MICROBIOTA

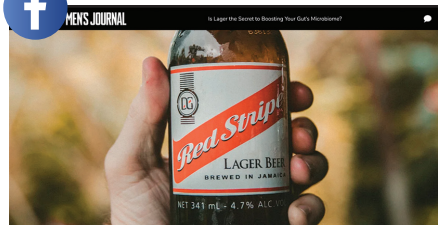
17 BIOCODEX NEWSLETTER | DECEMBER 2022

BIOCODEX Microbiota Institute

SUMMARY

Find this issue and previous ones here:

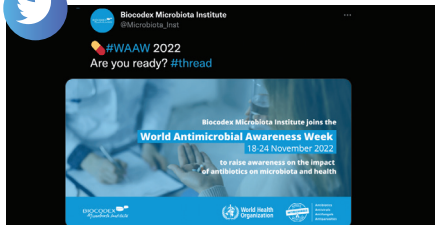
WHAT DID YOU MISS ON SOCIAL MEDIA?



IMPACT OF BEER ON THE GUT MICROBIOTA

Scientists reveal that beer increases gut microbiota diversity. Does that mean you could recommend your patients to drink half a pint every day?

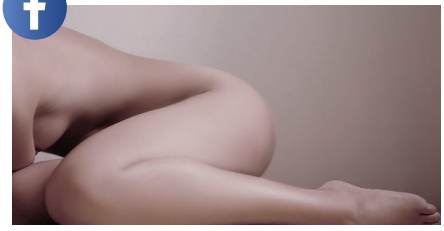
Pr. Schnabl gives you the right answer on p.18.



WAAW CAMPAIGN 2022

In November, Biocodex Microbiota Institute played an active role in the World Antimicrobial Awareness Week sharing exclusive content on the impact of antimicrobials on the gut microbiota.

3.7 k engagements



TAMPON, CUNNILINGUS, HAIR REMOVAL… How to take care of your vaginal microbiota?

By **France Inter** (French radio)

1 k engagements

EDITO

Dr Maxime Prost, MD
France Medical Affairs Director

Marion Lenoir, PhD
International Medical Affairs Manager

> “THE 1,000 FIRST DAYS OF LIFE ARE AT THE CENTER OF INTENSE INVESTIGATION. IT IS A TIME OF OPPORTUNITY AND VULNERABILITY.”

Dear readers,

Our understanding of the complex interplay between the microbiota and immunity is only beginning. The first two years of human life is at the center of intense investigation. The good news is that the veil is gradually lifting on the 1,000 first days of life, the crucial window of early childhood growth and development (period from conception to 2 years of age).

We know it is a time of opportunity and vulnerability.

We know that it is the beginning of everything, especially the start of microbial colonization.

We know that the first 1,000 days of life set up a dynamic crosstalk between gut microbiota (trillions of microorganisms) and the developing host.

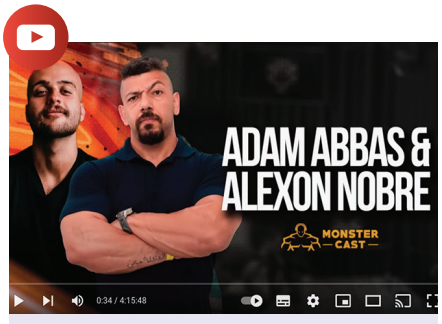
In this edition, Pr. Arrieta summarizes the evidence for early patterns of microbiome maturation that are conducive to host health, the causes and consequences of alterations from these patterns, as well as the restoration strategies aimed at improving dysbiosis.

Many factors shape the composition of the gut microbiota and the maturation of the newborn immune system during the first 1,000 days of life. One of them is the human milk. In the children’s commented article, Pr. Mas highlights a *Cell Host Microbe* article “human milk nutrient fortifiers alter the developing gastrointestinal microbiota of very-low-birth-weight infants”.

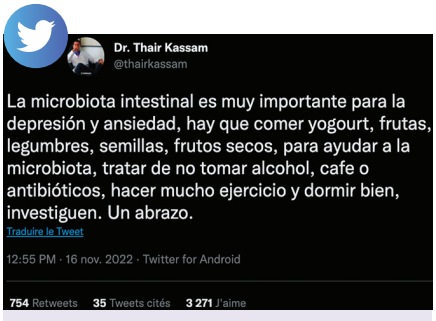
Another research area is at the heart of dynamic exploration: gut-brain axis. In the adult’s commented article, Pr. Sokol sheds light on a *Science Translational Medicine’s* article describing how the gut microbiota has been implicated in chronic pain disorders, including irritable bowel syndrome (IBS) whereas, in another commented article, Pr. Mazmanian analyses a *Science* article dedicated to gut brain axis and appetite.

We will close this edition on a lighter note with our new expert opinion section: Pr. Schnabl gives his views on the fact that nonalcoholic & alcoholic beer increased gut microbiota diversity, which has been associated with positive health outcomes. Does that mean he would recommend his patients to drink half a pint of beer everyday? You will find out in this edition.

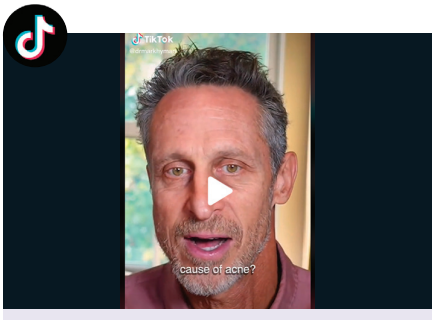
Enjoy your reading!



MICROBIOTA AND METABOLISM
By **Monster Cast**
3.6 k engagements and 62.1 k views



GUT MICROBIOTA, ANXIETY AND DEPRESSION
By **Dr. Thair Kassam**
3.8 k engagements



ACNE AND GUT MICROBIOME
By **Dr. Mark Hyman**
5.4 k engagements

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OVERVIEW

MICROBIAL COLONIZATION AS A DETERMINANT FACTOR FOR HEALTH DURING THE FIRST 1,000 DAYS OF LIFE

By Pr. Marie-Claire Arrieta

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Epidemiological and mechanistic studies during the past 20 years have demonstrated a role for the early-life microbiome in the pathogenesis of several non-communicable diseases (NCDs). This collection of trillions of microorganisms, residing mainly in the intestines, engages in a dynamic crosstalk with host cells. It is through this crosstalk that the host integrates microbial metabolites and structures to the early programming of immune, neurologic, metabolic and endocrine mechanisms that support host development. While this crosstalk occurs throughout life, there is a non-redundant period in early development, known as a "window of opportunity", during which microbial-host crosstalk sets the stage for host homeostasis, or deviations from it. This period lasts approximately 1,000 days, encompassing fetal growth and the first two years of human life, and it is at the center of intense investigation.

COMPOSITION AND FUNCTION OF THE EARLY-LIFE MICROBIOME

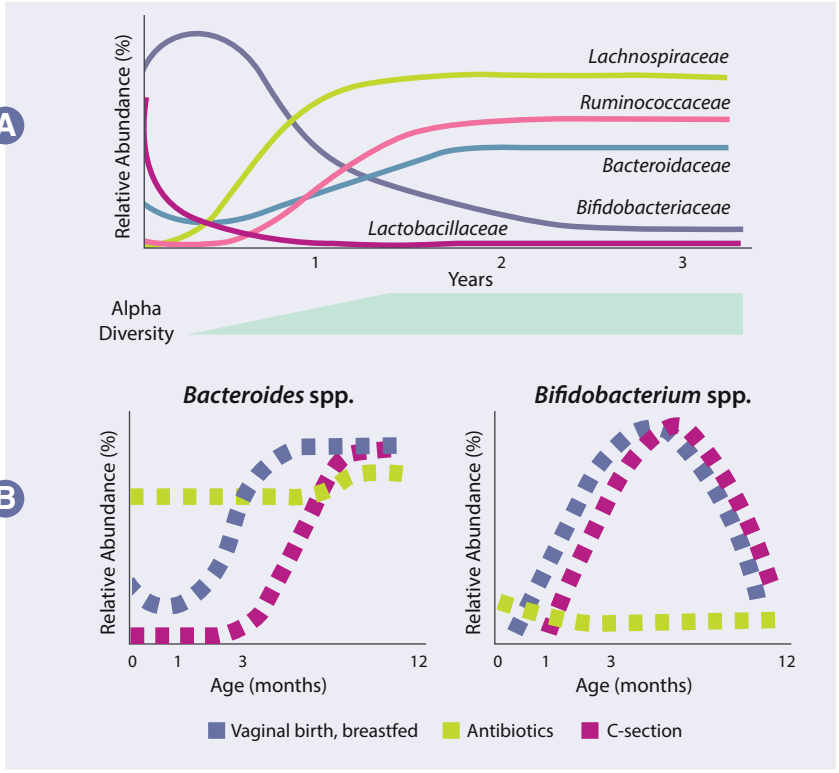
The infant gut microbiome starts developing at birth as a very simple ecosystem, gaining species diversity for about 2-3 years (box 1). This process occurs in a stepwise fashion, with common patterns identified across several human populations (**Figure 1**). Early colonization starts with pioneer species that primarily originate from the vaginal canal and maternal feces or the skin, depending on whether the infant is delivered vaginally or by Cesarean (C)-section, respectively. Vaginally-born exhibit higher abundance in *Lactobacillus, Prevotella*, and *Sneathia*, while those born by C-section are initially colonized by *Staphylococcus, Propionibacterium*, and *Corynebacterium*. Breastfed infants exhibit increased abundance of *Bifidobacterium* sp. and *Lactobacillus* sp., compared to formula fed infants, which display increased abundance of *Bacteroides*, *Enterobacteriaceae* and *Clostridiaceae*. As solid foods are introduced, the gut microbiome becomes increasingly diverse and shifts towards a state of *Bacteroidaceae, Lachnospiraceae*, and *Ruminococcaceae* dominance that persists into adulthood (**Figure 1**) [1].

