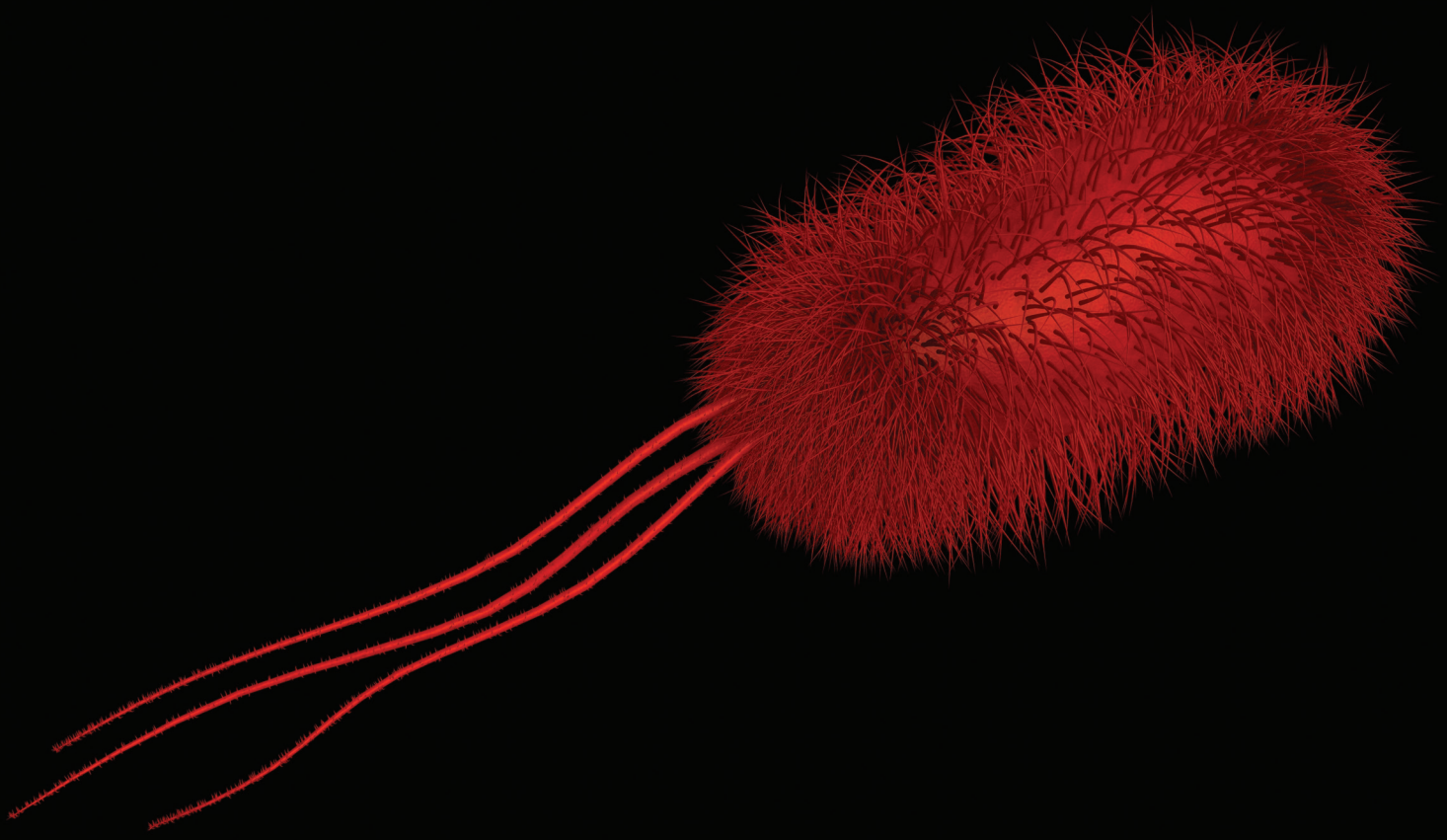
MICROBIOTA

13 BIOCODEX NEWSLETTER | SEPTEMBER 2021



BIOCODEX Microbiota Institute

SUMMARY

EDITO

Dr Maxime Prost, MD
France Medical Affairs Director

Marion Lenoir, PhD
International Medical Affairs Manager

> “ALTHOUGH THE PHYSIOPATHOLOGY OF IBS IS NOT YET COMPLETELY ELUCIDATED, AN EMERGING AVENUE OF RESEARCH IS CLEARLY THE GUT MICROBIOTA WHICH IS THOUGHT TO PLAY A MAJOR ROLE.”

Dear readers,

Irritable Bowel Syndrome (IBS) is a paradox. It is one of the most well-known gastro-intestinal disorders… but enigma for clinicians. A multifactorial disease, IBS is shrouded in mystery: the causes are poorly understood, diagnosis proceeds by the elimination of other diseases and the aim of treatments is an improvement in symptoms and not a cure.

Although the physiopathology of IBS is not yet completely clear, an emerging avenue of research is the role of the intestinal microbiota which is thought may play a major part.

In this edition, Professor Premysl Bercik (McMaster University, Hamilton, Canada) highlights the implication of the gut-microbiota-brain axis in this pathology and brings some responses to this medical enigma.

First and fundamental question, what is the role of the microbiota in IBS? Several lines of thought provide evidence that the microbiota may be involved. First, it is widely recognised that gut bacteria have an impact on the physiology of the intestine. Secondly, bacterial gastroenteritis is the most important risk factor for IBS. Thirdly, the composition and the metabolism of the microbiota are different in patients with IBS compared to those in good health. Lastly, treatments directed towards the microbiota (antibiotics, probiotics) may improve symptoms.

Another question, how do the gut and the brain communicate with each other? The microbiota appears to have a key role in these interactions as demonstrated by numerous studies on mouse models (animal/preclinical). Clinical data also suggest that the microbiota is implicated in cognitive and behavioural disorders related to hepatic encephalopathy, in depressive disorders and in some anxiety disorders.

Although other avenues remain to be explored concerning the use of probiotics to improve some depressive or anxiety behaviour linked to IBS, the veil is gradually lifting on this mystery pathology.

Enjoy your reading.

Photo: Shutterstock.

OVERVIEW

MICROBIOTA GUT-BRAIN AXIS IN IRRITABLE BOWEL SYNDROME

By Prof. Premysl Bercik
Faculty of Health Sciences, McMaster University, Farncombe Family Digestive Health Research Institute, Faculty of Health Sciences, Hamilton, Canada

Irritable bowel syndrome (IBS), characterized by abdominal pain and altered bowel habits, is the most common functional gastrointestinal disorder and is frequently accompanied by psychiatric comorbidities. Its pathophysiology is not fully understood but impairment in the gut-brain communication seems to underlie its genesis, with microbiota playing an important role in this process. Microbiota composition and its metabolic activity differ between patients with IBS and healthy controls, but no specific profiles have been identified. However, transplantation of fecal microbiota from IBS patients into germ-free mice induces gut dysfunction, immune activation and altered behavior in the murine host, similar to those observed in patients, thus suggesting its causal role. Furthermore, treatment with antibiotics or probiotics improve symptoms in some patients with IBS. Better understanding of the microbial-host interactions that lead to gut symptoms and psychiatric comorbidities, as well as discovery of new biomarkers that identify those who may benefit from microbiota directed treatments, are needed for optimized management of patients with IBS.

Photo: Shutterstock.

IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by recurrent abdominal pain, that is associated with changes in stool frequency or stool form, in the absence of any organic disorder. Using ROME IV criteria, IBS is classified into four subtypes: IBS with predominant constipation (IBS-C), IBS with predominant diarrhea (IBS-D), with mixed bowel habits (IBS-M) or IBS, unsubtyped (IBS-U) which does not meet the criteria for IBS-C, D, or M [1]. Psychiatric comorbidities, such as anxiety, depression and somatization are common in patients with IBS (**Figure 1**).

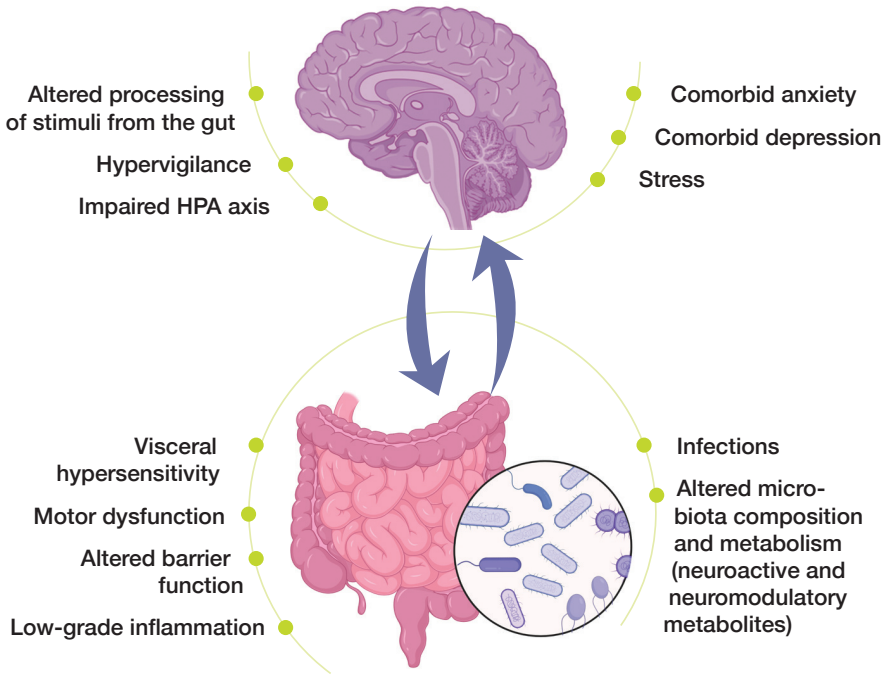
Although IBS prevalence rates appear to differ between countries, it is estimated to affect around 1 in 10 people globally [2]. IBS can develop at any age, but its onset is often usually between age of 20 and 30. Women are almost twice as likely as men to have symptoms of IBS, they also report to feel more fatigue and psychia-

tric comorbidities. The quality of life of IBS patients is severely affected, interfering with their everyday life, frequently resulting in missing work or school. The economic burden of IBS on healthcare systems and society is significant, with both direct and indirect costs. Mean annual direct cost for IBS patients was calculated at 1363 Euros, in addition to patients missing on average 8-22 days of their work per year.

