EDITORIAL

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It is with a great pleasure that we invite you to read and share this first "Microbiota Newsletter". Under the auspices of the BMI (Biocodex Microbiota Institute), this document will be released three times a year (two in 2017), it will be available in three languages (English, Spanish and French) and will also be downloadable from the BMI website: www.biocodexmicrobiotainstitute.com

The "Microbiota Newsletter" is focused on the importance of the various microbiota. It is intended to be "universal" and will therefore replace the newsletters that were proposed by Biocodex France ("Le Microbiote dans tous ses états") and by Biocodex International ("Biotascope"). We are very grateful to the authors of the French and international newsletters - in particular Professors Harry Sokol (Paris) and Emmanuel Mas (Toulouse) and Professor Serhat Bor (Turkey), Editor-in-chief, as well as the members of the ISGOP board.

We have decided, as it was the case in the previous formats, to entrust the best world experts with the drafting of the contents.

Several section will be included in this newsletter:

• An overview article: Dr. Pauline Jouët (Boulogne-Billancourt, France) explains the increasingly important role that the gut microbiota could play in the pathophysiology of irritable bowel syndrome in adults and in children.

• An analysis of two recent publications: in the first analysis, Prof. Harry Sokol (Paris, France) discusses the work done by G. de Palma et al. illustrating the changes in intestinal behavior and functions in mice that received fecal microbiota transplantation from adult patients with irritable bowel syndrome. In the second literature analysis, Prof. Emmanuel Mas (Toulouse, France) discusses the results obtained by M. Yassour et al. illustrating the impact of the use of antibiotics on the gut microbiome in infants.

• A review of 4 literature articles: Prof. Ener Dinleyici (Eskisehir, Turkey) discusses the interest that Akkermansia muciniphila could have in obesity and metabolic syndrome, the influence of the delivery mode on microbiota composition in the first 6 months of life, the new mechanisms of action of Saccharomyces boulardii on antibiotic-induced dysbiosis and the criteria defining the quality of a probiotic.

• A selection of the main communications related to the gut microbiota from the latest international congresses of gastroenterology or pediatrics, starting with the Gut Summit that was held in Paris on March 11-12, 2017 for which Dr. Alexis Mosca (Robert Debré Hospital, Paris) proposes a compilation of highlights.

We hope you will enjoy your reading!

"THE « MICROBIOTA NEWSLETTER » IS FOCUSED ON THE IMPORTANCE OF THE VARIOUS MICROBIOTA. IT IS INTENDED TO BE « UNIVERSAL »..."

OVERVIEW

MICROBIOTA AND IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome (IBS) combines abdominal pain and transit disorders, affects 5-10% of adults in France and is the leading cause of chronic abdominal pain in children. Its pathophysiology is complex with multiple abnormalities reported in the digestive tract and central nervous system (CNS). Microbiota abnormalities with bacterial overgrowth in the small intestine and dysbiosis related to qualitative and/or functional changes of the flora have recently been reported. They could be involved in the various pathophysiological mechanisms described in IBS. Some treatments may be successful through their effect on the microbiota, such as antibiotics, probiotics or dietary measures. The place of fecal transplantation remains to be determined.

By Dr. Pauline Jouët
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IBS is defined (Rome IV criteria) by abdominal pain associated with transit disorders (constipation: IBS-C, diarrhea: IBS-D, or alternation of both: IBS-M) evolving for at least 6 months. In France, its prevalence is of about 5-10% in adults. Although benign, it may lead to a significant impairment of the quality of life, the efficacy of current treatments being limited. Its pathophysiology is complex and could involve the microbiota.

WHAT ARE THE ARGUMENTS FOR A ROLE OF THE MICROBIOTA IN IBS?

