

Top 3 Considerations When Evaluating a Probiotic for Standard of Care in the NICU

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Routine neonatal care, antibiotics and prolonged hospitalization can have detrimental effects on the infant gut microbiome. These often-unavoidable practices, together with gestational age and immune immaturity, place preterm infants at uniquely elevated risk for developing gut dysbiosis.¹ In neonates, the consequences of dysbiosis range from feeding intolerance¹ to serious infections and life-threatening conditions, such as sepsis and necrotizing enterocolitis (NEC).² Evidence suggests administration of the appropriate probiotic can be an effective approach to shift the neonatal gut microbiome toward a more protective balance of microbes.³ However, with the variety of products available, as well as range of claims and formulations, choosing the right probiotic can be an overwhelming task. To facilitate this process, three important considerations are recommended when evaluating a probiotic for the NICU.

Scientific evidence of efficacy and proven mechanism of action

Arguably, the most important aspect when choosing a probiotic is the level of evidence-based data to support efficacy. Evidence from peer-reviewed and appropriately controlled studies is imperative, both for safety and to support anticipated beneficial effects. Importantly, data must be available at the strain-level, as the functions and benefits of a given strain are not generalizable to other probiotics of the same species.⁴

Clear mechanism of action for each strain is another key aspect in probiotic evaluation. In the NICU, pathogenic species from hospital surfaces invade the susceptible preterm gut, further exacerbating dysbiosis and contributing to nosocomial infections.⁵ The overabundance of pathogens triggers intestinal inflammation and enterocyte injury, which are thought to be significant risk factors in the development of NEC and sepsis.⁶ Probiotic strains with an elucidated mechanism to displace pathogenic bacteria in the infant gut, along with demonstrated immunomodulatory properties which in turn reduce enteric inflammation, are likely to have the most success improving outcomes in this population. Thus, it is recommended for probiotic products to contain strains that naturally colonize the healthy infant gut. These probiotics have a better chance of colonizing in high numbers and out-competing harmful bacteria, while having a favorable interaction with the immune system.⁷

Specific species of bifidobacteria are the first colonizers of the healthy infant gut and play key roles in early immunological development. *B. longum* subsp. *infantis* (*B. infantis*) is the most adept at colonizing the infant gut by utilizing oligosaccharides from human milk. *B. infantis* is also associated with improving gut barrier function.^{7,8} Feeding *B. infantis* in combination with human milk favorably alters the microbiome of term and preterm infants.^{7,9} In a clinical study, feeding *B. infantis* EVC001 was effective in significantly reducing the abundance of pathogenic bacteria¹⁰ known to carry virulence factors,¹¹ as well as reducing inflammatory responses.¹² Mechanistically, *B. infantis* EVC001 displaces pathogens by competing for nutritional resources in the gut and producing antimicrobial compounds in the form of organic acids, mainly lactate and acetate.¹³ These organic acids reduce the colonic and fecal pH, which furthers discourages the growth of acid-sensitive pathogens.¹⁴ Infants fed EVC001 also experienced significantly less degradation of the protective gut mucosal barrier compared to infants not fed the probiotic.¹⁵ The EVC001 strain was isolated from a healthy breastfed infant and its benefits in neonates are supported by a growing number of peer-reviewed studies,^{10-12,15,16} making *B. infantis* EVC001 an ideal probiotic strain for use in the NICU.

Product formulation and presentation

When it comes to probiotic formulation, powdered and liquid forms are the two main options. Powdered probiotics are more widely available due to the lower manufacturing costs. However, the use of powdered products in the NICU is heavily discouraged.¹⁷ Powdered probiotics can aerosolize up to three feet in distance when opened, contaminating surrounding surfaces and hands of the opening operator.¹⁸ This may increase the risk of central line infections and cross-colonization between patients. In the absence of alternatives, guidelines recommend handling powdered products at a designated location separate from patient care areas. These additional safety requisites often involve laborious multi-department logistical coordination which can be disruptive to day to day operations of the NICU staff. Additionally, careful sanitation steps and aseptic technique are required to prevent the inadvertent introduction of pathogens during preparation, and once reconstituted, some ingredients can serve as media for the multiplication of infectious bacteria. For these reasons official guidelines from the Academy of Nutrition and Dietetics (AND) and the Centers for Disease Control and Prevention (CDC) recommend, whenever possible, liquid product formulations should be chosen for use in the NICU.¹⁷

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Ask the following questions when evaluating probiotics for your NICU

- Is there sufficient and rigorous evidence-based data to support the mechanism of action and function of each individual strain?
- Is the CFU count of each strain clear and guaranteed at time of use?
- Are the other ingredients in the product safe & tolerable for preterm infants?
- What's the origin of the strain and is it a natural colonizer of the infant gut?
- Is the product manufactured on a dedicated line to prevent cross contamination during manufacturing?
- Does the manufacturer follow current Good Manufacturing Practices (cGMP)?
- Is the company able to provide a certificate of conformance, including stability and viability, for each batch of product?
- Is the product in the most appropriate form for the NICU (liquid) and does it comply with the official guidelines outlined by the Academy of Nutrition and Dietetics (AND) and Centers for Disease Control and Prevention (CDC)?

Liquid probiotic formulations have many advantages. In contrast to powdered probiotics, which require mixing with larger volumes, liquid formulations allow for small volume administration, compatible with initiation of trophic feeds.⁴ Liquid preparations in food grade oils, such as MCT oil, prevent aerosolization allowing bedside handling. MCT oil also creates a protective layer for oxygen sensitive organisms, ensuring probiotic viability, and facilitates flowability reducing the risk of clogging the enteral feeding tube. Finally, liquid formulations in single-serve vials eliminate the risk of product cross-contamination from repeated access to a central container.

Manufacturing, quality and safety

When providing a probiotic to vulnerable NICU patients, manufacturing, quality and safety are imperative. Key considerations when evaluating quality of a probiotic product include accurate labeling, transparent quality testing and verifiable bacterial counts for each individual strain listed on the product label. In a recent position statement, the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) stated, “manufacturers should provide certificates of compliance and analysis to be able to address at least strain identity, purity, viability at end of shelf life, and antibiotic susceptibility and resistance profiles”.¹⁹ These recommendations were issued in part in response to reports of manufacturers suspected of inflating the total bacterial counts (listed as colony forming units [CFU]) of multi-strain products and/or inaccurately listing bacterial strains on the label.²⁰ Health professionals should be wary of these unethical practices and ensure the probiotic label lists strain designation and visibility to the individual counts for each bacterial strain. Manufacturers must also be able to provide a certificate of conformance upon request, to confirm the product is labeled correctly, free of contamination and viable until time of administration to the NICU patient. Finally, because certain bacterial strains are particularly susceptible to temperature fluctuations, manufacturing and distribution must be protected by cold chain to ensure viability at time of administration.

Taken together, rigorous scientific evidence proving efficacy, product formulation and quality of manufacturing are critical aspects to consider when evaluating a probiotic and could make the difference in achieving important health outcomes in NICU

patients. Choosing probiotics from companies committed to verifying the identity and safety of their ingredients is of upmost importance. For the NICU, follow guidelines from the ADA and the CDC,^{17,21} and steer away from powdered products. Ensure your probiotic of choice is manufactured under the highest quality standards and is protected by cold supply chain to ensure viability. To make this process easier, the table below provides criteria for evaluating probiotic options for your unit.

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