The infant gut is stage of an important metabolism that contributes to digestion, energy metabolism and immune education. Through microbial digestion of breastmilk components, *Bifidobacterium* species decrease the intestinal luminal pH through the production of lactate and acetate, which is considered a crucial strategy in increasing intestinal nutrient absorption. Acetate accounts for the majority of the short-chain fatty acids (SCFA) produced in the infant gut, and is involved in preventing infections with enteropathogens [2]. Bifidobacteria are also involved in a process known as cross-feeding, in which the production of acetate and lactate serves as substrates for

▼ FIGURE 1

Compositional development of the early-life gut microbiome.

A. Trajectories of most abundant taxa during the first year of life.
B. Deviation for normal trajectories of two gut microbiome keystone taxa (*Bacteroides* spp. and *Bifidobacterium* spp) by C-section birth and antibiotic use.



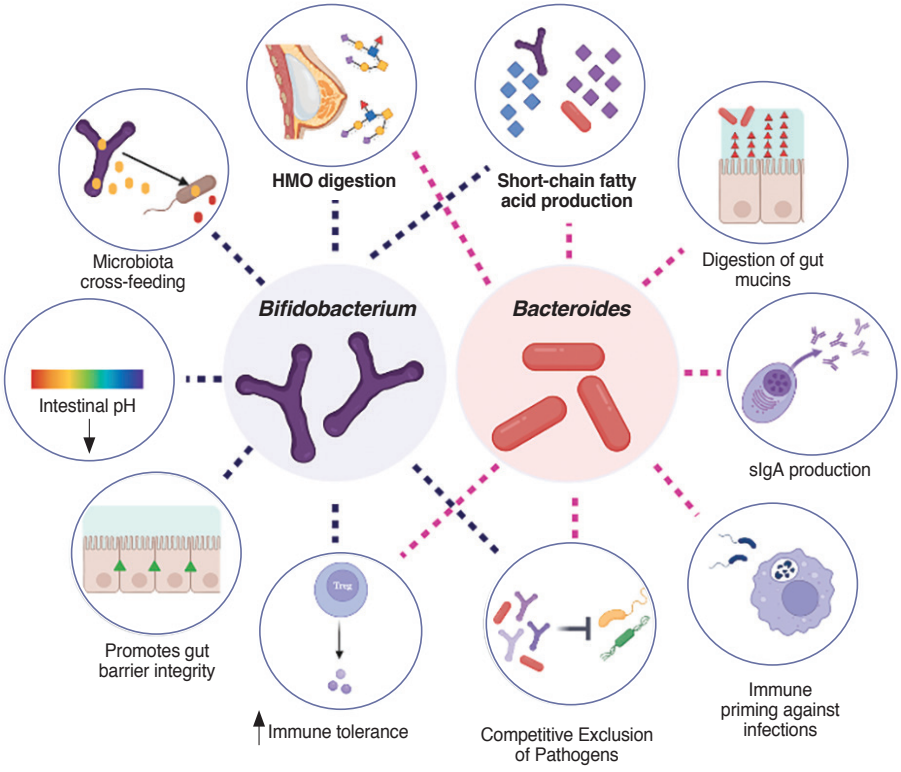
FACTORS THAT SUSTAIN THE EARLY-LIFE MICROBIOME

Early pioneer species can have long-lasting consequences to the trajectory of the infant gut microbiome through priority effects. This ecological process dictates that early arrival to a new ecosystem plays a fundamental role in the assembly of the community. This process explains the influence of mode of birth on the initial composition of the infant microbiome. Large cohort studies have identified microbiome differences linked to C-section delivery that last for months after birth, likely impacting this critical period in host development [5]. These include a lower of abundance of *Bacteroides* and *Bifidobacterium* spp., as well as an increased abundance of potential pathogenic species.

Besides mode of birth, the availability and abundance of nutritional substrates imposes a determinant effect on the early-life microbiome. Breastmilk contains more than 10 g/L of human milk oligosaccharides (HMOs), with 2'fucosyl lactose (2'FL) and trifucosyllacto-N-hexaose (TF-LNH) as the most abundant HMOs [6]. The majority of HMOs are digested by bifidobacterial and *Bacteroides* spp. into SCFAs. Bifidobacteria have a large repertoire of genes for the

▼ FIGURE 2

Functional profile of *Bacteroides* spp. and *Bifidobacterium* spp in the infant microbiome.



the growth of other species, such as *Roseburia*, *Eubacterium, Faecalibacterium,* and *Anaeroestipes*, favoring microbiome diversity. *Bacteroides* species can also ferment breastmilk, and are important producers of the SCFA propionate. Bacteroides species have a unique capacity to also metabolize mucin-derived oligosaccharides [3]. This metabolic plasticity improves their adaptability to the fluctuating intestinal conditions between meals, as well after weaning and introduction of solid foods. *Bacteroides* species are also key for immune education, constituting an important source of the microbial component lipopolysaccharide, as well as prompting for the development of tolerogenic adaptive immune responses in the gut [4]. Given their special adaptability to the infant gut environment, their demonstrated mother-to-infant strain transmission, their dominance in the infant gut, their importance to other members of this microbial ecosystem, and the benefits to the host, both *Bacteroides* spp. and *Bifidobacterium* spp. are likely keystone species of the human infant microbiome (**Figure 2**).

Is the infant colonized *in utero*?

• Microbial DNA has been detected in the placenta, amniotic fluid and meconium, prompting for the speculation of *in utero* colonization.

• Failure to culture microbes detected *in utero*, the consistent effect of mode of birth on the microbiome, and the successful generation of germ-free animals from embryos have led to the current consensus that healthy newborns start microbial colonization at birth [15].

digestion of HMOs. Several subspecies of *B. longum* are commonly found in the infant gut, with *B. longum* subsp. *infantis* (*B. infantis*), *B. longum* subsp. *longum* (*B. longum*), and *B. longum* subsp. *breve* (*B. breve*) commonly isolated from healthy breastfed infant feces, and formula-fed infants often colonized with *B. adolescentis*. Of these subspecies, *B. infantis* has the largest gene repertoire to digest all HMO structures in human milk [7]. Breastmilk also influences the composition of the infant microbiome through immune factors, such as antimicrobial compounds (lactoferrin and lysozyme), as well as immune effectors (sIgA, immune cells, and cytokines), which are critical for the immune exclusion of pathogenic microbes [1]. Notably, the lower abundance of *Bifidobacterium* in formula-fed babies is associated with a lower concentration of lactate, sIgA, and a higher gut luminal pH compared to breastfed babies.

Besides mode of birth and infant nutrition, other factors, such as maternal smoking, maternal body mass index, gestational diabetes, familial asthma and stress can influence the early-life microbiome [8]. The mechanisms underlying the associations between these factors and the infant microbiome remain unclear, but likely involve changes to the maternal microbiome and subsequent vertical transmission to the infant, as well as the increased risk of C-section rate and reduced success in breastfeeding linked to many of these factors. In general, the individual effects of factors such as birth mode, antibiotic use, and breastfeeding are relatively well characterized. However, the combinatory effects of these exposures remain poorly understood.

EARLY-LIFE DYSBIOSIS AS A CAUSE OF NON-COMMUNICABLE DISEASES

As a young ecosystem, the early-life microbiome is inherently less resilient. Ecological resilience refers to the capacity of an ecosystem to revert back to its original state after a perturbance occurs. This places the infant microbiome at a higher risk of permanently altering its trajectory during a critical developmental stage. Peri- and post-natal antibiotic use induce drastic compositional and diversity shifts to the infant microbiome, known as dysbiosis, decreasing the abundance of bifidobacteria and overall microbiome diversity, and increasing pathogenic species. This effect is observed even when antibiotics are only given to the mothers during vaginal birth (to prevent B-*Streptococcus* infections), and is augmented when given to infants during the first year of life, in a dose-response manner [9]. Notably, even a single course of amoxicillin to infants decreased bifidobacterial abundance for several months, highlighting the susceptibility of this important group of bacteria to these commonly used drugs [10].