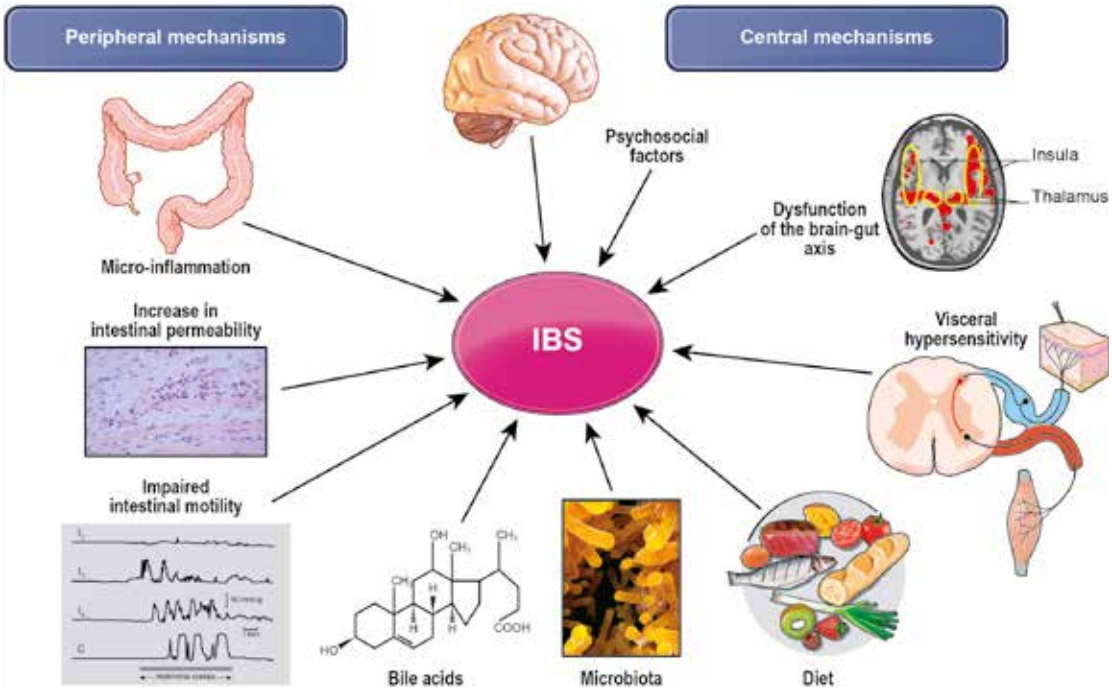
In 15-20% of cases, an episode of acute gastroenteritis precedes the onset of post-infectious IBS. In a systematic review [1] including 45 studies and more than 21,000 cases, this risk is estimated at 11.5%, especially after a bacterial or parasitic infection. Other risk factors include a severe and prolonged acute episode, antibiotic intake, female gender as well as anxiety and depressive disorders at the time of the episode. It could be increased by the presence of some genetic polymorphisms.

BACTERIAL OVERGROWTH

Bacterial overgrowth, defined by an excess of bacteria in the small intestine, seems to be three times more common in IBS in adults in a meta-analysis, but studies report highly variable prevalences [2]. The flora of the small intestine being poorly accessible, they usually use respiratory tests. Their diagnostic value varies according to the tests and the positivity thresholds used. The lactulose breath test may be falsely positive due to an accelerated transit in the small intestine. The use of proton pump inhibitors could be a contributing factor.

CHANGES IN FECAL FLORA

Qualitative and functional changes in fecal flora have been found in cases of IBS and between subgroups. The study results are very heterogeneous, depending on the methods used. Culture-based techniques should be interpreted with caution as most bacteria cannot be grown in culture. The use of more recent culture-independent techniques has allowed better analyzing bacteria, bacterial genes present and



◀ FIGURE 1
Pathophysiological mechanisms of irritable bowel syndrome (IBS)

their function, with different approaches assessing RNA transcription, proteins and metabolites of bacterial origin found in the bowel [3]. These changes could also be explained by differences in tested populations, individual changes in the microbiota, transit time or diet. In addition, the fecal flora is different from the more proximal flora and from those found next to the intestinal mucosa, which could play a more important role because of their vicinity with the intestinal wall. Most studies support a reduction in bacterial diversity with a decrease in bifidobacteria and an increase in some Firmicutes (Veillonella) and clostridia. Some functional abnormalities have also been described such as a reduction in bacteria producing and using lactate and an increase in hydrogen sulphide (H_2S) producing bacteria in case of IBS-C. Finally, a recent study has found the same microbial "signature" in the fecal and mucosal flora of IBS patients, associated with symptom severity, methane (CH_4) production, stool consistency and transit time [4].

DYSBIOSIS AND PATHOPHYSIOLOGY OF IBS

The pathophysiology of IBS remains poorly understood with multiple possible mechanisms (Figure 1). Dysbiosis could be involved at different levels due to the multiple intestinal functions of the microbiota, as suggested by studies often conducted in rodents.

• The microbiota influences intestinal motility. In axenic animals, gastrointestinal and colonic motor disorders have been found and they improve after reconstitution of the microbiota.

