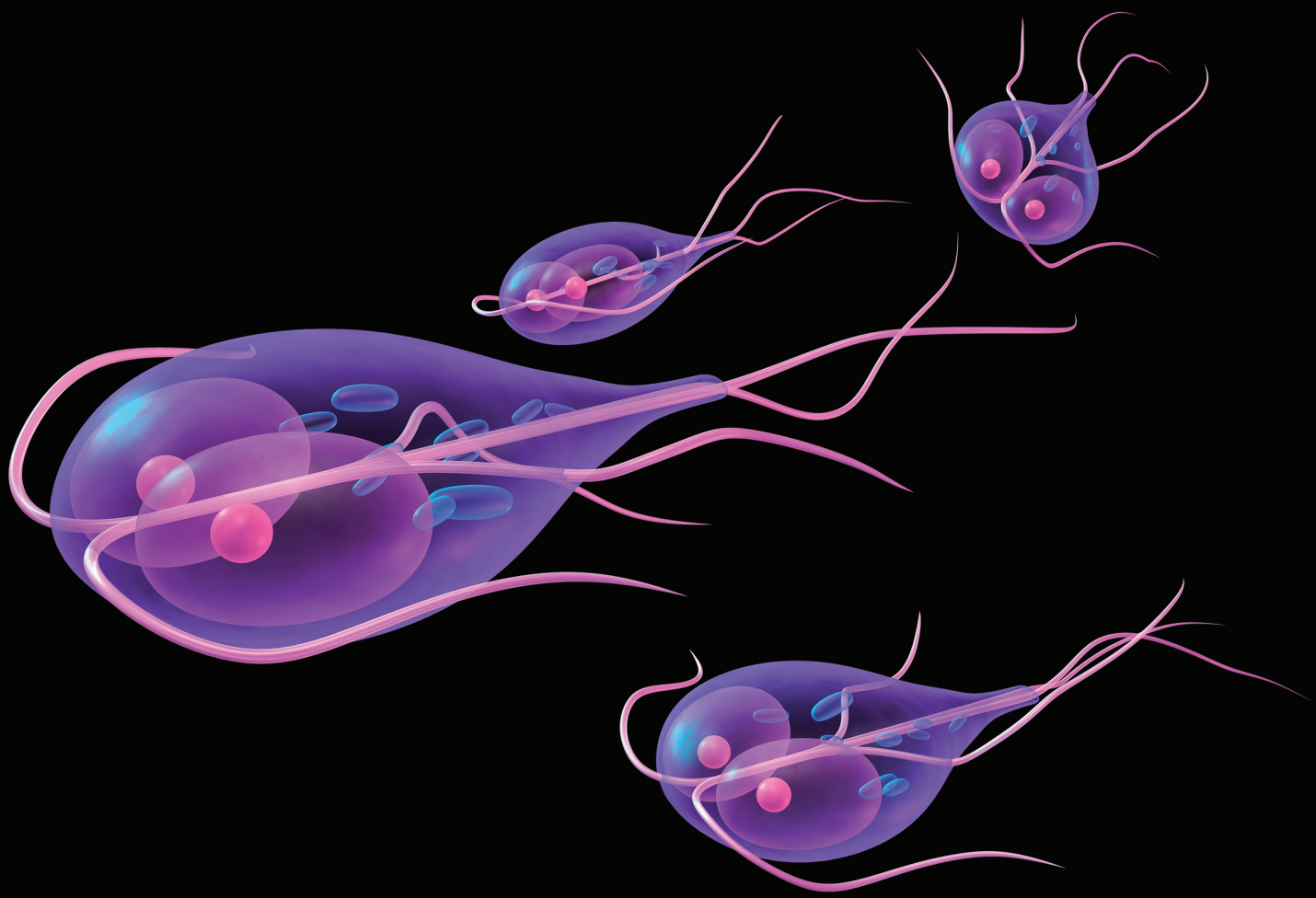
MICROBIOTA Mag

| 21 | JUNE 2024



| OVERVIEW |

Diarrhea and the role of microbiota

BIOCODEX Microbiota Institute

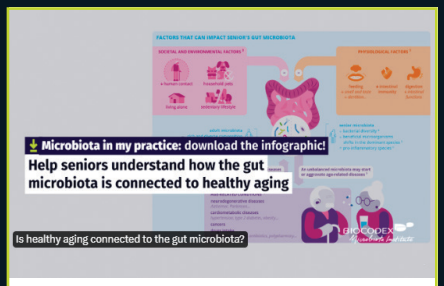
SUMMARY

Find this issue and previous ones here

WHAT DID YOU MISS ON SOCIAL MEDIA?

HOW TO GET THE EFFECTS OF OZEMPIC: FROM AN INTERNAL MEDICINE DOCTOR

In a video posted to her **TikTok** channel, internal medicine physician DrDeDeck explains how to get the "Ozempic effect" without having to take the drug.
Dr. Scanzi gives his point of view on p.18.



HEALTHY AGING

In February, the "healthy aging" X post from the Biocodex Microbiota Institute generated the most shares, comments and reactions.
2,7 k users engages, 317,3 k views

PANCREAS CANCER AND GUT MICROBIOTA

By **ESNM (GMFH)**
783 engagements, 26 k views

EDITO

Dr. Maxime Prost, MD
France Medical Affairs Director

Barbara Postal, PhD
International Medical Affairs Manager

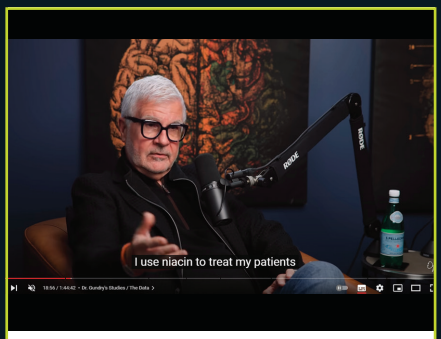
Dear readers,

After delving into diet in our previous issue, we turn our focus to digestive disorders, particularly diarrhea, in this new edition. Rest assured that there is no causal link between the two topics. Instead, consider this new overview as an updated review of research and promising avenues for treating a condition that, although known in benign forms, is anything but insignificant. According to the World Health Organization, diarrhea was responsible for 1.6 million deaths in 2016, primarily among malnourished children, immunocompromised individuals, or those living with HIV. The main reason for these deaths: severe dehydration due to the repeated loss of fluid in stools. The following overview covers the main diarrheal illnesses related to dysbiosis and some aspects regarding the management of microbiota to ameliorate gastrointestinal disorders.

Other topic and new section. “Gut Microbiota from post-Covid-19 patients induces lung inflammation and brain dysfunction in mice” is the first topic of our new section “Focus on young researchers”. With this new section, we want to highlight young researchers with an innovative and evidence-based research showing a clear link between gut microbiota and diseases or a link between digestive disorders and microbiota. A warm welcome to Viviani Mendes de Almeida, Angélica Thomaz Vieira and Daiane Fátima Engel who are opening this new section. This is also one of the missions of *Microbiota Mag*: encourage and promote new research on microbiota. And share it with you!

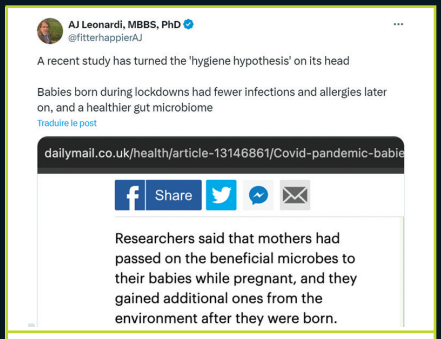
This is also one of the missions of *Microbiota Mag*: encourage and promote new research on microbiota.

Enjoy your reading.



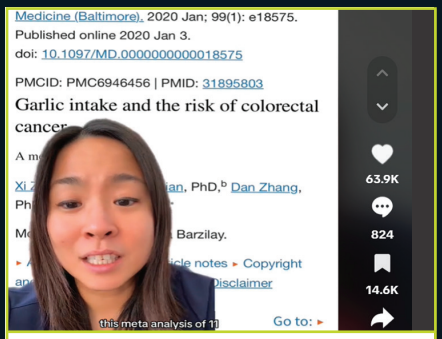
CONFRONTING DR. GUNDRY ON LECTINS - INFLAMMATION & LEAKY GUT

By **Dr. Mike**
11,9 M followers, 2,9 M views, 79 k likes



COVID-19 PANDEMIC BABIES AND GUT MICROBIOME

By **AJ Leonardi, MBBS, PhD**
4,4 k engagements, 106 k views, 957 retweets



COLORECTAL CANCER AND DIETARY CHANGES

By **socalgastrodoc**
67 k engagements, 541 k views

By Dr. Sanda Maria Cretoiu

Department of Morphological Sciences, Cell and Molecular Biology and Histology, "Carol Davila" University of Medicine and Pharmacy Bucharest, Romania

Diarrhea and the role of microbiota

Intestinal disorders can manifest symptoms such as frequent and loose stools, known as diarrhea. This signal from the digestive system can occur for many reasons, from infections and reactions to certain foods to adverse reactions to medications and pre-existing health conditions - summarized in [1]. The intestinal microbiota, *i.e.*, the totality of microorganisms present in the intestine, is essential for the preservation of digestive health and for its impact on the functioning of the intestine. Recent studies illustrate the link between the microbiota and diarrhea of diverse etiology. A balanced and diverse microbiota is vital for overall digestive health, nutrient absorption, and immune system regulation. Currently, there is a tendency towards the large-scale introduction of ways to reprogram the intestinal microbial community: prebiotics, probiotics and postbiotics or the transplantation of fecal matter in order to prevent or treat diarrhea. Research on microbiota modulation will offer actionable strategies for diarrhea prevention and treatment in the near future. The following overview covers the main diarrheal illnesses related to dysbiosis and some aspects regarding microbiota management to ameliorate these gastrointestinal afflictions.