Pathophysiology of IBS is not fully understood, but in general it stems from impaired gut-brain axis, a bidirectional communication between the digestive tract and the central nervous system. It likely involves multiple underlying mechanisms, including peripheral factors, such as visceral hypersensitivity, altered motility, increased intestinal permeability and low-grade inflammation. Among central factors, altered processing of signals from the gut, hypervigilance, stress, as well as psychiatric comorbidities, such as anxiety and depression, seem to play an important role. During the last decade, increasing attention has been given to gut microbiota as a key player in IBS.

▼ FIGURE 1

IBS: a bidirectional altered communication between the gut and the brain



- IBS is characterized by abdominal pain and altered bowel habits.
- Its prevalence is around 11%, predominantly affecting women, it has a significant socio-economic impact.
- Its pathophysiology is not fully understood, it is considered to be a disorder of the gut-brain interaction.

MICROBIOME IN IRRITABLE BOWEL SYNDROME

There are several lines of evidence, both from clinical studies and animal models, that implicate gut microbiota in IBS. First, bacterial gastroenteritis is the strongest risk factor for IBS, with 11-14% of patients developing chronic symptoms after acute infection with *Campylobacter, Salmonella, Shigella, Escherichia coli* or *Clostridioides difficile* infection [3]. Clinical data suggest that female sex, younger age, severity of infection and preceding psychiatric morbidity are risk factors for IBS. In addition, variants in genes related to the gut permeability, recognition of bacteria and innate immune responses have been identified.

Second line of evidence comes from clinical studies that demonstrated that certain antibiotics may improve symptoms in a proportion of patients with IBS [4]. On the other hand, clinical data also suggest that use of antibiotics, with likely subsequent intestinal dysbiosis, can lead to symptoms generation. And finally, multiple clinical trials have suggested that specific probiotics improve symptoms of IBS, such as abdominal pain, diarrhea or bloating.

The bacterial population thriving in the gut, collectively termed the gut microbiota is one of the major determinants of gut homeostasis. Accumulating data show that gut microbial composition and its metabolic activity differ between IBS patients and healthy controls, and that they associate with intestinal symptoms, as well as with anxiety and depression. However, the results from individual studies are highly variable and there seems to be no unique microbial profile that could be attributed to IBS. Despite this, a recent meta-analysis identified several microbial features, including increase in family *Enterobacteriaceae*, family *Lactobacillaceae*, and genus *Bacteroides* and decrease in uncultured *Clostridiales*, genus *Faecalibacterium*, and genus *Bifidobacterium* in patients with IBS compared to healthy controls (**Figure 2**) [5]. There are also multiple bacterial or host-microbial metabolites that are altered in patient with IBS, including phosphatidylcholine, dopamine, p-hydroxybenzoic acid, bile acids, tryptamine and histamine metabolites. However, all these findings are suggestive of association but not of causation.

The microbiota humanized mouse model is a valuable tool to establish the causal role of the gut microbiota in the IBS, and to study the underlying mechanisms leading to gut dysfunction. We used stool microbiota from patients with IBS-D and from age- and sex-matched healthy controls to colonize germ-free mice and studied them 4 weeks later. Mice colonized with IBS-D microbiota developed faster gastrointestinal transit, changes in gut barrier function and low-grade intestinal inflammation, compared to mice colonized with microbiota from healthy controls [6]. Furthermore, mice that were colonized with microbiota from patients with comorbid anxiety also developed anxiety-like behavior, suggesting that microbiome transplantation from IBS patients into the murine host not only alters the gut function, but also impairs the gut-brain communication. These functional ab-

normalities were associated with changes in multiple neuro-immune gene networks, as well as changes in many microbial and host metabolites. Interestingly, treatment with a probiotic normalized gastrointestinal transit and anxiety-like behavior in mice with IBS-D microbiota, which was associated with changes in microbiota profiles and bacterial indole production, reaffirming the notion that the gut microbiome plays a key role in the gut-brain communication [7].

- Bacterial gastroenteritis is the most significant risk factor for IBS.
- Microbiota-directed treatment (antibiotics, probiotics) can improve IBS symptoms.
- Microbiota profiles and metabolism differ in patients with IBS and healthy controls.
- Microbiota transplantation from IBS patients into germ-free mice can induce gut and brain dysfunction.

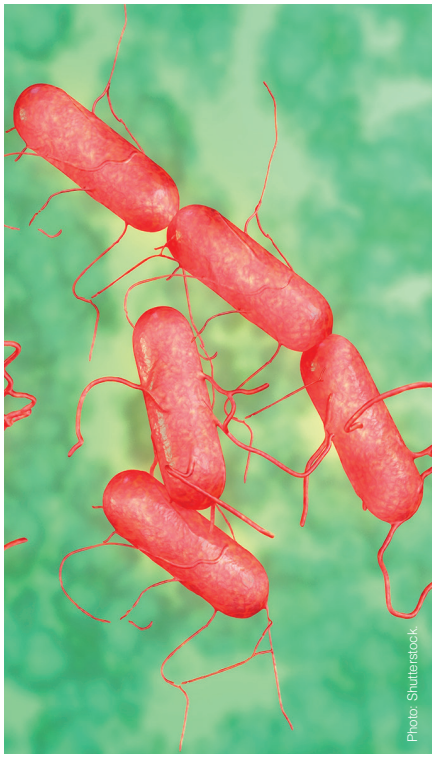
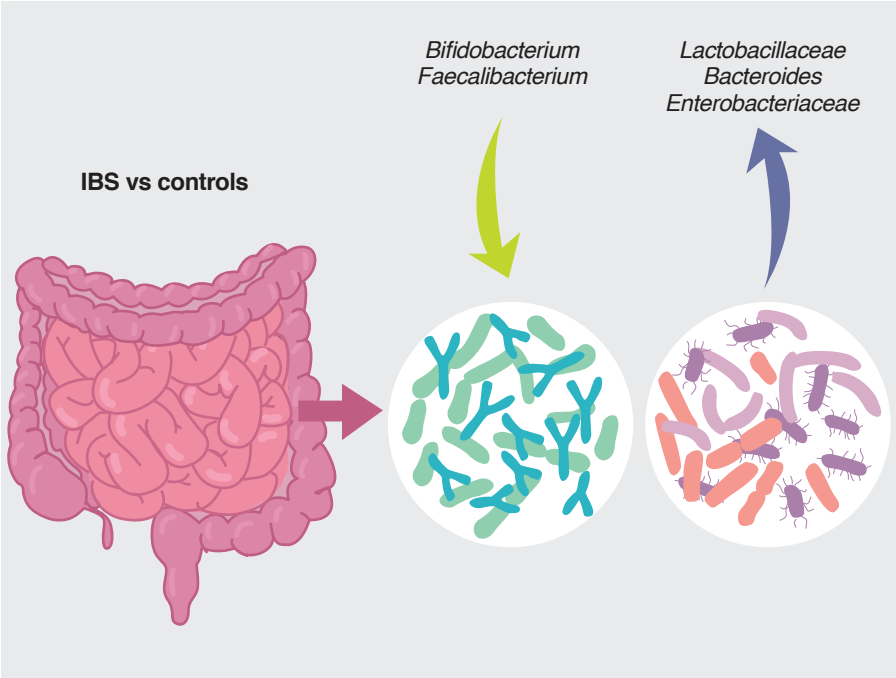


Photo: Shutterstock

▼ FIGURE 2
Gut microbiota in IBS patients.



MICROBIOTA-GUT-BRAIN AXIS

The gut-brain axis is a bidirectional communication system between the gut and the brain integrated via neural, hormonal, and immunological signalling. Growing evidence suggests that the gut microbiota plays a key role in the communication between the gastrointestinal tract and the central nervous system, with most data being obtained from animal studies [8]. Germ-free mice have abnormal behavior, associated with changes in expression of multiple genes and chemistry in the brain, altered blood-brain barrier, changes in morphology of brain regions involved in control of mood and anxiety (amygdala and hippocampus), altered myelination profile and plasticity, as well as global defects in brain microglia. Most of these abnormalities are normalized after bacterial colonization. Microbiota also modifies behavior in conventional mice, as administration of non-absorbable antimicrobials can increase their exploratory behavior, together with changes in Brain- Derived Neurotrophic Factor (BDNF) in the hippocampus and amygdala. Changes in behavior induced by antibiotics have been also described in patients treated for acute infections or during eradication of chronic *Helicobacter pylori* infection; this condition was coined "antibiotic-induced psychosis". Interestingly, a recent large population-based study found that use of antibiotics in early childhood was associated with an increased risk of developing mental health disorders in later life.

However, the most obvious case for the microbiota-gut-brain axis comes from patients with cirrhosis-associated hepatic encephalopathy that manifest with changes in behavior, mood and cognition [9]. These patients show dramatic improvement in brain function after administration of antibiotics or laxatives, and recent studies suggested that similar amelioration can be also achieved by fecal microbiota transplantation.

During recent years, multiple studies investigated gut microbiome in patients with psychiatric disorders, such as major depression and generalized anxiety, and found that the microbial profiles differed between patients and healthy controls. Furthermore, transferring microbiota from patients into germ-free or antibiotic treated rodents induced anxiety and depressive-like beha-

Photo: Shutterstock.

viors. This raises question whether those probiotics, which showed beneficial effects on behavior and brain chemistry in animal models, could be used to treat patients with psychiatric diseases. The results of the few studies completed so far suggest that probiotics, if used as an adjunctive treatment, might improve symptoms in some patients with major depressive disorder [10].

