MICROBIOTA Mag

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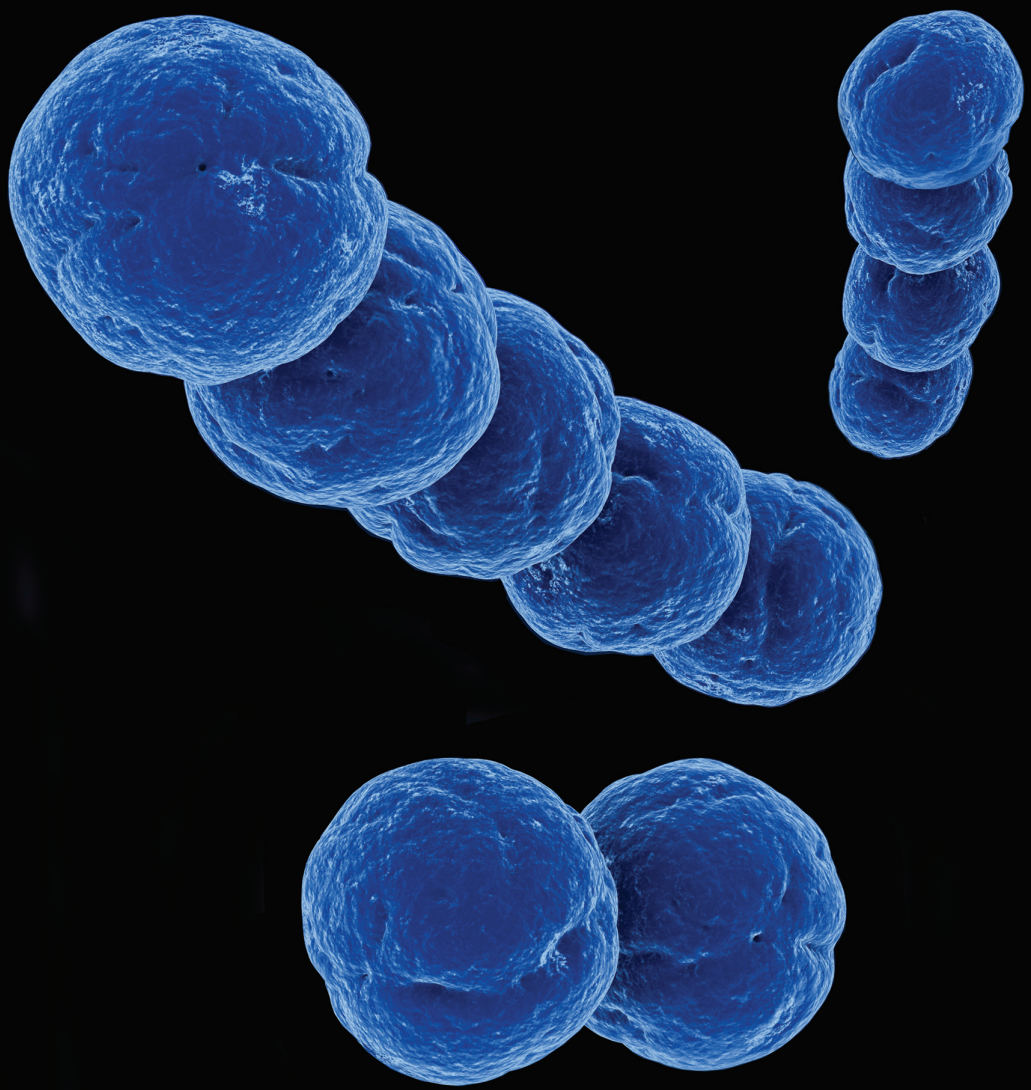


| OVERVIEW |

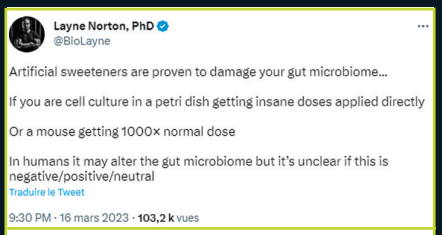
Oral microbiota and chronic conditions

BIOCODEX Microbiota Institute

SUMMARY

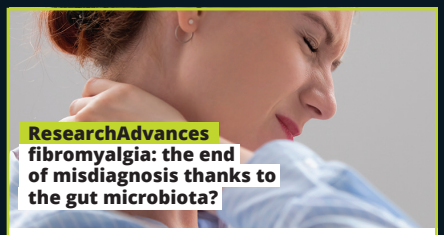
Find this issue and previous ones here

WHAT DID YOU MISS ON SOCIAL MEDIA?



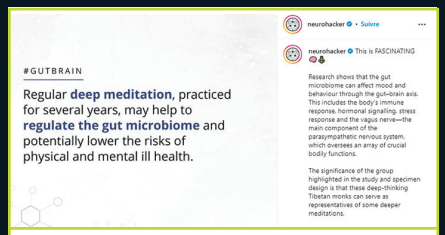
ARTIFICIAL SWEETENERS AND THE GUT MICROBIOME

In a recent study, non-nutritive sweeteners were shown to disrupt the gut microbiome of healthy people. Do you have to tell your patients not to use non-nutritive sweeteners? **Pr. Clément gives you the correct answer on p.18.**



FIBROMYALGIA AND GUT MICROBIOTA

In March, the "fibromyalgia" Facebook post from the Biocodex Microbiota Institute generated the most shares and comments with **4.5 k users engaged**



REGULATE THE GUT MICROBIOME THANKS REGULAR DEEP MEDITATION?

By **@neurohacker**
4.2k likes

EDITO

Dear readers,

Dr. Maxime Prost, MD
France Medical Affairs Director

Barbara Postal, PhD
International Medical Affairs Manager

Reading this new Microbiota Magazine, you might be surprised.

For the very first time, we have decided to broaden the strictly speaking gut microbiota research.

But don't worry, you will not be frustrated.

In this issue, we have tackled an exciting and expanding field of research: oral microbiome.

In recent decades, research have been inquiring the relationships between oral microbiome – oral health - and general health. For instance, a link was already established between *Porphyromonas gingivalis*, chronic periodontitis and Alzheimer's disease (AD) – a neurodegenerative disease which affects at least 30 million people worldwide.

Studies reveal that the oral microbiota is the second largest, most diverse, and most complex microbial community after the gut one. It is also the gatekeeper of the gut, the opening of the intestinal tract.

In the overview, Dr. Jay Patel told us that "an expanding body of evidence suggests that the relevance of this disturbance is not merely confined to local disease activity, but has a disseminated risk profile for other major chronic diseases of the body, with a high global burden of disease including diabetes, atherosclerotic cardiovascular disease, and rheumatoid arthritis."

In recent decades, research have been inquiring the relationships between oral microbiome – oral health – and general health.

From mouth to gut, from an oral microbiota dysbiotic to major chronic diseases, from a severe periodontitis to diabetes… Thanks to this unique overview, we hope you will acquire new skills to better integrate the interaction between oral microbiota and gut into your clinical practice.

Enjoy your reading!

DIETARY FIBER, BLOATING, AND INTESTINAL GAS

By **Dr. Eric Berg DC**
177.8k views, 8,1k likes, 9,9M followers

GUT MICROBIOME AND LONG COVID

By **Dr. Noha Aboelata, MD**
532 RT, 42 quotes, 1.453 likes

3 TYPES OF MYTHS ABOUT GUT HEALTH

By **Dr. Noc**
83,4k vues, 9,7k engagements

By Dr. Jay Patel

Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, United Kingdom

Oral microbiota and chronic conditions

Although the co-evolutionary role of the human microbiome as a determinant of human health is increasingly recognised in modern medicine, the oral microbiome remains a largely siloed factor contributing to general health and well-being. In health, the oral microbiome maintains a careful symbiotic equilibrium with the host, with harmful bacteria at clinically inconsequential levels. However, external environmental pressures readily turn the oral microbiome dysbiotic, where an improper proportional and diversity of microbes colonise the mouth. These environmental pressures are often highly modifiable risk factors. An expanding body of evidence suggests that the relevance of this disturbance is not merely confined to local disease activity but has a disseminated risk profile for other major chronic diseases of the body, with a high global burden of disease including diabetes, atherosclerotic cardiovascular disease, and rheumatoid arthritis.