The relationship between the microbiota and diarrhea

Diarrhea can involve various mechanisms (table 1), and the majority of them are related to the role of microbiota:

• *Protection of the microbial balance, this state*, known as eubiosis, is fundamental for the health of the human body because it prevents and slows down the expansion of pathogens. Disturbance of the balance between the main microbial strains, known as dysbiosis, can increase susceptibility to infections and contribute to diarrhea. The literature generally indicates that diarrhea represents a major dysbiosis and that the degree of dysbiosis is related to the etiology and the stage of diarrhea [6]. Following acute diarrhea, the taxonomy of the microbiota changes a lot. In early stages of diarrhea, facultative fast-growing anaerobes such as Proteobacteria (mostly *Enterobacteriaceae/Escherichia coli*) and *Streptococcus* (mainly *Streptococcus salivarius* and *Streptococcus gallolyticus*) dominate and favor the drastic disappearance of obligate anaerobic gut commensals (*Blautia, Prevotella, Faecalibacterium, Lachnospiraceae, Ruminococcaceae,* etc.) [2, 3]. The consequence is that short-chain fatty acid (SCFA) also decreases, and the integrity of the intestinal barrier starts to be under threat, possibly leading to gut permeability. In the recovery phase after diarrhea, a proposed model shows that in the mid-stage, there is an abundance of *Bacteroides* (the 7th day since disease onset). At the same time, in the late-stage *Prevotella* and SCFA-producing Firmicutes dominate [4, 5].

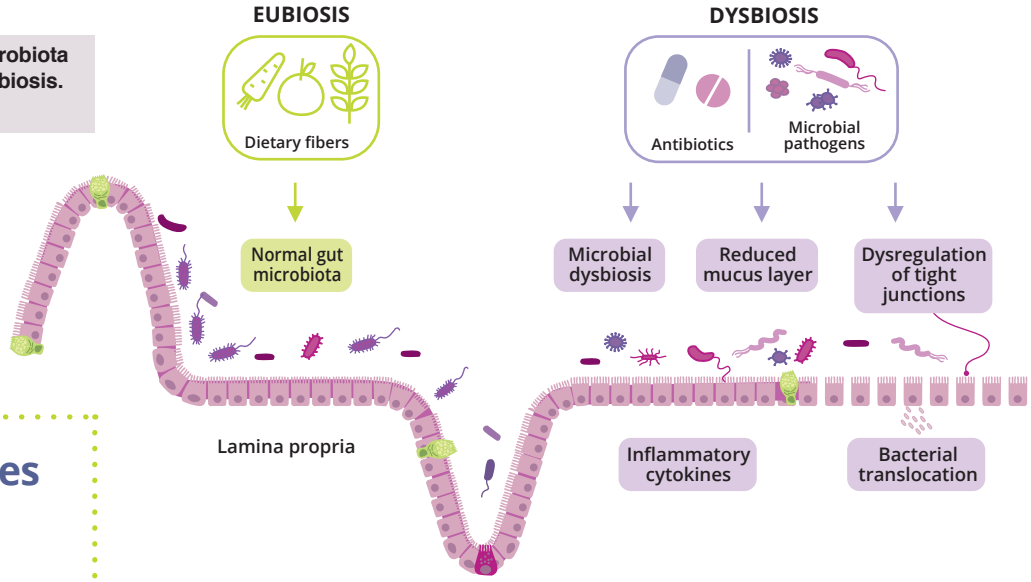
• *Protection against pathogenic invaders.* The microbial community of the gut microbiota competes for resources, produces antimicrobial substances, and acts as a barrier against enteropathogens. Beneficial bacteria in the gut, such as certain strains of *Bifidobacteria* and *Lactobacilli*, have been demonstrated to have beneficial effects on infectious diarrhea caused by rotavirus in young children. However, there are no clinical trials to demonstrate it [6].

• *Regulating the immune system.* The gut microbiota helps educate and modulate immune responses, promoting tolerance to harmless substances and defending against pathogens. Dysregulation of the immune response due to microbiota imbalances can contribute to inflammation and diarrhea. After antibiotics for *Clostridioides difficile*-induced diarrhea, such as vancomycin, a reduced relative abundance of *Bacteroidetes* and *Firmicutes* is observed, while *Proteobacteria* and *Fusobacteria* increase and leading to a decrease in SCFA propionate, creating premises for inflammation [7].

• *Maintenance of gut function and metabolism.* Beneficial bacteria ferment dietary fibers to produce short-chain fatty acids (SCFAs), such as acetate, propionate, and butyrate. SCFAs contribute to maintaining a healthy intestinal lining, promote water absorption, and provide an energy source for colonocytes. Imbalances between bacterial strains may impact these functions, leading to functional diarrhea due to decreased SCFA production. Increasing its production enhances colonic fluid absorption. [8].

FIGURE • 1

Factors influencing the gut microbiota in the eubiosis state and in dysbiosis. Created with Biorender.com.



Diarrheal illnesses and microbiota management

Infectious diarrhea

Bacterial, viral or parasitic gut infections cause acute diarrhea and are frequently spread through contaminated water. Most cases of diarrhea are improved in a few days, but severe diarrhea can lead to serious dehydration and can become lethal [9].

Rotaviruses remains the primary cause of diarrhea-associated deaths in children [11], and management of this viral disease generally involves oral or intravenous hydration, tailored to the severity of dehydration [12]. Furthermore, based on the latest conclusions from the ESPGHAN committee (2023) [13], healthcare providers might suggest certain probiotic strains for acute gastroenteric episodes in children, acknowledging their potential (certainty of evidence: low; grade of recommendation: weak) to decrease the duration of diarrhea, and/or hospital stay, and/or volume of fecal discharge. However, a randomized, double-blind, controlled trial of Bolivian children with acute rotavirus diarrhea demonstrated a decreased duration of diarrhea by using an oral rehydration solution plus a mixture of probiotics by comparison with simple rehydration solution [11].

TABLE 1 • DYSBIOSIS AND DIARRHEA

- Dysbiosis refers to an imbalance or disruption in the composition of the normal gut microbiota, often characterized by a decrease in beneficial bacteria and an increase in harmful microorganisms.
- Imbalances in the microbiota can lead to inflammation, compromised gut barrier function, and an increased susceptibility to infections, all of which may contribute to diarrhea.
- Infections caused by pathogenic bacteria (*Campylobacter, Salmonella, Shigella, Vibrio, Escherichia coli*), viruses (rotavirus, norovirus), or parasites (*Cryptosporidium, Entamoeba, Giardia*) can disrupt the balance of the gut microbiota and result in **acute diarrhea.**
  - *Clostridium difficile* - Causes dysbiosis by producing toxins that disrupt the gut microbiota and lead to diarrhea
  - *Salmonella* - Provokes gut microbiota imbalance and inflammation, leading to diarrhea and potential systemic complications
  - *Escherichia coli* - Triggers inflammation and disturbs the gut microbial balance, contributing to diarrhea development
- Antibiotic use, while essential for treating infections, can also disrupt the normal microbiota, leading to antibiotic-associated diarrhea.
- Persistent digestive disorders, such as diarrhea-predominant irritable bowel syndrome (known by the acronym IBS-D), diarrhea caused by osmotic imbalances, diarrhea induced by bile acids, as well as diarrhea that occurs after antibiotic treatment, are known as **chronic diarrhea**.

Travelers diarrhea

More than 60% of the adults from developed countries who travel to developing countries experience acute diarrhea, also known as traveler's diarrhea (TD). The most frequently identified pathogens implicated in traveler's diarrhea episodes are *Escherichia coli, Campylobacter jejuni, Salmonella species* and *Shigella* species. Thus, the recommended treatment strategies include antibiotic therapy with azithromycin or fluoroquinolones for moderate to severe cases [14]. However, antibiotics are not recommended to prevent TD, due to insufficient evidence of their prophylactic efficacy and partially due to the risk of antibiotic resistance [15].

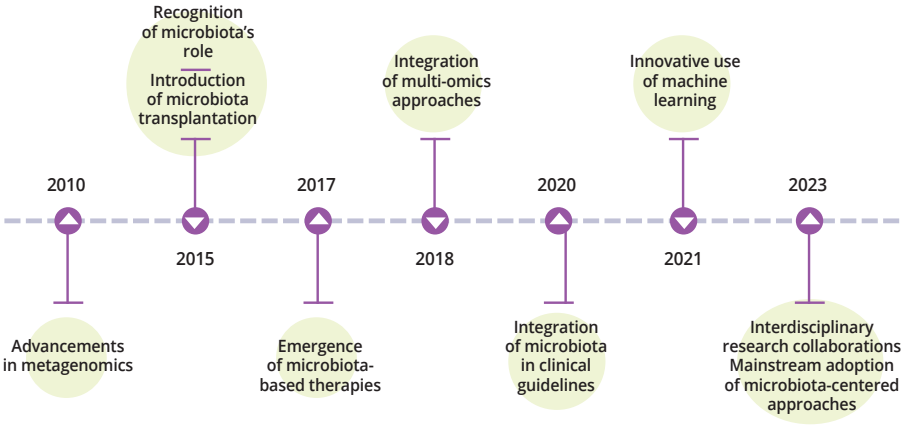
There is conflicting data regarding the efficacy of probiotics in preventing traveler's diarrhea [16]. One systematic review and meta-analysis compared the efficacy of rifaximin and probiotics in preventing TD. [15].