We conducted a pilot RCT study in patients with IBS and comorbid depression to assess effects of a probiotic that showed beneficial effects on behavior and brain chemistry in several mouse models [11]. We found that compared to placebo, a 6-week probiotic treatment improved depression scores and overall symptoms of IBS. This was associated with changes in neuronal activation in the amygdala and other brain regions involved in mood control, as assessed by functional magnetic resonance imaging. This suggest that some probiotics may produce neuroactive metabolites that could be harnessed not only for treatment of patients with functional bowel disorders, but also for those with mental health issues. However, more rigorous clinical studies are needed to confirm and validate these findings.

- Gut microbiota modifies behavior, as well as brain chemistry and structure in animal models.
- Clinical data suggest that microbiome is involved in cognition and mood disorders, such as hepatic encephalopathy, major depression and generalized anxiety.
- Specific probiotics might improve depressive behavior in patients, but more clinical data are needed to confirm these findings.

CONCLUSION

Irritable bowel syndrome is a common functional gastrointestinal disorder with frequent psychiatric comorbidities, that negatively affects patients quality of life and has significant socio-economic impact. Its pathophysiology is not fully understood, but it is likely multifactorial and is considered to be a disorder of the gut-brain interaction. Gut microbiota appears to play a key role in IBS, possibly through interactions with the immune or neural system, although the exact underlying mechanisms have to be clarified. Gut bacteria have the capacity to affect behavior and brain structure, and some probiotics might be beneficial for treatment of both gut and brain dysfunction.

References

• **1**. Lacy BE, Mearin F, Chang L, *et al.* Bowel disorders. *Gastroenterology* 2016: 150: 1393-407. • **2**. Black CJ, Ford AC. Global burden of irritable bowel syndrome: trends, predictions and risk factors. *Nat Rev Gastroenterol Hepatol* 2020; 17: 473-86. • **3**. Barbara G, Grover M,Bercik P, *et al.* Rome Foundation Working Team Report on Post-Infection Irritable Bowel Syndrome. *Gastroenterology* 2019; 156: 46-58. • **4**. Ford AC, Harris LA, Lacey BE, *et al.* Systematic review with meta-analysis: the efficacy of prebiotics, probiotics, synbiotics and antibiotics in irritable bowel syndrome. *Aliment Pharmacol Ther* 2018; 48: 1044-60. • **5**. Pittayanon R, Lau JT, Yuan Y, *et al.* Gut microbiota in patients with irritable bowel syndrome - a systematic review. *Gastroenterology* 2019; 157: 97-108. • **6**. De Palma G, Lynch MD, Lu J, *et al.* Transplantation of fecal microbiota from patients with irritable bowel syndrome alters gut function and behavior in recipient mice. *Sci Transl Med* 2017; 9: eaaf6397. • **7**. Constante M, De Palma G, Lu J, *et al.* Saccharomyces boulardii CNCM I-745 modulates the microbiota-gut-brain axis in a humanized mouse model of irritable bowel syndrome. *Neurogastroenterol Motil* 2021; 33: e13985. • **8**. Morais LH, Schreiber HL, 4th, Mazmanian SK. The gut microbiota-brain axis in behaviour and brain disorders. *Nat Rev Microbiol* 2021; 19: 241-55. • **9**. Acharya C, Bajaj JS. Chronic liver diseases and the microbiome-translating our knowledge of gut microbiota to management of chronic liver disease. *Gastroenterology* 2021; 160: 556-72. • **10**. Nikolova VL, Cleare AJ, Young AH, Stone JM. Updated review and meta-analysis of probiotics for the treatment of clinical depression: adjunctive vs. stand-alone treatment. *J Clin Med* 2021; 10: 647. • **11**. Pinto-Sanchez MI, Hall GB, Ghajar K, *et al.* Probiotic Bifidobacterium longum NCC3001 reduces depression scores and alters brain activity: a pilot study in patients with irritable bowel syndrome. *Gastroenterology* 2017; 153: 448-59.

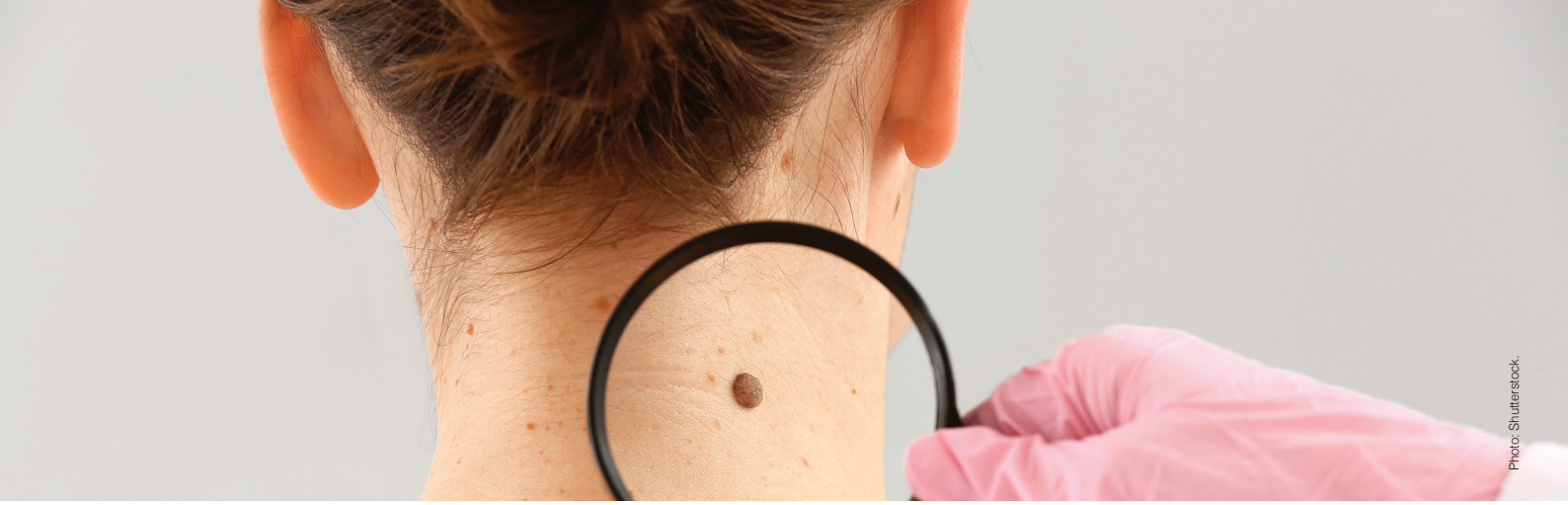


Photo: Shutterstock.

COMMENTED ARTICLE
ADULTS' SECTION

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

FAECAL MICROBIOTA TRANSPLANTATION OVERCOMES RESISTANCE TO ANTI-PD-1 TREATMENT IN PATIENTS WITH MELANOMA

Comments on the article of Davar et al. Science 2021 [1]

Anti-programmed cell death protein 1 (PD-1) immunotherapy offers long term clinical benefits to patients with advanced melanoma even though some patients are resistant to these treatments. The composition of the intestinal microbiota correlates with the efficacy of this therapy in preclinical models and in cancer patients. With the aim of determining if the anti-PD-1 resistance could be overcome by modifying the intestinal microbiota, this clinical trial evaluated the safety and efficacy of anti-PD-1 responder-derived faecal microbiota transplantation (FMT) in patients with PD-1-refractory melanoma.
This combination was well tolerated, produced a clinical benefit in 6 of the 15 patients evaluated and induced a rapid and durable microbiota perturbation. Responders exhibited increased abundance of taxa that were previously shown to be associated with response to anti-PD-1, such as *Faecalibacterium prausnitzii* and *Akkermansia muciniphila*, increased CD8+ T cell activation and decreased frequency of interleukin-8-expressing myeloid cells. Responders had distinct proteomic and metabolomic signatures, and transkingdom network analyses confirmed that the gut microbiome regulated these changes. Collectively, these results show that FMT associated with anti-PD-1 changed the gut microbiome and reprogrammed the tumour microenvironment to overcome resistance to anti-PD-1 in a sub-set of melanoma.

WHAT DO WE ALREADY KNOW ABOUT THIS SUBJECT?

Immune-checkpoint blockade with monoclonal antibodies targeting programmed cell death protein 1 (PD-1), results in long term clinical benefits in nearly 40% of patients with advanced melanoma [2]. In addition to the intrinsic tumour mechanisms underlying resistance to anti-PD-1 agents, the gut microbiome is a major extrinsic tumour regulator of responses to anti-PD-1 agents [3]. In mice, the composition of the gut microbiome modulates the therapeutic activity of the anti-PD-1 and antibodies directed against its ligand (PD-L1). Moreover the administration of certain commensal intestinal bacteria or the transplantation of faecal microbiota (FMT) enhances the efficacy of anti-PD-1 agents in mice with melanoma [4]. Although several studies have reported that a favourable gut microbiome was associated with a response to anti-PD-1 in cancer patients, its precise composition is not yet fully understood. Specifically, in melanoma, key bacterial species belonging to various phyla, in particular the Actinobacteria (*Bifidobacteriaceae* spp. and *Coriobacteriaceae* spp.) and the Firmicutes (*F. prausnitzii*), are associated with a favourable response to anti-PD-1 agents with limited concordance between the species identified in various studies. The question of whether microbiota transfer therapy can overcome anti-PD-1 resistance in patients with advanced melanoma has not been studied. To respond to this question, the authors designed an open label single-arm clinical study to evaluate the safety and efficacy of FMT derived from melanoma patients showing long-term response to anti-PD-1 agents (R), in patients with metastatic melanoma refractory to anti-PD-1.