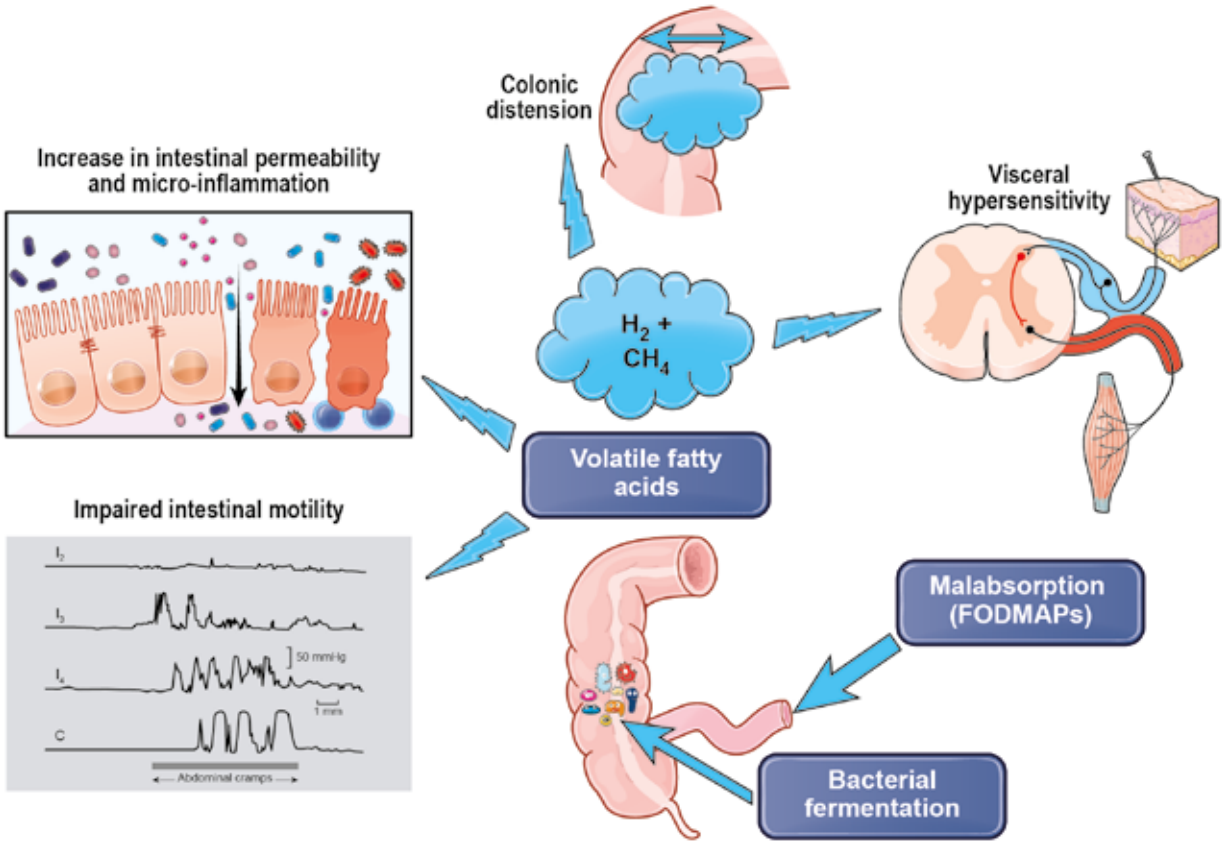
• There is a potential link between dysbiosis and visceral hypersensitivity. Administering some bacterial strains such as Lactobacillus acidophilus NCFM or Lactobacillus paracasei NCC2461 decreases visceral hypersensitivity in mouse models of stress-induced hypersensitivity. This effect is associated with an increased expression of the colonic mu-opioid receptors.

• A micro-inflammation of the intestinal wall infiltrated by lymphocytes, enterochromaffin cells and mast cells, found inconsistently, could be more common in case of post-infectious IBS. It could be promoted by a greater interaction between the immune system and the microbiota [5]. Changes in intestinal immunity have been described in IBS, with increased colonic expression of TLR4 involved in the recognition of bacterial lipopolysaccharides and systemic immunity, with an increase in circulating anti-flagellin antibodies, suggesting a greater recognition of bacterial components. These abnormalities could play a role in the augmented intestinal permeability frequently described in IBS-D.

• The colonic bacterial fermentation results in gas production that could be increased in IBS as some studies have shown a correlation between hydrogen (H_2) levels and symptoms, with a possible role of gas-induced colonic distension. This excess H_2 could be the result of an increase in colonic fermentation substrates, in particular in case of carbohydrate malabsorption. The fermentation may stimulate colonic motility, induce visceral hypersensitivity through the production of volatile fatty acids such as butyrate or promote a micro-inflammation and an increase in intestinal permeability (Figure 2).

