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POSITION STATEMENT

Gastroenterology

Reevaluating the FDA's warning against the use of probiotics in preterm neonates: A societal statement by ESPGHAN and EFCNI

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Abstract

The recent advisory issued by the United States Food and Drug Administration, cautioning against the routine administration of probiotics in preterm neonates, has sparked a lively debate within the scientific community. This commentary presents a perspective from members of the Special Interest Group on Gut Microbiota and Modifications within the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and other authors who contributed to the ESPGHAN position paper on probiotics for preterm infants, as well as representatives from the European Foundation for the Care of Newborn Infants. We advocate for a more nuanced and supportive approach to the use of certain probiotics in this vulnerable population, balancing the demonstrated benefits and risks.

KEYWORDS

live biotherapeutic product, necrotizing enterocolitis, premature infants, probiotic drug, probiotic sepsis

1 | INTRODUCTION

The recent advisory issued by the United States Food and Drug Administration (FDA), cautioning against the routine administration of probiotics in preterm neonates,[1] has sparked a lively debate within the scientific community and among other advocates for preventing necrotizing enterocolitis (NEC).[2–6] This commentary presents a perspective from members of the Special Interest Group on Gut Microbiota and Modifications within the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and other authors who contributed to the ESPGHAN position paper on probiotics for preterm infants,[7] as

For affiliations refer to page 3.

well as representatives from the European Foundation for the Care of Newborn Infants (EFCNI). Both organizations endorsed this commentary. We advocate for a more nuanced and supportive approach to the use of certain probiotics in this vulnerable population, balancing the demonstrated benefits and risks.

2 | CONSIDERATIONS ABOUT THE FDA WARNING

The FDA's warning refers to a case of a preterm infant who had been administered the probiotic strain *Bifidobacterium longum* subsp. *infantis* EVC001, developed sepsis from this specific strain and subsequently died.[1] Although this incident is very tragic, it is important to note that it represents an isolated case. No further details are provided on concomitant diseases, actual cause of death, or causality assessment. Adverse effects can occur with any treatment or drug, although causality can be difficult to prove. In contrast, during probiotic sepsis, the specific probiotic strain can be directly detected and genotyped, resulting in a uniquely identifiable fingerprint. Most published cases of probiotic sepsis were successfully treated,[8,9] which may be because of low pathogenicity of many of the organisms involved (especially *Bifidobacterium* species) and their sensitivity to standard antibiotics.[8,10,11]

Benefit-risk assessment (BRA) is a complex and continuous process that occurs after a drug or intervention is launched onto the market. Detailed and extensive postmarketing surveillance is required to establish the occurrence, frequency and severity of adverse effects. However, an important limitation in all BRAs is the degree of subjectivity in reporting adverse events, including the likely underreporting of cases of probiotic sepsis, even those cases which were fatal. Quantitative benefit assessment relies heavily on randomized controlled trials (RCTs), whereas claims based on observational studies are more prone to bias and have lower degrees of certainty. The potential benefits of certain probiotic strains in very preterm infants are high. In fact, there are few therapies in neonatal medicine that have been studied as extensively as probiotics. More than 55,000 preterm infants studied in over 60 RCTs and 30 high-quality non-randomized studies, including trials from the United States, have received prophylactic probiotics.[12–15] Meta-analyses show that the risk of severe NEC can be reduced by 30%–50% when appropriate probiotic strains are used. Simultaneously, none of these studies report an increased incidence of sepsis, but for several strains rather a reduction.

We concur with the FDA and others on the concerns regarding the unregulated probiotic market.[16,17] However, we emphasize that the FDA's efforts to establish pharmaceutical-grade probiotic drugs, also known as live biotherapeutic products,[18] is unlikely to mitigate the risk of sepsis from a probiotic strain. Classifying probiotics as pharmaceuticals will foremost address several potential product quality issues, such as verification of the presence and concentration of the intended strain while avoiding inadvertent contamination with other bacteria. In addition, more attention will be directed to several strain safety concerns, including the potential transfer of antibiotic resistance genes and the avoidance of strains that produce D-lactic acid or may have other adverse metabolic side-effects.[7,19]

3 | ESPGHAN'S POSITION

In the ESPGHAN position paper on probiotics for preterm infants,[7] specific recommendations of a few efficacy-based probiotic strains for clinical use were made, whilst simultaneously recognizing the need for more high-quality research. Nonetheless, the current data strongly suggest that the number of adverse events associated with probiotics is several magnitudes lower than the reported reduction in NEC rates. The 2020 ESPGHAN position paper also addressed potential safety and quality control concerns by providing recommendations and emphasizing the importance of their confirmation by manufacturers before implementation. These can be summarized as:

- Use only products manufactured according to current Good Manufacturing Practices to ensure correct strain identity with lack of contamination. Certificates of analysis should address strain identity, purity, viability, and antibiotic susceptibility and resistance profiles;
- Do not provide probiotic strains, which produce D-lactate, as its potential risk or safety has not been adequately studied in preterm infants and remains uncertain;
- Use only strains devoid of any plasmids containing transferable antibiotic resistance genes. This information should be confirmed and provided by the manufacturer;
- Use only strains with proven effectiveness as determined by strain specific analyses.

Similar guidance was published recently from the United States.[20–22] As noted above, probiotic sepsis is an inherent risk of any probiotic product, is largely unrelated to product quality and may not be avoided with more stringent regulations, or by registration as pharmaceutical-grade. Probiotic sepsis most likely occurs after either intestinal translocation or contamination of intravenous catheters. As this latter route may be more common,[23] a hygienic workflow from preparation to administration to the preterm infant may have more impact on preventing catheter-related probiotic sepsis than a regulated product by itself.

4 | OTHER ORGANIZATIONS (AMERICAN GASTROENTEROLOGICAL ASSOCIATION [AGA], WORLD HEALTH ORGANIZATION [WHO], AND AMERICAN ACADEMY OF PEDIATRICS [AAP])

In 2020, the AGA advocated in a practice guideline for the use of certain probiotic strains in preterm infants to reduce NEC incidence.[24] Similarly, the WHO provided a conditionally positive recommendation for using probiotics in all human milk-fed preterm infants.[25] These recommendations were largely in line with those posed by ESPGHAN.[7,26] However, shortly after, the AAP stated that current evidence does not support routine administration of probiotics to preterm infants, particularly those with a birth weight of <1000 g.[27] However, this does not imply that probiotics should not be considered as a potential treatment in this group. These particularly vulnerable preterm infants have the highest morbidity and mortality risks, and may also stand to benefit most from efficacy-based probiotic strains. Although more rigorous mechanistic and clinical studies should be conducted to determine safety and efficacy of optimal strain combinations, there is already guidance available to allow a logical decision regarding which available strains have the best prophylactic potential and safety profile, as well as on the most relevant manufacturing standards.[7]

5 | RIGHTS OF THE PARENTS

Decisions regarding which extremely preterm infants should be offered active intensive care, whether invasive procedures such as laparotomy are appropriate, and whether all therapeutic treatments should be used must always be made in partnership with parents. Parents are capable of balancing benefits and risks when data are explained in lay language so they can be involved in decision making for their babies. Denying parents the option of advocating for their babies to receive a well-tested and safe intervention is not appropriate. We do not recommend that all very preterm infants must receive probiotics, as the recommendations are conditional, but we do suggest that every neonatologist should be prepared to discuss this option with every parent.

6 | CONCLUSION

In the absence of new, well-designed studies, we reconfirm that the available evidence has a highly favourable benefit-risk ratio thereby justifying the use of some well-identified, efficacy-based probiotic strains for the prevention of NEC in very preterm infants. Although caution and a hygienic workflow should be exercised when considering and implementing probiotics for preterm neonates, the exclusion of probiotics based on rare but tragic cases does not appear to be the optimal approach for preterm infants. An extremely low risk of probiotic sepsis is likely to be accepted by nearly all parents if this is compared to the relatively large reduction in short and long-term burden arising from NEC. Currently, 400 preterm infants die of NEC in the United States annually,[28] whereas this might be reduced by 30-50% through using probiotic strains with proven efficacy.[7,12–14] Abandoning evidence-based, high-quality products that are already currently available, while waiting for pharmaceutical-grade probiotic drugs, will cost many lives in the coming years. In addition, allowing neonatal intensive care units to only use future FDA-approved pharmaceutical-grade probiotic drug therapies will very likely increase daily costs substantially, while the risk of probiotic sepsis will likely not be lower. Besides, escalated costs will limit patient access to receiving evidence-based probiotics. Rather than delaying evidence-based interventions in favour of pharmaceutical-grade products, embracing probiotics with vigilance, guided by evidence and practicality, can harness their life-saving potential while still ensuring safety and efficacy.