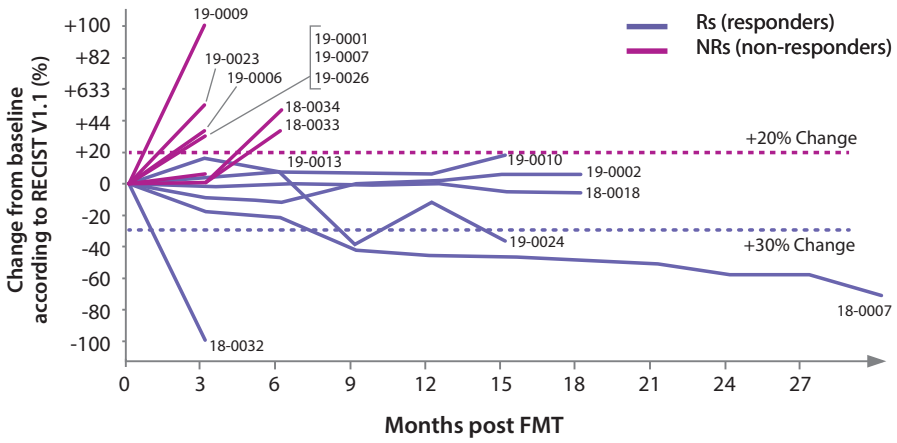
WHAT ARE THE MAIN INSIGHTS FROM THIS STUDY?

Sixteen patients with melanoma primo-refractory to anti-PD-1 treatment were included between June 2018 and January 2020. Seven donors, of whom four exhibited complete response (CR) and three, partial response (PR), with a median pro-

KEY POINTS

- The gut microbiota is involved in the anti-PD-1 response in cancerology
- FMT may overcome anti-PD-1 resistance in a sub-set of patients with refractory melanoma
- Some intestinal bacteria, such as *F. prausnitzii* and *A. muciniphila*, may be implicated in these effects

▼ FIGURE 1
Change from baseline of radiographic tumour burden.



gression-free survival (PFS) of 56 months (range: 45 to 70 months) were used to treat the 16 patients. One FMT obtained from a single donor was administered to each patient with pembrolizumab, followed by additional pembrolizumab every 3 weeks until progression of the disease or unbearable toxicity. Radiographic evaluations were performed every 12 weeks and the response was classified according to RECIST v1.1 criteria (**Figure 1**). The intestinal microbiota of the recipients (collected before FMT and then each week for 12 weeks, and then at 3-week intervals) and the donors was analysed using shotgun sequencing. Patients were followed up for an average of 12 months. One patient was not assessable and the results therefore concerned 15 patients.

No serious side effect was attributed to the FMT. Objective responses were observed in 3 patients and stabilisation lasting > 12 months was observed in 3 additional patients.

The composition of the intestinal microbiota in the recipients was modified by the FMT. The composition of the intestinal microbiota was significantly similar to that of the donor in the responders (Rs) but not in the non-responders (NRs). Most of the taxa which were significantly augmented in the Rs belonged to the phyla Firmicutes (*Lachnospiraceae* and *Ruminococcaceae families*) and Actinobacteria (*Bifidobacteriaceae* and *Coriobacteriaceae* families), whereas most of the bacteria which were reduced in the Rs belonged to the Bacteroidetes phylum.

Overall, although successful colonisation after FMT did not always restore sensitivity to patients with melanoma resistant to anti-PD-1, clinical response was associated with FMT implantation. Several bacterial species associated with a clinical response have already been reported (*B. longum, Colinsella aerofaciens* and *F. prausnitzii*).

Immunological analysis showed that the response to FMT was associated with CD8+ T-cell activation. The levels of several circulating cytokines and chemokines decreased after FMT in Rs, including MCP1, IL-8 and IL-18 (associated with anti-PD-1 resistance), and IL-12p70 and IFN-γ (associated with a T-cell antitumour response).

Lastly, transkingdom network analysis showed that the abundance of commensals which increased in Rs patients (*F. prausnitzii* and *A. muciniphila*) correlated with the favourable laboratory parameters, such as a fall in IL-8 levels.

WHAT ARE THE CONSEQUENCES IN PRACTICE?

This study suggests that FMT could overcome resistance to anti-PD-1 in a sub-set of patients with refractory melanoma. Although these results remain preliminary, they confirm the results of a previous study, published recently [5] and encourage the conduct of controlled studies on a larger scale.

CONCLUSION

This single arm, open label study, suggests that FMT may overcome anti-PD-1 resistance in a sub-set of patients with refractory melanoma. If the results are confirmed in controlled studies conducted on a larger scale, modulation of the microbiota concomitant with immunotherapy is a combination which may revolutionise cancer therapy.

References
• **1**. Davar D, Dzutsev AK, McCulloch JA, *et al.* Fecal microbiota transplant overcomes resistance to anti–PD-1 therapy in melanoma patients. *Science* 2021; 371 : 595-602. • **2**. Larkin J, Lao CD, Urb a WJ, *et al.* Efficacy and Safety of Nivolumab in Patients With BRAF V600 Mutant and BRAF Wild-Type Advanced Melanoma. A Pooled Analysis of 4 Clinical Trials. *JAMA Oncol* 2015 ; 1 : 433-40. • **3**. Finlay BB, Goldszmid R, Honda K, *et al.* Can we harness the microbiota to enhance the efficacy of cancer immunotherapy? *Nat Rev Immunol* 2020 ; 20 : 522-8. • **4**. Gopalakrishnan V, Spencer CN, Nezi L, *et al.* Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients. *Science* 2018 ; 359 : 97-103. • **5**. Baruch EN, Youngster I, Ben-Betzalel G, *et al.* Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients. *Science* 2021 ; 371 : 602-9.

COMMENTED ARTICLE
CHILDREN'S SECTION

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

HIGH-FIBRE DIET MITIGATES MATERNAL OBESITY-INDUCED COGNITIVE AND SOCIAL DYSFUNCTION IN THE OFFSPRING *VIA* GUT-BRAIN AXIS

Comments on the original article of Liu et al. (Cell Metabolism 2021) [1]

Developmental disorders in children appear to be related to maternal obesity. However, the underlying mechanisms and possible actions remain unclear. This cross-sectional study in 778 Chinese children aged 7 to 14 years indicates that maternal obesity is strongly correlated with lower cognition and socialisation in the children. Moreover, it has been demonstrated in mice that maternal obesity disrupted both behaviour and gut microbiota in the offspring. These two phenomena were restored by a high-fibre diet in either the dams or the pups, by reducing synaptic impairments and microglial maturation defects. Faecal microbiota transplantation (FMT) experiments revealed a causal relationship between the microbiota and behavioural changes. Moreover, treatment with the microbiota-derived short-chain fatty acids also alleviated the behavioural deficits in the offspring of obese mice. This study indicates that the microbiota-metabolites-brain axis may underlie maternal obesity-induced cognitive and social dysfunction and that high dietary fibre intake could be a promising intervention.

WHAT DO WE ALREADY KNOW ABOUT THIS SUBJECT?

Obesity is increasingly frequent in women of child-bearing age, which leads to a higher risk of diabetes, hypertension, and behavioural changes in the offspring. Nationwide studies have shown that these children had a greater risk of having lower intellectual capacities and autism spectrum disorders. This intellectual deficit was reproduced in mice when the mothers were fed a maternal high-fat diet (mHFD).

The gut microbiota is affected by the diet and by maternal obesity. Moreover, data exist which have identified a link between the gut microbiota and brain function. A high-fibre diet enhances the production of short-chain fatty acids (SCFA) which may be the metabolites involved in this gut-brain axis.

WHAT ARE THE MAIN INSIGHTS FROM THIS STUDY?

The authors firstly included 778 children aged 7-14 years, 79 mothers of whom were obese or overweight. The children of these obese or overweight mothers had lower social or learning abilities ($p < 0.05$), more pronounced in boys than girls.

In mice, when the mothers received a mHFD for 12 weeks, memory and social interactions in the offspring were impaired compared with those of mothers fed a control diet (mCD) ($p < 0.01$). The use of 4 types of diet in the mothers, mCD, mHFD, mFFD (high-fat and high- fibre) and mFD (high-fibre), for 12 weeks, showed that a high-fibre diet in the mother (mFFD and mFD) corrected these memory and social interaction deficits in the offspring ($p < 0.01$). This was associated with an elevated post-synaptic density in the hippocampus of mFFD offspring compared with mHFD offspring ($p < 0.05$), and with differences in gene expression in the microglia in the hippocampus and the prefrontal cortex.

This effect of a high-fibre diet is associated with a modification in the composition of the gut microbiota as shown by 16S sequencing analysis. Analysis of OTU (operational

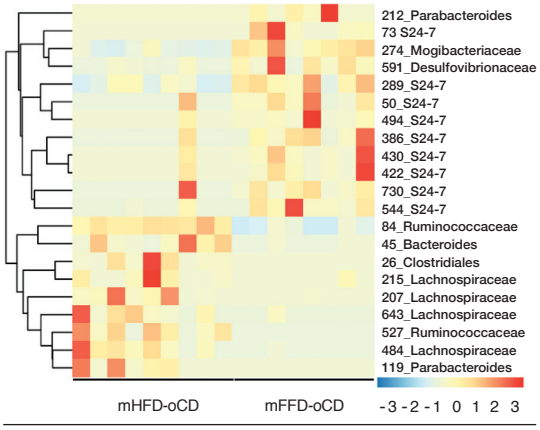
KEY POINTS

- The gut-brain axis is implicated in the cognitive and social deficit of children of obese mothers
- A high-fibre diet corrects this effect via the gut microbiota

▼ FIGURE 1

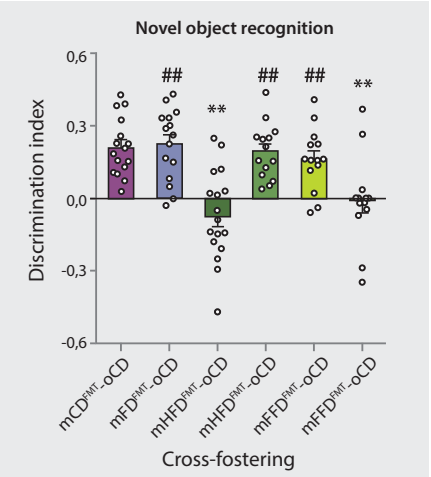
High-fiber intake in maternal diet restores synaptic impairments and re-shapes the gut microbiome of offspring.