Antibiotic exposure during gestation or in the pre-weaning stage of rodents can exacerbate allergic immune responses (IgE, Th2 and Th17 lymphocytes), adiposity and obesity, autoimmune responses, and chronic colitis [1]. These systemic responses to early-life dysbiosis are in line with consistent epidemiological findings associating early-life antibiotic use with several NCDs. For example, a systematic review and metanalysis of 13 studies identified a dose-response association between antibiotic use and obesity, which ranged between an 11% increased risk for infants receiving only one dose, to a 24% increased risk with more than one treatment [9]. More recently, a systematic review and metanalysis of 160 studies, encompassing over 22 million children, revealed significant associations between pediatric antibiotic use and atopic dermatitis, food allergies, allergic rhinoconjuntivitis, asthma, juvenile arthritis, psoriasis and autism spectrum disorder [11].

Establishing directionality and causality from epidemiological studies is very difficult. However, the combined results of preclinical studies, with the consistent and dose-response associations between antibiotic use with asthma and obesity, in particular, support for the application of more strict antibiotic stewardship measures. A recent study in Canadian children reported a parallel decrease in asthma incidence as antibiotic prescriptions decreased at the population level between the years 2000 and 2014. Importantly, the microbiome composition at 1 year of age mediated the association between antibiotic exposure and asthma diagnosis at five years [12]. This important study provides strong evidence for a causal relationship between antibiotic use and asthma in humans and reveals the need for a prudent antibiotic use as a strategy to reduce asthma rates.

RESTORING DYSBIOSIS – ARE WE THERE YET?

The detrimental consequences of early-life dysbiosis warrants further study, but also action. Decreasing C-section rates, formula feeding and antibiotic prescriptions, while a worthy goal, have limited potential as successful strategies given societal needs. Several avenues of microbiome restoration have been attempted, with mixed results. Two methods of ecosystem restoration have been tested in planned C-section deliveries: vaginal seeding and fecal microbiota transplantation (FMT). Vaginal seeding involves impregnating the skin and/or oral cavity of a newborn with collected maternal vaginal secretions. The three vaginal seeding trials currently published showed that this method does not restore the C-section microbiota into one resembling that of a vaginal birth [8]. In contrast, a mother-to-infant FMT (given once during the first feed) was sufficient to correct the C-section microbiome [13]. However, while authors carried out pathogen screening in the FMT samples, this controversial practice carries significant and unnecessary infectious risk to an otherwise healthy newborn infant, and it is unlikely to become a viable option.

The use of pre- and probiotics may provide a more practical and feasible approach to microbiome restoration, especially when informed from the studies summarized above. A recent study showed that depletion of bifidobacteria and HMO-utilizing genes could be ameliorated through the combination of administration of a strain of *B. infantis* and breast feeding [14]. This strategy also dampened pro-inflammatory responses conducive to allergy at 1-year, showing long-term beneficial immune mechanisms. Still, there is insufficient evidence that current microbiome restoration strategies will help curve the alarming rates of pediatric NCDs.

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CONCLUSION

The early-life microbiome is an integral component of child health. Our knowledge on the compositional and functional patterns of early colonization, as well as the factors sustaining or perturbing these patterns has grown considerably. In contrast, the mechanisms that explain how dysbiosis contributes to disease pathogenesis are poorly understood. Ecologically-informed measures to replenish keystone species of the infant microbiome lost through antibiotic use, *C*-section of formula feeding, as well as their nutritional substrates, may prove as effective measures. However, current microbiome restoration strategies are insufficient, and have yet to show effectivity in reducing the risk of NCDs. This is the next crucial step to prompt changes in medical policies and practices.

Sources
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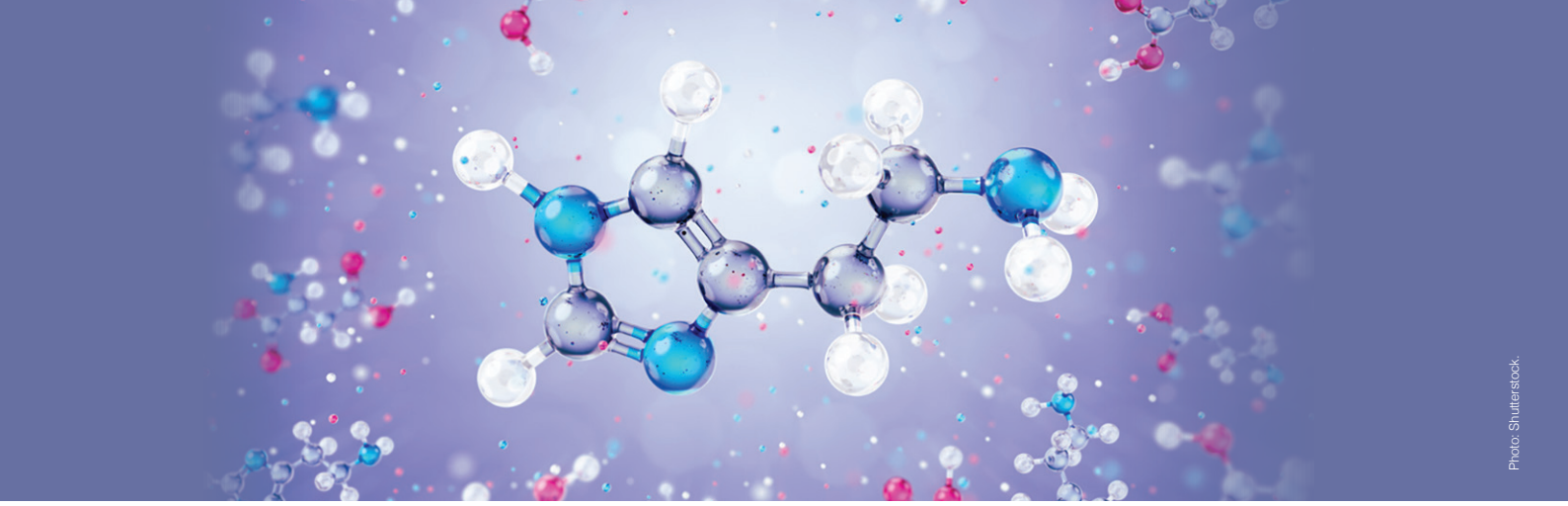

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COMMENTED ARTICLE
ADULTS' SECTION

HISTAMINE PRODUCTION BY THE GUT MICROBIOTA INDUCES VISCERAL HYPERALGESIA THROUGH HISTAMINE 4 RECEPTOR SIGNALLING IN MICE

Comment on the article by De Palma et al. Science Translational Medicine 2022 [1]

By Pr. Harry Sokol
Gastroenterology and Nutrition Department, Saint-Antoine Hospital, Paris, France

Gut microbiota has been implicated in chronic pain disorders, including irritable bowel syndrome (IBS), yet specific pathophysiological mechanisms remain unclear. In this article, the authors showed that decreasing intake of fermentable carbohydrates improved abdominal pain in patients with IBS, and this was accompanied by changes in the gut microbiota and decreased urinary histamine concentrations. Germ-free mice colonised with faecal microbiota from patients with IBS were used to investigate the role of gut bacteria and the neuroactive mediator histamine in visceral hypersensitivity. Germ-free mice colonised with the faecal microbiota of patients with IBS who had high urinary histamine developed visceral hyperalgesia and mast cell activation. When these mice were fed a diet with reduced fermentable carbohydrates, the animals showed decreased visceral hypersensitivity and mast cell accumulation in the colon. The authors then observed that faecal microbiota from patients with IBS with high urinary histamine produced large amounts of histamine *in vitro*. The authors identified *Klebsiella aerogenes*, carrying a histidine decarboxylase gene variant, as a major producer of this histamine. This bacterial strain was highly abundant in the faecal microbiota of three independent cohorts of IBS patients compared with healthy individuals. Pharmacological blockade of the histamine 4 receptor *in vivo* inhibited visceral hypersensitivity and decreased mast cell accumulation in the colon of germ-free mice colonised with the high histamine-producing IBS faecal microbiota. These results suggest that therapeutic strategies directed against bacterial histamine could help treat visceral hyperalgesia in a subset of IBS patients with chronic abdominal pain.

WHAT DO WE ALREADY KNOW ABOUT THIS SUBJECT?

Gut microbiota has been implicated in the pathophysiology of some chronic pain disorders, including pain associated with irritable bowel syndrome (IBS) and fibromyalgia [2]. This assumption is largely based on studies reporting an association between pain levels and changes in the composition of gut microbiota, on differences in pain thresholds between conventionally bred and germ-free mice, which return to normal after bacterial colonisation, and on the ability of bacteria to produce neuroactive metabolites *in vitro* [3]. However, there is a lack of data demonstrating causality, the precise mechanisms involved in visceral pain induced by the gut microbiota, or identifying the specific bacterial species involved. The authors of this article previously reported that abdominal pain in IBS patients improved after restriction of fermentable carbohydrate intake. This improvement was associated with changes in gut microbiota profiles and lower concentrations of urinary histamine [2], a known mediator implicated in visceral hypersensitivity [4]. In this article, the authors investigated gut microbiota functions triggering histamine production and visceral hypersensitivity using germ-free mice colonised with the faecal microbiota of IBS patients or healthy individuals.