> In health, the oral microbiome represents a carefully balanced, diverse community protecting the mouth from disease. Modern lifestyle choices can readily upset this balance, rendering the community less protective and increasingly harmful.

Mechanism

The morphology, warmth and moisture of the mouth affords the oral microbiota a highly diverse habitat for colonisation and growth. From birth, children acquire a simple oral microbiome, and with age, the eruption of teeth, and the additive role of external factors, this community becomes increasingly complex. Both host-derived and microbially-derived factors maintain the homeostatic equilibrium of the oral microbiome required for health.

Poor oral hygiene can be a profound ecological pressure that steers complex microbial communities in the mouth into dysbiosis [1].

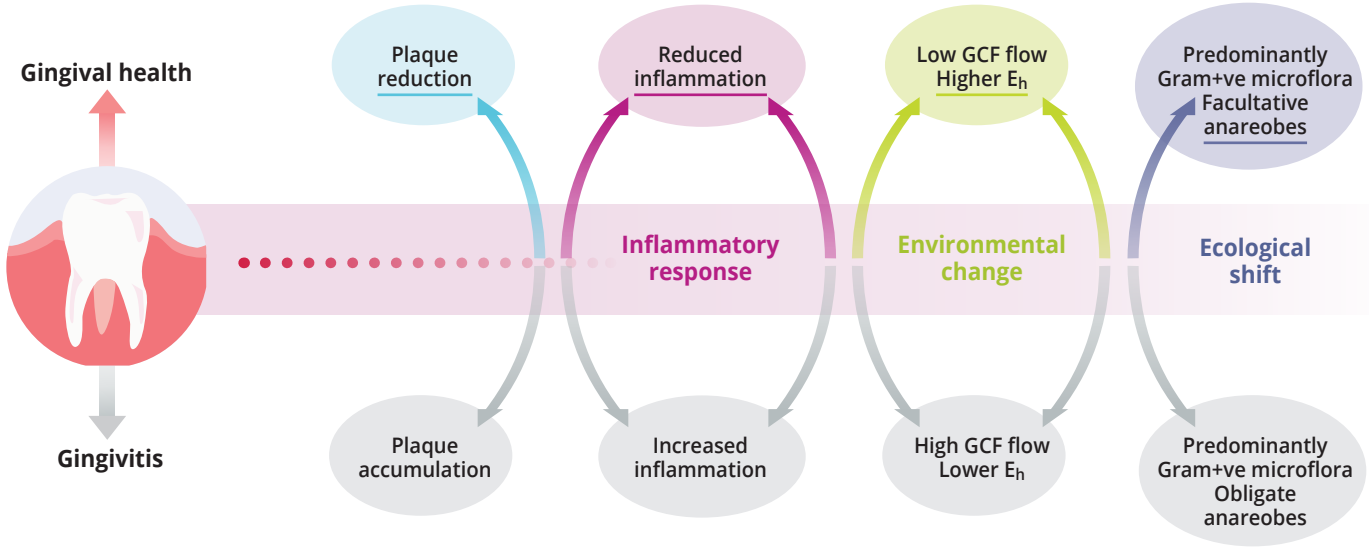
Photo: Shutterstock

Ecological shifts in a dysbiotic ecosystem favour the colonisation and proliferation of pathogenic oral bacteria (**figure 1**). When these species increase in quantity, the risk of oral disease significantly increases. Periodontal disease is a chronic, non-resolving, inflammatory process leading to tissue breakdown of the tooth-supporting apparatus, and can lead to tooth loss, if untreated. Routine activities including chewing, flossing, and toothbrushing can induce bacteraemia, which facilitate haematogenous dissemination of oral bacteria and inflammatory mediators, inducing systemic inflammation in some patients [2]. Patients with periodontal disease—the sixth most prevalent condition affecting humankind globally [3]—show micro-ulcerated sulcular epithelia and damaged periodontal tissues, and thus seem more susceptible to bacteraemia. Therefore, the inflammatory state from periodontal disease metastasises to other sites of the body, which can occur at clinically-relevant levels. Good oral hygiene is therefore essential for controlling the total bacterial load in the mouth, maintaining or re-establishing the oral symbiotic equilibrium, and preventing the dissemination of oral bacteria to other sites in the body.

The characteristics of the oral microbiome are not only confined to oral pathological changes but can influence systemic health, and in cases, this influence is measurable in both positive and negative directions.

FIGURE • 1

Schematic overview of the ecological plaque hypothesis relevant to periodontal health and disease. Adapted from Clerehugh V, Tugnait A, Genco RJ. *Periodontology at a Glance*. Oxford: Wiley–Blackwell, 2009.



GCF = gingival crevicular fluid • E_h = redox potential • +ve = positive • -ve = negative

Compared to individuals with periodontal health, **patients** with **severe periodontitis** are at a

19–33%

elevated risk of developing diabetes [6].

Diabetes

> The strongest evidence supporting a bidirectional role between oral and systemic health exists for the dose-dependent relationship between the severity of periodontitis and complications arising from diabetes.

Type II diabetes is a metabolic disorder characterised by an insufficiency of insulin production and the subsequent inability for the body to metabolise glucose, leading to elevated levels of blood glucose (chronic hyperglycaemia). Severe periodontitis strongly influences glycated haemoglobin (HbA1c) and fasting blood glucose levels in people with and without diabetes [4]. Periodontitis is thus recognised as the sixth major complication of diabetes, as the risk for periodontitis is raised by 2-3 times for people with the condition [5]. Compared to individuals with periodontal health, patients with severe periodontitis are at a 19–33% elevated risk of developing diabetes [6].

Untreated severe periodontitis is associated with an increase in the circulating levels of bacteria and bacterial antigens, pro-inflammatory mediators and cytokines, and increased levels of interleukin 6, tumour necrosis factor alpha, C-reactive protein, and oxygen free radicals. This combined effect fosters the conditions for systematic inflammation, impairing insulin signalling and resistance [6]. Clinically, this is recognised through increased HbA1C and the progression of diabetes, with greater risk of diabetic complications. Periodontal treatment reduces the oral bacterial load, and therefore lowers the circulating levels of inflammatory mediators, thereby reducing the degree of the systematic inflammatory state (**figure 2**). Hence, the dental management of periodontitis can lead to a clinically-relevant improvement in glycemic control, where patients with diabetes experience HbA1c reductions of 0.3–0.4% up to four months after treatment.

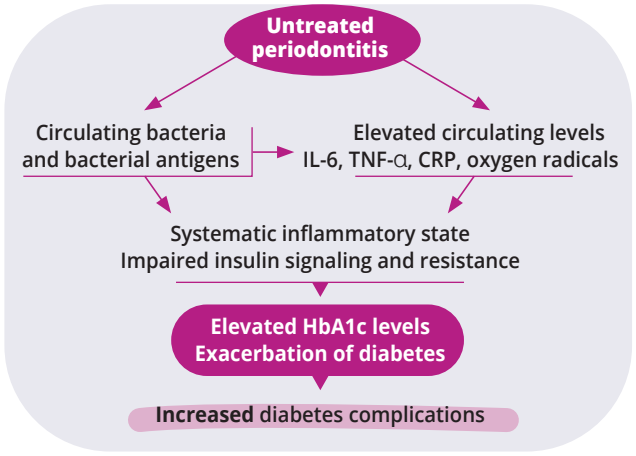
Atherosclerotic cardiovascular disease

Atherosclerosis describes the accumulation of fats, cholesterol, and blood cells that form hardened plaque deposits within the artery walls, occluding blood flow through the vessels, increasing the risk of cardiovascular complications.

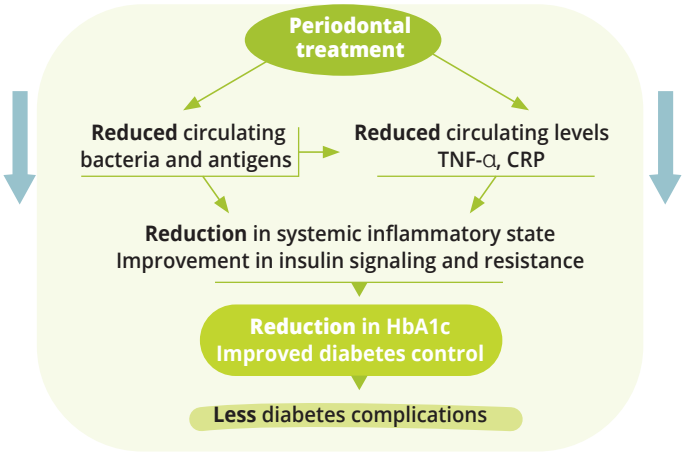
FIGURE • 2

The mechanistic association between periodontitis and diabetes, and the impact of non-surgical periodontal therapy on diabetes control. Reproduced from Preshaw P, Bissett S. Periodontitis and diabetes. *Br Dent J* 2019; 227(7): 577–584.