A Z score-scaled heatmap of different OTUs identified using the Wilcoxon rank-sum test between mHFD-oCD and mFFD-oCD, with p ≤ 0.01.



▼ FIGURE 2

Cognitive impairment transmitted by the gut microbiota, in mothers by faecal transplantation and in infants by cross-fostering of the offspring.



taxonomic units) data revealed 21 bacterial taxa which differed between the mHFD and mFFD groups, 9 of which belonged to the S24-7 family, with an increase in the group receiving the mFFD diet (**Figure 1**); the abundance of 5 OTUs was positively correlated with cognitive and social behavioural deficit ($p < 0.05$). The high-fibre diet corrected the fall in propionate and acetate in the stools of the offspring, but butyrate was unaffected ($p < 0.01$).

Using faecal microbiota transplantation (FMT) analysis, the authors showed that this effect of a high-fibre diet was transmitted via the maternal gut microbiota. Firstly, transplantation of stools from mHFD mothers changed the cognitive and social behaviour of the offspring, and this was corrected by a high-fibre diet; secondly, cross-fostering of the offspring between mHFD^{FMT} and mFFD^{FMT} induced behavioural changes in the offspring of mFFD^{FMT} mothers raised by mHFD^{FMT}, and behavioural improvement in the offspring of mHFD^{FMT} mothers raised by mFFD^{FMT} mothers (**Figure 2**), an effect due to transfer of the microbiota by coprophagy.

The addition of fibre to the diet of the offspring of mHFD mice corrected the behavioural and social deficits. These mHFD-oFD pups (o = offspring fed a high-fibre diet (FD)) also exhibited an increase in S24-7 levels. Specifically, mHFD-oCD stool samples were rich in *Bacteroides* and poor in *Ruminococcus*, and for those of mHF-oFD the reverse was true (**Figure 3**). This was also associated with differences in cognitive and social behaviours. As in the mothers, fibre supplementation in the diet of the offspring produced an increase in SCFA levels. Dietary supplementation with a mixture of acetate and propionate in the drinking water improved cognitive and social abilities, and also the composition of the hippocampus and the prefrontal cortex.

WHAT ARE THE CONSEQUENCES IN PRACTICE?

Modification to the diet of obese mothers or their children by fibre supplements, or even the correction of their dysbiotic microbiota, opens new perspectives for the improvement in cognitive and social capacities of these children.

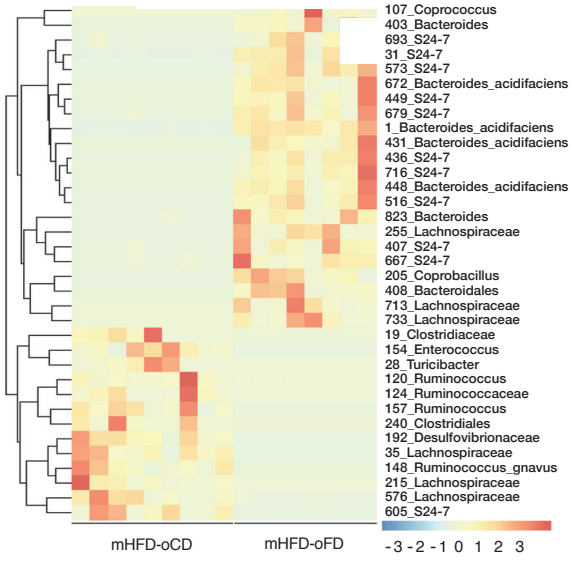
CONCLUSION

The cognitive and social deficits of children born to obese mothers are induced by changes in the gut microbiota transmitted from the mother to the child. These abnormalities are corrected by dietary supplementation with fibre, in the mother or the child. This effect is mediated by short-chain fatty acids, acetate and propionate.

▶ FIGURE 3

High-fiber intake in offspring's diet re-shapes the gut microbiome.

A Z score-scaled heatmap of different OTUs identified by the Wilcoxon rank-sum test between mHFD-oCD and mHFD-oFD with p ≤ 0.001.



Reference

1. Liu X, Li X, Xia B, *et al*. High-fiber diet mitigates maternal obesity-induced cognitive and social dysfunction in the offspring via gut-brain axis. *Cell Metab* 2021 ; 33 : 923-38.

Photo: Shutterstock.

By Prof. Gerard D. Wright
M.G. DeGroote Institute for Infectious Disease Research, McMaster University, Hamilton, Canada

WHAT IS THE IMPACT OF COVID-19 ON THE HUMAN MICROBIOME?

The COVID-19 pandemic is impacting human health in profound ways. Finlay *et al.* explore how COVID-19 and our response to it are affecting the human microbiome and what the results of the pandemic may be on maintaining our health beyond acute viral infection [1]. Both SARS-CoV-2-infected and uninfected persons have the potential to have their microbiomes significantly altered by the pandemic with ensuing effects on health. There is growing evidence that the diversity of the human microbiome is decreasing in individuals across the globe, with an acceleration over the past several decades and concomitant increase in chronic non-communicable diseases. The COVID-19 pandemic can exacerbate these concerns of diminished microbial diversity through several mechanisms (increased hygienic procedures, changes in food access, general decrease in social and community interactions…). What is less evident at this stage is what the long-term effects of the pandemic will be on the microbiome and, as a result, human health. The current situation of COVID-19 offers a unique "living laboratory" opportunity to study in real-time how pandemics can impact human health in the short- and long-term and across the lifespan and what these effects might have on individuals, communities, and societies.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT?

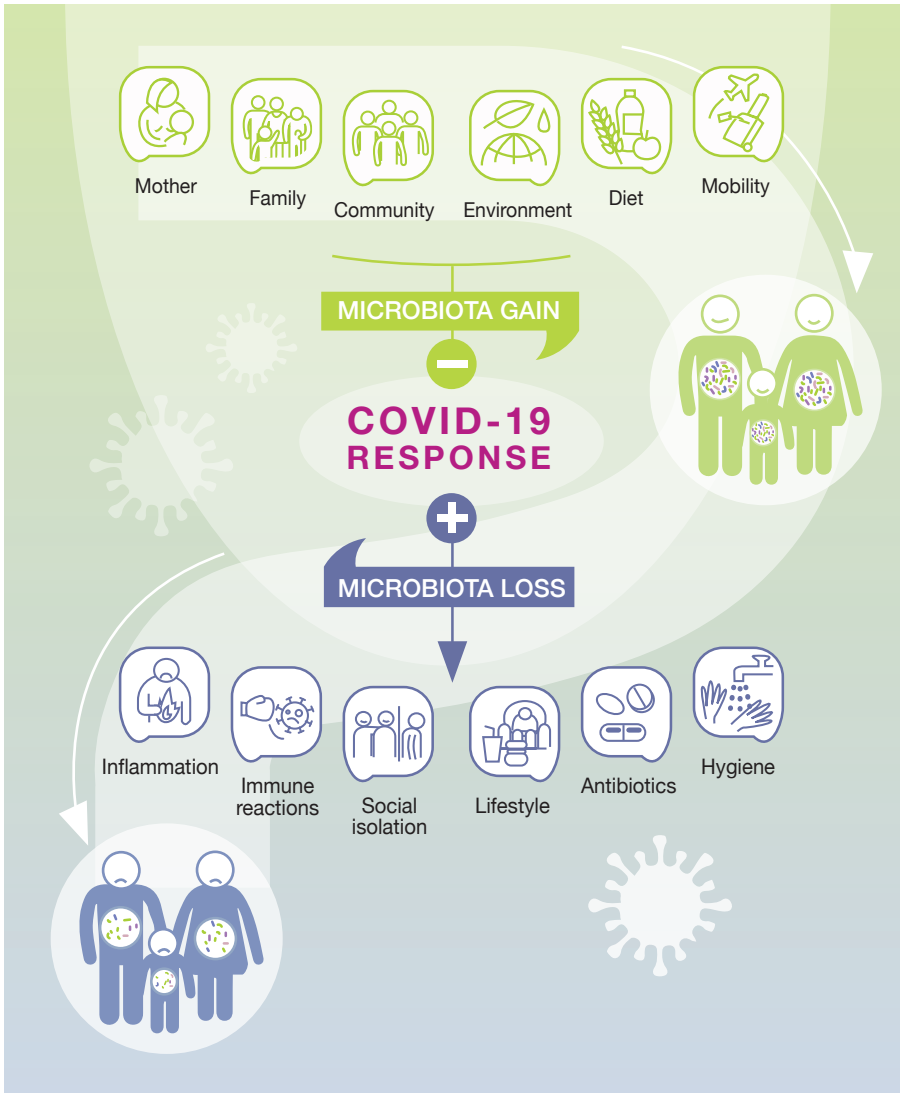
The diversity of the human microbiome varies across the globe. It is impacted by nutrition, geography, income and wealth, and societal structures [2]. A general trend of loss of microbiome diversity, especially in wealthy countries, is correlated with changes in diet (increased consumption of processed food), access to clean water, antibiotics use (and abuse), and general improvement in hygiene. The original "hygiene hypothesis" and its more recent elaborations suggest that this reduction in microbial diversity is directly linked to insufficiently "trained" immune responses, especially in the early stages of life that are manifested in susceptibility to a range of downstream chronic conditions (obesity, asthma, cardiovascular disease) [3]. Such conditions are also known to increase susceptibility to infections. Similarly, aging is often associated with a shift towards diminished genetic diversity of the human microbiota and increased susceptibility to infection [4]. From the past year's experience, we know that individuals with underlying chronic conditions and the elderly – and thus are predicted to harbor a less diverse microbiome – have been disproportionally affected by SARS-CoV-2 infection with adverse outcomes. This observation may not be coincidental. Moreover, SARS-CoV-2 infection is frequently associated with gastrointestinal disorders [5] correlated with the presence of ACE-2 receptors [6], and associated with gut dysbiosis.

WHAT ARE THE MAIN RESULTS OF THIS STUDY?