KEY POINTS

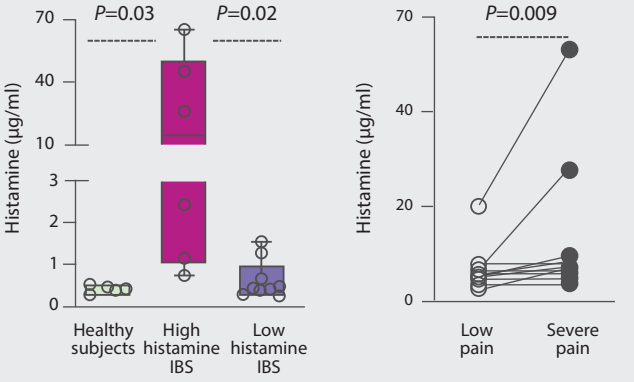
- Gut microbiota is involved in chronic pain in IBS patients
- In the context of a diet rich in fermentable carbohydrates, some bacteria in the microbiota, including *Klebsiella aerogenes*, contribute to histamine production
- Histamine produced by the microbiota plays a role in visceral hypersensitivity by boosting mast cell recruitment by activation of the H4 receptor
- Pharmacological blockade of the histamine 4 receptor *in vivo* inhibits visceral hypersensitivity and reduces mast cell accumulation in the colon of germ-free mice colonised with the high histamine-producing IBS faecal microbiota. These results suggest that therapeutic strategies directed against bacterial histamine could help treat visceral hyperalgesia in a subset of IBS patients with chronic abdominal pain

▼ FIGURE 1

The gut microbiota of patients with IBS and high urinary histamine levels produce large amounts of histamine *in vitro*.

A Histamine production in the coecal contents of mice colonised with the microbiota of IBS patients with high or no urinary histamine levels.

A *In vitro* histamine production by the faecal microbiota of IBS patients relative to pain levels.



WHAT ARE THE MAIN INSIGHTS FROM THIS STUDY?

A positive correlation was first observed between visceral pain severity and urinary histamine concentration in a cohort of IBS patients.

Visceral hypersensitivity and gut mechanosensation, evaluated using action potential measurements in colonic afferent nerves, was higher in germ-free mice colonised with faecal microbiota from IBS patients with high urinary histamine levels compared with mice colonised with microbiota associated with low urinary histamine levels. It was shown that the microbiota was responsible for the production of histamine in IBS patients with high urinary levels of this metabolite (**Figure 1**). In addition, a diet low in fermentable carbohydrates reduced histamine-mediated visceral hypersensitivity.

Using culturomics, *Klebsiella* bacteria were then identified as the main producer of histamine in IBS patients with elevated urinary levels of this molecule.

Compared with healthy subjects, IBS patients had a higher prevalence of *K. aerogenes* and a higher relative abundance of the *histidine decarboxylase* (*hdc*) gene, responsible for histamine production. Mechanistically, histamine produced by *K. aerogenes* was implicated in mast cell recruitment, which plays a role in the pain phenotype in mice. H4R (histamine receptor 4) expression was elevated in the colon of mice colonised with the faecal microbiota of IBS patients with high levels of urinary histamine. *In vitro*, H4R blockade blocked mast-cell chemotaxis. Finally, *in vivo*, H4R blockade reduced visceral-motor responses to colorectal distension in mice colonised with the faecal microbiota of IBS patients with high levels of urinary histamine.

WHAT ARE THE CONSEQUENCES IN PRACTICE?

This study reveals the specific role of histamine production by some bacteria in the gut microbiota in the painful symptoms suffered by a subgroup of IBS patients, in the context of a diet rich in fermentable carbohydrates. It suggests that gut distension related to gas production is not the main nociceptive trigger in these patients. Identifying *K. aerogenes*, or other histamine-producing bacteria, could help guide dietary recommendations as well as therapies targeting the microbiota or the use of H4 receptor antagonists in this subgroup of IBS patients.

CONCLUSION

Gut microbiota is involved in visceral pain in IBS patients. In a subset of patients, it is linked to histamine production in the context of a diet rich in fermentable carbohydrates. Targeting histamine-producing bacteria or blocking the H4 receptor could offer a therapeutic strategy to such patients.

Sources

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COMMENTED ARTICLE
CHILDREN'S SECTION

HUMAN MILK NUTRIENT FORTIFIERS ALTER THE DEVELOPING GASTROINTESTINAL MICROBIOTA OF VERY-LOW-BIRTH-WEIGHT INFANTS

Comment on the article by Asbury et al. (Cell Host Microbe) [1]

By Pr. Emmanuel Mas
Gastroenterology and Nutrition Department, Children's Hospital, Toulouse, France

Nutrient fortifiers are added to human milk to support the development of very-low-birth-weight infants. At present, bovine-milk-based fortifiers (BMBFs) are predominantly administered, but there is an increasing interest in adopting human-milk-based fortifiers (HMBFs). Although beneficial for growth, their effects on the gastrointestinal microbiota are unclear. This triple-blind, randomised clinical trial (NCT02137473) tested how nutrient-enriching human milk with HMBFs *versus* BMBFs affects the gastrointestinal microbiota of infants born <1,250 g during hospitalisation. These results highlight how nutrient fortifiers impact the microbiota of very-low-birth-weight infants during a critical developmental window.

WHAT DO WE ALREADY KNOW ABOUT THIS SUBJECT?

Breast milk (BM) is recognised as the best choice for feeding infants, especially those with a very-low-birth-weight (VLBW), *i.e.* <1,250 g. In intensive care units, when breastfeeding is impossible, it is recommended using pasteurised human breast milk (PHBM) donated from a breast-milk bank. BM or PHBM often requires enrichment to ensure optimal growth. Bovine-milk-based fortifiers (BMBFs) have traditionally been used for enrichment; however, more recently, human-milk-based fortifiers (HMBFs) are also used.

While it is well established that VLBW infants have abnormal gut microbiota, it is not known how to improve the composition of this gut microbiota with the nutrients used in VLBW infants.

Clinical studies are needed to determine the impact of these different enrichments on the gut microbiota of VLBW infants.

WHAT ARE THE MAIN INSIGHTS FROM THIS STUDY?

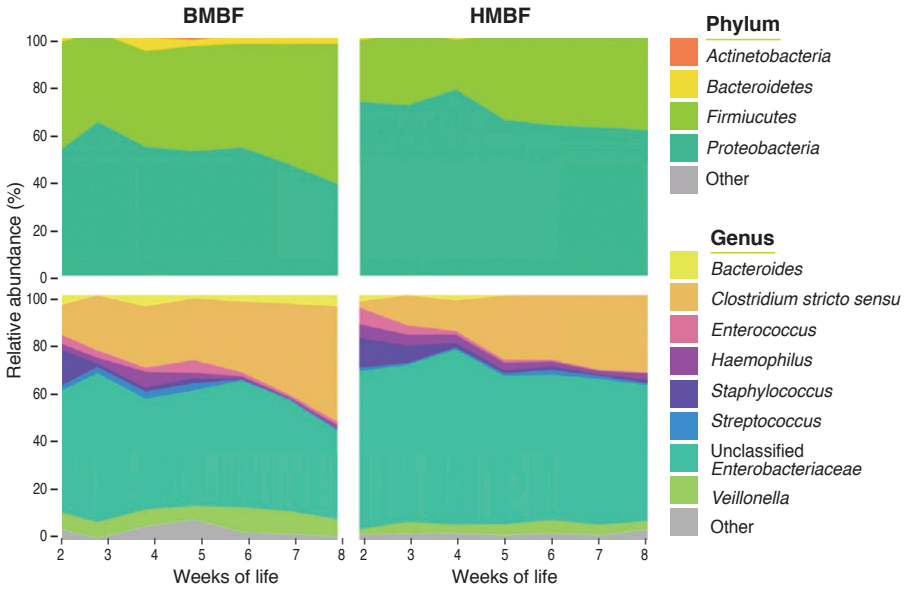
The OptiMom randomised controlled trial included 119 infants with a birth weight <1,250g (56 BMBFs and 63 HMBFs). The median term and birth weight were 880 g and 27.9 weeks, with no differences in any of the parameters between the two groups.

HMBF infants had lower microbial diversity (Shannon index) ($p < 0.005$). A predominance of *Proteobacteria* and *Firmicutes* was observed in both groups, with a higher relative abundance of *Proteobacteria* ($p = 0.0003$) including unclassified *Enterobacteriaceae* ($p = 0.005$) and a lower abundance of *Firmicutes* ($p = 0.001$) including *Clostridium stricto sensu* ($p = 0.04$) in HMBFs compared to BMBFs (**Figure 1**). Bacterial abundance increased steadily over time in the BMBF group but changed little in the HMBF group ($p = 0.03$). The relative abundance of *Clostridium stricto sensu* ($p = 0.04$) was higher in BMBF infants compared to HMBF infants, and unclassified *Enterobacteriaceae* were lower ($p = 0.005$)(**Figure 2**). After normalising the abundance of taxa, other differences emerged on a genus level with higher concentrations of unclassified *Eubacteriaceae* ($p < 0.0001$), *Streptococcus* ($p = 0.0002$) and *Staphylococcus* ($p = 0.002$), and lower concentrations of *Clostridium stricto sensu* ($p = 0.04$) in HMBF infants compared to BMBF infants. These changes in bacterial abundance were associated with changes in microbial function. Finally, it was possible to predict the type of fortifier received based on microbial abundance in stools.

