BPD. Every day of antibiotic treatment increased the risk of NEC (OR 1.28) and BPD (OR 1.6). The increased risk is thought to be due to the reduction in bacterial diversity, leading to overgrowth of pathogenic species. This effect was most significant at 30 days postnatally which the authors conclude coincides with the general timing of NEC. They also included babies given probiotics, but the use of probiotics

** DISCLAIMER: This brief review was produced for Biofloratech Ltd who manufacture and supply Labinic Drops, a multispecies liquid bio-flora 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

did not offset the effect, because broad-spectrum antibiotics were used for prolonged periods, which would have also killed the probiotic organisms.

They conclude that the use of narrower spectrum and shorter courses of antibiotics are essential to enable the gut diversity to be protected and strengthened by the addition of probiotics in line with existing evidence.

++

Probiotics reduced dysbiosis in neonates with congenital surgical gastrointestinal conditions

Rao S et al. Probiotic supplementation in neonates with congenital gastrointestinal surgical conditions: a pilot randomised controlled trial. Pediatr Res (2022)

This paper:

61 babies over 35 weeks with congenital gastrointestinal conditions were randomised to receive a multistrain probiotic containing Bifidobacteria (breve, longum and infantis) or a placebo. Stool was analysed sequentially and was found to have reduced levels of pathogenic bacteria in the babies who received probiotics. SCFA levels were higher in the probiotic group, in particular acetate (Bifidobacteria are not butyric acid producers unlike Lactobacillus).

This study also concluded that probiotic administration was safe, with no Bifidobacterial sepsis episodes seen, which was a previous concern in this population of babies.

++

Antibiotic Resistance Genes are more prevalent in the neonatal microbiome but can be reduced with breastfeeding and probiotics

Leo S et al. The neonatal intestinal resistome and factors that influence it - a systematic review. Clin Microbiol Infect. 2022 Jul 19:S1198-743

This review article included 23 cohort studies showing high levels of antibiotic resistance genes (ARGs) in the neonatal microbiome, even in babies not exposed to direct antibiotics, with evidence of transferance of ARGs from mother to baby. The prevalence of ARGs was reduced by breastfeeding and in babies who were given probiotics.

** DISCLAIMER: This brief review was produced for Biofloratech Ltd who manufacture and supply Labinic Drops, a multispecies liquid bio-flora 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

Impact of gestational age on the gut microbiome

Jia Q et al. Dynamic Changes of the Gut Microbiota in Preterm Infants With Different Gestational Age. Front Microbiol. 2022 Jun 30;13:923273

In this study, the authors evaluated 616 stool samples at different time points up to 365 days, from 166 preterm and 50 term infants, with 27 of the preterm babies born less than 27 weeks gestation. The gut microbiome in the preterm cohort was signficantly affected by the mode of delivery, and the gestational groups were significantly different during the first 28 postnatal days. Whilst the preterm groups showed microbiome maturation patterns developing more like those of term babies over time, there was a persistant difference at the age of 1 year between the preterm and term-born microbiota in terms of bacterial composition and diversity.

++

Preventive factors for NEC – a mixture of Lactobacillus and Bifidobacteria species reduces NEC

Campos-Martinez AM et al. Evaluation of Risk and Preventive Factors for Necrotizing Enterocolitis in Premature Newborns. A Systematic Review of the Literature. Front. Pediatr. 17 May 2022

This systematic review of recent literature evaluated the risk and preventive factors for NEC in preterm babies. 19 studies met the criteria for inclusion out of 113 found. The authors conclude from their review that there are known factors which reduce the risks of NEC, which are:

- The enteral consumption of human milk oligosaccharides
- The administration of multistrain probiotics, especially the combination of Lactobacillus and Bifidobacteria
- The supplementation of human milk with lactoferrin
- The use of donor milk fortified appropriately for the infant's nutritional needs

They also conclude that tests such as faecal calprotectin can lead to an earlier diagnosis of NEC.

For probiotics, the review covered 7 studies with 134,000 patients. This showed that the combination of different strains of a combination of Lactobacillus and Bifidobacteria, reduces the incidence of NEC Bell stage ≥2, especially in babies less than 28 weeks gestation and birth weight <1000g. Furthermore, the incidence of reduced deaths and late-onset sepsis were lower in the groups receiving a mixture of Lactobacillus and Bifidobacterium.

** DISCLAIMER: This brief review was produced for Biofloratech Ltd who manufacture and supply Labinic Drops, a multispecies liquid bio-flora 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

++

Labinic is a multi-strain probiotic with Lactobacillus and two Bifidobacteria strains. It is manufactured to stringent high-quality control standards in a GMP manufacturing licenced pharmacy.

Labinic has an excellent safety profile with over 2 million doses administered. It 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.

Biofloratech Ltd

** DISCLAIMER: This brief review was produced for Biofloratech Ltd who manufacture and supply Labinic Drops, a multispecies liquid bio-flora 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