Antibiotic-associated diarrhea

Antibiotics are one of the most prescribed medications and represent an effective treatment for several infectious pathologies [17]. One of the complications associated with antibiotic therapy is antibiotic-associated diarrhea (AAD), which occurs in 5%-35% of the patients who receive antibiotherapy [18]. AAD can be defined as three or more watery or loose stools per day for at least two consecutive days, which is strictly related to antibiotics administration and no other cause [14]. The highest risk is attributed to aminopenicillins, cephalosporins and clindamycin, which primarily target anaerobes [19].

FIGURE • 2

Timeline depicting key dates in the evolution and recognition of the microbiota significance and its integration into gastroenterology. Created with Biorender.com.



The lack of an infectious agent identified in AAD may be explained by the direct toxic effect of the antibiotics on the intestinal mucosa, which may cause diarrhea. Due to their beneficent properties, probiotics are now being researched and used for both treatment and prophylaxis of AAD [16, 18].

Clostridium difficile-associated diarrhea

Clostridioides difficile (CD) infection is the most common cause of nosocomial antibiotic-associated diarrhea in adults. Risk factors include age over 65 years, long hospitalization in intensive care, and administering antibiotics (fluoroquinolones, clindamycin, cephalosporins, and beta-lactams in particular) or proton pump inhibitors.

During antibiotherapy, anaerobes that produce SCFAs may disappear due to antibiotic-induced alterations in the gut microbiota, which may also disturb the metabolism of carbohydrates and bile and cause an osmotic imbalance. Following antibiotic intake, all three intestinal barriers are affected: the epithelial intestinal cells, the mucus and antimicrobial peptides layer, and the immunoprotective layer composed of different immune cells and various biomolecules (**figure 1**). This event can interfere with the production of mucin, cytokines, and antimicrobial peptides, dysregulating intestinal function and leading to other infections or even causing recurrent episodes of infections. The American Gastroenterological Association (AGA) conditionally recommends specific probiotics for preventing CD infection in individuals on antibiotics, noting that the quality of evidence is low [20].

Emerging discoveries and the future of diarrhea management

Recent breakthroughs in microbiota research, including metagenomic analysis and microbial transplantation, are revolutionizing our approach to diarrhea treatment (**figure 2**).

Treatment options for diarrhea should take into account the causative mechanisms involved in the genesis of diarrhea, from infectious toxins capable of disrupting fluid and electrolyte balance to patients who developed dysbiosis due to other causes and patients with large amounts of non-absorbed carbohydrates in the lumen triggering osmotic diarrhea.

There is limited data regarding the prebiotics and fibers in treating diarrhea (**table 2**). Apparently, prebiotics are more prone to prevent and treat the recurrence of diarrhea. At the same time, fibers, mainly the viscous ones, are more indicated during acute episodes due to their water-retaining capacity. Other therapeutic options involve, in some cases, the probiotic administration and (**table 3**), in severe cases, the use of fecal microbiota transplantation (FMT).

The fascinating journey of FMT discovery has roots in ancient China, where Ge Hong treated patients with severe diarrhea using a "yellow soup" consisting of feces suspension. In modern times, Dr. Ben Eiseman used fecal enemas from healthy individuals to treat pseudomembranous enterocolitis back in 1958. Nowadays, there is growing interest in fecal microbiota transplantation (FMT) as a treatment for recurrent *Clostridioides difficile* infection (CDI), which points out its utility [22]. Research is ongoing regarding its efficacy towards inflammatory bowel disease, diabetes, cancer, liver cirrhosis, and brain diseases such as Parkinson's [23]. The benefits of using FMT in patients with diarrhea are based on the idea that the healthy microbial flora introduced via FMT has the ability to outcompete pathogens and restore the composition of a healthy gut microbiome (**figure 3**).


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TABLE 2. PREBIOTICS AND FIBERS IN DIARRHEA

- Usually, there is an overlap between the definition of prebiotics and fibers
- "Dietary fibers mean carbohydrate polymers with 10 or more monomeric units, which are not hydrolyzed by the endogenous enzymes in the small intestine of humans" CODEX Alimentarius Commission in 2009 [21]. Some examples include guar gum, psyllium, β-glucans, pectin, resistant starch, and wheat dextrin.
- Prebiotics are alimentary non-digestible substances, that are not hydrolyzed nor absorbed in the stomach and small intestine, and promote the growth and activity of beneficial bacteria in the gut. In this category, one includes usually inulin, fructooligosaccharides (FOS), galactooligosaccharides (GOS), and lactulose.
- Consuming a diet rich in prebiotics, such as fruits, vegetables, and whole grains, can support a healthy gut.

FIGURE • 3

Gut microbiota restoration in diseased patients.
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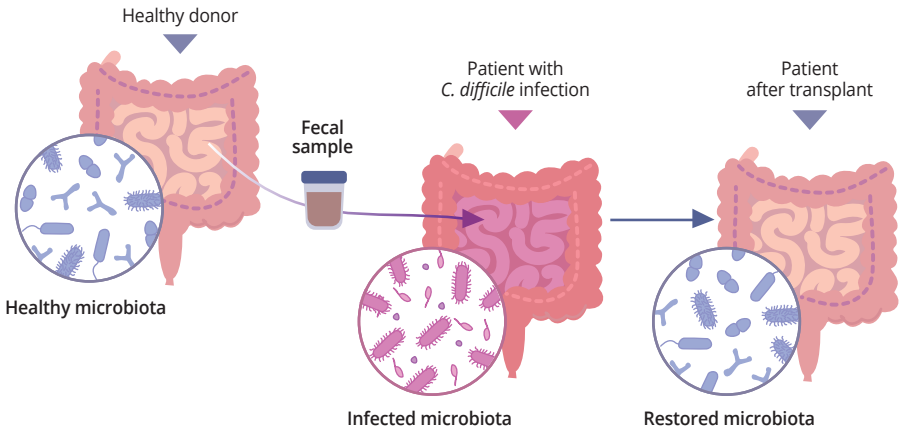

TABLE 3 • PROBIOTICS AND DIARRHEA

- Probiotics are live microorganisms that, when administered in adequate amounts, confer health benefits on the host, including improving gut microbiota balance.
- Some studies suggest that certain probiotics may help prevent or alleviate infectious and antibiotic-associated diarrhea by promoting the restoration of a healthy microbial balance. Probiotics can alleviate diarrhea through a number of anti-pathogen effects (production of antimicrobial substances, limiting access to nutrients for pathogens and competitive exclusion) and through general effects like reduction of gut permeability, stimulating the mucosal immune response.
- Modulation of the microbiota in cases of diarrhea is possible by taking probiotics. Several recommendations are provided by medical societies, such as the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition - ESPGHAN, for the use of probiotics for the prevention of AAD in children [13, 24].
- According to the ESPGHAN working group, the modulation of the microbiota in AAD can moderately benefit from using *Lactobacillus rhamnosus* GG or *Saccharomyces boulardii* [13, 24].


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Conclusion

Research reveals that reduced gut microbiota diversity is associated with increased susceptibility to diarrhea, paving the way for potential diagnostic and therapeutic interventions. Maintaining a balanced and diverse gut microbiota prevents diarrhea and promotes overall digestive health. Imbalances in the microbiota, known as dysbiosis, can result from infectious acute diarrhea or dysbiosis due to other factors (frequent antibiotic use, unhealthy diet, malabsorption) that can contribute to chronic diarrhea. Understanding the complex interplay between microbial composition and clinical symptoms is crucial for personalized patient management of diarrhea. Tailored approaches based on unique microbiota profiles can lead to more effective strategies or interventions. The introduction of probiotics and a diet rich in prebiotics, microbiota transplantation, integration of multi-omics approaches, innovative use of machine learning, and the growing trend of interdisciplinary research collaborations may help restore microbial balance and support gastrointestinal well-being. Hopefully, in the future, one could design microbiome-based therapies as suggested by Peter J. Turnbaugh, laying the base for new treatment principles [25].

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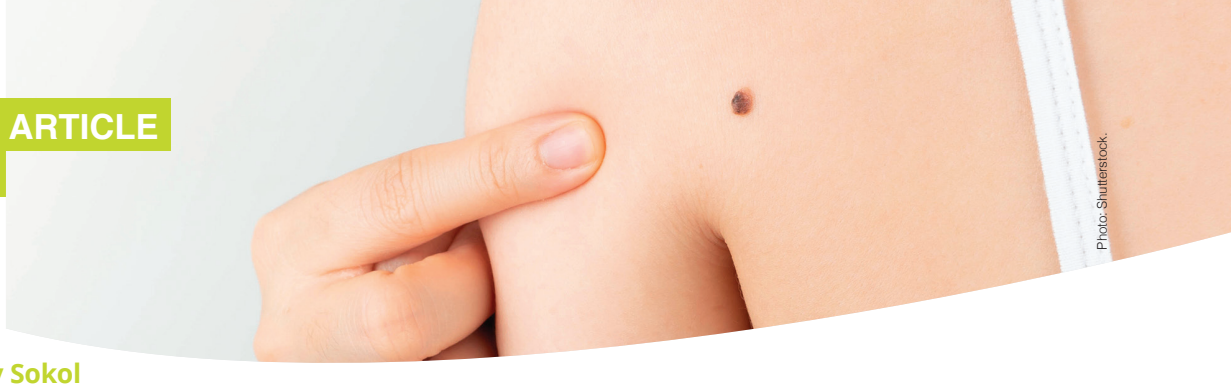
COMMENTED ARTICLE