A The up-regulated systemic inflammatory state from untreated periodontitis.



B The reduced systemic inflammatory state following non-surgical periodontal therapy, resulting in improved insulin resistance, HbA1c and overall diabetes control.



- CRP = C-reactive protein
- HbA1c = glycated haemoglobin
- IL-6 = interleukin-6
- TNF-α = tumour necrosis factor-α

Oral bacteria are contributory infectious agents in the pathogenesis of atherosclerosis, through the invasion of cardiovascular host cells, namely endothelial cells [7].

Chronic periodontal disease can lead to endothelial dysfunction, through an elevated systematic inflammatory state, which can be shown through increased levels of IL-6, fibrinogens, and periodontopathic bacterial products, such as outer membrane vesicles and gingipains [8]. Much of the atherosclerotic pathology appears to be attributable to *Porphyromonas gingivalis*. However, *Aggregatibacter actinomycetemcomitans, Prevotella intermedia, Tannerella forsythia* and *Fusobacterium nucleatum* have each been studied in relation to this association. The primary microbial implications are endothelial dysfunction and the promotion of atherosclerosis in cardiovascular cells. *P. gingivalis* has the ability to attach to endothelial target cells, and external factors mediate its cellular entry, where it induces pro-coagulant effects. The results of a parallel-group, single-blind, randomised, controlled trial found that although intensive periodontal therapy led to systemic inflammation and endothelial dysfunction in the immediate term, 6 months after treatment, clinical and biochemical improvements in endothelial function were noted [9]. This study added to the theory that periodontal control may modulate atherosclerotic cardiovascular processes.

Rheumatoid arthritis

Rheumatoid arthritis is a chronic, autoimmune inflammatory condition affecting the synovial fluid of joints in a symmetrical pattern, and if untreated, other organs. *Porphyromonas gingivalis* is implicated in the pathophysiology of rheumatoid arthritis, where the bacteria produce enzymes with the capacity of citrullinating proteins, increasing the probability of reductions in the host immune tolerance and promoting the release of autoantibodies characteristic to the condition [10]. Several studies have shown that periodontitis caused by dysbiotic oral biofilms, can trigger rheumatoid arthritis with systemic inflammation and increased bone erosion. A bidirectional relationship has been postulated between the inflammatory conditions, but further evidence is needed to verify this [11]. Clinicians involved in the rheumatological care of arthritis patients should be aware of the role of periodontitis as a fac-

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Cross-sectional data from the United States showed an 82% increase in rheumatoid arthritis associated with periodontitis, identified through gain in periodontal attachment loss [12].

tor modulating the efficacy of biologic disease-modifying anti-rheumatic therapies, since the maintenance of systemic inflammation could affect treatment response.

> Non-surgical periodontal therapy appears to improve the biochemical expression of rheumatoid arthritis, but its role in improving clinical outcomes remains to be fully understood.

In patients with dysbiotic oral biofilms, where the proportions of periodontopathic bacteria capable of citrullinating proteins are higher than in health, preventive and curative treatment to stabilise the oral microbiome and periodontal inflammation would be prudent to include as a core aspect of the rheumatological care plan.

Prevention

Scientific advances in the understanding of the oral microbiome demonstrate its contribution to both oral and general health and well-being. The ecological plaque hypothesis is the currently accepted theory desiring microbiological changes in the mouth, where shifts in the ecology of the oral microbiome result in disharmony, which foster key harmful pathogens to increase in number [13]. The dissemination of oral bacteria to systemic bodily sites is substantially reduced by enhancing control of the oral microbial load. Daily mechanical removal of plaque, through a systematic and comprehensive toothbrushing and interdental cleaning technique, reduces the volume of this load, and prevents the colonisation of pathogenic species. Good plaque control also prevents the risk of developing periodontal diseases, characterised by micro-ulceration of the gingival architecture, thereby producing channels for the leakage of bacteria and inflammatory mediators.

Supplemented with professional interventions by dental practitioners (commonly oral hygiene instruction, risk factor control, and mechanical plaque removal), periodontal disease processes can be stabilised and if mild, reversed.

> **Where the microbial balance has been disturbed in disease, the symbiotic equilibrium of the oral microbiome can be re-established and stabilised through relatively simple personal and professional interventions**

Conclusion

Research exploring the association between changes in the oral microbiome and systemic chronic conditions continues to expand.There are multiple plausible reasons to justify the bidirectionality of these putative connections. Dysbiosis in the oral microbiome, the primary driver for local and general disease onset and progression is mediated by highly modifiable risk factors, reinforcing the value of prevention, and the need for health systems to re-orient their mode of care delivery to accommodate the delivery of preventive oral health care.

Sources

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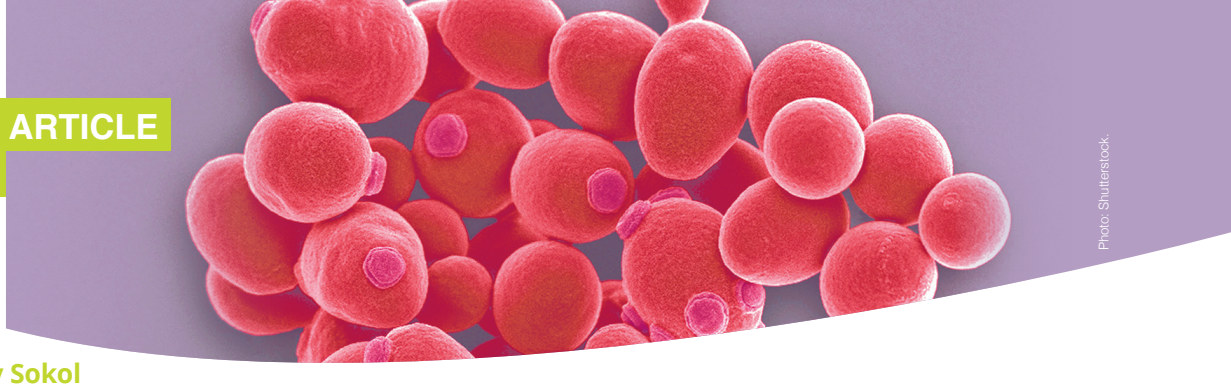

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By Pr. Harry Sokol

Gastroenterology and Nutrition Department, Saint-Antoine Hospital, Paris, France

A pan-cancer mycobiome analysis reveals fungal involvement in gastrointestinal and lung tumours

Comment on the article by Dohlman et al. (Cell 2022 [1])

Fungal microorganisms (mycobiota) comprise a small but immunoreactive component of the human microbiome, yet little is known about their role in human cancers. Pan-cancer analysis of multiple body sites revealed tumour-associated mycobiomes at up to 1 fungal cell per 10^4 tumour cells. In lung cancer, *Blastomyces* was associated with tumour tissues. In stomach cancers, high rates of *Candida* were linked to the expression of pro-inflammatory immune pathways, while in colon cancers *Candida* was predictive of metastatic disease and attenuated cellular adhesions. Across multiple GI sites, several *Candida* species were enriched in tumour samples and tumour-associated *Candida* DNA was predictive of decreased survival. The presence of *Candida* in human GI tumours was confirmed by external ITS sequencing of tumour samples and by culture-dependent analysis in an independent cohort. These data implicate the mycobiota in the pathogenesis of GI cancers and suggest that tumour-associated fungal DNA may serve as diagnostic or prognostic biomarkers.

What do we already know about this subject?

