The best from nature.
The best for nature.

57th Annual Meeting of ESPGHAN

Welcome to the HiPP Symposium

Gut talk – relevance of the intestinal communication axes for pediatric practice

May 16, 2025, Messukeskus Helsinki

Chair: Seppo Salminen,
Turku/Finland

Videos of the lectures available as of August 2025

www.hipp.com/hcp

Hania Szajewska,
Warsaw/Poland

Gut communication axes: the role of microbiota

Objectives

This presentation aims to:

1. Define the gut microbiota and explain the challenges in distinguishing between a healthy and dysbiotic microbiota.
2. Introduce the concept of gut-organ communication axes and describe their mechanisms.
3. Highlight the clinical relevance of gut-organ cross-talk in early life, especially in pediatrics.
4. Explore the potential of microbiota-targeted strategies to support child health.

Abstract

The gut microbiota — the diverse community of microorganisms living in the gastrointestinal tract — plays a central role in shaping human health from the very beginning of life. Beyond its role in digestion, it influences immune development, metabolism, neurodevelopment, and gut barrier function through a range of biochemical and molecular interactions.

Despite growing research, defining what constitutes a health-associated gut microbiota remains challenging. Traditional approaches based mainly on microbial composition are now considered too limited. As recent studies highlight, what microbes do may matter more than who is there. Key microbial functions — such as the production of short-chain fatty acids (SCFAs), transformation of bile acids, and immune modulation — are emerging as more meaningful markers of gut health than taxonomic profiles alone. Defining dysbiosis is equally complex. This lack of clear definitions has important clinical implications.

The gut is increasingly seen not as a separate organ but as a central communication hub that interacts with multiple body systems. This presentation focuses on the best-characterized gut-organ axes, including the gut-brain, gut-liver, and gut-lung axes, while also acknowledging that other connections are emerging. These axes are bidirectional, with the gut microbiota and distant organs exchanging signals through microbial metabolites, immune pathways, and neuroendocrine mechanisms.

The gut-brain axis is explored in the context of neurodevelopment, highlighting how microbial metabolites — such as SCFAs and tryptophan derivatives — affect neuronal signaling, the vagus nerve, and neuroimmune function. The hypothalamic—pituitary—adrenal (HPA) axis also plays a role, particularly in stress regulation.

Early-life disruptions — such as C-section delivery, lack of breastfeeding, or antibiotic exposure — may increase the risk of conditions like autism spectrum disorder, attention-deficit hyperactivity disorder, or depression.

The gut-lung axis illustrates how SCFAs and immune cell trafficking can modulate airway inflammation and support respiratory immune function. In turn, pulmonary infections and systemic inflammation can disrupt the gut microbiota. Early-life imbalances, such as those caused by antibiotic exposure, have been associated with an increased risk of asthma and other respiratory diseases.

The gut-liver axis is especially active during infancy, when the gut barrier is still developing. Increased gut permeability allows microbial products such as lipopolysaccharide and butyrate to reach the liver, influencing immune tolerance and metabolic programming. In response, the liver produces bile acids, which affect microbial composition and support gut homeostasis. Disruption of this axis may contribute to chronic inflammation and the development of metabolic-associated steatotic liver disease.

As our understanding of the microbiota deepens, so does interest in translating this knowledge into clinical practice. A growing number of microbiota-targeted strategies — such as prebiotics, probiotics, synbiotics, and dietary modifications — are being explored for their potential benefits. In pediatrics, early life presents a unique window of opportunity, when careful support of gut-organ communication may help reduce the risk of long-term disease. Still, the guiding principle remains: first, do no harm. All clinical decisions must be guided by evidence, safety, and the individual needs of each child.

References

- Britton RA, Verdu EF, Di Rienzi SC, et al. Biotherapeutics Subcommittee of the AGA Center for Gut Microbiome Research and Education. Taking Microbiome Science to the Next Level: Recommendations to Advance the Emerging Field of Microbiome-Based Therapeutics and Diagnostics. Gastroenterology. 2024 Nov; 167(6): 1059—1064.
- O'Riordan KJ, Moloney GM, Keane L, Clarke G, Cryan JF. The gut microbiota-immune-brain axis: Therapeutic implications. Cell Rep Med. 2025 Mar 18; 6(3): 101982.
- Özçam M, Lynch SV. The gut-airway microbiome axis in health and respiratory diseases. Nat Rev Microbiol. 2024 Aug; 22(8): 492—506.
- Tripathi A, Debelius J, Brenner DA, et al. The gut-liver axis and the intersection with the microbiome. Nat Rev Gastroenterol Hepatol. 2018 Jul; 15(7): 397—411. doi: 10.1038/s41575-018-0011-z. Erratum in: Nat Rev Gastroenterol Hepatol. 2018 Dec; 15(12): 785.
- Van Hul M, Cani PD, Petitfils C, et al. What defines a healthy gut microbiome? Gut. 2024 Oct 7; 73(11): 1893—1908.

Monika Schaubeck,
Pfaffenhofen/Germany

How can we positively influence the microbiota of non-breastfed infants?