Adults' section



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By Pr. Harry Sokol

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

Faecal microbiota transplantation plus anti-PD-1 immunotherapy in advanced melanoma: a phase I trial

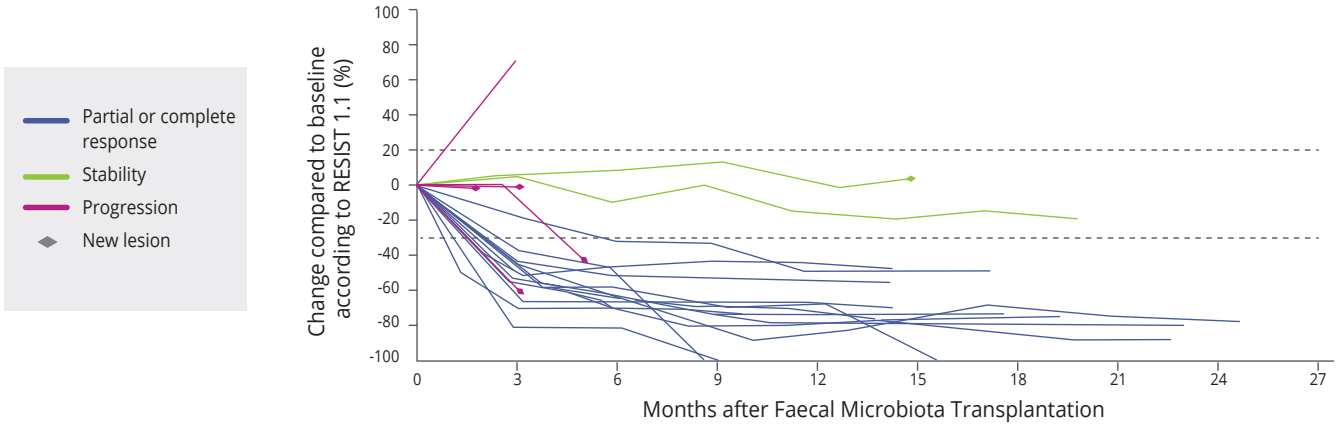
Comments on the article by Routy et al., Nature Medicine 2023 [1]

Faecal microbiota transplantation (FMT) represents a potential strategy to overcome resistance to immune checkpoint inhibitors in patients with refractory melanoma; however, the role of FMT in first-line treatment settings has not been evaluated. The authors conducted a multicentre Phase I trial combining healthy donor FMT with the PD-1 inhibitors nivolumab or pembrolizumab in 20 previously untreated patients with advanced melanoma. Safety was the primary endpoint. No grade 3 events were reported during the FMT. Five patients (25%) experienced grade 3 immune-related adverse events from the combination therapy. Key secondary endpoints were objective response rate, changes in gut-microbiome composition and systemic immune and metabolomics analyses. The objective response rate was 65% (13 out of 20), including four (20%) complete responses. Longitudinal microbiome profiling revealed that all patients engrafted strains from their respective donors. However, the acquired similarity between donor and patient microbiomes was only increased over time in responders. Responders experienced an enrichment of immunogenic bacteria and a loss of deleterious bacteria after FMT. The results showed that FMT from healthy donors is safe in a first-line setting and warrants further investigation when used in combination with immune checkpoint inhibitors.

What do we already know about this subject?

••• Almost half of patients with advanced melanoma receiving anti-PD-1 monotherapy develop primary resistance, highlighting the need to develop new therapeutic strategies to improve the response to immune checkpoint inhibitors (ICIs). Although the combination of anti-PD-1 and anti-CTLA4 (*cytotoxic T lymphocyte-associated antigen-4*) increases the response rate, this therapy is limited by the high number of immune-related adverse events (IR-AEs). The gut microbiome has emerged as an essential regulator of local and systemic immune responses. Several studies in cancer patients treated with ICIs have shown that specific gut bacteria are associated with both immune system response and adverse events [1]. More specifically, the presence of certain commensal genera, such as *Ruminococcus, Faecalibacterium* and *Eubacterium*, has been associated with positive outcomes in melanoma patients [2]. The therapeutic potential of the gut microbiome was first demonstrated in mouse models combining ICIs with FMT using faeces from non-responder (NR) patients who were associated with ICI resistance [1]. Two studies showed that FMT in patients with a long-term response to ICI therapy circumvented anti-PD-1 resistance in almost 30% of patients with ICI–refractory melanoma [3, 4]. In these studies, the mi-

FIGURE 1 Radiological response determined according to RECIST v.1.1 criteria.
The figure shows the response in terms of change in size of the target lesions from baseline.



crobiota of patients changed after FMT, and an increase in *Ruminococcaceae* and *Bifidobacteriaceae* was observed in responder (R) patients plus a reprogramming of the tumour microenvironment with increased CD8+ T-cell infiltration and interferon-γ signalling. These clinical findings confirm the potential of microbiome-based interventions to overcome ICI resistance in melanoma.

What are the main insights from this study?

••• In this article, the authors reported the clinical and translational findings from a Phase I trial (NCT03772899) combining FMT from healthy donors with the PD-1 inhibitors nivolumab or pembrolizumab in treatment-naive patients with advanced melanoma (**figure 1**). The toxicity observed (85% IR-AEs, of which 25% grade 3 toxicity and zero grade 4 or 5 toxicity) was similar to that reported in the Phase III trials for anti-PD-1. The observed clinical efficacy (objective response 65%) was higher to that of nivolumab and pembrolizumab monotherapy in Phase III trials (objective response 42-45%) and in real-world data (objective response 17.2-51.6%). However, the absence of a control arm and the small size of the study hindered the interpretation of the results.

Unlike the previous studies [3, 4], it included patients receiving first-line treatment, a single FMT was performed by oral capsule, donors were healthy subjects (and not ICI responders) and, finally, only PEG (without the use of antibiotics) was used for the preparation. By studying the microbiota of donors and recipients, the authors observed that the microbiota of responders was enriched in *Ruminococcus* SGB15234 and SGB15229, *Alistipes communis, Eubacterium ramuleus* and *Faecalibacterium* SGB15346, while the abundance of *Enterocloster aldensis* and *Enterocloster clostridioformis* decreased. In previous studies, the increase in *Faecalibacterium* was also associated with the response to ICI [3, 4].

The authors then experimented on mice colonised with human microbiota and observed a similar efficacy of the faecal transplantation from healthy subjects in this context, with an effect associated with an increase in the infiltration of CD8+ T memory lymphocytes in the tumour microenvironment..

What are the consequences in practice?

••• Despite its limitations, this study suggested that microbiota modulation via FMT could increase ICI efficacy when administered in a first-line setting for metastatic melanoma. Although the wide-scale use of FMT seems difficult in current practice, modulating the microbiota, in particular with new-generation probiotics, in combination with ICI could become a standard treatment.

Key points

- Gut microbiota plays a role in ICI response
- FMT from healthy donors is feasible and safe in patients treated with ICI in a first-line setting for metastatic melanoma
- Despite the limitations associated with the absence of a control arm and the small size of the study, the clinical efficacy observed in patients receiving FMT in combination with ICI was greater than that of ICI monotherapy in Phase III trials and in real-world data

[CONCLUSION]

This study has shown that FMT from healthy donors is feasible and safe in patients treated with ICI in a first-line setting for metastatic melanoma. Modulating the microbiota through FMT or other methods could increase ICI efficacy although larger controlled studies are required to confirm the data.

Sources

• **1**. Routy B, Lenehan JG, Miller WH Jr, *et al.* Fecal microbiota transplantation plus anti-PD-1 immunotherapy in advanced melanoma: a phase I trial. *Nat Med* 2023; 29: 2121-32. • **2**. 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. • **3**. Baruch EN, Youngster I, Ben-Betzalel G, *et al.* Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients. *Science* 2021 ; 371 : 602–9. • **4**. 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.

COMMENTED ARTICLE

Children's section

Photo: Shutterstock.

By Pr. Emmanuel Mas

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Longitudinal analysis of the gut microbiome in adolescent patients with anorexia nervosa: microbiome-related factors associated with clinical outcome

Comments on the original article by Andreani et al. [1]

The gut microbiome is increasing recognised as playing a role in anorexia nervosa (AN). Studies have reported that AN patients present with dysbiosis compared to healthy controls. However, the underlying mechanisms are unclear and data on influencing factors and the longitudinal impact of microbiome alterations are rare. In this article, the authors presented longitudinal data from 57 hospitalised adolescents diagnosed with anorexia at nine different time points (including a one-year follow-up examination) and compared them to six different time points in 34 healthy controls.

The study concluded that characterising prognostically relevant taxa could help stratify patients at admission and potentially identify candidate taxa for future supplementation studies to improve the treatment of anorexia nervosa.

What do we already know about this subject?

••• Anorexia nervosa (AN) is a very common psychiatric condition in adolescence, with a high mortality rate. AN is characterised by dysmorphia, reduced calorie intake and malnutrition. Although the pathophysiology of AN is poorly understood, the gut microbiome (GM) is thought to play an important role. GM is actually involved in the gut-brain axis, in malnutrition and also in excess weight, and is altered by diet.

The aim of the study was to analyse GM alterations over time in AN patients. It was a one-year study conducted on inpatients until they were discharged from hospital, with an assessment of the clinical parameters associated with the GM in AN.