••• Cancer is one of the leading causes of death worldwide. The tumorigenesis, progression and treatment-response of cancer are influenced by various interactions between the immune system of the host and bacteria in the microbiota. However, the role of fungi (mycobiota) in these processes remains largely unexplored. Fungi and bacteria co-colonise the gastrointestinal tract, skin epithelium, airways and reproductive organs of mammals, forming a complex ecosystem of microbe-microbe and host-microbe interactions with significant implications for human health. While fungal infections account for over 1.5 million deaths worldwide each year, they only account for 0.1% of microbial DNA in the gut, suggesting a disproportionate influence of species from this kingdom on the overall gut microbiome and host immunity. Whether referring to viruses, bacteria or fungi, an ever growing body of scientific evidence suggests a link between the human microbiome and cancer and its outcomes. Several cases showing the association between bacterial species and cancer development/progression have been observed in recent years. *Helicobacter pylori* is responsible for approximately 75% of the risk attributable to gastric cancer, while genotoxic *Escherichia coli, Bacteroides fragilis, Streptococcus bovis/gallolyticus* and *Fusobacterium nucleatum* have been implicated in colorectal carcinogenesis [2]. The common feature of these bacteria is their ability to trigger chronic inflammation, a feature considered to contribute to their tumorigenic capacity. Recent reports have also identified intracellular bacteria in many types of tumour [3].

The mycobiome plays a key role in the activation of innate immunity in the gut. Mycotoxins and bioactive amines have been associated with carcinogenesis. Recent experimental studies support fungal involvement in cancer in some contexts [4]. Sequencing data from tumour banks have revealed the presence of microbial sequences, although the fungal component has not yet been explored.

What are the main insights from this study?

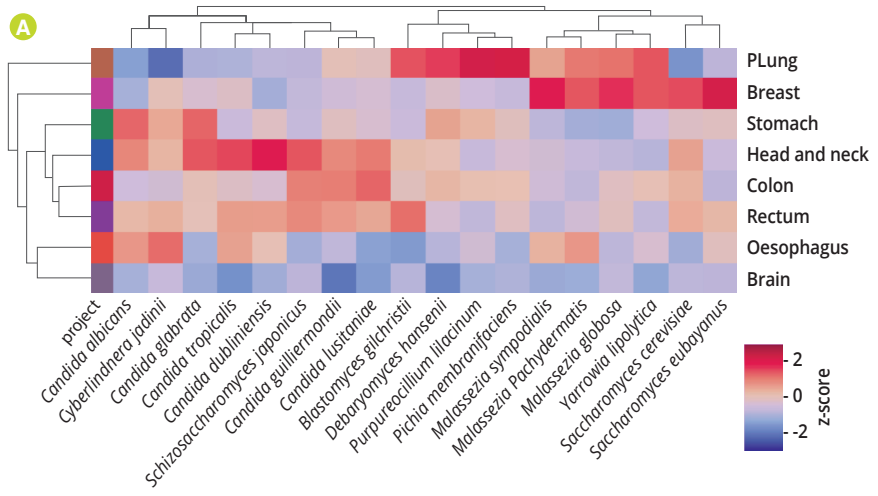
••• By analysing several types of cancer using "The Cancer Genome Atlas" (TCGA), the authors extracted tumour-associated mycobiome profiles with a species-level

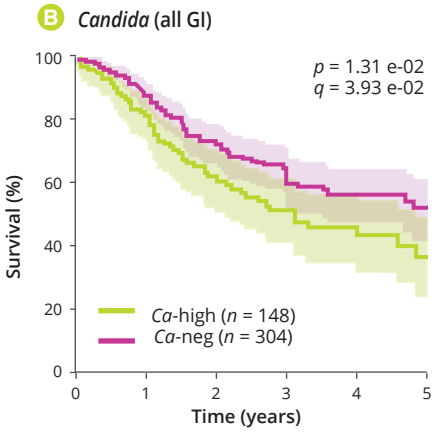
Key points

- A pan-cancer analysis of the mycobiome revealed the presence of fungi within tumour tissue
- Gastrointestinal tumours contain live and transcriptionally active *Candida*
- Abundant *Candida* DNA is found in some tumour tissue, and could be indicative of poor prognosis

FIGURE 1 The fungal mycobiota associated with cancer differs between tumour types, and Candida abundance may be predictive of survival.

• **A**. Heatmap showing the difference in relative abundance of fungal species between tissues of each cancer type. • **B**. In patients with gastrointestinal cancers overall, patients with high levels of tumour-associated *Candida* (Ca-high) have decreased survival compared to patients with no *Candida* in their tumour (Ca-neg).





resolution. After eliminating contamination and false-positive signals, the authors reported that fungal compositions varied according to the type of cancer, and that some fungi were tumour-type specific, in both gastrointestinal and non-gastrointestinal locations (**figure 1A**). Overall, up to one fungal cell per 10^4 human tumour cells were observed, a rate consistent with the finding that fungi make up 0.1-1% of the microbiome, while bacteria are estimated to make up less than 1% of tumour cells [2, 3]. Abundant numbers of several species of *Candida*, *Saccharomyces cerevisiae* and *Cyberlindnera jadinii* have been found in gastrointestinal tumours, while *Blastomyces* and *Malassezia* species are abundant in lung and breast tumours, respectively. The authors then showed that several *Candida* species are alive and transcriptionally active in the tumour. Finally, the abundance of some fungi within the tumour could predict host tumour gene expression, disease status and survival (**figure 1B**), although these findings still need to be confirmed. Overall, these results suggest an involvement of fungi, especially *Candida*, in the pathogenesis of gastrointestinal cancers but also highlight their potential as a therapeutic target and prognostic tool.

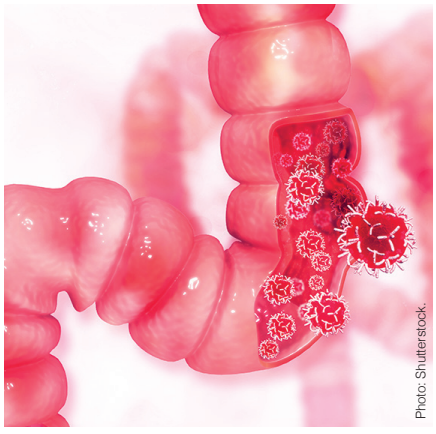


Photo: Shutterstock.

What are the consequences in practice?

••• Alongside bacteria, this study reported the presence of fungi in many gastrointestinal and non-gastrointestinal tumours, with some degree of specificity across tumour types and a potential for predicting severity. These results suggest that fungi play a role in the cancer process and its severity. They could also pave the way for the development of new biomarkers or new cancer treatments targeting the fungal component.

[CONCLUSION]

An analysis of multiple gastrointestinal and non-gastrointestinal tumours identified tumour-associated fungi, especially *Candida* enrichment in gastrointestinal cancers. Fungi may also play a role in carcinogenesis. Tumour-associated fungal DNA could serve as a prognostic marker in this context and fungi could represent a new therapeutic target in cancer.

Sources

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COMMENTED ARTICLE

Children's section

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By Pr.Emmanuel Mas

Gastroenterology and Nutrition Department, Children's Hospital, Toulouse, France

Rural environment reduces allergic inflammation by modulating the gut microbiota

Comment on the article by Yang et al. (Gut Microbes [1])

Rural environments and microbiota are linked to a reduction in the prevalence of allergies. However, the mechanism underlying this reduction is unclear. The authors assessed gut bacterial and fungal composition in urban and rural children in Southern China (EuroPrevall-INCO cohort). The bacterial and fungal composition of airborne dusts from homes in the city and countryside (including mattress dust) as well as dust from henhouses (rural environment) were analysed by 16S rRNA sequencing. Mice were repeatedly exposed to intranasal dust extracts and evaluated for their effects on ovalbumin (OVA)-induced allergic airway inflammation. It was found that children in rural areas had fewer allergies and unique gut microbiota with fewer *Bacteroides* and more *Prevotella*. Dusts from rural environments contained a higher level of endotoxins and diversity of bacteria and fungi, whereas indoor urban dusts were enriched with *Aspergillus* and contained a higher number of potentially pathogenic bacteria. Intranasal administration of rural dusts before OVA sensitisation reduced respiratory eosinophils and blood IgE level in mice and also led to a recovery of gut bacterial diversity and *Ruminiclostridium* in the mouse model. Faecal microbiota transplant restored the protective effect by reducing OVA-induced lung eosinophils in recipient mice. These results support a cause-effect relationship between exposure to dust microbiota and allergy susceptibility in children and mice. Specifically, rural environmental exposure modulated the gut microbiota, which was essential in reducing allergy in children.