The near-universal increased use of hand sanitizers, deep cleaning of buildings and public places, and even the wholesale application of anti-infective agents in open outdoor spaces have unknown effects on microbial diversity. Changes in food access and intake are also predicted due to increased home cooking, alcohol consumption, and potential food security concerns for some parts of the world due to reduced travel and access to goods. Altered social patterns may also have profound impacts on microbiome diversity. Lockdowns, lack of human contact in the workplace,

▼ **FIGURE 1**

How COVID-19 measures influence microbiota diversity during the lifetime of an individual.



cloistering of long-term care facilities have the potential to modulate human microbiomes in ways that increase inflammation and risk of infection. It is also important to recognize that there remain hygiene inequalities across the globe, and by implication different impacts on human microbiomes. These are playing out in different relationships with COVID-19 disease, for example water quality scores were inversely correlated with COVID-19-related deaths in one study [7]. All these areas require significant study and attention.

WHAT ARE THE PRACTICAL CONSEQUENCES?

Finlay *et al.* argue that the effects of the COVID-19 pandemic on microbiome diversity and health should be investigated in real-time and over the long term across the lifespan (**Figure 1**). It offers the opportunity to look back to the impacts of past infectious disease events with more clarity and to guide response and resilience in future pandemics. Longitudinal studies can also be marshaled to address future challenges armed with information on how the microbiota can impact human health beyond acute infection. Already reports are emerging on pandemic-related changes to the human microbiome, including how travel patterns are influencing microbiome diversity [8] that even after six months post-disease that SARS-CoV-2-infected patients do not have fully recovered microbiome diversity [9]. Altered practices in neonatal care, at least in the early stages of the pandemic, such as limited skin-to-skin contact and reduced breastfeeding, have the potential to alter the infant microbiota, with potential health effects over the long-term. On the other hand, increased contact with household pets and children in cases where parents can work from home may have a balancing effect. Finally, the effect on younger children and adolescents who often have not had an opportunity to attend school or engage in sporting and social events have diminished normal contact with others is unknown. The influences that sustained stress induced by isolation, decreased social engagement, etc., may have on the long-term health of individuals due to microbial changes will need to be measured for years to come.

CONCLUSION

The diversity of the microbiome is essential to human health, and there is a correlation between diminished microbial diversity with increased risk to develop chronic diseases and susceptibility to infections. The intersection of the COVID-19 pandemic and microbiome health exposes vulnerabilities to this line of defense to acute infection and long-term health. While the pandemic is global, it is being felt unequally across nations and communities. How the inequities in age, health, nutrition, hygiene access and societies manifest themselves in short and long-term health impact related to microbiome disruption is unknown at present, but they must be recognized and studied.

References

• **1**. Finlay BB, Amato KR, Azad M, *et al.* The hygiene hypothesis, the COVID pandemic, and consequences for the human microbiome. *Proc Natl Acad Sci USA* 2021; 118: e2010217118. • **2**. Porras AM, Brito IL. The internationalization of human microbiome research. *Curr Opin Microbiol* 2019; 50: 50-5. • **3**. Stiemsma LT, Reynolds LA, Turvey SE, *et al.* The hygiene hypothesis: current perspectives and future therapies. *Immunotargets Ther* 2015; 4: 143-57. • **4**. DeJong EN, Surette MG, Bowdish DME. The gut microbiota and unhealthy aging: disentangling cause from consequence. *Cell Host Microbe* 2020; 28: 180-9. • **5**. Cha MH, Regueiro M, Sandhu DS. Gastrointestinal and hepatic manifestations of COVID-19: A comprehensive review. *World J Gastroenterol* 2020; 26: 2323-32. • **6**. Vuille-Dit-Bille RN, Lischty KW, Verrey F, *et al.* SARS-CoV-2 receptor ACE2 gene expression in small intestine correlates with age. *Amino Acids* 2020; 52: 1063-5. • **7**. Kumar P, Chander B. COVID 19 mortality: Probable role of microbiome to explain disparity. *Med Hypotheses* 2020; 144: 110209. • **8**. Peng Y, Zhang D, Chen T, *et al.* Gut microbiome and resistome changes during the first wave of the COVID-19 pandemic in comparison with pre-pandemic travel-related changes. *J Travel Med* 2021 [Epub ahead of print]. • **9**. Chen Y, Gu S, Chen Y, *et al.* Six-month follow-up of gut microbiota richness in patients with COVID-19. *Gut* 2021 [Epub ahead of print].

DDW2021 Digestive Disease Week®
Centered on Growth
May 21-23, 2021

CONGRESS REVIEW

DDW

MAY 2021

By Dr. Ericka Montijo Barrios
Pediatric Gastroenterology and Endoscopist, Department of Gastroenterology and Nutrition, Instituto Nacional de Pediatría, Mexican council NASPGHAN, Mexico city, Mexico

DDW CONGRESS

The Digestive disease week 2021 moves online this year and was held from May 21-23, 2021. It is the first meeting for physicians and researchers in the fields of gastroenterology, hepatology, endoscopy and surgery.
DDW features more than 300 original lecture sessions and interesting posters [1-7].

MICROBIOTA AND FUNCTIONAL GASTROINTESTINAL DISEASE

The gut microbiome can be viewed as a dynamic organ capable of mediating a wide variety of biochemical transformations that directly impact host physiology and disease. A disruption in this equilibrium can lead to alteration of host physiology resulting in disease such as functional gastrointestinal disorders (FGIDs).

Modifying factors in adult microbiota includes psychological stress, infectious gastroenteritis, physical activity, tobacco use, alcohol consumption, antibiotic exposure and the diet (including low fermentable oligosaccharides, disaccharides, monosaccharides and polyols diet). It is well known that antibiotic induced dysbiosis could lead to hyperalgesia. Jones *et al.* presented that more FGID patients are over prescribed antibiotics relative to non-FGID patients and more than 25% recorded antibiotic within prior their first FGDI diagnosis [4].

Microbial mediators of gastrointestinal motility are: short chain fatty acids (SCFAs) that increase serotonin biosynthesis, increase colonic hypersensitivity and decrease visceral sensitivity; bile acids, promotes propagating and non-propagating colonic contractions, stimulate secretion; methane augments small bowel contractility and slows intestinal transit and hydrogen gas shortens transit.

GASTROINTESTINAL DISORDERS WITH PAIN AS THE KEY SYMPTOMS

Pain in some FGIDs has been attributed to visceral hypersensitivity to mechanical and chemical stimuli. Most of the evidence for a role of the gut microbiome in regulating GI sensation comes from gnotobiotic studies showing that the visceral hypersensitivity phenotype can be transferred after transplantation of gut microbiota from patients with FGIDs into germ free mice.

FGIDs, are the most frequent diseases associated with visceral pain. Inflammatory pain results from the altered activity of ion channels within peripheral nociceptive sensory fibers by inflammatory mediators, which leads to increased excitability and pain. The list of pro-inflammatory mediators includes TNF-α, IL-1β, CCL2, chemokine, ligand 1 and prostaglandin E2. It has been shown that inflammatory pain induced by these mediators is lower in germ-free mice and showed increased levels of the anti- inflammatory cytokine IL-10.

Microbial dysbiosis can trigger a localized immune response associated with the production of dietary antigenic specific IgE antibodies, leading to mast cell mediated hyperalgesia. Bacterial histamine can induce hyperalgesia trough H4R mediated pathways. It is shown that injection of food antigens (gluten, wheat, soy and milk) into the rectosigmoid mucosa of patients with irritable bowel syndrome induced local oedema and mast cell activation.

CONCLUSION

Antibiotics frequently precede first diagnosis of functional gastrointestinal disorders.
There is emerging evidence that small intestinal dysbiosis plays an important role in the pathophysiology of FGIDs.
Accumulating data suggest that gut microbiota may play a role in the abdominal pain modulation.
Microbial dysbiosis can trigger hyperalgesia inducing low grade inflammation.

References
• **1**. Shin A, Preidis GA, Shulman R, Kashyap, P. The gut microbiome in adult and pediatric functional gastrointestinal disorders. *Clin Gastroenterol Hepatol* 2019; 17: 256-74. • **2**. Santoni M, Miccini F, Battelli N. Gut microbiota, immunity and pain. *Immunol Lett* 2021; 229: 44-7. • **3**. Gurusamy S, Shah A, Talley N, *et al.* Small Intestinal Bacterial Overgrowth in functional Dyspepsia: A systematic review and meta-analysis. *DDW ePoster Library* 2021; 320192; Sa389. • **4**. Jones M, Walker M, Holtmann G, *et al.* Antibiotics frequently precede first diagnosis of functional gastrointestinal disorders. *DDW ePoster Library* 2021; 319221; Fr071. • **5**. Bercik P. Host-microbe interactions as a means of understanding visceral hypersensivity. Conference. *DDW2021* virtual. May 21-23. • **6**. Kashyap P. Small Intestinal Bacterial Overgrowth Hype: Role of dietary fiber. Conference. *DDW2021* virtual. May 21-23. • **7**. Microbes and functional GI disease: The science behind the hype. Lecture. *DDW2021* virtual. May 21-23.

6th WORLD CONGRESS
of Pediatric Gastroenterology, Hepatology and Nutrition
02–05 June 2021

FISPGHAN
ESPGHAN

CONGRESS REVIEW

ESPGHAN

By Dr. José Francisco Cadena León
Dept. Gastroenterology and Nutrition, Head of of the Endoscopy Unit Digestive Endoscopy Unit, Instituto Nacional de Pediatría, Mexico City, Mexico

MICROBIOTA HIGHLIGHTS FROM THE 6TH WCPGHAN 2021 SUMMIT

JUNE 2021

During the WCPGHAN it was highlighted the importance of early changes in infant gut microbiota associated with immune programming and the emergence of chronic non communicable diseases, and the need of new nutritional and therapeutic interventions.