FIGURE 1 **Microbiome of AN patients during the study and controls.**

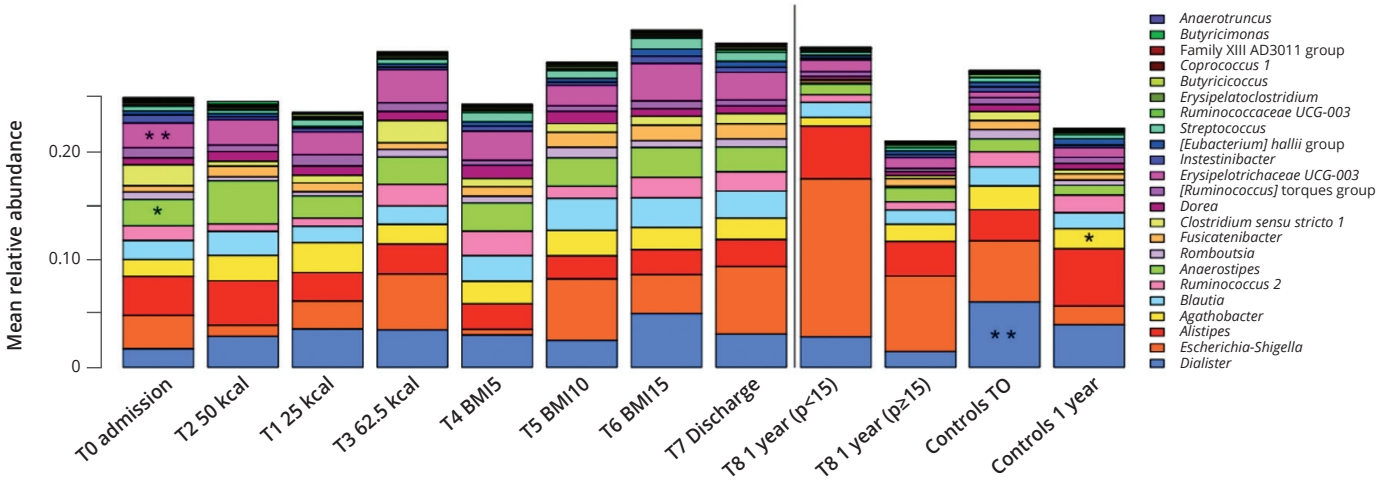
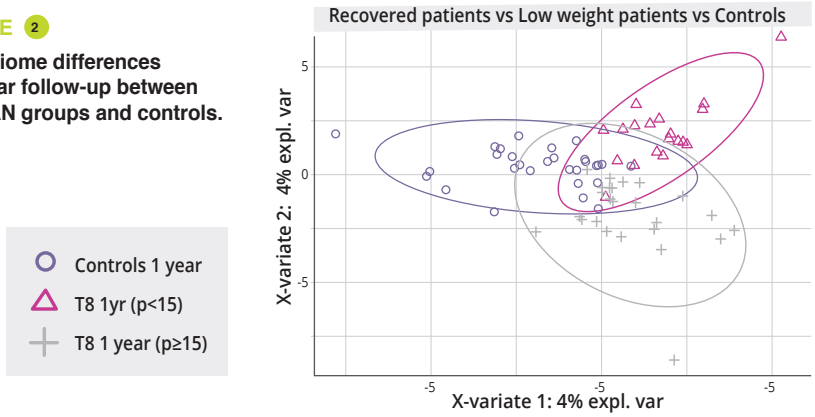


FIGURE 2

Microbiome differences at 1 year follow-up between the 2 AN groups and controls.



What are the main insights from this study?

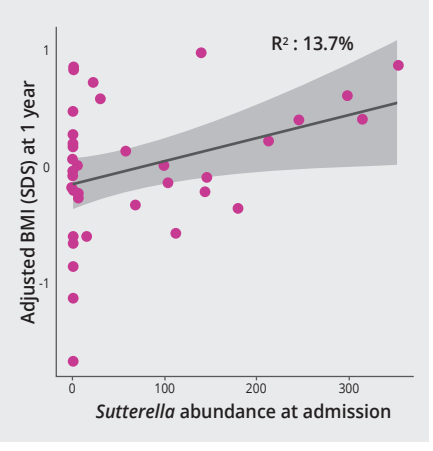
••• This is the first longitudinal study on gut microbiome (GM) alterations in AN patients, conducted over such a lengthy time frame (one year). The study included 56 patients aged between 12-20 years and 34 controls. Stools were collected at admission and discharge (T0-T7) then one year after admission (T8). Eight patients were re-admitted during the study; patients were separated into those who had recovered their weight (BMI≥15th p [percentile]) and those who still had a low weight (BMI<15th p).

GM composition differed significantly at admission during the acute malnutrition phase, with no difference in terms of alpha-diversity (**figure 1**). GM differences observed in AN patients compared to controls, even when non-significant, persisted throughout the study. In adolescents with a BMI<15th p at one year, alpha-diversity (Chao1 index) was significantly reduced during hospitalisation compared to admission, discharge and at the 1-year follow-up. A similar trend was observed in AN patients who recovered a BMI≥15 compared to the controls. At admission, the PERMANOVA analysis showed a significant reduction in the genera *Legionella, Dialister, Ruminococcaceae UCG-003* and *Limnobacter* compared to the controls. During in-hospital treatment, the differences between AN patients and controls were reduced, and only remained in the amplicon sequences variants (ASVs). At one year, significant differences were still observed between AN patients with a BMI<15th p and controls in terms of the phyla, classes and orders (p = 0.001 to <0.001), whereas smaller differences were observed between AN patients with a BMI≥15th p and controls (p = 0.063 in terms of ASVs) (**figure 2**).

Between admission and the 1-year follow-up, AN patients with a BMI<15th p had a significant abundance of the genera *Anaerostipes, Clostridium sensu stricto 1* and *Romboustia* (p = 0.02) while surprisingly, the GM of AN patients who recovered a BMI≥15th p was more similar during the follow-up. The same was true for changes in GM between hospital discharge and the 1-year follow-up: with a four fold greater abundance of the genus *Escherichia-Shigella* (p = 0.04) and two fold greater abundance of *Alistipes* (p = 0.03) in AN patients with a BMI<15th p.

GM analysis at admission revealed a significant association between illness duration (phylum-family level, p = 0.011 to 0.022) and amount of weight loss (class-genera level, p = 0.030 to 0.047). A longitudinal PERMANOVA analysis, with correction for the use of laxatives, showed a significant association between GM and the amount of ingested calories (p = 0.003, R^2 = 0.009), the BMI-SDS (p = 0.006, R^2= 0.008) and leptin concentration at admission, discharge, and 1-year follow-up (p = 0.02, R^2 = 0.02). The genera *Ruminiclostridium 5* (p=0.006) and *Intestinibacter* (p= 0.03) were associated with the risk of hospital readmission. A linear model analysis, with correction for laxative use, illness duration, weight loss and BMI-SMS at admission, identified that at admission four genera were associated with BMI-SDS at the 1-year follow-up: *Sutterella, Parasutturella, Lachnospiraceae FCS020 group* and *Clostridium stricto sensu* (p = 0.008 to 0.04) (**figure 3**).

FIGURE 3 **BMI-SDS prediction at 1 year by *Sutterella* abundance at admission.**



What are the consequences in practice?

••• Dysbiosis is observed in acute-phase AN patients and improves partly with treatment. GM composition at admission can help predict the risk of relapse in the first year and improvement in BMI at one year. Thus, a GM analysis at admission could identify the genera and taxa *Parasutturella, Lachnospiraceae FCS020 group*, *Clostridium stricto sensu* and uncultured *Alistipes* as indicative of a poorer prognosis. As a higher abundance of *Sutterella* is indicative of a positive outcome, it could be used as a probiotic target.

Key points

- GM analysis could be worthwhile in adolescents with AN
- Certain microbes could be predictive of negative outcome factors while *Sutterella* could be positive and used as a probiotic target

[CONCLUSION]

This study showed that GM composition was associated with the duration of the AN and weight loss at admission, but also that GM alterations during treatment was influenced by the calories ingested, weight gain and leptin.

Source

• **1**. Andreani NA, Sharma A, Dahmen B, *et al.* Longitudinal analysis of the gut microbiome in adolescent patients with anorexia nervosa: microbiome-related factors associated with clinical outcome. *Gut Microbes* 2024; 16: 2304158.

Focus on young researchers

Photo: Shutterstock.

Gut microbiota from post-Covid-19 patients induces lung inflammation and brain dysfunction in mice [1]

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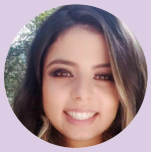


Viviane is a PhD student under Pr. Angélica Thomaz Vieira's supervision.
Viviani Mendes was selected from the special call of paper of the *Microbiota Mag*. She gives us a tour from her recent publication about the influence of microbiota in post-Covid effects. Her study was recently published in *Gut Microbes* [1].

> What do we already know about this subject?

Covid-19 has wreaked havoc on a global scale, resulting in millions of confirmed cases and fatalities as of March 2023. Long-term complications of Covid-19 are pervasive, affecting even individuals with mild or asymptomatic cases. Among pathophysiological responses triggered by Sars-CoV-2 infection, several studies have linked gastrointestinal symptoms and altered gut microbiota in Covid-19 during and after the infection. On SARS-CoV-2 infection, growing evidence supports the role of gut microbiota in influencing Covid-19 severity and post-Covid effects [2].

Dysbiosis, an imbalance in the gut microbiota composition, is a critical factor in the development of various diseases. Severe Covid-19 cases have been associated with alteration of the intestinal microbiota that may persist for up to a year following the initial infection [3, 4]. However, until now, it was known that Covid-19 can alter the composition of the intestinal microbiota, but we were unaware of the causal effects that the post-Covid microbiota can have on the host's physiology.