What do we already know about this subject?

••• The prevalence of allergic diseases has increased dramatically. It has been shown that children living in the countryside are less prone to asthma than those living in cities. Indoors, dust is the main source of bacteria and fungi. Its composition reflects the outdoor environment and is influenced by external activities (e.g., agricultural), building materials and animals.

The establishment of gut microbiota during the first 1,000 days of life shapes the subsequent development of allergic diseases. Some well-known factors influence the composition of the gut microbiota of infants including antibiotics, delivery method and diet. Any resulting dysbiosis is thought to increase the subsequent likelihood of developing allergic diseases. In contrast, breastfeeding and vaginal delivery protect against the subsequent development of allergic diseases. The intestinal microbiota of these types of infants is characterised by a predominance of bifidobacteria, especially *Bifidobacterium breve*. Decreased contact with nature was seen to favour intestinal dysbiosis with a dysregulation of Th1/Th2 immune balance in favour of Th2, which is the adaptive immune response involved in allergic diseases (Cukrowska Nutrients).

The mechanisms by which gut dysbiosis in early life influences the development of allergies and asthma are little understood. Farm dust and bacterial lipopolysaccharide are known to induce endotoxin tolerance, thus reducing allergic asthma.

Key points

- Chinese children living in rural areas develop fewer allergic diseases than those living in urban areas
- The composition of the dust microbiota is different
- In mouse models, exposure to rural house dusts reduces allergic inflammation in the airways by modulating the gut microbiota

FIGURE 1 Composition of gut microbiota in allergic children and controls in urban and rural areas of Southern China.

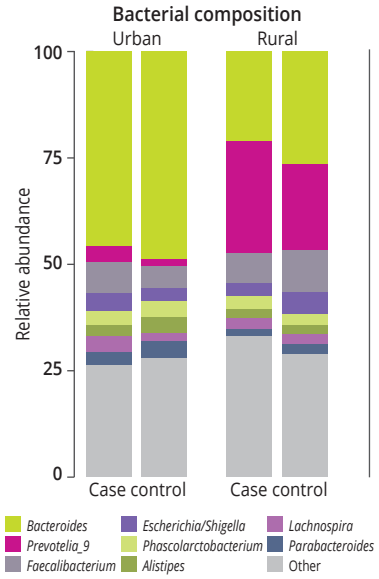
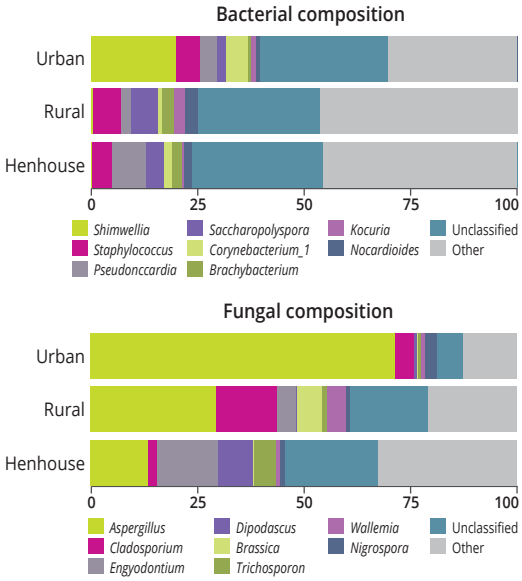


FIGURE 2 Characterisation of environmental dust microbiota from urban and rural homes and henhouses.



What are the main insights from this study?

••• The authors compared urban and rural environmental exposures in China in a human and mouse study. The EuroPrevall-INCO human cohort included 5,139 urban and 5,542 rural school-age children. The prevalence of food allergies and especially asthma, rhinitis, and eczema were higher in urban children ($p < 0.001$).

A case-control study included 225 children: 151 urban and 74 rural children. The gut microbiota of all children was analysed via 16S rRNA sequencing and metabolic pathways were assessed via shotgun sequencing. Clinical data and allergen sensitizations were collected. The *Prevotella*-to-*Bacteroides* ratio was significantly higher in rural children ($p < 0.001$). This difference was due to *Prevotella_9* accounting for 25% of amplified variants in rural children and <5% in urban children (**figure 1**). However, no significant difference was observed in gut microbiota composition between cases and controls in both urban and rural participants. The analysis of metabolic pathways identified 14 different pathways between urban/rural participants and nine between controls/cases. Among these, the L-lactate producing pathway was strongly associated with allergy and pathways involved in sugar degradation and lipopolysaccharide synthesis were abundant in the microbiota of control children.

To mimic the microbial exposure of children in urban and rural environments, mattress dusts were collected from ten urban and ten rural families and dusts from five henhouses from rural families (on the assumption that these may contribute to the microbial environment in rural families). *Enterobacteriaceae* and *Rhizobiaceae* were predominant only in urban house dusts (**figure 2**). A significantly higher α diversity and endotoxin content was observed in rural house dusts compared to urban house dusts and henhouse dusts. Finally, urban house dusts had a significantly higher proportion of potentially pathogenic bacteria. In addition, *Aspergillaceae* dominated in urban house dusts, whereas *Trichocomaceae* (*genus Penicillium*) was more abundant in rural house dusts (hence the higher diversity) and henhouse dusts (**figure 2**).

To test the impact that exposure to environmental dusts may have on allergic disease by altering the gut microbiota, the researchers exposed mice to dust by intranasal exposure (OVA-induced allergic model). Prior exposure to house dust in rural areas attenuated allergic inflammation (eosinophilic infiltration of airways, in bronchoalveolar lavage (BAL), increased sIgE). Mice exposed to rural dusts showed the lowest increase in the proportion of potentially pathogenic bacteria. The abundance in the gut of *Bacteroidales* increased and while *Clostroidales* (including species belonging to both *Lachnospiraceae* and *Ruminococcaceae* families) decreased in control mice exposed to PBS as well as those exposed to urban dusts. Finally, the relative abundance in the gut microbiota of *Bacteroides* and *Ruminiclostridium* was correlated to eosinophils in BAL ($r = 0.59$ and $p = 0.001$ and $r = -0.45$ and $p = 0.05$ respectively).

What are the consequences in practice?

••• Early modulation of the gut microbiota, targeting the beneficial effect of rural house dusts could prevent the development of allergic diseases..

[CONCLUSION]

This study reported differences in the composition of dust microbiota between urban and rural areas in China. These modulate differently the gut microbiota and its immune response in allergic diseases.

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GUT MICROBIOTA FOR HEALTH World Summit 2023

By Dr. Nicolas Benech

Gastroenterology and hepatology,
Microbiota Study Group,
Hospices Civils de Lyon, Lyon, France

GUT MICROBIOTA FOR HEALTH

MARCH 2023

Highlights of Gut Microbiota for Health - World Summit 2023

The science of the microbiota is a rapidly evolving area and currently encompasses a wide range of scientific and medical expertise, meaning there is now a need to structure and raise awareness of discoveries and bring emerging concepts to the attention of as many people as possible. Gut Microbiota for Health (GMFH) is an off-shoot organisation of the European Society for Neurogastroenterology & Motility (ESNM) whose remit is to promote information and scientific discussion in the area of gut microbiota, especially within the scientific and medical community. Founded in 2012, GMFH organises an annual symposium to gather experts in microbiota science and encourage optimal interactions between both scientists and clinicians. The eleventh edition of Gut Microbiota for Health - World Summit took place in Prague, Czech Republic, on the 11th and 12th of March, and focused on recent developments in innovative treatments targeting the microbiota. A selection of highlights in terms of research and concepts during these two days are presented below.

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Gut microbiota research is now developing complex clinical applications such as faecal microbiota transplantation (FMT), next-generation probiotics derived from the human microbiota, medicines developed from microbial products (postbiotics) and also diets based on our current knowledge of host/microbiota interactions. The challenges and issues raised by the arrival in clinical practice of these new forms of medicines today bring up a large number of regulatory, ethical and scientific questions which were developed throughout the congress. At the opening of the symposium, Professor Eugène B. Chang (Chicago, USA) introduced the challenges and new concepts involved in the development of this new type of medicine. Some of these include: the pressing need to establish a specific regulatory framework and design industrial standards capable of underpinning the development of new probiotics; and the need to understand treatments targeting the microbiota in an ecological and dynamic manner, *i.e.* evolving products that fit into an ecological niche which, in turn, they help to modify.