The authors were interested in the effects of milk volumes. In both groups, higher volumes of BM for three days were associated with higher alpha diversity but were unrelated to total bacterial density. With higher BM volumes, a higher relative and

▼ FIGURE 1

Relative abundance of bacterial taxa between groups of fortifiers, human-milk-based fortifiers (HMBFs) or bovine-milk-based fortifiers (BMBFs) over time.



KEY POINT

- The use of human-milk based fortifiers or bovine-milk based fortifiers in the diet of very-low-birth-weight infants alters differently the bacterial composition of the gut microbiota during the first weeks of life

normalised abundance of *Veillonella* was observed in both groups, and *Streptococcus* in the BMBF group. A positive link between BM volumes and *Staphylococcus* concentrations was observed in the HMBF group, and with unclassified *Eubacteriaceae* in the BMBF group.

PHBM volumes were only associated with higher diversity in the BMBF group and bacterial density. Similarly, lower relative and standardised abundances of unclassified *Eubacteriaceae*, *Streptococcus* and higher abundance of *Clostridium stricto sensu* were reported in BMBF infants with higher PHBM volumes.

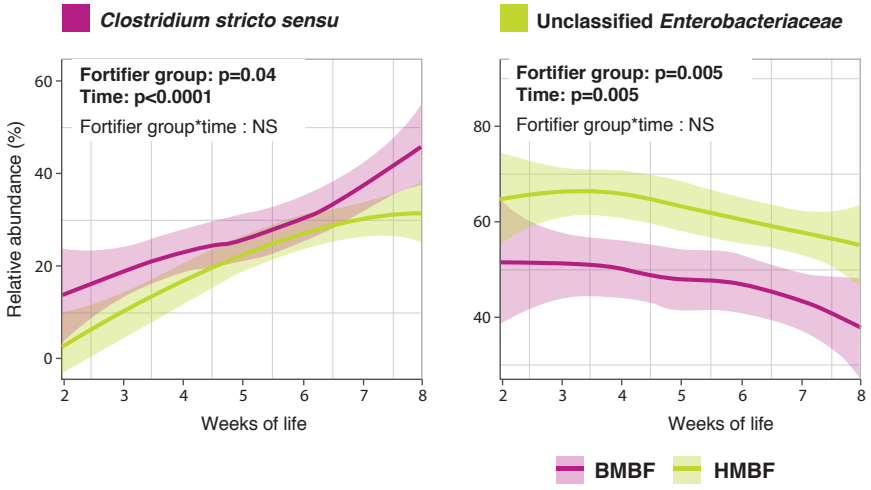
Higher volumes of BMBF were positively related to bacterial diversity and density in the BMBF group but not in the HMBF group. BMBF volumes were positively associated with relative and standardised abundances of *Firmicutes* and *Clostridium stricto sensu*, whereas HMBF volumes were positively associated with relative and standardised abundances of *Clostridium stricto sensu* and negatively associated with *Staphylococcus*.

WHAT ARE THE CONSEQUENCES IN PRACTICE?

This study shows the importance of understanding the impact of the different nutrients used in the gut microbiota of VLBW infants to achieve a beneficial effect on their short- and long-term health.

▼ FIGURE 2

Relative abundance of bacterial genera according to the fortifier, expressed as mean density over time (line) and 95% confidence interval (coloured areas).



CONCLUSION

This study showed that nutritional fortifiers alter the development of the gut microbiota in very-low-birth-weight infants. It also showed that associations exist between amounts of enteral nutrition components in these children, BM, PHBM and bacterial communities.

Source

• **1**. Asbury MR, Shama S, Sa JY, *et al.* ; OptiMoM Feeding Group. Human milk nutrient fortifiers alter the developing gastrointestinal microbiota of very-low-birth-weight infants. *Cell Host Microbe* 2022; 30: 1328-39.e5.

Photo: Shutterstock.

FOCUS ON

THE GUT-BRAIN AXIS

Comment on the article by Gabanyi et al. Science 2022 [1]

The microbiota affects metabolism and recent data has implicated gut bacteria in feeding behaviors in mice. A challenge in the field is to define gut-brain pathways that link microbial compounds to neuronal processes that impact appetite. In this study, Gabanyi and co-workers identified a functional role for Nod2, a pattern recognition receptor for bacterial muropeptides, bacterial cell wall components, in regulating appetite and thermoregulation in aged, female mice. The authors found that muropeptides accumulate in the brains of aged mice and regulate the activity of arcuate hypothalamic inhibitory neurons. Targeted Nod2-deficiency in these neurons results in increased appetite, weight gain, and reduced body temperature response that is dependent on the presence of the microbiota. These results suggest that the regulation of neuronal activity by Nod2 signaling in the brain affects complex behaviors in mice and warrants further investigation.

By Pr. Sarkis K. Mazmanian, John W. Bostick, Nadia Suryawinata

Biology and Biological Engineering, California Institute of Technology, Pasadena, CA, USA

WHAT DO WE ALREADY KNOW ABOUT THE SUBJECT?

Food intake is essential to the survival of animals, and the inappropriate regulation of feeding behavior leads to serious metabolic and psychiatric consequences, such as obesity and anorexia [2]. Food intake involves complex processes from nutrient processing and uptake in the gut and its periphery to the central nervous system that regulates appetite and drives feeding. Much focus in the field of appetite biology has centered on the characterization of neural circuits involved in feeding, such as the agouti-related peptide (AgRP)-expressing neurons in the arcuate hypothalamus that are necessary for homeostatic feeding [3]. More recently, the gut and its resident microbes have been shown to regulate metabolism [4] and aspects of feeding behavior [5]. Whether compounds produced by microbes are influencing appetite remains less well-established. Short chain fatty acids as a byproduct of microbial fermentation reduce food intake in mice [6]. However, a gut-brain pathway that links microbial compounds to neuronal processes that regulate appetite and feeding behavior has not been previously shown. The microbial pattern recognition receptor Nod2 is suggested to mediate feeding, as Nod2 knockout mice shows enhanced weight gain when fed a high fat diet [7]. Furthermore, the downstream signaling component of Nod2, nuclear factor kB (NFkB), is expressed in neurons of the hypothalamus, and its hypothalamic activation regulates energy balance [8]. This suggests that the hypothalamus may present a unique integration point for signals derived from the microbiome and feeding behaviors.

WHAT ARE THE MAIN INSIGHTS FROM THIS STUDY?

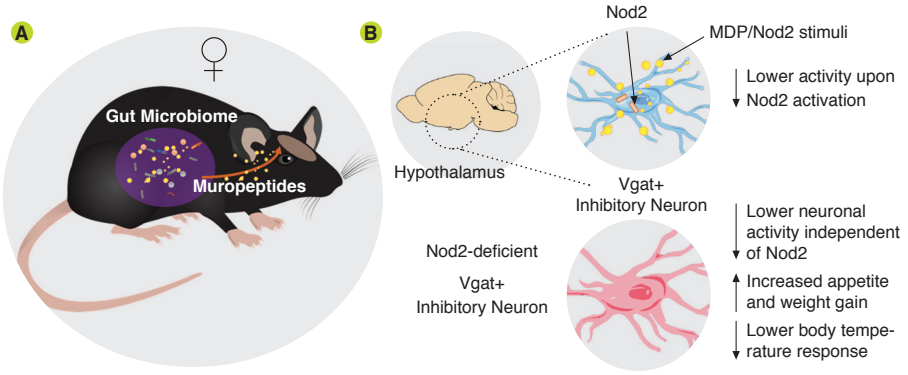
The authors demonstrated that activation of Nod2 signaling in the hypothalamus affected feeding and thermoregulatory behavior in mice (**Figure 1**). Nod2 was found to be expressed in neurons in multiple regions of the mouse brain, including the striatum, thalamus, and hypothalamus. The authors then investigated whether radiolabeled muropeptides could reach the brain, when introduced through the gastrointestinal tract directly or via radiolabeled bacteria. Both methods of delivery resulted in the accumulation of muropeptides in the brain.

To investigate the functional role of Nod2 in neurons, conditional knockout mouse models that targeted Nod2 for deletion were utilized to show that older female mice with Nod2 deleted in inhibitory neurons expressing the vesicular GABA transporter (Vgat/Slc32a1) display increased weight gain and dysregulated temperature control. Measurement of Fos expression in the brain revealed that older female mice have higher neuronal activity in the arcuate and dorsomedial regions of the hypothalamus. Next, the authors injected Cre-expressing adeno-associated viruses (AAVs) into $Nod2^{flox}$ mice to knockout Nod2 expression locally in inhibitory neurons of the arcuate hypothalamus, demonstrating that Nod2 deficiency in hypothalamic neurons was sufficient to cause weight changes and temperature dysregulation (**Figure 2**).