> What are the main insights from this study?

Microbiota analysis of 72 individuals with a history of Covid-19 (post-Covid group) and 59 healthy controls showed no significant differences in gut microbiota diversity (α and β diversity) between the groups, while post-Covid subjects exhibited a higher prevalence of *Enterobacteriaceae* strains with drug-resistant phenotypes. A higher proportion of post-Covid individuals reported antibiotic use, likely due to Covid-19 treatment. Importantly, *Klebsiella* strains, associated with antimicrobial resistance (AMR), were notably increased in post-Covid gut microbiota (**figure 1**).

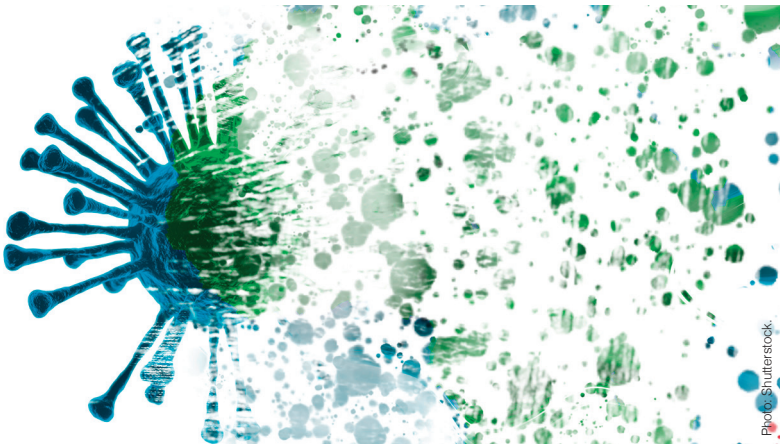
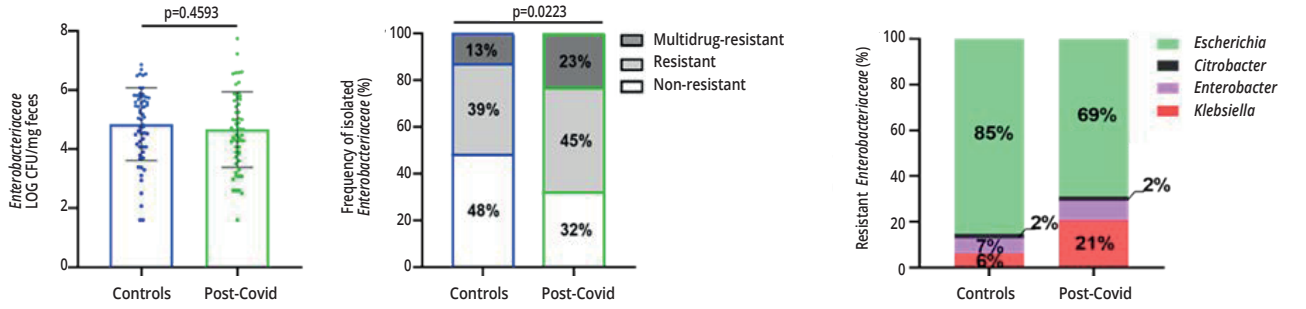


Photo: Shutterstock.

FIGURE 1



To understand the direct contribution of post-Covid microbiota to the host, fecal microbiota transplantation (FMT) was performed in germ-free mice using samples from post-Covid and control donors. Post-Covid mice exhibited lung inflammation (**figure 2A**).

They were also more susceptible to infection with multidrug-resistant Klebsiella pneumonia displaying a more severe lung pathology and inflammatory cell infiltration but were less efficient at clearing the bacteria. Increased *Enterobacteriaceae* levels in the blood of post-Covid mice suggested systemic translocation. In addition, reduced serum acetate levels were observed in post-Covid *Klebsiella pneumonia*-infected mice (**figure 2A**).

Post-Covid mice exhibited memory impairment in cognitive behavioral tests, along with increased TNF expression and decreased neuroprotective factors in the hippocampus (**figure 2B**). Administration of a strain probiotic to mice infected with a murine coronavirus prevented memory impairment, reduced weight loss and lung tissue inflammation.

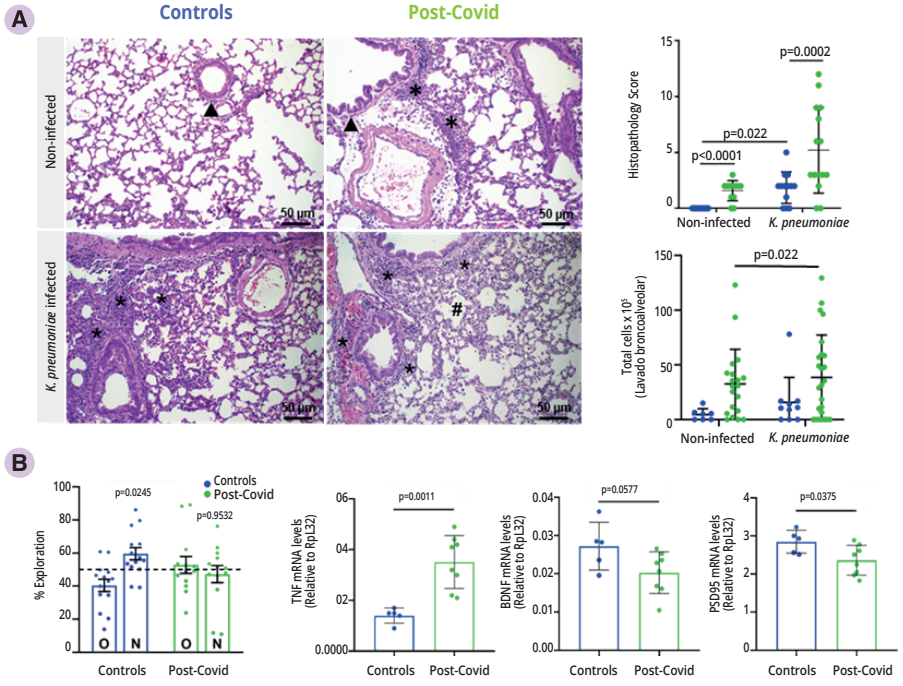
> What are the consequences in practice?

This study warns about the relationship between Covid-19 and the global burden of antimicrobial resistance. Furthermore, it highlights for the first time the causal effect of post-Covid microbiota on lung and nervous system alterations.

Key points

- *Enterobacteriaceae* strains with an antibiotic resistance phenotype are highly present in the intestinal microbiota of post-Covid subjects
- Transplanted mice with post-Covid samples showed lung inflammation and difficulty dealing with a pulmonary infection by multidrug-resistant *Klebsiella pneumoniae*
- Transplanted mice with post-Covid samples also exhibited cognitive performance impairment, even after viral clearance

FIGURE 2



[CONCLUSION]

The study provides compelling evidence that gut microbiota from individuals following SARS-CoV-2 infection, even after viral clearance, can lead to lung inflammation, cognitive impairment, and increased susceptibility to secondary infections in mice. It highlights the potential for microbiome-based interventions, such as probiotics, to mitigate post-Covid sequelae.

Source

- **1**. Mendes de Almeida V, Engel DF, Ricci MF, *et al.* Gut microbiota from patients with Covid-19 cause alterations in mice that resemble post-Covid symptoms. *Gut Microbes* 2023; 15: 2249146.
- **2**. Zuo T, Liu Q, Zhang F, *et al.* Depicting SARS-CoV-2 faecal viral activity in association with gut microbiota composition in patients with Covid-19. *Gut* 2021; 70: 276-84.
- **3**. Chen Y, Gu S, Chen Y, *et al.* Six-month follow-up of gut microbiota richness in patients with Covid-19. *Gut* 2022; 71: 222-5.
- **4**. Liu Q, Mak JWY, *et al.* Gut microbiota dynamics in a prospective cohort of patients with post-acute Covid-19 syndrome. *Gut* 2022; 71: 544-52.

By A/Pr. Dao Viet Hang, MD, PhD
Hanoi Medical University, Vietnam

APDW summary

DECEMBER 2023

In December 2023, more than 3,000 physicians representing over 60 countries attended the Asia Pacific Digestive Week in Bangkok. The event provided a rich and diverse program, with many updated lectures spanning various fields including hepatology, endoscopy, gastrointestinal (GI) diseases, and motility/surgery. Besides the lectures on newly released guidelines, many new topics are integrated into the program with various formats – interactive sessions with case-based discussion, debate sessions on different aspects and approaches, and keynote lectures from well-known panellists worldwide.

Gastrointestinal motility and functional disorders

One of the highlights of this year's event are numerous sessions dedicated to GI motility, with a main focus on functional diseases. In the opening ceremony, an update on refractory gastroesophageal reflux disease (GERD) was presented as a presidential lecture from Prof Somchai Leelakusolvong, President of Local Organizing Committee. Prof Somchai emphasized the importance of the Lyon consensus version 2.0, which has expanded the criteria of endoscopic findings to include Los Angeles reflux esophagitis grade B, which is more practical in Asian countries. The event also introduced many updated data on optimizing the treatment of refractory GERD based on various mechanisms. The advancements in treatment strategies were also highlighted, including the use of drugs targeting lower esophageal sphincter (LES) pressure, esophageal contractions, endoscopic interventions, and electrical stimulation. Transient lower esophageal sphincter relaxations were considered as one of the key mechanisms of GERD. This condition can be improved by baclofen by increasing resting LES pressure, thus reducing episodes of reflux. Preliminary data on a small cohort of patients suggested that electric stimulation could improve LES pressure; however, the practical application of this intervention in the future is still debated.