HUMAN MILK: ROLE ON GUT COLONIZATION AND NUTRITION

Human milk (HM) is the gold standard for infant feeding during the first six months of life, supporting optimal growth and development, and should be continued until 2 years of age, alongside complementary feeding. HM contains multiple bioactive components as Human Milk Oligosaccharides (HMOs) and microorganisms (10^4-10^5 UCF) that exerts multiple long and short-term benefits.

Some studies suggests that HM microbiota differs from oral, vaginal, skin and meconium microbiota, with species closer to each other, integrating a specific HM microbiota (Hunt KM *et al. PLoS One* 2011:6.e21313).

HM shapes the growth and development of infant gut microbiota from birth until 6 months of life. During this period, the microbial profile of exclusively breastfed infants differs from the partially breastfed or formula- fed infants, promoting an immunologic and metabolic programming.

PERINATAL FACTORS THAT MODULATE HM MICROBIOTA

While C-section promotes colonization with a specific bacterial profile, vaginal birth lead to one resembling to the mother´s vaginal microbiota. Some studies have demonstrated that C-section and maternal antibiotic administration (*G-O-084 abstract*) prior skin incision induces a delayed colonization and a less diverse microbiota.

In addition, yeast and fungi (21.4%) have been reported in HM and associated with early antibiotic use and lower bacterial load, outdoor environment, city population, density, season, maternal atopy.

In a cross-sectional study Zelca *et al.* (N-ePwP-049) examined the characteristics of the gastrointestinal microbiota in infants (0-12 months) and pre-school children (under 5 years-old) related with diet and environmental factors. The authors reported a greater composition of *Bifidobacterium* in the infant group whose mothers did not receive antibiotics during pregnancy or with siblings, and a larger amount of *Bacteroides*, *Blautia* and *Ruminococcus* in pre-school children.

HMOS AND BIOTICS

In a study, Kawata MS, (N-ePwP-042) using a simulator of the human gut ecosystem, analyzed the impact of an infant formula enriched with 2 HMOs [2' fucosyllactose (Nnt; 05.g/L)] in the microbiota and metabolites. The author reported an increase of the taxa of Actinobacteria and Firmicutes, mainly *Bifidobacterium* and *Lactobacillus*; short fatty acids as butyrate, acetate and, propionate and reduction of *Enterobacteriaceae* spp.

HMOs are specific for *Bifidobacterium* spp, whereas, combination of both could bring a metabolic effect, producing short-chain fatty acids similar to those contained in HM (Walsh C. *et al*, N-eP-133).

The future implications of understanding the early gut colonization of the infant during the first 6 months and the risk factors that could modify the immune programming allow us to generate new therapeutic interventions.

PRESS REVIEW

By Prof. Markku Voutilainen
Turku University Faculty of Medicine; Turku University Hospital, Department of Gastroenterology, Turku, Finland

GUT MICROBIOTA

GUT MICROBIOTA, MEDITERRANEAN DIET AND CARDIOVASCULAR DISEASE

Top contributors of disease burden worldwide, cardiometabolic disease such as cardiovascular disease (CVD) and type 2 diabetes (T2D) have been linked to the individualized nature of the gut microbiome (metabolism and immune interactions). While preclinical studies suggest that gut microbiome and diet engage in a two-way relationship, strong clinical evidence is still lacking especially towards cardiometabolic disease risk.

The aim of the study was to examine the interplay of a Mediterranean diet (MedDiet), the gut microbiome and cardiometabolic disease risk in a subpopulation of over 300 men from the long-running Health Professionals Follow-up Study (HPFS).

A significant interaction between a healthy dietary pattern and the gut microbiome in relation to cardiometabolic disease risk was identified. This study shows that long-term adherence to a healthy MedDiet was associated with the taxonomic and enzymatic variation of the gut microbiome. Dietary patterns explained 0.7% of the variation which is higher than that caused by antibiotic use. Adherence to MedDiet was associated with the enrichment of microbial degradation of dietary fibers and short chain fatty acid fermentation run by anaerobic fiber metabolizers such as *F. prausnitzii* and *E. rectale*. Low adherence to MedDiet with use of red or processed meat was associated with increased microbial synthesis of hepatotoxic secondary bile acids carried mainly by *C. aerofaciens*. The study underlines the ability of the MedDiet to mitigate cardiometabolic disease risk in the absence of *Prevotella copri;* while increase in the MedDiet index was associated with decreased myocardial infarct risk in *P. copri* non-carriers, the *P. copri* carriers had increased risk.

Consequently, individual's gut microbial profile could be used to tailor dietary interventions to prevent CV disease. For *P. copri* non-carriers, a MedDiet would be the first-line preventive measure, while *P. copri* carriers might benefit more from exercise or statins to control CV risk.

Wang D, Nguyen LH, Li Y, *et al*. The gut microbiome modulates the protective association between a Mediterranean diet and cardiometabolic disease risk. *Nature Medicine* 2021; 27: 333-43.

ANTIBIOTIC PROPHYLAXIS AND RESISTANCE IN LEUKAEMIA PATIENTS

Although antibiotic prophylaxis (AP) can reduce the risk of serious infection in immunocompromised patients the major drawback is antibiotic resistance. Prophylaxis with a broad-spectrum fluoroquinolone may select for antibiotic-resistant microbes and lead to cross-resistance to other antibiotics. In this study, the authors have examined gastrointestinal resistome of children with acute lymphoblastic leukaemia (ALL) to determine the impact of AP on the antibiotic resistance genes (ARGs).

Amongst the 49 children with ALL, 31 (63%) received levofloxacin prophylaxis during induction therapy and 18 received no prophylaxis. Trimethoprim-sulfamethoxazole was given for *Pneumocystis jirovecii* prophylaxis. An increase in the relative abundance of

trimethoprim-sulfamethoxazole resistance genes of gut microbiota was detected, which was not modified by levofloxacin prophylaxis. Topoisomerase point mutations of stool bacteria increased during therapy in levofloxacin recipients, but not in the rest of the study population. Levofloxacin target bacterial topoisomerase enzymes that catalyze DNA double-strand break. The increase in the prevalence of fluoroquinolone resistance genes was low and the number of patients with topoisomerase mutations remained small. Although the selective effect of levofloxacin appeared small, an increase in the frequency of fluoroquinolone resistance persisted for at least 2 months after exposure. By contrast, no changes were detected in the aminoglycoside, β-lactam, vancomycin, or multidrug resistance genes after induction therapy suggesting no cross-class resistance to any other antibiotics.

In conclusion, fluoroquinolone prophylaxis gives short-term protection against infections but does not increase the risk of cross-resistance to other antibiotics.

Margolis EB, Hakim H, Dallas RH, *et al.* Antibiotic prophylaxis and the gastrointestinal resistome in paediatric patients with acute lymphoblastic leukaemia: a cohort study with metagenomics sequencing analysis. *Lancet Microbe* 2021 [Epub ahead of print].

THE ROLE OF FECAL MICROBIOTA TRANSPLANTATION (FMT) IN MELANOMA TREATMENT

Immunotherapy to inhibit the programmed cell death-1 (PD-1) checkpoint protein is used for melanoma patients, but only 10-20% obtain complete remission. To increase therapy success, modulation of the gut microbiota has become one of the most promising leads as it shows positive results in preclinical models. However, it has not been investigated in clinical trials. The authors wanted to evaluate immune cell impact of FMT followed by anti-PD-1 immunotherapy in patients with refractory metastatic melanoma.

FMT was performed both via colonoscopy and with oral administration of stool capsules followed by reinduction of anti-PD-1 therapy. Stool was obtained from two donors (donor 1 and 2) whose metastatic melanoma had been treated and complete remission reached. No moderate or severe adverse events from FMT were observed. Objective melanoma treatment responses were detected in three patients, they all had received FMT from the same donor (1). One patient achieved complete and two partial remission. After FMT gut microbiota differed from the baseline in all patients and was different depending on the donor (1 or 2). Responders had higher relative abundance of *Enterococcaceae*, *Enterococcus*, and *Streptocccus australis* and lower abundance of *Veillonella atypica*, but no association between microbial taxa and treatment response was detected. After FMT up-regulation of genes related to the presentation of peptides by antigen-presenting cells (APC) was detected. Responders up-regulated also genes related to APC-activity, innate immunity and interleukin-12. Tumor analysis of all available recipients revealed post-treatment up-regulation of many immune-related gene sets.

The study shows that FMT combined with anti-PD-1 therapy is a safe and potentially effective treatment for refractory metastatic melanoma. Modulation of the gut microbiota may overcome resistance to immunotherapy.

Barruch EN, Youngster I, Ben-aBetzalel G, *et al.* Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients. *Science* 2021; 371: 602-9.

MICROBIOTA AND BREAST CANCER

In this review, the authors focus on human microbiota throughout life, the links between gut/breast microbiota and breast cancer (BC), and the impact of metabolomics and pharmacomicrobiomics on BC risk and prognosis and treatment choices. While estrogens, high breast density, western-style diet, obesity, alcohol and genetic factors are risk factors for BC, gut microbiota dysbiosis has emerged as a key player in development, treatment, and prognosis of BC through diverse biological processes. β-glucuronidase (BGUS) bacteria modify the enterohepatic circulation of estrogens and may increase the risk of hormone dependent BC. As in the gut, local microbial signatures of breast microbiota in BC patients differ from that of healthy controls. While it is not known whether these findings are a cause or a consequence, a link between breast dysbiosis and BC might exist and is influenced by bacteria and/or their components in local immune microenvironment.

Human estrobolome[1] denotes enteric bacterial genes whose products metabolize estrogens. BGUS of intestinal bacteria deconjugate xenobiotics and estrogens leading to reuptake via enterohepatic circulation. Estrogen produced by BGUS may increase the risk of hormone-dependent BC. Other intestinal bacteria metabolize phytoestrogens that may protect against BC. Some gut bacteria produce equol and enterolignans that may diminish hormone-dependent BC risk. Twenty to 30% of western population have microbes (*Coriobacteriaceae* family) converting isoflavone to equol that has affinity to estrogen receptors, and antiandrogenic and antioxidant activity. Gut free fatty acid receptors are activated by short chain fatty acids and may participate in tumor suppression. Breast and gut microbiota may modulate BC microenvironment: activate aberrant epithelial proliferation, secretion of growth factors, genome mutations, local metabolic microenvironment and angiogenesis. Gut bacteria may inactivate, *e.g.*, doxorubicin and gemcitabine. Gut microbiota has even a double role in radiotherapy efficacy either beneficial and protective or detrimental and resistant.