Finally, to examine the role of the microbiota in the Nod2-dependent changes in appetite and temperature regulation, the authors treated hypothalamic neuron-specific Nod2 knockout mice with broad-spectrum antibiotics. Hypothalamic Nod2-deficent mice that underwent antibiotic treatment

▼ FIGURE 1 Nod2 signaling in the hypothalamus regulates brain function and metabolism.

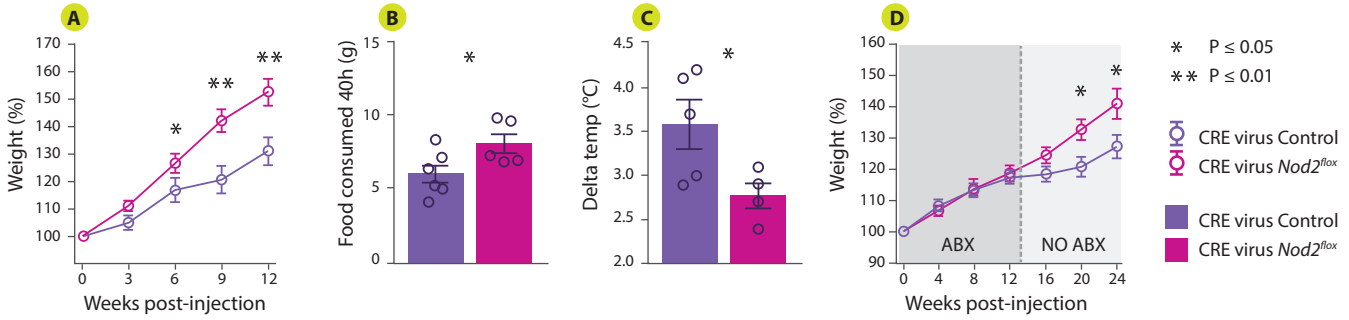
A. Microbiome-derived muropeptides accumulate in the brain of aged female mice.
B. Nod2-deficiency in Vgat+ inhibitory neurons in the hypothalamus promotes weight gain and temperature dysregulation in aged female mice.



▼ FIGURE 2

Hypothalamic, Nod2 expressing inhibitory neurons regulate weight and temperature.

A. Knockout of Nod2 in the arcuate (ARC) hypothalamic Vgat+ inhibitory neurons (pink) of older, female mice induces weight gain, compared to control mice (blue).
B. ARC-Nod2 knockout female mice consume more food compared to control mice.
C. ARC-Nod2 knockout female mice display higher body temperature variation compared to control mice.
D. ARC-Nod2 knockout female mice gain more weight post-antibiotics treatment, compared to control mice.



KEY POINTS

- Nod2 is expressed in neurons in multiple regions of the mouse brain, including the striatum, thalamus, and hypothalamus
- Nod2 ligands, such as muropeptides, accumulate in the brains of aging mice
- The activity of hypothalamic inhibitory neurons is regulated by Nod2 expression
- Appetite and temperature regulation is perturbed in Nod2-deficient aged female mice

display normal appetite and weight gain until the antibiotics are removed, at which point they exhibit increased appetite and weight gain compared to Nod2-sufficient control mice. This data suggests that microbiota-derived products can modulate appetite in female mice via a Nod2-dependent mechanism.

WHAT ARE THE CONSEQUENCES IN PRACTICE?

In this interesting new work, Gabanyi *et al.* identified a functional role for Nod2 expression in neurons of the hypothalamus in regulating appetite and temperature in aging female mice, but not in male mice. The cellular and molecular mechanisms that determine this effect remain to be elucidated. Sex differences in microbiome composition may play a role in the dissimilarities in response to neuronal Nod2 deficiency; however, microbial composition was not investigated by the authors. Moreover, in addition to muropeptides, other microbe-derived products and endogenous stimuli can regulate the expression or activation of Nod2 [9], though are not addressed in this study. Additional data is needed to distinguish the activity and contribution of these alternative stimuli from muropeptides. Other possible contributors to the outcomes reported in the paper may include the increased gut and blood-brain barrier permeability that occurs with age, which may allow more microbe-derived molecules to enter the circulation from the gut and accumulate in the brain [10]. Further investigation is required to clarify the roles of sex and age in the observed phenotypes.

CONCLUSION

This study reports that Nod2-deficiency in hypothalamic neurons is sufficient to induce changes in appetite and temperature regulation in aged female mice. Replication in mice and future work in humans is needed to validate these exciting findings.

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ueg week
VIRTUAL 2022

CONGRESS REVIEW

HIGHLIGHTS FROM THE UEGW

By Dr. Lucas Wauters
Gastroenterology and Hepatology, University Hospitals Leuven, Leuven, Belgium

OCTOBER 2022

After 2 years of virtual editions, the UEG Week 2022 was not only organized in-person (in Vienna) but also as the very first hybrid congress. With over 10,000 registrants (of which 19% virtual), it is the biggest European and "the best gastroenterology congress in the world" according to the organization and many others. Many highlights focused on the microbiome, of which a selection is discussed here.

A GLIMPSE AT THE HEALTHY MICROBIOME

Despite the timing on the last day, the high attendance of the popular session on "The microbiome as modulators of gut function" is easily explained by the selection of experts. Chaired by Pr. Harry Sokol (Paris, France) and Prof. Tim Vanuytsel (Leuven, Belgium), the first lecture by Pr. Jeroen Raes from the VIB Center for Microbiology (Leuven, Belgium) focused on the healthy gut microbiome. He stated that a definition of normal microbiota variation is essential to allow robust diagnostics, but that we do not even know what a healthy flora means. Indeed, only <10% of microbiota variation could be explained by host and environmental factors in the population-level analysis of the Flemish Gut Flora Project [1]. He showed that many of these variables replicated in the Dutch Microbiome Project, which recently confirmed the important effects of the environment and cohabitation [2].

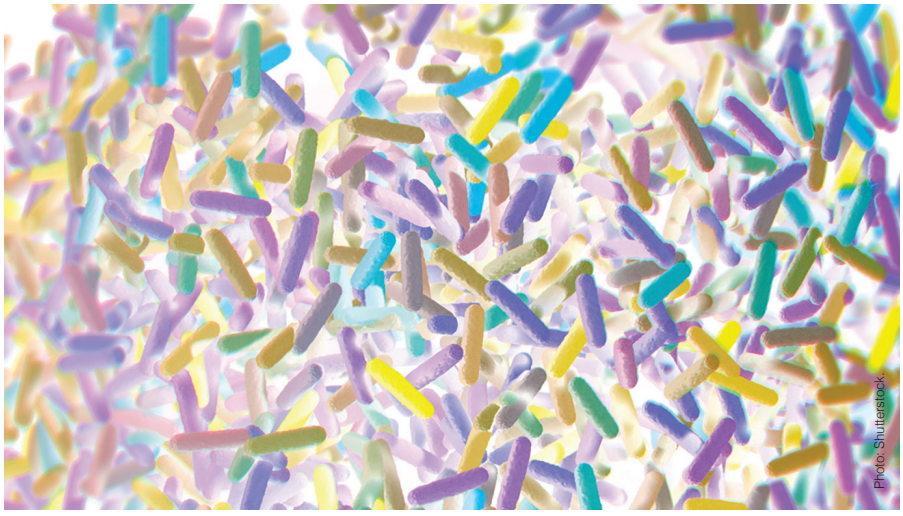

Photo: Shutterstock

In addition to the high between-individual variability, Pr. Raes showed evidence for substantial within-individual variation in the quantitative presence of microbial genera [3]. He explained that gut transit time was not only the primary confounder for microbiota composition but also the driver of temporal variation in healthy individuals. While the enterotypes (preferred community compositions) remained relatively stable, he richly illustrated the dysbiotic nature of the novel high-*Bacteroides* and low microbial load or B2-enterotype. Besides the diagnostic value of this marker across different diseases, he presented surprising findings of statins as a modulator of the microbiome. Finally, he stressed

the need for more *in vitro* ecology work, as identification and isolation of species and their interactions is crucial to refine probiotic treatments and fecal microbiota transplantation (FMT).

FOCUS ON MICROBIAL STRAINS AND METABOLITES

As an alternative to *in vitro* work, Italian researchers presented improved strain-level metagenomics or the identification of subtypes of species in relation to FMT. As the first of many strong abstracts in the session on "Gut microbiome as pathogenic and therapeutic player", the engraftment or strain sharing events within donors and recipients of FMT were nicely illustrated for different diseases. Interestingly, clinical success of FMT was associated with higher donor strain engraftment, which further improved with multiple routes of delivery and after antibiotics for infectious diseases [4]. Based on these findings, future donor-selection may not only optimize the microbiota composition but also the response after FMT, with specific protocols for different diseases.