New pre- and probiotics to boost anti-tumour immune response

We have known about the important role played by gut microbiota in modulating anti-tumour immune response for around 10 years; however, the underlying mechanisms are still poorly understood. During the first session of the congress, Dr. Michael Scharl (Zurich, Switzerland) and Professor Harry Sokol (Paris, France) presented their latest findings regarding the identification of microbiological and metabolic candidates for combination therapies with conventional treatments to stimulate anti-tumour immunity. Thus, by studying differences in tumour development in murine models from different animal houses, Dr. Scharl's team identified four bacterial strains which, when administered alone, reduced tumour development in mice (*Eubacterium hallii, Faecalibacterium prausnitzii, Roseburia intestinalis, Anaerostipes caccae*) [1].

Interestingly, administration of the supernatant of these strains was sufficient to obtain a stimulatory effect on the anti-tumour immune response.

The metabolism of 3-OH dodecanoic acid has been identified as one of the mechanisms potentially responsible for this effect, paving the way to the development of specific postbiotics.

In line with these findings and the bacterial consortium identified, Professor Sokol presented unpublished work confirming the beneficial impact of *Faecalibacterium prausnitzii* in the response to immunotherapy.

The re-analysis of metagenomic data from several studies comparing responder and non-responder patients treated with immunotherapy confirmed that the presence of F. prausnitzii was associated with superior tumour response and survival in patients with a dose effect.

In addition to the plenary scientific sessions, several workshops were organised to foster lively exchanges with the experts. Thus, the session on "Engineered microorganisms as therapeutic agents" explored the current advances and perspectives in the development of new genetically engineered microbiological therapeutic agents. During this session, Dr. Nicholas Arpaia (New York, USA) presented an engineered strain of *Escherichia coli* developed with a lysis cycle coordinated between the different bacteria *via* a quorum sensing mechanism resulting in the release of a nano-antibody (anti-CD47 antibody fragment) inhibiting an immune tolerance signal in phagocytes [2]. In mice, injection of these bacteria at the tumour graft site resulted in the complete elimination of implanted tumours by the immune system via phagocytosis stimulation but also through adaptive immunity recruitment, thus suggesting the generation of a sustained immune and anti-tumour response. However, the ethical and regulatory framework required to allow the clinical evaluation of this type of treatment has yet to be defined, and this point was specifically discussed during the remainder of the workshop.

Faecal microbiota transplantation, gaining a better understanding of mechanisms underpinning its effectiveness

Among microbiota-based therapies, FMT is currently the most widely evaluated treatment in clinical practice across many indications. Despite a large number of studies, the factors determining the effectiveness of FMT and its mechanism of action

The beneficial effect of FMT was correlated to the engraftment capacity of donor strains in the recipient.

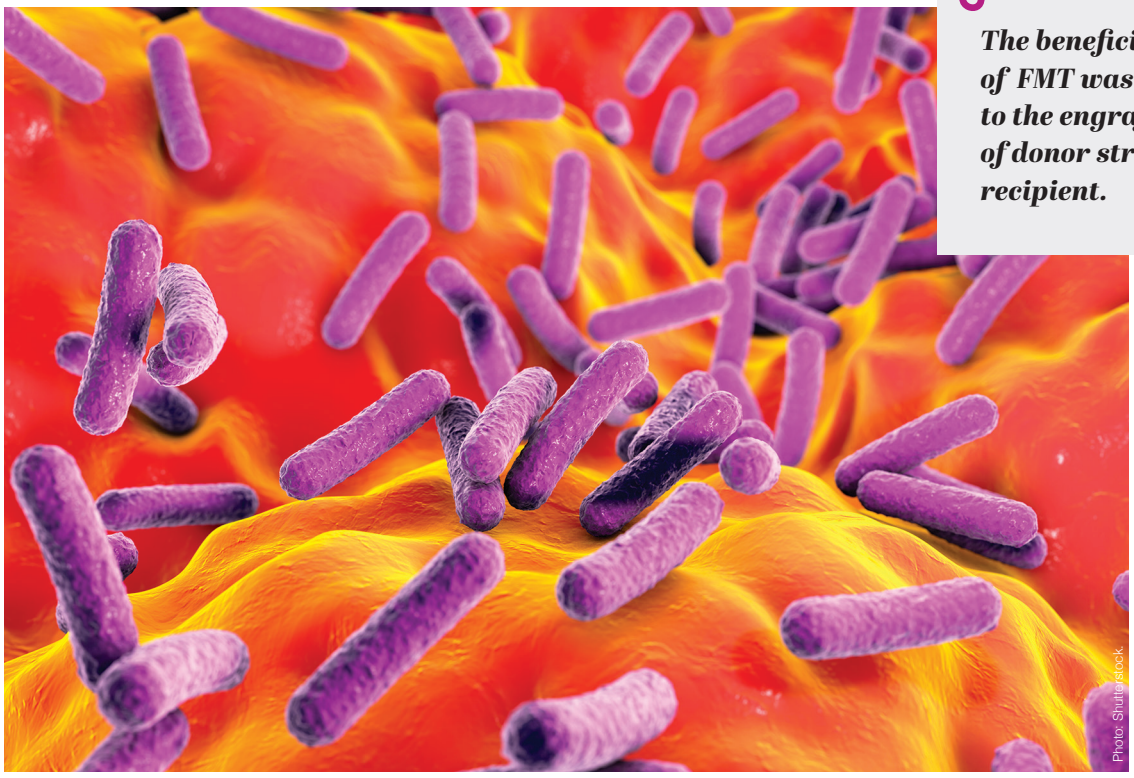

Photo: Shutterstock

are not yet fully understood. The work presented by Dr. Gianluca Ianiro on the combined analysis of 226 FMTs provided new insights into understanding this therapy by showing that the beneficial effect of FMT was correlated to the engraftment capacity of donor strains in the recipient and that this could be enhanced by the prior administration of antibiotics to open up the intestinal ecological niche, along with the combination of several methods when administering FMT [3].


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Foods preserving intestinal barrier integrity

Several presentations also explored the importance of dietary factors in maintaining the intestinal barrier integrity and its consequences on health. Especially a fibre-rich diet has been shown to prevent the degradatation by *Akkermansia muciniphila* of the mucus layer that protect the colonic epithelium (presentation of Dr. Mahesh S. Desai, Luxembourg). Conversely, some food additives can boost the penetration of bacteria in the mucous layer in contact with the epithelium and predispose to the development of inflammatory colitis (presentation of Dr. Benoit Chassaing, Paris, France) [4].

The GMFH - World Summit 2023 provided an opportunity to put the major advances in recent years into the development of therapies based on microbiota science into perspective, providing solid guiding principles that are still being confirmed and further refined.

This better understanding of the mechanisms underpinning the efficacy of microbiota-targeted therapies and the complexity of their use in clinical practices illustrates the need for clinical experts able to develop and use microbiota-based applications in the routine care. Dr. Ianiro, a world expert in FMT suggested that such qualifications should be grouped together under the concept of «microbiome clinician».

At this 11th congress, the GMFH symposiums, by creating a rich and accessible space for exchange between clinicians and researchers, contribute to the emergence of this type of expertise.


Photo: Shutterstock.

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By Pr. Satu Pekkala

Academy of Finland Research Fellow, Faculty of Sport and Health Sciences, University of Jyväskylä, Finland

GUT MICROBIOTA

Diet-induced modifications to human microbiome reshape colonic homeostasis in irritable bowel syndrome

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder that can be classified to different subtypes: diarrhea- or constipation-predominant IBS (IBS-D and IBS-C, respectively), IBS with mixed bowel habits, and unclassified IBS. Many IBS patients benefit from low-fermentable oligo-, di- and monosaccharides as well as polyols (FODMAP) diet. However, only about 60-70% of patients clinically respond to the diet.

This study examined the effects of 6-weeks low-FODMAP diet on the gut microbiota in therapy-naive patients with IBS-D. The diet led to an increase in the abundance of *Acutalibacter timonensis* and *Oscillibacter* species, as well as a decrease in *Bifidobacterium adolescentis, Eubacterium ventriosum,* and *Clostridium disporicum*. Seventy percent of the patients showed improvements in disease manifestations.