The first months of life have a lasting impact on the development of the infant's immune system, known as the neonatal window of opportunity.[1] This coincides with the rapid development of body-associated microbial communities.[2] The maturation of the gut microbiota during early life is of great interest as it may be associated with the risk of pathologies in later life.[3,4]

Factors such as diet are known to modulate the gut microbiome of infants; however, the point at which their influence wanes has rarely been determined.[5] Therefore, it is important to investigate strategies to positively modulate colonization in early life.

Human milk (HM) is the gold standard for infant nutrition. Due to its prebiotic and probiotic components, it is the most important extrinsic factor influencing microbial communities in infants. If breastfeeding is not possible, infant formula should support similar development of the intestinal ecosystem. Therefore, supplementation of infant formula with probiotics originally isolated from HM is a reasonable approach to positively modulate colonization in early life, for infants who cannot be breastfed.[6]

Limosilactobacillus (L.) fermentum CECT5716 is one such HM-isolated bacterium, for which probiotic properties have been demonstrated in several studies in vivo, in vitro and ex vivo.[7] These studies provide mechanistic plausibility for previously observed probiotic effects in humans, demonstrating, for example, modulatory effects on isolated immune cells or barrier-enhancing effects on intestinal cell culture systems.

To test the effects of a synbiotic intervention in early life on the long-term development and maturation of the infant's microbiome maturation and immune health development, the GOLF-III trial followed infants from the age of 1—36 months of age (prospectively registered: NCT02221687). Infants were randomised to one of two formula groups at one month of age. The synbiotic intervention formula (IF) contained *L. fermentum* CECT5716 (≥2x108 cfu/day) + galacto-oligosaccharides (GOS)). The trajectory of the infants' faecal microbiota was assessed by 16S rRNA sequencing at 4, 12, 24 and 36 months of age. The effects of age, mode of birth and diet on community assembly and predicted functional capacity (PICRUST2) were determined. At 4 months of age, there were significant effects of the synbiotic IF compared to the control formula (CF). These included a higher abundance of Bifidobacterium spp. and Lactobacillaceae in the IF group. De-novo clustering of the bacterial communities at 4 months of age showed that the phylogenetic profiles of infants fed IF were closer to those of infants fed HM (reference group) than to those fed CF.[8]

The sampling performed in this project allowed us to investigate the effects of nutritional intervention and other early life factors on the development of the gut microbiota of infants up to toddler age. We showed that the microbiota profiles of infants converged towards those of adult samples. The most dramatic shift in distance, both phylogenetically and in terms of predicted function, occurred between 4 and 12 months of age. The diversity of the microbiota gradually increased until 36 months, at which point it resembled adult community states, indicating that microbiota maturation had occurred. Distinct gut microbiota community states were observed that differed at each stage of maturation. Interestingly, the microbial community state at one time point was not predictive of the next; instead, we observed hopscotching of the infant microbiota between different community states.[9]

This work provides new longitudinal data on the infant gut microbiome in relation to diet and shows that early life events influence the community state of an individual's gut microbiota beyond infancy. Thus, well-defined probiotic microbes represent a sound intervention strategy to modulate the gut microbiota during infancy.

References

1 Torow, N., T.W. Hand, and M.W. Hornef, Programmed and environmental determinants driving neonatal mucosal immune development. Immunity, 2023. 56(3).

2 Roswall, J., et al., Developmental trajectory of the healthy human gut microbiota during the first 5 years of life. Cell Host Microbe, 2021. 29(5).

3 Alcazar, C.G., et al., The association between early-life gut microbiota and childhood respiratory diseases: a systematic review. Lancet Microbe, 2022. 3(11).

4 Depner, M., et al., Maturation of the gut microbiome during the first year of life contributes to the protective farm effect on childhood asthma. Nat Med, 2020. 26(11).

5 Xiao, L., et al., Deterministic transition of enterotypes shapes the infant gut microbiome at an early age. Genome Biology, 2021. 22(1).

6 Lyons, K.E., et al., Breast Milk, a Source of Beneficial Microbes and Associated Benefits for Infant Health. Nutrients, 2020. 12(4).

7 Ozen, M., H. Piloquet, and M. Schaubeck, *Limosilactobacillus fermentum* CECT5716: Clinical Potential of a Probiotic Strain Isolated from Human Milk. Nutrients, 2023. 15(9).

8 Lagkouvardos, I., et al., Early life gut microbiota profiles linked to synbiotic formula effects: a randomized clinical trial in European infants. The American Journal of Clinical Nutrition, 2023. 117(2).

9 Intze, E., et al., The infant microbiota hopscotches between community states toward maturation — longitudinal stool parameters and microbiota development in a cohort of European toddlers. ISME Communications, 2025. 5(1).

Metehan Özen,
Istanbul/Türkiye

Clinical benefit of a synbiotic formula in terms of preventing respiratory and gastrointestinal infections

The impact of upper and lower respiratory tract infections (URTIs & LRTIs) on the pediatric community is still as evident today as it has been for decades. A major cause of morbidity, URTIs and LRTIs also have a significant impact on public health by increasing days off school, costs of treatment and loss of workdays for parents.[1] Coupled with the increasing occurrence of antibiotic resistance after inappropriate use of antimicrobial drugs poses a considerable threat for the future treatment of certain life-threatening infections.