During the main microbiome session, Pr. Nicolas Cenac (Toulouse, France) elaborated on the role of bacterial lipopeptides in irritable bowel syndrome (IBS), one of the most common gastrointestinal disorders. Following evidence of analgesic properties of these metabolites, his group explored the link between stress-induced dysbiosis during pregnancy and the development of colonic visceral hyper-sensitivity (VHS), a hallmark of IBS. He nicely illustrated that prenatal stress induced IBS-like symptoms in mice, with a decrease in *Ligilactobacillus murinus*, which was associated with VHS. This also led to a lower production of lipopeptides containing γ-aminobutyric acid (GABA), with reversal of VHS after colonic administration in mice. Pr. Cenac explained how translation in humans was needed and confirmed by lower GABA-lipopeptides in feces of IBS-patients. The microbial metabolites are exciting new players in IBS and were fully published after the congress.[5]

MICROBIOME, MEDITERRANEAN DIET AND IMMUNOTHERAPY

Important abstracts of UEG Week covered the potential factors related to the success of immuno-therapy in melanoma, a type of skin cancer. Dr. Johannes R. Björk (Groningen, The Netherlands) presented changes in the gut microbiome in response to immunotherapy. As one of the Top Abstract awardees, he kicked off the second part of the opening session by showing evidence of baseline gut microbial biomarkers predictive of response. However, he explained that microbiota dynamics over the treatment course are still unexplored. Based on a multi-center cohort study, his longitudinal analysis of repeated stool sampling showed that species from the family *Lachnospiraceae* increased in responders, while species from the family *Bacteroides* increased in non-responders. Besides these novel potential targets (*e.g.*, for FMT), the microbiota changes in those affected by immunotherapy-induced colitis may also provide diagnostic markers for the future.

Interestingly, the increased butyrate producers in responders suggested a role of fiber degradation. Therefore, the same groups of researchers from the Netherlands and UK focused on the role of dietary intake in a separate analysis. They showed that patients who responded to immunotherapy were more likely to adhere to a Mediterranean diet, which is high in mono-unsaturated fatty acids, polyphenols, and fiber. In addition, immune-related side effects were less likely with intake of whole grains or legumes and more likely with high red and processed meat. Future clinical trials will show whether this translates to treatment benefits for various tumor types, including gastrointestinal cancers.

In conclusion, important and novel findings on microbial strains, metabolites and the role of diet have advanced our understanding of the gut microbiome in disease, while taking important confounders (even in the healthy microbiome) into account.

Photo: Shutterstock.

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PRESS REVIEW

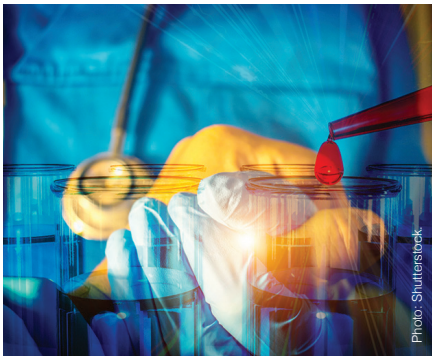
By Pr. Satu Pekkala
Academy of Finland Research Fellow, Faculty of Sport and Health Sciences, University of Jyväskylä, Finland

GUT MICROBIOTA

LINKING GASTROINTESTINAL MICROBIOTA AND METABOLOME DYNAMICS TO CLINICAL OUTCOMES IN PAEDIATRIC HAEMATOPOIETIC STEM CELL TRANSPLANTATION

Haematopoietic stem cell transplantation (HSCT) is used to treat many pathological conditions. At post-HSCT graft-*versus*-host disease and infections can develop, being major causes of mortality. The current understanding of the role of the gut microbiota (GM) on adverse outcomes in paediatric patients post-HSCT is scarce. In a longitudinal study, Vaitkute *et al*. determined whether the GM and fecal metabolome associates with the clinical outcomes in 64 paediatric HSCT patients during ~ 66-days inpatient stay.
Following HSCT, the GM alpha-diversity decreased. There were compositional shifts in the GM, and most of the patients did not return to their initial GM composition. The GM was clustered into community state types [CST(s)]. CST1 was common before HSCT, and included abundant *Clostridium XIVa, Bacteroides* and *Lachnospiraceae*. The lack of total parenteral nutrition contributed to CST1. CST2 was common at post-HSCT and was characterized by abundant *Streptococcus* and *Staphylococcus* as well as the use of vancomycin and metronidazole. CST3 was also common at post-HSCT and included abundant *Enterococcus*, *Enterobacteriaceae* and *Escherichia*. CST3 associated with a higher risk of viraemia, total parenteral nutrition and various antimicrobials.
The metabolomic analyses revealed that fecal butyrate at baseline associated with a lower risk of viraemia. Longitudinally, acetate and butyrate decreased, and glucose increased after HSCT.
The identified GM taxa and metabolites may be useful biomarkers for predicting the risk of complications post-HSCT. However, larger longitudinal studies are warranted.

Vaitkute G, Panic G, Alber DG, *et al.* Linking gastrointestinal microbiota and metabolome dynamics to clinical outcomes in paediatric haematopoietic stem cell transplantation. *Microbiome* 2022; 10: 89.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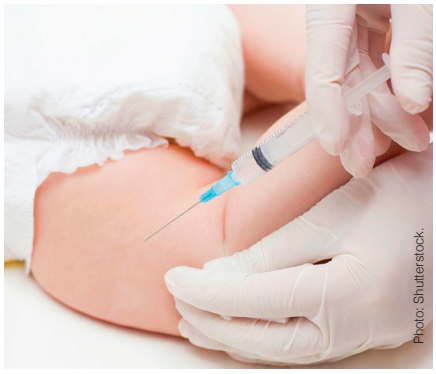
A PROSPECTIVE STUDY OF THE INFANT GUT MICROBIOME IN RELATION TO VACCINE RESPONSE

The establishment of infant gut microbiota (GM) early in life is essential for the developing immune system. In addition, GM contributes to immune responses to vaccination, such as polio vaccine. However, research in this field is still scarce. Moroishi *et al.* enrolled 83 infants and studied the composition and functions of the early-life (6-weeks of age) GM in relation to infant antibody response to pneumococcal capsular polysaccharide (PCP) and tetanus toxoid (TT) at 1-year of age.
PERMANOVA analyses of pair-wise GM community composition showed a weak association with PCP and TT antibody responses. In metagenome analyses, the authors found a negative association between TT response and *Aeriscardovia aeriphila*, whereas the association was positive with *Staphylococcus aureus, Escherichia coli, Streptococcus thermophilus*, and *Anaerococcus vaginalis*. However, only *A. aeriphila* remained significant after FDR correction. Lower PCP vaccine response associated with nine pathways, such as phenylalanine biosynthesis and pyrimidine deoxyribonucleotides de *novo*

biosynthesis. In contrast, pantothenate and coenzyme A biosynthesis III, pyrimidine ribonucleosides degradation, methylphosphonate degradation II, and pyrimidine ribonucleotides de *novo* biosynthesis pathways were associated with higher PCP response. Five pathways associated positively with TT response, including especially CDP-diacylglycerol biosynthesis I and CDP-diacylglycerol.
As a conclusion of this study, *A. aeriphila* could be used as a biomarker of TT response. Further, the early-life GM functions may influence an infant's vaccine response.

Moroishi Y, Gui J, Nadeau KC, *et al.* A prospective study of the infant gut microbiome in relation to vaccine response. *Pediatr Res* 2022 [Epub ahead of print].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META-ANALYSIS OF MUCOSAL MICROBIOTA REVEALS UNIVERSAL MICROBIAL SIGNATURES AND DYSBIOSIS IN GASTRIC CARCINOGENESIS

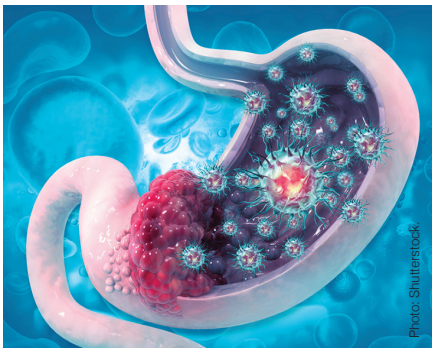


Photo: Shutterstock.

