A Nutritional Approach to Feeding a Targeted Bacterial Strain in the NICU

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Probiotic use in the NICU has been considered as a promising tool for the prevention of necrotizing enterocolitis (NEC) with a focus on the very low birth weight (VLBW) population of infants <32 weeks or <1500 grams, and the data appear to show a lower risk of NEC in preterm infants fed a probiotic. However, from a pharmaceutical perspective, the evidence and precision on which strains, or how much of each strain, to use for NEC prevention is inconclusive, primarily due to a lack of understanding or focus on the mechanism of action. As a result, expert groups have conflicting viewpoints.

This dichotomy is clear from two recently published articles regarding the use of probiotics in the NICU. The first was a meta-analysis of 56 RCTs and 30 observational studies (including over 80,000 patients total) on the use of probiotics to prevent NEC, published in the Journal of the American Medical Association (JAMA) Pediatrics. After evaluating the results, Razak et al. suggested that the evidence supports the routine use of probiotics for preterm infants. The authors further referenced support for this recommendation by citing the Canadian Pediatric Society guidelines, the American Gastroenterology Association, and the European Society for Paediatric Gastroenterology Hepatology and Nutrition.

A contrary viewpoint was written by the American Academy of Pediatrics (AAP) Committee on Fetus and Newborn. The Committee took the position that, due to the lack of FDA-regulated pharmaceutical products and the heterogeneity of the clinical data between different probiotics, the current evidence does not support routine administration of probiotics to preterm infants.

Given that preterm infants are a particularly vulnerable population, the cautionary tone from the AAP committee regarding safety is well warranted. However, the specific and narrow pharmaceutical perspective on probiotic use to treat NEC does not represent the whole story of patient care in the NICU. Proposed here is a new lens through which to view NICU probiotic use, focusing on a nutritional rather than pharmaceutical intervention to provide comprehensive management of the preterm gut microbiome, leading to overall improved health outcomes in preterm infants, including NEC.

Differentiating between a pharmaceutical vs nutritional approach when utilizing probiotics as standard of care:

It is well established in the literature that preterm infants acquire high levels of nosocomial pathogenic bacteria in their gut microbiome. This may disrupt evolutionarily appropriate gut assembly, resulting in microbiome instability and a loss of function. This imbalance of pathogenic and beneficial bacteria causes enteric inflammation and puts preterm infants at risk for a number of adverse outcomes. Managing this microbial imbalance in the preterm gut should be a clear patient care goal in the NICU. Said another way, if a Bifidobacterium dominant microbiome in a breast-fed infant is natural and developmentally appropriate in early infancy, it stands to reason that achieving this should be a milestone in the care of premature infants.

Research published by Nguyen et al. in 2021 shows that modulation of the gut microbiome is achievable in preterm infants without the use of antibiotics through the nutritional approach of feeding a targeted bacterial strain, activated B. infantis EVC001 (EVC001) in addition to human milk. Contrary to most probiotic strains on the market, which have been selected based on availability and production characteristics rather than function, the EVC001 bacterial strain was determined as an infant gut symbiont that works synergistically with human milk to provide benefits to the infant, including colonization resistance to opportunistic pathogens. EVC001 was selected specifically for its growth characteristics on human milk oligosaccharides (HMO), the third most abundant class of nutrients in human milk, as evidenced in the EVC001 genome. Compared to other B. infantis strains, EVC001 has a functional H5 gene cluster important in the ability to use HMO, which highlights the importance of selecting specific strains for their ability to modulate the microbiome in an age- and diet-appropriate manner. The EVC001 strain is commercially available in the product Evivo with MCT Oil which is designated as a Food for Special Dietary Use (FSDU) specifically to meet dietary needs that exist due to age of infancy and lactation. Evivo with MCT Oil is regulated as a food under the FDA Food Safety Modernization Act, not under dietary supplement regulations.

Feeding EVC001 along with human milk is a nutritional solution with an established mechanism of action, unique in providing a comprehensive approach to improving newborn gut health. This nutritional approach provides a broad spectrum of biological benefits to the infant through the ability to completely break down HMO. As a result of these biological changes in the gut, observational studies
from NICUs using EVC001 as standard of care have reported significant improvements in intrinsic factors related to the onset of NEC, including reduction in enteric inflammation and reduced abundance of *Enterobacteriaceae*, such as *E. coli* and *Klebsiella oxytoca*. In addition to NEC-related benefits, clear indicators of improved gut health, such as significant reduction in diaper dermatitis and antibiotic usage, have been seen in preterm infants receiving EVC001.

Given the above clinical outcomes and the known mechanisms of action, numerous prominent healthcare institutions have successfully introduced the routine use of *B. infantis* EVC001 in their NICUs, including use in extremely low birth weight (ELBW) infants.

In conclusion, comprehensive management of the preterm infant gut through nutritional intervention aimed at modulating the microbiome can yield health benefits to the infant, including the reduction or elimination of known causative factors related to NEC. As demonstrated in clinical studies using EVC001, this is possible due to the unique capacity of the EVC001 strain to utilize specific components of human milk (i.e., HMOs), colonize the infant gut, displace hospital acquired microorganisms, and produce specific metabolites that lower enteric inflammation and modulate the immune system.

**Addressing the safety of activated *B. infantis* EVC001 as a high-quality nutritional product:**

Routine use of high-quality food-grade nutritional products is commonly practiced in NICUs across the United States. The targeted EVC001 bacterial strain in Evivo with MCT Oil was selected for use in the NICU at Edward-Elmhurst because of the manufacturer’s commitment to high quality standards with rigorous testing throughout the end-to-end product life cycle and transparent labeling with 8 billion CFU of the designated EVC001 strain guaranteed through the ‘best if used by’ date.