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CONFLICT OF INTEREST STATEMENT

Chris H. P. van den Akker has participated as a clinical investigator and/or consultant, and/or advisory board member and/or speaker for ELGAN Pharma, Nutricia Early Life Nutrition, Nestlé (Nutrition Institute), and Baxter. Nicholas D. Embleton has provided expert advice to WHO regarding probiotics; Nicholas D. Embleton employer received institutional research grant from Danone Early Life Nutrition and Prolacta Bioscience; Nicholas D. Embleton received three speaker honoraria from Nestle Nutrition Institute donated to charity; Nicholas D. Embleton provided nonremunerated personal opinion to Neobiomics. Alexandre Lapillonne has no conflict of interest related to this work. Walter A. Mihatsch has participated as a clinical investigator and/or advisory board member, and/or consultant and/or speaker for Alzchem, Danone, Nestle Nutrition Institute, Neobiomics. Silva Salvatore has participated as consultant and/or speaker for Danone Nutricia, Nestle Nutrition Institute, Aurora Biofarma, Bioproject, Noos, DMG and, in the last 2 years, she has received consultant fee from Nestle Nutrition Institute. Roberto B. Canani has participated as a clinical investigator and/or consultant, and/or speaker for CHR Hansen, iHealth, Nestle Health Science, Nestle Nutrition Institute, Novalac, Nutricia, Mead Johnson Nutrition, United Pharmaceuticals (Novalac). Ener C. Dinleyici has participated as an advisory board member and/or consultant, and/or speaker for Biocodex, Nutricia, BioGaia and Nestle Health Science. Magnus Domellöf has received research funding from Arla Foods Ingredients and Prolacta Bioscience, as well as speaker or consultation fees from Baxter, Chiesi, Nestlé and Mead Johnson. Alfredo Guarino has received research grants or honoraria for educational presentations by IPSEN, Biocodex, Mayoli and Dicofarm. Pedro Gutiérrez-Castrellón has participated as a clinical investigator and/or consultant, and/or advisory board member and/or speaker for Biogaia Sweden, AB-Biotics, Abbott Nutrition and Nestle. Iva Hojsak has received honorarium for lectures from Abbott, BioGaia, Nestle, Nutricia, Sandoz and Takeda. Flavia Indrio has participated as consultant and/or speaker for Biogaia, Danone Nutricia, Nestle Nutrition Institute and Novalac. Alexis Mosca has participated as an advisory board member and/or consultant, and/or speaker for Biocodex, Nutricia, BioGaia, Nestle Health Science, Havea, PiLeJe and AdareBiome. Rok Orel has participated as consultant or speaker for Lek Sandoz, Ewopharma, Abbvie, Kefo, Medis, Merit and Inspharma. Johannes (Hans) B. van Goudoever is founder and director of the Dutch National Human Milk Bank and member of the national Health Council, and has received financial research support from Danone (not related to this topic). Zvi Weizman has participated as a clinical investigator and/or advisory board member, and/or consultant and/or speaker for BioGaia, BioCodex, Hipp, Mead Johnson, Nestle, Sensus and Materna. Silke Mader has no direct personal conflict of interest. Silke Mader is member of the EFCNI Trustee and Executive Board, but both functions are nonpaid. EFCNI as an organization received educational grants and has sponsorship agreements with DSM, Nestle Nutrition Institute, Philips and Prolacta Bioscience. Luc J. I. Zimmermann has no direct personal conflict of interest. Luc J. I. Zimmermann is a member of the EFCNI Executive Board, but this function is nonpaid. EFCNI as an organization received educational grants and has sponsorship agreements with DSM, Nestle Nutrition Institute, Philips and Prolacta Bioscience. Raanan Shamir has participated as a clinical investigator and/or advisory board member, and/or consultant and/or speaker for Abbott, Elgan, Else, Nestlé, Nestle Health Science, NGS, Soremartec and Nutricia. Yvan Vandenplas has participated as a clinical investigator and/or advisory board member, and/or consultant and/or speaker for Abbott Nutrition, Alba Health, Arla, Ausnutria, Biogaia, By Heart, CHR Hansen, Danone, ELSE Nutrition, Friesland Campina, Nestle Health Science, Nestle Nutrition Institute, Nutricia, Mead Johnson Nutrition, Pileje, Sanulac, United Pharmaceuticals (Novalac), Yakult and Wyeth. Hania Szajewska has participated as a clinical investigator and/or advisory board member, and/or consultant and/or speaker for: Arla, BioGaia, Biocodex, Danone, Dicofarm, Nestlé Nutrition Instutite, Nutricia, Mead Johnson/RB, Novalac, and Winclove. HS serves as a board member of the International Scientific Association for Probiotics and Prebiotics (unpaid, volunteer position).

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