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

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Do we need more trials of probiotics for NEC – or do we have enough evidence? Important questions addressed.

Razak A, Patel RM, Gautham KS. Use of Probiotics to Prevent Necrotizing Enterocolitis Evidence to Clinical Practice. JAMA Pediatr. 2021;175(8):773-774.

A discussion paper which reviews the current evidence and tackles the usual questions raised by clinicians who are trying to assess the evidence for their own practices. This was accompanied by further discussion on the lead author's twitter feed.

Approximately 88,000 babies have partcipated in research across 56 RCTs and 30 non-RCTs.

"Will further RCT's change the evidence that probiotics reduce NEC?" – almost certainly not – it would take a study with 80,000 participants to show no effect. Funding for trials could be better spent elsewhere.

"What about the variations in strains?" The Cochrane review in 2020 inlcuded trials with 27 different strains, but the heterogeneity was low (<20%). Therefore despite strain and population differences, the effects were similar.

"What about the effects of poorly designed studies causing bias?" Under 21% of the meta-analysis contained highly biased studies. Furthermore, the effects of the non-RCTs cannot be disregarded.

"What about safety?" No RCT has reoorted probiotic sepsis and only 2 observational studies reported a total of 5 cases.

"Our rates of NEC are low so we don't need to use probiotics." For the babies who do get NEC, this type of statement is of little comfort to their parents who might find out that a relatively cheap and safe treatment could have prevented, or reduced the severity of their baby's NEC.

Comment:

It is useful when papers are published that try to take a pragmatic view of the current evidence, as sometimes it can feel that we have reached an impasse and decision making, faced with what seems like a lot of evidence, becomess even harder because of the various permutations and combinations. Safety and cost-effectiveness are important, and the cost-benefit ratio works even when rates of NEC are low for lower cost preparations like Labinic Drops. Rather than waiting for trials that may never happen or may not change the meta-

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analysis, it is suggested in this viewpoint paper that clinicians can give parents the choice, can introduce probiotics without significant expense, or risk and then review their practice data after several years of "real world" experience have accumulated.

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AAP position paper on probiotics

Brenda Poindexter and COMMITTEE ON FETUS AND NEWBORN. Use of Probiotics in Preterm Infants. Pediatrics June 2021, 147 (6)

Poindexter and colleagues, on behalf of the AAP, state that the current evidence does not support the routine, universal adminsitration of probiotics to preterm babies. They cite the potential for harm, although they also note that multistrain probiotics showed efficacy in reducing necrotising enterocolitis and all-cause mortality in trials. They focus on the regulatory challenges of fulfilling the need for a pharmaceutical, notwithstanding the dramatic cost implications of clinical trials required to gain FDA approval.

They recognised the issue of CFU count of viable probiotics not only at time of manufacture but also during shelf life, and also the consistency of products – although they cited lots of evidence and product evaluations which were over 5 years old.

In the absence of a "probiotic drug", they are unable to recommend the use of probiotics, although they do say that centres who decide to use probiotics can do so with appropriate caution and monitoring. Centers should choose preparations that are at low risk for contamination and have high accuracy of dose and stability.

Comment:

The AAP position recognises the unique challenge of a live probiotic preparation meeting the criteria for a stable, consistent, predictable drug. The concerns about harm are interesting, given the low number of sepsis episodes reported in trials, which they felt were likely to underreport but do not explain why. The cost of achieving FDA pharmaceutical approval would make probiotics extraordinarily expensive (given their niche market), which would potentially "shift" the cost-benefit away from routine use in most babies, even though targeted use in the highest risk babies has not been tested and may not be as effective.

However in 2020 the American Gastroenterological Association (AGA) conditionally recommended the use of probiotics to prevetn NEC in babies <37 weeks and in those with low birth weight. The AGA also wrote there was evidence that probiotics may reduce mortality and severe NEC, may improve feed tolerance and speed up discharge to home.

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Reduction in NEC in >28-week babies in retrospective review

Granage C et al. Necrotising enterocolitis, late-onset sepsis and mortality after routine probiotic introduction in the UK. Archives of Disease in Childhood - Fetal and Neonatal Edition Published Online First: 25 August 2021. doi: 10.1136/archdischild-2021-322252

This was a retrospective study from a UK neonatal unit, which examined a pre- and post-introduction of probiotics (including in 1/3 of babies the use of Labinic) population, with over 500 babies in each group under 32 weeks. The headline was that the rates of NEC were unchanged (9.2% vs 10.6%) and that mortality (9.2% vs 9.7%) and Late Onset Sepsis (LOS) (16.3% vs 14.1%) were unchanged. However babies >28 weeks did show significantly lower rates of NEC and there was signfiicantly lower LOS in babies <1000g. The median age for starting probiotics was 6 days.