Gastric cancer (GC) is the 4th leading cause of cancer death. The developmental stages of GC are superficial gastritis (SG), atrophic gastritis (AG), intestinal metaplasia (IM), dysplasia and gastric carcinoma. *Helicobacter pylori* infection is a common player in GC that reduces secretion of stomach acid, allowing overgrowth of non-*H. pylori* microbes. Studies on the associations between gastric microbiota and GC have been inconsistent. Liu *et al.* did a meta-analysis of gastric microbiota from six independent studies to identify microbial signatures in GC. Alpha-diversity was lower in GC than in SG, AG and IM. *Veillonella, Dialister, Granulicatella, Herbaspirillum, Comamonas, Chryseobacterium, Shewanella* and *Helicobacter* were newly identified in this study as universal biomarkers discriminating GC from SG. In addition, opportunistic pathobionts *Fusobacterium, Parvimonas, Veillonella, Prevotella* and *Peptostreptococcus* were more abundant in GC than in SG. Contrarily, the abundance of *Bifidobacterium, Bacillus* and *Blautia* were lower.
The microbial functions were inferred using PICRUSt2. Compared to SG, the most enriched pathway in GC was peptidoglycan maturation of peptidoglycan biosynthesis. The most depleted pathway in GC was *Helicobacter* specific tricarboxylic acid cycle, which agrees with the very low abundance of *Helicobacter* in GC patients. The authors further found that *Helicobacter* seems to affect gastric microbiota as *H. pylori*-negative patients had higher microbial diversity than the *H. pylori*-positive.
To conclude, gastric microbiome can be a biomarker capable of distinguishing patients across disease stages.

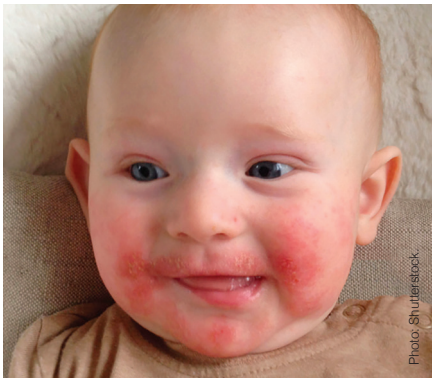
Liu C, Ng SK, Ding Y, *et al.* Meta-analysis of mucosal microbiota reveals universal microbial signatures and dysbiosis in gastric carcinogenesis. *Oncogene* 2022; 41: 3599-10.

SKIN MICROBIOTA

ATOPIC DERMATITIS: SKIN MYCOBIOTA UNDER THE MICROSCOPE

Atopic dermatitis (AD) is a complex and multifactorial inflammatory skin disease in which genetics, the immune system, and microbes play a role. For example, the skin of AD patients generally has an increased abundance of *Staphylococcus aureus*. But what about fungal communities? A recent study has shed some light on this little-known area.
Skin swabs were taken from 16 AD patients and 16 healthy individuals at four skin sites (antecubital crease, dorsal neck, glabella, and vertex). To observe the course of the disease, the AD patients were sampled at three time points (weeks 0, 2, and 4) and the controls at two time points (weeks 0 and 4).
An analysis of the 320 swabs showed that the *Malassezia* fungus predominated in all subjects, whether healthy or ill. However, in patients suffering from severe AD, this dominance was reduced in favor of fungi such as *Candida* or *Debaryomyces*, resulting in greater fungal diversity.
As for bacteria, AD was characterized by lower levels of *Cutibacterium* and a greater relative abundance of *Staphylococcus*, particularly *S. aureus* and *S. epidermidis*. A higher presence of *S. aureus* may favor the proliferation of *Candida*, a synergistic activity between the two microorganisms having previously been shown.
The study also showed a link between skin dysbiosis and the severity of AD: the bacterial and fungal communities of patients with severe AD differed significantly from those of controls and patients with mild-to-moderate forms of the disease. The skin communities of the latter two groups (mild-to-moderate AD and controls) were similar overall, with some distinctions in the bacterial communities (more staphylococci and less cutibacteria in mild-to-moderate AD *versus* no AD). Thus, a pronounced dysbiosis of the microbiota is characteristic of severe forms of AD, but not of less severe forms.

Schmid B, Künstner A, Fähnrich A *et al.* Dysbiosis of skin microbiota with increased fungal diversity is associated with severity of disease in atopic dermatitis. *J Eur Acad Dermatol Venereol.* 2022 Jun 21.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EXPERT OPINION

IMPACT OF BEER AND NONALCOHOLIC BEER CONSUMPTION ON THE GUT MICROBIOTA

By Pr. Bernd Schnabl
Division of Gastroenterology, San Diego Digestive Diseases Research Center (SDDRC), UC San Diego, USA

Alcohol is known to affect the gut microbiota. Larger amounts of alcohol (*e.g.*, more than 2 drinks per day for men and 1 drink per day for women) have negative effects on the gut microbiota, which is accompanied by a decrease in bacterial diversity and an increase of potentially harmful microbes. However, the effect of moderate alcohol consumption on the gut microbiota is less known.

What is your opinion regarding the fact that nonalcoholic & alcoholic beer increased gut microbiota diversity, which has been associated with positive health outcomes? Does that mean you could recommend your patients to drink 330 mL of beer every day?

A recent randomized clinical trial investigated the effect of one daily beer (330 mL) with alcohol (5.2%) or without alcohol (0.0%) during a 4-week period [1]. Twenty-two healthy men were enrolled and the fecal microbiota was assessed. Bacterial diversity increased when baseline stool was compared with samples collected 4 weeks after the intervention in each group. However, diversity was not different between subjects consuming alcoholic or non-alcoholic beer. As the only difference between the two groups was alcohol, other substances present in both beverages might explain these differences. Bioactive compounds such as polyphenols and phenolic acids, which are present in alcoholic and non-alcoholic beer, might have a positive health effect possibly mediated via an increase in bacterial diversity. Some of these bioactive compounds develop during the brewing process and can originate from hops or malt. Bacteria in our gut are known to metabolize dietary compounds and might utilize them for their own metabolism. More experimental evidence is required to determine the effects of these bioactive compounds on gut bacteria. Ideally, such a trial should be done in a larger cohort of subjects who do not consume alcohol at baseline.

More studies are required before a recommendation for daily consumption of one beer can be made. This should be preferably non-alcoholic beer as alcohol, even in small amounts, has been associated with worse health outcomes.

How do you explain that drinking nonalcoholic or alcoholic beer daily during 4 weeks did not increase body weight and body fat mass and did not significantly change serum cardiometabolic biomarkers?

Comparison of the nine subjects in the non-alcoholic beer group *versus* ten subjects in the alcohol containing beer group finishing the aforementioned study showed largely no differences on liver function, inflammatory or metabolic markers. There are several possibilities why increased bacterial diversity did not translate into improvement of these markers. The study duration might have been too short and the number of participants in each group might have been too small. Although subjects in both groups were overweight, most other markers were within normal range. It would therefore be interesting to assess the effects in patients with metabolic syndrome, whether there is an improvement in intestinal dysbiosis, increase in bacterial diversity and a concomitant improvement in metabolic parameters.

Photo: Shutterstock.

Source

- **1**. Marques C, Dinis L, Barreiros Mota I, *et al.* Impact of beer and nonalcoholic beer consumption on the gut microbiota: a randomized, double-blind, controlled trial. *J Agric Food Chem* 2022; 70: 13062-70.

BIOCODEX MICROBIOTA INSTITUTE

WAAW CAMPAIGN 2022: LET'S BREAK THE MYTHS ON ANTIBIOTICS!

In November, Biocodex Microbiota Institute joined the World Antimicrobial Awareness Week (WAAW) to improve understanding of antimicrobial resistance. Held on 18-24 November, this WHO campaign encourages the general public, healthcare professionals and decision-makers to use antibiotics, antivirals, antifungals and antiparasitics carefully in order to prevent the further emergence of antimicrobial resistance. During the WAAW campaign, Biocodex Microbiota Institute federated its physicians' community with new dedicated pages highlighting antibiotic resistance, antibiotics impact on microbiota and dysbiosis topics. How to monitor antibiotic-resistant genes? What is the connection between antibiotic resistance and microbiota? To mark WAAW campaign, Biocodex Microbiota Institute also handed the floor to two antibiotic resistance's experts: Dr. Windi Muziasari, PhD, CEO of Resistomap, and Pr. Christian G. Giske from Karolinska Institute in Sweden.

BIOCODEX MICROBIOTA FOUNDATION

HENRI BOULARD AWARDS 2022: AND THE WINNERS ARE…

The second edition Henri Boulard Awards came to an (happy) end with three winners:

1 • **CLIFFORD-NKEMDILIM Jennifer (Nigeria)** "Curbing the menace of rotavirus disease in Agbor community and raising awareness on the need for early childhood vaccination"
2 • **BESONG Michael (Cameroon)** "Vaginal microbiota and Cameroonian women's health: mapping increased awareness"
3 • **VIVEROS CONTRERAS Rubi (Mexico)** "Validation of a screening questionnaire designed to assess the risk of gut dysbiosis and its correlation with the gut ecosystem of Mexican children"

Again this year, this three awardees have presenting very convincing projects to support global health in their country for vulnerable communities. Each project has been awarded €10,000.

Launched in 2021, the Henri Boulard Awards aims at recognizing local initiatives dedicated to improving the management of disorders associated with gut microbiota. Awards are opened to all healthcare professionals. With the Henri Boulard Awards, the Biocodex Microbiota Foundation is pursuing its ambition of highlighting the critical role of the human microbiota in health. More information available on the Biocodex Microbiota Foundation: **https://www.biocodexmicrobiotafoundation.com/henri-boulard-public-health-award**

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