The event also paid considerable attention to the comparison between proton pump inhibitors (PPI) and potassium-competitive acid blockers (PCAB) in different studies, with the target population being patients with erosive esophagitis. Current evidence showed a higher efficacy of PCAB compared to PPI in treating severe erosive esophagitis with acceptable adverse events.

One of the most engaging sessions was "All about GERD", chaired by Prof Somchai Leelakusolvong and Prof Kwang-Jae Lee on December 8th. This session primarily focused on the updates of the modern Lyon consensus, non-acid reflux management, and optimizing treatment of functional heartburn.

Dr. Ping-Huei Tseng, Taiwan, presented the detailed changes of the Lyon consensus 2.0 with the clarification on the expanded criteria in endoscopic findings for Los Angeles grade B esophagitis. The role of high-resolution manometry to exclude mimic esophageal disorders and identify risk factors of GERD such as low LES pressure, hiatal hernia, or weak oesophageal contraction was also explained with case examples for further clarity. Some promising metrics on 24-hour pH impedance, such as mean nocturnal baseline impedance (MNBI) and post-reflux swallow-induced peristalsis (PPSW) index, are still debating and require further clinical data.

For non-acid reflux management, Prof. Justin Wu from Hong Kong highlighted the differences between the definition of refractory GERD and refractory GERD symptoms, of which the latter can be caused by various diseases. The roles of high-resolution manometry (HRM), endoscopy, and 24-hour pH impedance in the diagnosis and management of these conditions are explained in detail by the ESNM/ASNM guideline. The decision to perform 24-hour pH impedance on or off PPI depends on the diagnostic aim, whether to confirm GERD in patients with no prior diagnosis, or to confirm refractory GERD. It will be helpful to have a stepwise

Panelists of ASPDE-WEO International Clinical Symposium Artificial Intelligence in Endoscopy.

strategy for patients with refractory GERD to determine the optimal time for endoscopic interventions or surgery. Non-acid reflux management should be considered comprehensively for possible mechanisms, including characteristics of reflux episodes, oesophageal motility patterns, and overlapping symptoms. Furthermore, Prof Wu emphasized the need to establish a cut-off value for acid exposure time (AET) in GERD diagnosis for the Asian population, which can be a debating point when compared to the Lyon consensus.

Functional heartburn is also a challenging condition due to several factors: overlapping with other functional gastrointestinal disorders, presenting with mental disorders (anxiety, depression, stress) in the scope of the "gut-brain pathway" mechanism, and requiring exploration tests for exclusion. According to recent data, 70% of patients with functional symptoms had normal endoscopic findings. Within this population, 50% had normal 24-hour pH impedance results, and 60% showed no correlation with the occurrence of symptoms, meaning only 21% was classified as functional heartburn. That is why, besides PPI, neuromodulators play an essential role. Tricyclic antidepressants (TCAs) and selective serotonin uptake inhibitors (SSRIs) have shown efficacy in treating functional heartburn. However, their potential side effects should be carefully considered. For prevention, it is recommended to initiate treatment with a low dose and maintain follow-up during treatment.

Artificial intelligence in Endoscopy: ASPDE – WEO Symposium Highlight

Artificial intelligence (AI) is also a hot topic with many invited speakers. On the final day of APDW, December 9th, ASPDE co-hosted with WEO to organize a session called "ASPDE-WEO International Clinical Symposium Artificial Intelligence in Endoscopy: Implementation in the Asia Pacific and the World". This session was moderated by Prof Hisao Tajiri, Prof Yuichi Mori, and Assoc. Prof Nonthalee Pausawasdi. Prof Yuichi Mori gave the first presentation to introduce the WEO AI committee to the two ongoing projects. One project is an international study aimed at evaluating the perceptions of endoscopists and patients regarding the use of AI in endoscopy. The other is a longitudinal study on the role of AI in real-world settings. The WEO AI committee focuses on implementing AI in clinical practice, considering different aspects including accuracy, cost-effectiveness, doctor-machine interactions, training programs, and ethical considerations.

Prof Han-Mo Chiu, Prof Rungsun Rerknimitr, and Prof Kherk-Yu (Lawrence) Ho each presented different topics on developing and using AI effectively in several fields, including colorectal cancer screening, gastric cancer screening, and biliary endoscopy. The presentations showed many updated data, inspiring clinicians and endoscopists to consider implementing AI in the near future.

Assoc. Prof Dao Viet Hang presented another aspect of utilizing AI in endoscopy training, especially in limited-resources settings. She highlighted that the conventional metrics in endoscopy training, based on the minimum number of cases or the duration of practice, do not reflect the skills and personal development over time, requiring a more interactive approach. E-learning training programs and simulation-integrated activities have shown promising results in enhancing junior endoscopists' knowledge and lesion detection skills. Until now, AI has shown promising data on improving lesion detection with more and more data in clinical practice; however, its integration in endoscopy training is still lacking. Some key considerations for applying AI in endoscopy training include economic feasibility, safety and accountability, technical concerns and validation, and clinicians' role in digitalization. The framework suggested that adopting AI in endoscopy training should balance users' factors, technology factors, social factors, and contextual factors (educational environment and standards). A needs assessment is required to outline educational needs and establish clear educational goals to inform AI's technology selection. AI should be integrated into training based on the best evidence and within a curriculum, incorporating user training for both trainees and trainers to promote uptake.

All the talks in this session received substantial feedback, comments, and questions, reflecting a great interest in the future application of AI in endoscopy.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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

Gut microbiota as predictor of acute pancreatitis severity

Severe acute pancreatitis (AP) patients are at risk of elevated mortality, for which determining the course of disease within the first few hours would be very important. The current complex scoring systems cannot predict AP severity early enough, and thus, novel markers are needed.

While there seem to be a bilateral link between AP and gut microbiome, larger prospective clinical studies have been lacking. This paper presents results of orointestinal microbiome from 450 patients with AP from 15 European centers. The samples were sequenced by full-length 16S rRNA and metagenomic sequencing using Oxford Nanopore.

The revised Atlanta classification (RAC) redefines severity of AP into three categories: mild, moderate, and severe (RAC I-III, respectively). This study found that Bray-Curtis distance of the rectal microbiomes was different in RAC III compared with RAC I and RAC II. Further, several bacterial species were differentially abundant depending on the RAC category. Bray-Curtis distances were also different between alive and deceased patients in rectal but not buccal microbiomes. In addition to mortality, the length of hospital stay associated with early alterations of rectal microbiome.

In the end, the authors found that 16 bacterial species were differentially abundant in severe vs. non-severe AP. In Ridge regression, these species together with systemic inflammatory response syndrome could faithfully predict disease

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severity. Interestingly, all these species are producers of short-chain fatty acids (SCFA). Accordingly, functional pathways of SCFA production were more expressed in severe AP. While the finding is intriguing, it is still unknown whether SCFA producing bacteria are cause or consequence of severe AP.

Ammer-Herrmenau C, Antweiler KL, Asendorf T, *et al.* Gut microbiota predicts severity and reveals novel metabolic signatures in acute pancreatitis. *Gut* 2023 : gutjnl-2023-330987.

GUT MICROBIOTA

Links between gut microbiome in type 2 diabetic Emirates

The incidence of type 2 diabetes (T2D) is increasing drastically in Middle East countries. Several Western studies have shown the contribution of gut microbiome in T2D-associated insulin resistance and low-grade inflammation, but studies in Middle East populations are scarce. Further, the existing studies show inconclusive results of how the microbial community composition and functions contribute to the pathogenesis of T2D.

To gain more insight, the authors analyzed stool samples of 84 individuals from the United Arab Emirates with or without T2D using nanopore metagenomic sequencing. Unlike many earlier Western

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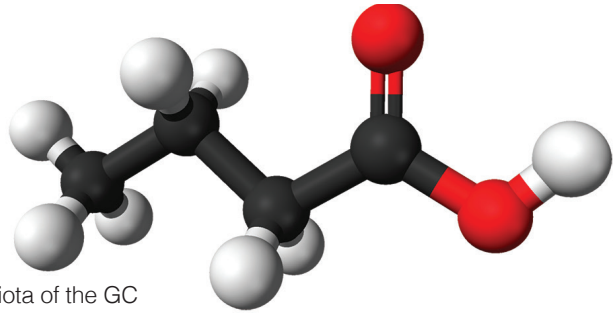
studies, this study reported no differences in gut microbiota alpha-diversity between healthy controls and T2D. Further, after correcting for multiple comparisons, the authors did not find differential abundance of any microbial species or KEGG orthology (KO) features between the groups. However, a gene set enrichment analysis revealed 8 functions with higher abundance in the control group and 5 in the T2D group. These differentially abundant modules associated with the degradation of amino acids, such as arginine, the degradation of urea and homoacetogenesis. These functions seem to have pro-inflammatory effects, and thus, may contribute to low-grade inflammation, a hallmark of T2D. Ultimately, the authors used prediction analysis to identify 3 potential biomarkers of T2D. These included a depletion of *Enterococcus faecium* and *Blautia* as well as an enrichment of *Absiella* spp or *Eubacterium limosum* in T2D. Interestingly, *E. faecium* is shown to have lipid-lowering and anti-obesity effects, and therefore, might partly contribute to the pathogenic T2D phenotype.

To conclude, this study was successful in identifying specific microbial biomarkers, including functions and taxa that may help in predicting the development of specific T2D-associated disease conditions.