Comment:

The results from this study contrast to the data published by Robertson et al. The background rates of NEC in this study are substantially higher, which suggests that either the populations are very different, or the diagnosis of NEC is different (although NEC and FIP were well defined in this study). The later administration of probiotics may also be a factor, and it is a paradox that the babies who are at greatest risk of NEC and LOS tend to be those who are slow to achieve enteral feeds. What is also interesting is that only 19% of the babies with NEC who received probiotics only recevied their mother's milk; donor milk was not used. The potential for different causes for NEC between different units, warrant deeper understanding of this condition. In more mature babies (over 28 weeks) there was less NEC and in the smaller babies there was less sepsis, which are positive findings in line with the Robertson data.

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Intrapartum Antibiotics have a negative effect on the Newborn Microbiome

Diamond L, Wine R, Morris SK. Impact of intrapartum antibiotics on the infant gastrointestinal microbiome: a narrative review. Arch Dis Child. 2021 Oct 29:archdischild-2021-322590. doi: 10.1136/archdischild-2021-32259

This review study included 30 publication which showed that intrapartum antibiotic exposure seems to reduce Bifidobacteria presence and led to reduced bacterial diversity. The long term effects of such an effect are unknown.

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Korpela K. Impact of Delivery Mode on Infant Gut Microbiota. Ann Nutr Metab. 2021 Aug 30:1-9. doi: 10.1159/00051849

Another paper published in August 2021 notes that breastfeeding and probiotics are important to "fix" an intestinal dysbiosis arising from antibiotic exposure, regardless of the mode of delivery.

Comment:

We have had regular feedback from clinicians who report that babies delivered by Caesarean section (where there is routine antibiotic exposure prior to the procedure and through the maternal breastmilk after delivery) are more likely to show symptoms of a dysbiosis with feed intolerance, wind, pain and cramps.

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And finally – some science and detailed information about Bifidobacterium infantis Bi-26 – one of the components in Labinic Drops. Strain differences are considered to be important, and the strains in Labinic were chosen for a combination of safety but also gut-efficiency/colonisation advantages.

Bifidobacteria were first found in infant stool in 1899 and are known to be the most abundant bacteria (up to 80% of the total) in the first few weeks after birth, and this period for colonisation appears to be critical. Bifidobacteria can be vertically transmitted.

Loss of Bifidobacteria in the microbiome is associated with higher rates of later-onset autoimmune disease and allergies. B. infantis is dominant in breast fed babies and has immunomodulation effects, such as suppressing inflammation, reducing intestinal permeability, reducing gut luminal pathogens and maturing the immune response. HMO's (see previous Newsletters) are the main substrate for B. infantis and the metabolic activity of B. infantis reduces gut pH. B. infantis has not been associated with antibiotic resistance and is widely considered to be clinically safe.

Bi-26 is the strain used in Labinic, which has some significant advantages to the ATCC Type strain (ATCC 15697) B. infantis in terms of the utilisation of 2'-fucosyllactose (2'FL), 3-fucosyllactose (3FL) and difucosyllactose (DFL). We previously commented on a paper from this group in the April 2020 newsletter and further examination of the Bi-26 is summarised below, with a full text link also available.

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B. infantis Bi-26 grows faster than the Type strain of B. infantis and it produces additional metabolites due to its adaptation characteristics which use these FLs efficiently and quickly, producing higher levels of acetate, lactate and formate than the Type strain comparator and potentially giving the Bi-26 a competitor advantage.

The low pH environment is also considered to exclude potential pathogens. The production of pyruvate and L-fucose by Bi-26 are additional factors considered to be important.

Zabel, B.E., Gerdes, S., Evans, K.C. et al. Strain-specific strategies of 2'-fucosyllactose, 3-fucosyllactose, and difucosyllactose assimilation by Bifidobacterium longum subsp. infantis Bi-26 and ATCC 15697. Sci Rep 10, 15919 (2020). https://doi.org/10.1038/s41598-020-72792-z

Full text here https://www.nature.com/articles/s41598-020-72792-z

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Labinic is a multi-strain probiotic manufactured to stringent high-quality control standards in a GMP manufacturing environment. 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-professional colleagues and we wish you a very happy and productive 2022.

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Labinic Drops
Now on the NHS Supply Chain

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