Infant mortality is often recognized as an important indicator of general health status and is used as an indicator of life expectancy. Breastfeeding is known to decrease the incidence of RTIs, which may involve complementary immunological mechanisms of action. Studies have shown that using several probiotics with formulas may reduce the risk of nonspecific infections and reduce the risk of using antibiotics.[2] Recently, the manipulation and modification of the intestinal microbiota of infants via the administration of probiotic strains and prebiotics has been noticed as a potential program for the prevention of infant's infectious diseases.[3]

Milk powders and formulas supplemented by probiotics are now marketed in various countries to mimic some of the advantageous impacts of human milk. Hence far, only a limited number of studies have investigated the efficacy of infant formula supplemented with prebiotics, probiotics and synbiotics in diminution the risk of RTI, but the results are contradictory. A previous systematic review found that certain probiotics have a protective effect on the incidence of respiratory tract infections (RTI) in children.[4] The immune-stimulating effect of probiotics such as Lactobacillus has been shown to prevent recurrent infections in children referred to child care centers.[5]

Similarly, it was demonstrated that a *L. fermentum* CECT 5716-supplemented formula can reduce the incidence of upper respiratory tract infections by 27 % in infants aged 6 to 12 months (the incidence rate during the study period: in the probiotic group, 0.969 ± 0.96; in the control group, 1.330 ± 1.23).[2] This was not confirmed in a different formula trial using *L. fermentum* CECT5716 in infants aged 1 to 6 months, where no significant difference in incidence of respiratory tract infections was observed[6], probably due to the low incidence of respiratory tract infections in this age group. Another formula study reported no general difference in incidence of respiratory tract infections, although a subgroup analysis of infants born by caesarean section revealed a reduction in URTIs after *L. fermentum* CECT5716 administration from 1—12 months of age.[7]

In a recent large study[8], 460 infants were randomized to receive a synbiotic formula containing *L. fermentum* CECT 5716, The incidence rate of lower respiratory tract infections was lower in IF than in CF [0.79 compared with 1.01, IR ratio 0.77 (0.60—1.00)].

Given the potential of synbiotic-containing formulas supporting immune system in infants, consumption of a synbiotic formula containing *L. fermentum* CECT5716 and GOS may reduce the incidence of upper and lower respiratory tract infections.[9] Additional research is warranted to further investigate the potential interaction of the gut—lung axis and the importance of medical nutrition for prevention and treatment for RTIs. The situation is similar for gastrointestinal infections. While a significant reduction was observed in some studies[2,6], there was no significant difference in another study.[8]

References

1 Díez-Domingo, J., Pérez-Yarza, E.G. Melero, J.A & et al. Social, economic, and health impact of the respiratory syncytial virus: a systematic search. BioMed Central Infectious Diseases 2014; 14: 544.

2 Maldonado J, Canabate ˜ F, Sempere L, et al. Human milk probiotic Lactobacillus fermentum CECT5716 reduces the incidence of gastrointestinal and upper respiratory tract infections in infants. J Pediatr Gastroenterol Nutr. 2012; 54(1): 55—61.

3 Ozen M, Kocabas GS, Dinleyici EC. Probiotics for the prevention of pediatric upper respiratory tract infections: a systematic review. Expert opinion on biological therapy 2015; 1: 9—20.

4 Emre IE, Eroğlu Y, Kara A, Dinleyici EC, Özen M. The effect of probiotics on prevention of upper respiratory tract infections in the paediatric community — a systematic review. Beneficial microbes 2020 11 (3), 201—211.

5 Rashidi K, Darand M, Garousi N, et al. Effect of infant formula supplemented with prebiotics and probiotics on incidence of respiratory tract infections: A systematic review and meta-analysis of randomized clinical trials. Complement Ther Med. 2021 Dec; 63: 102795.

6 Gil-Campos, M.; López, M.Á.; Rodriguez-Benítez, M.V.; et al. Lactobacillus fermentum CECT 5716 is safe and well tolerated in infants of 1—6 months of age: A Randomized Controlled Trial. Pharm. Res. 2012, 65, 231—238.

7 Maldonado, J.; Gil-Campos, M.; Maldonado-Lobón, J.A.; et al. Evaluation of the safety, tolerance and efficacy of 1-year consumption of infant formula supplemented with *Lactobacillus fermentum* CECT5716 Lc40 or *Bifidobacterium breve* CECT7263: A randomized controlled trial. BMC Pediatr. 2019, 19, 361.

8 Piloquet H, Vrignaud B, Gillaizeau F, et al. Efficacy and safety of a synbiotic infant formula for the prevention of respiratory and gastrointestinal infections: a randomized controlled trial. Am J Clin Nutr. 2024 May; 119(5): 1259—1269.

9 Ozen M, Piloquet H, Schaubeck M. *Limosilactobacillus fermentum CECT5716*: Clinical Potential of a Probiotic Strain Isolated from Human Milk. Nutrients 2023 15 (9), 2207.

47238-04.2025