To conclude, in BC patients, microbiota could serve as prognostic and predictive factors of treatment response. In the future, microbiota modulation may improve the outcomes of BC patients.

Costa DA, Nobre JG, Batista MV, *et al.* Human microbiota and breast cancer – is there any relevant link? – A literature review and new horizons toward personalized medicine. *Frontiers Microbiol* 2021; 12: 584332.

Photo: Shutterstock.

1"the aggregate of enteric bacterial genes whose products are capable of metabolising oestrogens" (Plottel and Blaser, 2011).

VAGINAL MICROBIOTA

USING RECOMBINANT ENDOLYSINS TO TREAT BACTERIAL VAGINOSIS

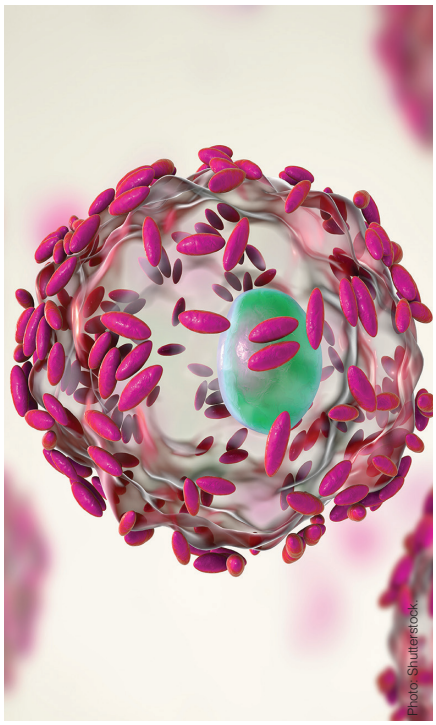


Photo: Shutterstock.

A study has shown that by using recombinant endolysins of the type 1,4-beta-N-acetylmuramidase encoded on *Gardnerella* prophages it is possible to eliminate the bacterial biofilm responsible for bacterial vaginosis without damaging the beneficial bacteria of the vaginal microbiota.

To this end, the authors generated several engineered endolysins, bacteriophage enzymes that lyse the bacterial wall, via domain shuffling. They compared their bactericidal activity on *Gardnerella* strains to that of wild-type endolysins. The bactericidal activity of the recombinant endolysins was 10 times that of any wild-type enzyme. When tested against a panel of 20 Gardnerella strains from 4 species (*G. vaginalis, G. leopoldii, G. piotii* and *G. swidsinski*), the most active endolysin, called PM-477, showed superior efficacy compared to the antibiotics tested (metronidazole, tinidazole, clindamycin). Furthermore, PM-477 had no effect on beneficial lactobacilli or other species of vaginal bacteria. According to the authors, PM-477 is highly selective for *Gardnerella* and kills strains of each of the four main species without affecting beneficial lactobacilli or other species typical of the vaginal microbiota. The effect of PM-477 was confirmed by microscopy in mixed cultures of *Gardnerella* and *lactobacilli*.

To go further and analyze the efficacy of PM-477 in a physiological environment closely resembling the *in vivo* situation, the researchers treated vaginal swabs from 15 bacterial vaginosis patients and analyzed them by fluorescence *in situ* hybridization (FISH). They showed that in 13 of the 15 cases, PM-477 eradicated the *Gardnerella* bacterium and physically dissolved the biofilms without affecting the vaginal microbiota. According to the authors, endolysins are a promising therapeutic alternative to antibiotics for the treatment of bacterial vaginosis.

Landlinger C, Tisakova L, Oberbauer V. Engineered phage endolysin eliminates *gardnerella* biofilm without damaging beneficial bacteria in bacterial vaginosis ex *vivo*. *Pathogens 2021*; 10: 54.

SKIN MICROBIOTA

COCONUT OIL FOR THE SCALP MICROBIOTA!

A recent study has shown that coconut oil can help maintain a healthy scalp by improving the scalp microbiota. The researchers compared the impact of coconut oil and a neutral shampoo on the scalp bacterial and fungal microbiota of 140 women with and without dandruff. The scalps of the women with dandruff had a much higher abundance of uncharacterized *Malassezia* species, fungus known to accelerate the development of dandruff and inflammation. Conversely, the fungus species *M. globosa*, was found in abundance on the scalps of the women with no dandruff or itching. Treatment with coconut oil brought the ratio of *M. globosa* to other groups of *Malassezia* in line with that of healthy scalps. Although no significant differences were observed between the bacterial microbiota of the healthy group and that of the dandruff group, both groups saw an increase in bacteria involved in the metabolism of biotin following coconut oil treatment. Biotin, a B vitamin that is essential for the maintenance of healthy skin and a healthy scalp, is also known to reduce inflammation. Further studies are required to understand the underlying mechanisms, but for the researchers, the positive effect of coconut oil on the composition and function of the scalp microbiota is the first step towards the longer-term restoration of scalp health.

Saxena R, Mittal P, Clavaud C. *et al.* Longitudinal study of the scalp microbiome suggests coconut oil to enrich healthy scalp commensals. *Sci Rep* 2021; 11: 7220.

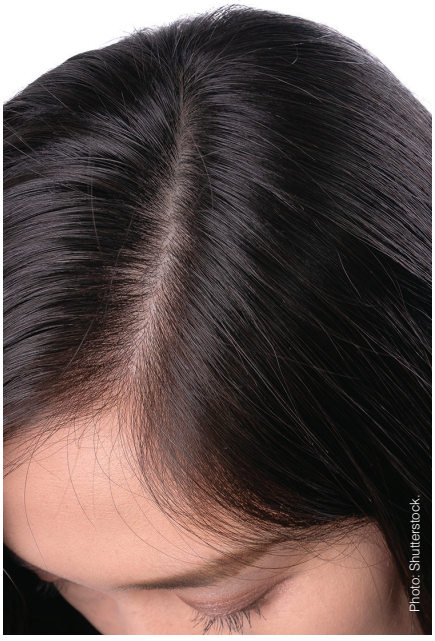
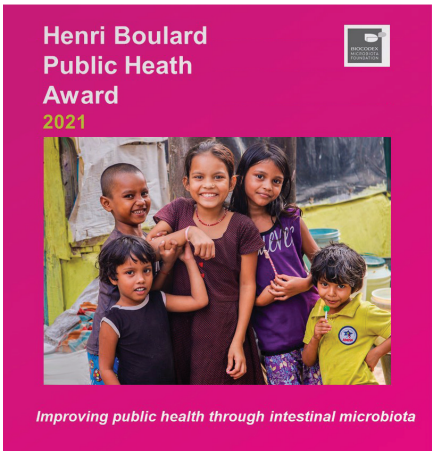


Photo: Shutterstock.

BIOCODEX MICROBIOTA FOUNDATION

HENRI BOULARD PUBLIC HEALTH AWARD

"To support and reward innovative projects that aim to improve public health by addressing issues linked to the intestinal microbiota": this is the goal of the Henri Boulard Public Health Award, launched in May 2021 by the Biocodex Microbiota Foundation. This new award focuses on programs promoting good nutritional practices, wastewater treatment projects, campaigns to reduce infant mortality caused by infectious diarrhea, among others. It is aimed at projects linked to the intestinal microbiota that have the potential to significantly impact public health at a local level. With the Henri Boulard Public Health Award, the Biocodex Microbiota Foundation continues its mission to highlight the importance of the microbiota and remind us of its role in current public health issues. Open to all health professionals, the award is aimed at projects linked to the gut microbiota. Worth €10,000 each, the award will be granted each year. Applications can be submitted until September 30, 2021. For more information regarding application rules, click **here**.



BIOCODEX MICROBIOTA INSTITUTE

CME: GET CERTIFIED IN MICROBIOTA!

Looking for a practical training on microbiota? Want to update your knowledge in a few hours? **Xpeer Medical Education** and the **Biocodex Microbiota Institute** are launching the second session of training courses to improve doctors' knowledge of the importance of the human microbiota for health. After the inaugural session "Health outcomes of drugs-gut microbiota interactions" led in May 2021 by Professor Francisco Guarner Aguilar, gastroenterologist and senior researcher at the Vall d'Hebron Research Institute (Barcelona), the second session will focus on «Obesity/overweight and microbiota in clinical practice». Under the direction of Professor Karine Clément, endocrinologist and professor of nutrition Inserm nutriOmics Unit, Pitié-Salpêtrière Hospital (Paris), this course is intended for health professionals with an intermediate level of knowledge about the microbiota. Only 5 minutes available? Each one-hour course includes several microlearning videos. The evaluation test at the end of the course allows you to obtain European Continuing Medical Education Credits (ECMEC) granted by the European Accreditation Council for Continuing Medical Education (EACCME). Totally free of charge and exclusively accessible on the Xpeer application, the courses are available in 7 different languages: English, French, Spanish, Russian, Polish, Turkish and Portuguese.

INTERNATIONAL CALL FOR PROJECTS 2022

"Structure and function of the gut microbiota resistome". The topic for the Biocodex Microbiota Foundation International Grant for 2022 came out! The research projects will have to explore the functional role of antibiotic resistance genes within the gut microbiome, with a focus on anaerobic microorganisms that are difficult to assess in routine clinical microbiology. Amount of the grant: €200,000. Researchers can apply until 30 November 2021:

apply@BiocodexMicrobiotaFoundation.com

ISSN : 2782-0505

7 avenue Gallieni – 94250 Gentilly – Tél. : +33 1 41 24 30 00

BIOCODEX Microbiota Institute

BMI-21.38 (09-21) - Code SAP : 98397 - Achevé d'imprimer par Corlet, Imprimeur, S.A. en septembre 2021