The authors then studied using *ex vivo* gut organ cultures how the fecal samples affected gene expression. The post-diet microbiota induced expression of genes implicated in enteric neuronal and muscle functions and suppressed the expression of many genes encoding pro-inflammatory proteins. Gene ontology analysis revealed that post-diet microbiota increased pathways related to extracellular matrix organization, cellular adhesion, and junction assembly.

Because many pathways and genes associated with the abundance of *B. adolescentis*, the authors co-cultured colonic epithelial cells with *B. adolescentis* and administered mice with the bacterium to find a mechanistic link between the bacterium and gut health. Both *in vitro* and *in vivo*, *B. adolescentis* disrupted epithelial tight junction integrity and gut barrier functions.

Ultimately, using *in vitro* cultures it was found that fructose avoidance under low-FODMAP diet explained the reduced *B. adolescentis* levels in patients' post-diet microbiota.

The study provides a mechanistic link between diet, microbiome and intestinal functions which will help, in the future, the development of personalized microbiome-based therapies for human diseases.

Bootz-Maoz H, Pearl A, Melzer E, *et al.* Diet-induced modifications to human microbiome reshape colonic homeostasis in irritable bowel syndrome. *Cell Rep* 2022; 41: 111657.

Photo: Shutterstock.

GUT MICROBIOTA

Altered functional connectivity strength in chronic insomnia associated with gut microbiota composition and sleep efficiency

Little is known about the link between the gut microbiota and resting-state brain activity in patients with chronic insomnia (CI). CI manifests with, for instance, difficulties in initiating or maintaining sleep, obtaining refreshing sleep, and a hyperarousal state. Moreover, CI can impair social, cognitive, and behavioral functioning of the patients.
This study investigated associations between the brain functions, gut microbiota composition and neuropsychological performance in patients with CI.
The gut microbiota composition strongly associated with neuropsychological performance in CI patients. Specifically, the abundance of *Intestinibacter, Lachnospiraceae* UCG-003 and *Faecalicoccus* correlated with the functional connectivity strength (FCS) in the left superior parietal gyrus. This part of the brain is involved in aspects of attention and visuospatial perception, including the representation and manipulation of objects. As expected, the FCS was lower in CI patients than in healthy controls. At the genus level, *Alloprevotella*, members of *Lachnospiraceae* family and *Faecalicoccus* associated with mood and sleep assessment scores. Because *Alloprevotella* and members of *Lachnospiraceae* are producers of short chain fatty acids (SCFA), the authors hypothesized that these genera could affect brain functions by modulating SCFA metabolism in CI patients. However, no mechanistic link was established in the study.
While the findings of the study were interesting, longitudinal studies are needed to determine whether interventions could affect the gut microbiota of the CI patients and whether the gut microbiota could be targeted, *e.g.*, with probiotic interventions to improve the brain functions in insomnia patients.

Chen Z, Feng Y, Li S, *et al.* Altered functional connectivity strength in chronic insomnia associated with gut microbiota composition and sleep efficiency. *Front Psychiatry* 2022; 13: 1050403.

Photo: Shutterstock.

GUT MICROBIOTA

Mode of delivery modulates the intestinal microbiota and impacts the response to vaccination

Photo: Shutterstock.

Various factors influence infant's vaccine responses, such as genetics, birth weight, maternal antibodies, and feeding type. Less is known on the role of gut microbiota in immune responses to vaccination though the microbes importantly affect the development of the immune system early in life.
This study determined whether the mode of delivery-induced differences in gut microbial colonization patterns in early life are associated with antigen-specific IgG responses to the pneumococcal 10-valent PCV (PCV-10) and the meningococcal MenC conjugate vaccine. Among many variables studied, the mode of delivery and feeding type were the only early life factors significantly associated with IgG responses against one or more serotypes. The diversity of the gut microbiota was not associated with the PSV or MenC IgG responses. The infants, whose gut microbiota was characterized by low abundances of *Bifidobacterium* and *Escherichia coli* had the lowest IgG concentrations against both vaccines.
Contrarily, anti-MenC IgG concentrations in infants with high abundance of *E. coli* were ~2-fold higher, which was also associated with vaginal birth. However, at the age of one year, the gut microbiota did not associate with vaccine responses, confirming that early life microbiota is more related to vaccine responses than the microbiota close to the time of vaccination. Regarding the early life gut microbiota, higher abundances of *E. coli* and *Bifidobacterium* associated with high anti-pneumococcal responses, while *Clostridium, Prevotella* and *Streptococcus pyogenes* associated with low responses. In high anti-MenC responders, higher abundances of many low abundant OTUs belonging to the *Lachnospiraceae* family were observed.
The study proves that understanding the microbial factors driving immune maturation and vaccine immunogenicity is key to improve vaccine performance in children.

de Koff EM, van Baarle D, van Houten MA, *et al.* Mode of delivery modulates the intestinal microbiota and impacts the response to vaccination. *Nat Commun* 2022; 13: 6638.

VAGINAL MICROBIOTA

Pregnancy and Covid-19: is vaginal dysbiosis a source of complications?

And what if the harmful effects of Covid-19 in pregnant women required the intervention of the vaginal microbiota? In order to check this hypothesis, researchers conducted a prospective case-control study including 28 non-infected pregnant women and 19 pregnant women suffering from Covid-19.
A sample of the vaginal microbiota was obtained with a swab during the active phase of the disease in the month following recovery and evaluated by 16S rRNA gene sequencing. The Covid-19 group displayed significantly greater diversity than the control group. In addition, the Bacteroidetes had gained the upper hand over the Firmicutes, and, at bacterial genus level, the *Lactobacillus sp.* were significantly less abundant than in the control group. Well, previous studies showed that there was an increased risk of miscarriage or premature birth in pregnant women whose vaginal microbiota were depleted in *Lactobacilli*. These data corroborate this finding, since 3 women in the Covid-19 group gave birth prematurely (*versus* 0 in the control group).
Despite the small size of the sample, the investigators observed other differences in the composition of the vaginal microbiota in the Covid-19 group. In particular, the women suffering from moderate to severe forms of Covid-19 displayed much higher levels of *Ureaplasma* spp.: 2.05% vs 0.1% in case of asymptomatic to mild forms. The genus *Ureaplasma* is involved in different gynecological infections (salpingitis, urethritis, and cervicitis), its over-representation in case of severe Covid-19 also argues in favor of an association of vaginal dysbiosis both with SARS-Cov-2 infection and risks of pregnancy complications. All the more as, in the 3 premature births that occurred in this study, 2 were in the moderate to severe Covid-19 subgroup (n=6).
Thus, although this study does not allow the conclusion that a causal relationship exists, these results suggest that Covid-19 may trigger an unfavorable disruption of the vaginal microenvironment in pregnant women. This would be even more pronounced when the infection is severe, and could lead to an increased risk of complications, such as premature birth.


Photo: Shutterstock.

Deng H, He L, Wang C, *et al.* Altered gut microbiota and its metabolites correlate with plasma cytokines in schizophrenia inpatients with aggression. *BMC Psychiatry* 2022; 22: 629.

URINARY AND URETHRAL MICROBIOTA

Idiopathic urethritis in men: new infectious etiologies?

Some Australian researchers sought to determine which infectious agents, apart from those already known, might contribute to non-gonococcal urethritis in men, taking into account their sexual practices and the biological sex of their partner. For this, they conducted a case study including 199 men, 96 of whom had symptoms of idiopathic urethritis and 103 of whom did not, who served as controls. The median age of participants was 31 years, 73 had had a sexual relationship with a man in the month prior to inclusion (classified as MSM), and the remainder were classified as MSW. For all of them, the researchers had samples of urinary and urethral microbiota available for sequencing analysis.
Their results revealed that *Haemophilus influenzae*, which naturally colonizes nasopharyngeal microbiota, was more abundant in MSM participants with idiopathic urethritis. In addition, *H. influenzae* was clearly associated with clinical features such as urethral burning, dysuria and purulent discharge. The researchers believe having oral sex without a condom could be the main mode of contamination by this bacterium. They observed more of the genus *Corynebacterium* in affected MSW, which they found surprising since it is considered commensal in male genital microbiota. The scientists conclude that some specific species of Corynebacterium may become pathogenic when present in abundance. There were also more *Ureaplasma, Staphylococcus haemolyticus, Streptococcus pyogenes, Escherichia* and *Streptococcus pneumoniae* in the urinary and urethral microbiota of symptomatic subjects, so they may all promote urethritis.
Possible infectious causes of non-gonococcal urethritis, previously described as idiopathic, have thus been discovered. If these results are confirmed by other studies, doctors may eventually be able to offer their patients more targeted treatments.