Dash NR, Al Bataineh MT, Alili R, *et al.* Functional alterations and predictive capacity of gut microbiome in type 2 diabetes. *Sci Rep* 2023; 13: 22386.

GUT MICROBIOTA

Microbial butyrate inhibits immunosuppressive factors in gastric cancer



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Gastric cancer (GC) is one of the leading causes of cancer death worldwide. Early detection is important for successful treatment of GC. Programmed death-ligand 1 (PD-L1), a target of cancer immunotherapy, is highly expressed in tumor-associated macrophages that can be regulated by the gut microbiome. One possible way through which the microbiome may have anti-cancer effects is the production of short-chain fatty acids, including butyrate.

In this study, advanced GC patients expressed more immunosuppressive markers, namely PD-L1 and interleukin (IL)-10, in macrophages, dendritic cells and cancer mucosa than healthy controls. The gut microbiota of the GC patients was characterized by lower diversity and dysbiosis. At genus level, lower abundances of butyrate-producing bacteria, such as *Faecalibacterium* and *Bifidobacterium* were detected in GC patients. Interestingly, administration of butyrate and *Faecalibacterium* into the peripheral blood mononuclear cells of GC patients decreased the number of PD-L1- and IL-10-expressing macrophages. In addition, butyrate suppressed the growth on cultured GC cells. However, it remained unclear which *Faecalibacterium* strain was used in the *in vitro* experiment. Ultimately, a humanized tumor mouse model was injected with GC cells and peripheral blood mononuclear cells of from healthy controls or GC patients with or without butyrate. The experiment showed that butyrate significantly decreased tumor size and the immunosuppressive markers PD-L1 and IL-10. Thus, butyrate may have therapeutic potential via suppressing cancer cell growth in GC.

Lee SY, Jhun J, Woo JS, *et al.* Gut microbiome-derived butyrate inhibits the immunosuppressive factors PD-L1 and IL-10 in tumor-associated macrophages in gastric cancer. *Gut Microbes* 2024; 16: 2300846.

VAGINAL MICROBIOTA

Predicting the risk of preterm birth through vaginal microbiota

Photo: Shutterstock.

Respiratory, gastrointestinal and neurodevelopmental complications: preterm birth is the main cause of neonatal morbidity and mortality. The vaginal microbiota seems to be involved, but the underlying mechanisms remain poorly understood.

A team of American researchers tracked the genome of the vaginal microbiota of 175 American women throughout their pregnancies (40 of whom subsequently experienced spontaneous preterm delivery, and 135 of whom delivered at full term). The study shows that the two types of pregnancy differ in terms of vaginal microbiota composition: certain bacterial species of the *Lactobacillus* genus, such as *L. helveticus, L. crispatus, L. gasseri* and *L. jensenii*, are associated with full-term pregnancies, while *Megasphaera genomosp, Gardnerella* spp. and *Atopobium vaginae* are linked to preterm births. Another finding is that the genetic diversity of the vaginal microbiota is higher in the first half of pregnancies that end preterm, due to *Gardnerella* species. More precisely, the nucleotide diversity of *Gardnerella* spp. increases at the start of pregnancies that end preterm whereas it remains stable in pregnancies that are carried to term. The genetic diversity of *Gardnerella* spp. could perhaps be used as a biomarker for the early diagnosis of preterm birth.

But how can we explain this peak in *Gardnerella* nucleotide diversity? Compared to other bacteria, *Gardnerella* shows a 1.5-fold higher growth rate at the start of pregnancy, more frequent genetic recombination and greater selection of mutations that benefit this bacterium (and increased elimination of deleterious mutations). Antibiotics and other xenobiotics are thought to be involved. In fact, the more diversified gene pool of *G. swidsinskii* seems to correspond to an adaptation to drugs, confirming a previously suggested effect of xenobiotics in the vaginal environment; and vaginal microbiota associated with preterm birth exhibit higher antibiotic resistance potential. Genomic variation in vaginal bacteria is therefore believed to affect the host's phenotypes (including pregnancy outcomes). However, the authors do not rule out another explanation, even if they consider it unlikely: the associations between microbial genetic diversity and pregnancy outcomes could also result from unmeasured confounding factors (drugs, chemical compounds, etc.) that might act on both variables.

Liao J, Shenhav L, Urban JA, *et al.* Microdiversity of the vaginal microbiome is associated with preterm birth. *Nat Commun* 2023; 14: 4997.

By Dr. Julien Scanzi

Department of Gastroenterology, Clermont-Ferrand University Hospital, Clermont-Ferrand, France

Can you "hack" into your gut to obtain the slimming effects of a drug for diabetes?

Dr. DeDecker, an internal medicine specialist, has posted a short video on her TikTok channel explaining how people can benefit from the slimming effect of a drug without actually taking it. The drug in question is a GLP-1 analogue in the form of an injectable pen. It is indicated for the treatment of diabetes but is widely misused for its slimming effect, particularly in the United States, with female influencers even promoting it on social networks. The doctor explains that it is possible to achieve the slimming effect of this drug, which can help people lose up to 20% of their bodyweight, using two "natural" methods, thanks to the gut microbiome, by taking a specific probiotic and by eating a fibre-rich diet.

> Could you talk about the claims made on the video from a clinical perspective?

This drug increases GLP-1, which is a hormone primarily produced by the endocrine cells (also called enteroendocrine cells) in the gut. It boosts the secretion of insulin (incretin effect), slows down gastric emptying and stimulates the sensation of being full, making you feel less hungry.

> What about fibre and taking a probiotic?

It is well known that dietary fibre, especially soluble fibre, can slow down gastric emptying, making you feel full and help control your appetite. Fibre can also help stabilise blood sugar levels by slowing down the absorption of carbohydrates, which can be beneficial in diabetic patients. What's more, fibre-rich food often has a lower energy density, which can help reduce the overall calorie intake and potentially help patients to lose weight when eaten as part of a balanced diet. In terms of the gut microbiota, I agree with Dr. DeDecker about the fact that most fibre has a prebiotic effect and will nourish certain gut bacteria, which are then able to produce short-chain fatty acids (SCFAs) through fermentation, and these SCFAs can increase GLP-1 levels.

I would, however, qualify the statements about the bacterium she mentions, *Akkermansia muciniphila*, which she credits with tremendous benefits in terms of regulating energy metabolism and insulin sensitivity, as some studies have suggested it plays an indirect role in regulating the secretion of intestinal peptides such as GLP-1. However, this is preclinical data, and the link could be a fairly indirect one. Thus, there is no evidence to claim that supplementation with this bacterium could increase GLP-1 secretion and lead to weight loss.

> Why do you think that this video has attracted so much attention?

In my opinion, it was very easy for this video to create a buzz because it deals with weight loss, and in the West with our high rates of overweight and obese people (50-60% of the population), there are many who dream of being able to lose weight without changing their lifestyle, particularly their diet. So if you suggest that a natural method exists to lose 20% of your bodyweight without taking a drug, you can easily see why it appealed to so many people.

> Would you give this information to your patients? What could be the risks and/or pitfalls?

That's my personal opinion and I think that Dr. DeDecker's comments are somewhat misleading, because neither taking any kind of probiotic nor increasing dietary fibre has shown any benefit in terms of weight loss, let alone a 20% one. However, despite these misgivings, I do think what she has to say is interesting as it could have the positive effect of reducing the misuse of anti-diabetic medication, as well as raising public awareness of the impact of the gut microbiota on our health. And, more importantly, she is encouraging people to eat more fibre. The current consumption of fibre in Western countries (less than 20 g/day) is well below the World Health Organisation's recommendations (25-30 g/day), and only 5% of Americans eat enough fibre.

BIOCODEX MICROBIOTA FOUNDATION

Henri Boulard Awards: 4 awards to protect microbiota and preserve global health

Launched in 2021 by the Biocodex Microbiota Foundation, the Henri Boulard Awards are dedicated to improving the human health related to microbiota equilibrium. From Nigeria to Thailand, 8 laureates have already won these awards. Recent research shows that some factors such as diet, lifestyle, drugs or environmental conditions may impact microbiota leading to clinical disorders or diseases. This is the reason why, in 2024, the Biocodex Microbiota Foundation takes another step towards supporting 4 Henri Boulard Awards in 3 different topics: Microbiota & Human Health, Microbiota & Antimicrobial Resistance, Microbiota & Environmental Concerns. Open to all health professionals, these awards are limited to projects taking place in Asia, Latin America or Middle East Africa. Sixty-six countries are eligible. These 4 projects will each be awarded €10,000. Applications can be submitted **until September 15th, 2024**. An independent and renewed jury will evaluate the proposed projects at the end of November based on several criteria. All information available here: **https://www.biocodexmicrobiotafoundation.com/henri-boulard-award/henri-boulard-award-call-projects**

2024 International grant: French researcher Nicolas Cenac awarded!

The Biocodex Microbiota Foundation is delighted to announce that French researcher Nicolas Cenac, working in the Inserm UMR 1220 (Toulouse) dedicated to the physiopathology of the gut-brain axis has just been awarded the Foundation's International Grant for 2024. The topic of the 2024 Biocodex Microbiota Foundation's international call for projects was "Role of the gut microbiota in the mechanisms of pain". Nicolas Cenac's project will explore the link between functional microbiota dysbiosis and visceral pain, and more specifically the role of maternal milk on microbiota implantation under stress condition. The €200,000 award will help support his research. Once again, Biocodex Microbiota Foundation is rewarding innovative research in order to gain a better understanding of the impact of microbiota on human health.

Nicolas Cenac

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