Selecting a NICU-appropriate form was also important when adopting Evivo as part of the feeding protocol at Edward-Elmhurst. Contrary to other products, Evivo with MCT Oil is designed with the neonate in mind, manufactured in a single-use, ready-to-feed liquid which facilitates adherence to the Infant and Pediatric Feeding 3rd Edition recommendation. Finally, but most importantly, *B. infantis* is an infant gut symbiont and the EVC001 strain is a non-pathogenic species, lacking virulence factors and has been fed under the care and direction of health professionals as a microbiome management product many thousands of times to preterm infants, including ELBW infants, as a nutritional product.

**Pointing to recent and future research of EVC001 in preterm infants:**

A series of strong and consistent data on the unique benefits of activated *B. infantis* EVC001 have been presented in recent published clinical trials, and recently presented at neonatology conferences such as Cool Topics in Neonatology, Hot Topics in Neonatology and the NEC society.

Furthermore, a clinical trial was recently completed at Winnie Palmer Hospital in Orlando FL, which systematically assessed safety and tolerability of the product among preterm infants <1500 grams or gestational age at birth <33 weeks. This study adds to a growing body of data that demonstrates how feeding EVC001 to preterm infants in the NICU provides care givers with a new tool to address comprehensive management of the infant gut microbiome, leading to improved global gut health and overall healthier infants. Additionally, the beneficial impact of actively managing the preterm infant gut microbiome was obvious from a recent study at Oregon Health and Science University which showed significant reductions in NEC and NEC-related mortality among VLBW and especially ELBW infants fed Evivo with MCT Oil.

**Concluding remarks**

While the AAP Committee Report wisely raises awareness over the need for high quality probiotics for the preterm population, their view on probiotics solely as a drug for the prevention of NEC is very narrow. A drug implies a certain amount of accepted risk to solve the indication; however, if missing symbionts and overabundance of hospital acquired bacteria are a root cause and key to the overall health of the preterm infant, a more global approach needs to be considered.

Over the past few years, it has become clear that the gut microbiome is an important “microbiological organ” that, if managed properly, has been implicated in many beneficial aspects of neonatal health, including the reduction of opportunistic pathogens, antimicrobial resistance, enteric inflammation, diaper dermatitis and feeding intolerance, all issues that greatly affect preterm outcomes in the NICU. Given that the AAP’s Committee on Fetus and Newborn may not issue another report for several years and gut microbiome science and clinical usage is rapidly developing, clinicians are encouraged to follow new research carefully to make the best evidence-based, informed decisions for their patients. Finally, we should consider nutritional-based approaches to comprehensively manage the infant gut microbiome for the improvement of all health outcomes, including NEC, in addition to the pharmaceutical approach as suggested by the recent AAP Committee Report. If indeed, the effective nutritional management of the preterm infant gut sets up conditions that do not allow the overgrowth of pathogenic bacteria that contribute to NEC, there may no longer be a need for a pharmaceutical intervention to treat it.

**References**

7. Grier, A. *et al.* Impact of prematurity and nutrition on the


Feed additives are used to balance diets, increase nutrient absorption, and reduce toxicity and bacterial contamination of feed (Borda et al., 2019). The use of bacterial enzymes as a feed additive attracts more increased attention. Enzymes play an important role in the digestibility of nutrients, which helps to reduce the cost of the diet. A common group of enzymes used as nutritional supplements are pro-enzymes that catalyze protein hydrolysis. Exogenous proteases are thought to not only supplement the digestive enzymes of animals, such as pepsin and trypsin, but also destroy nutrients such without loss of nutritional value. Moringa is especially promising as a food source in the tropics because the tree is in full leaf at the end of the dry season when other foods are typically scarce. A large number of reports on the nutritional qualities of Moringa now exist in both the scientific and popular literature. Any readers who are familiar with Moringa will recognize the oft-reproduced characterization made many years ago by the Trees for Life organization, that “ounce-for-ounce, Moringa. Insecticide activity of B. thuringiensis bacterial strains grown on the medium based on the wastes from the production of alcohol - the bard, after 7 days of exposure was 48.71%, after 14 days - 87.53%. The cell quantity and the insecticidal activity of B. thuringiensis bacterial strains grown on a nutrient medium based on skimmed milk powder was higher than the above-mentioned nutrient media. So, the Bt 26 strain, grown on a medium based on dry milk, showed the highest growth titer - 5.7 x 108 CFU / ml. The insecticidal activity of local strains of B. thuringiensis was determined using the method of V. Guliy et al. [7]. Apple leaves pretreated with 70% ethanol were used as feed for the caterpillars. Health care professionals should aim to provide adequate nutrition to every patient unless prolongation of life is not in the patient’s best interest (grade C). It should be hospital policy that the results of an admission nutritional screening are recorded in the notes of all patients with serious illness or those needing major surgery (grade C). Artificial nutrition support is needed when oral intake is absent or likely to be absent for a period >5–7 days. Earlier instigation may be needed in malnourished patients (grade A). Support may also be needed in patients with inadequate oral intake over longer periods. PDF | A practical approach for nutritional assessment in preterm infants under intensive care, based on anthropometric measurements and commonly used | Find, read and cite all the research you need on ResearchGate. A Practical Approach in the NICU. Luis Pereira-da-Silva 1,2,3,* , Daniel Virella 3 and Christoph Fusch 4. 1Medicine of Woman, Childhood and Adolescence, Faculdade de Ciências Médicas NOVA Medical School attributed to inadequate nutrient intake and lack of standardization in feeding practices. [1, 2]