Plummer EL, Ratten LK, Vodstrcil LA, *et al.* The urethral microbiota of men with and without idiopathic urethritis. *mBio* 2022; 13: e0221322.


Photo: Shutterstock.

By Pr. Karine Clément

Sorbonne University, Inserm, Unité de recherche nutrition et obésités ; approches systémiques [Nutrition and Obesity Research Unit (systemic approaches)], Paris, France; Nutrition Department, Assistance-Publique - Hôpitaux de Paris, Pitié-Salpêtrière Hospital, Paris, France

Artificial sweeteners, gut microbiota and metabolic health: an interaction requiring close examination

Sweeteners are considered as a worthy alternative to the excessive use of simple sugars, which are considered to be harmful to cardiometabolic health [1]. Sweeteners can be consumed directly or in processed products [2] In *Cell*, Suez *et al.* reported the results of a randomised controlled trial which showed that, paradoxically, some sweeteners may disturb glucose tolerance and that some effects are mediated by changes in the gut microbiota [3].

> How do you explain that only two sweeteners have an effect on blood sugar levels (saccharin and sucralose) while the four sweeteners tested had an impact on the composition and functions of the gut microbiota?

The use of sweeteners can be suggested in people with metabolic diseases to help them reduce their calorie intake, lose weight and improve their metabolic risk [4]. However, over time, concerns have emerged due to the fact that sweeteners do not have a neutral effect [5, 6]. In 2014, the authors of this publication had already shown that mice consuming high doses of aspartame, saccharin and sucralose developed glucose intolerance due to disturbances in the gut microbiota [7]. In this new research, they have gone one step further by carrying out a well-conducted clinical study in humans. In 120 healthy participants, the researchers assessed the effects on glucose tolerance of sucralose, saccharin, stevia and aspartame administered for 14 days (5 study arms, 20 participants per group and one control group). Sweeteners were used at levels lower than the recommended daily intake. The ingestion of sucrose and sucralose aggravated glucose tolerance, while aspartame and stevia had a neutral effect. These sweeteners had distinct effects on the composition of the oral and faecal microbiota and on key functions (such as purine and pyrimidine metabolism, glycolysis, and amino-acid metabolism). The most significant effect was observed with sucralose. Microbiota transfer studies (human to mouse) have established the causality of effects. Animals colonised with samples from sweetener-supplemented subjects showed varying degrees of altered glucose tolerance. The chemical composition of sweeteners appears to influence the microbiota; however, the precise mechanism by which they exert these variable effects on the host through changes in the faecal microbiota requires further detailed study. More specifically, sucralose, saccharin and stevia are partially metabolised in the upper digestive tract and only a tiny proportion reaches the colon.

> Does this mean you recommend that your patients should not use non-nutritive sweeteners, since they may not be physiologically inert?

In my clinical practice, we do not systematically suggest patients use sweeteners, as there is no evidence that they are an effective weight-loss tool. Although, in patients who are unable to lose their sweet tooth, we prefer suggesting the use of natural sweeteners such as steviol glucoside, which can be used on a short-term and reasonable basis. However, the above discussed results highlight the need for a rigorous assessment of the short- and long-term impact of the available sweeteners on human health before deciding whether or not to recommend their continued use as an aid to reducing metabolic risks.

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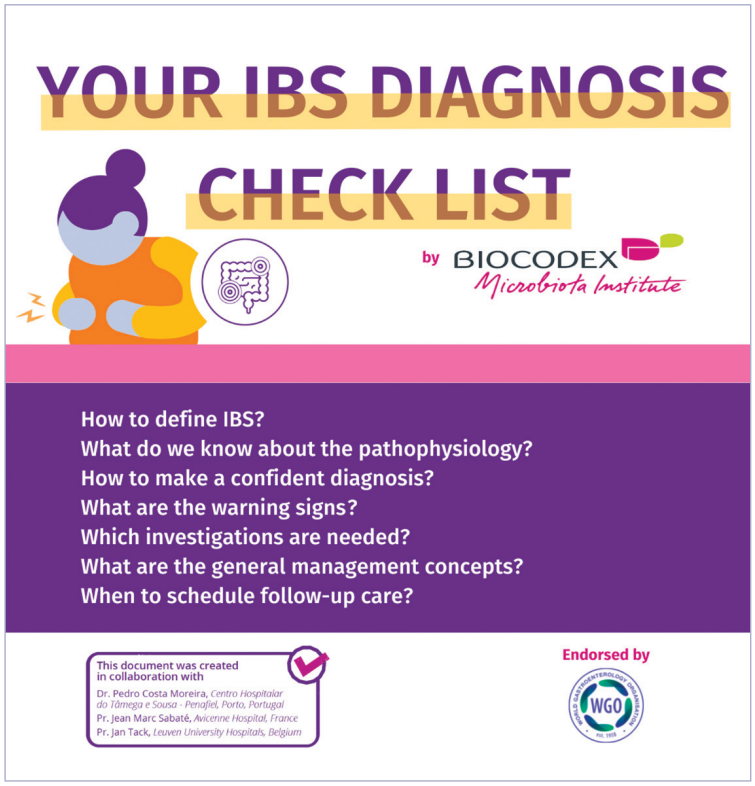


An easy-to-use and practice-oriented IBS diagnostic tool

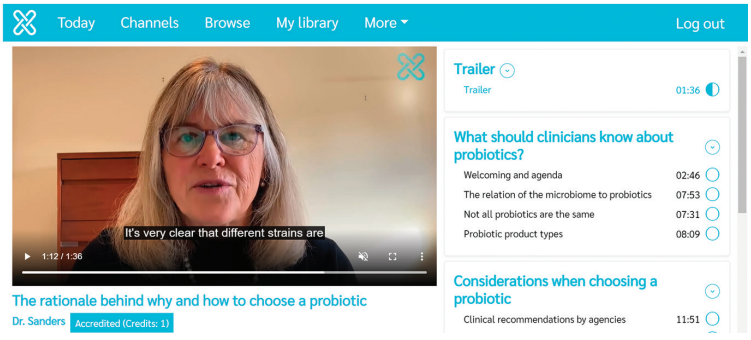
How many patients suffering with bowel disorder do you see each week? Do you know that up to 75% of individuals with Irritable Bowel Syndrome (IBS) may be undiagnosed and may struggle more than 4 years before receiving a formal medical diagnosis? A correct diagnosis of IBS can be challenging and uncertain for several reasons: the disorder with symptoms often difficult to objectively quantify, it might be difficult to explain during an average consultation… This is why Pr. Jean-Marc Sabaté, Pr. Jan Tack and Dr. Pedro Costa Moreira with the support of the Biocodex Microbiota Institute have **created an easy-to-use and practice-oriented IBS diagnostic tool** with a dual objective for healthcare professionals: better diagnose IBS and improve dialogue with their patients.

Up to 75% of individuals with Irritable Bowel Syndrome (IBS) may be undiagnosed

CME Course: How to choose a probiotic?

Today, people are drowning in contradictory information and recommendations about how to choose a probiotic. In this new CME course, Mary Ellen Sanders, PhD, founding President and executive science officer of ISAPP, reminds physicians that the choice of a probiotic should be determined by on clinical recommendations based on their efficacy to treat certain pathologies. This course is a great opportunity to learn from a renowned expert some misconceptions and practical recommendations regarding probiotics use! Relations between probiotics and microbiota, probiotic product types, clinical recommendations, probiotic safety… In a very attractive format full of references, Mary Ellen Sanders reviews what clinicians should know about probiotics. She goes further with a "misconceptions and recommendations" session in which she sums up all the ideas avoid.

The rational behind **why an how to choose a probiotic**
Dr. Mary Ellen Sanders



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