BACTERIAL OVERGROWTH IN THE SMALL INTESTINE

- It seems to be more common in IBS
- It may be investigated using a glucose breath test
- If present, a discontinuation of proton pump inhibitors should be discussed
- The use of poorly absorbable antibiotics may decrease symptoms



▲ FIGURE 2

Colonic bacterial fermentation and pathophysiology of irritable bowel syndrome (IBS).

H_2 : hydrogen ; CH_4 : methane ; FODMAPs : Fermentescible Oligo or Di or Monosaccharides And Polyols.

• Dysbiosis could modify the metabolism of bile acids as bacteria are involved in the deconjugation and transformation of primary bile acids into secondary bile acids. Some bile acids have a laxative effect because they can stimulate colonic motility as well as intestinal secretions, and increase intestinal permeability. They can also modify visceral sensitivity. In a recent study, dysbiosis was associated with different fecal and serum bile acid profiles according to the IBS-C or -D subtype [6].

• The interaction of the microbiota with the CNS is complex and may pass through neurological, metabolic, immunological or endocrine mechanisms. The development of the CNS is influenced by the microbiota as neurological dysfunctions have been described in axenic mice as well as behavior changes after transfer of the flora from IBS patients to mice. The microbiota may be influenced by stress, possibly through its effects on intestinal motility and secretions. It may also limit its effects as, in rats, administering a probiotic (L. paracasei NCC2461) corrects the increase in intestinal permeability, visceral hypersensitivity and/or stress-induced mucosal inflammation.

TREATMENTS OF IBS AND MICROBIOTA CHANGE

The efficacy of drug treatments in IBS, compared to placebo that improves symptoms in one-third of the patients, is often limited. Dysbiosis and its possible involvement in most pathophysiological mechanisms make the microbiota a promising therapeutic target. Some treatments such as antibiotics and probiotics act directly on the microbiota, others such as diets limit the intake of substrates for bacterial fermentation.

DIETS

In two-thirds of cases, patients have found a link between the diet and their symptoms. Australian studies suggest the efficacy of the low-FODMAP diet, an acronym for carbohydrates likely to be poorly absorbed in IBS, with an osmotic effect in the small intestine and an increase in substrates for colonic bacterial fermentation that may explain abdominal pain, bloating and transit disorders. However, its efficacy remains controversial and may lead to a change

EFFICACY OF PROBIOTICS: BEWARE OF PRECONCEIVED IDEAS!

- The efficacy of the treatment does not necessarily increase with the administration of a higher amount of bacteria or a strain combination compared to a single strain
- The benefit of a prolonged treatment duration (>8 weeks) has not been proven
- Probiotics are not always marketed in the form/dose with which their efficacy has been demonstrated

in the microbiota with a decrease in bacterial abundance [7] with uncertain long-term consequences.

ANTIBIOTICS: RIFAXIMIN

Rifaximin is a broad-spectrum antibiotic that is poorly absorbed in the small intestine and associated with a low risk of developing bacterial resistance. Its efficacy on symptoms, that is superior to that of the placebo after 14 days of treatment, is however modest (delta of 9%). The effects could persist for 18 weeks after treatment discontinuation in almost one-third of patients [8]. It seems well tolerated but it is not currently available in France.

PROBIOTICS AND PREBIOTICS

Numerous studies have assessed the effect of probiotics and they are highly heterogeneous because they use different strains, with variations in doses, administration mode and duration as well as main objectives studied, making any comparison or pooled analysis difficult. The strains are tested alone or in combination, generally with Lactobacilli and bifidobacteria.
There may be publication biases with an overrepresentation of small positive studies. With these reservations, they support a significant effect of probiotics on symptoms and quality of life compared to placebo. A short treatment duration seems more effective. Among the studies with the best quality criteria, bifidobacteria such as Bifidobacterium infantis 35624 are more effective; in other studies, probiotics combining several strains seem interesting [3].
Probiotics, that are available without prescription and are usually well tolerated, are not always marketed in the form with which their efficacy has been demonstrated. In addition, their efficacy and safety in case of prolonged use should be assessed in well-conducted studies. The data on the benefit of prebiotics in IBS are too limited to draw conclusions.

FECAL TRANSPLANTATION

Fecal transplantation, currently used in some cases of Clostridium difficile colitis, could allow correcting dysbiosis and improving patient condition. To date, only encouraging preliminary studies conducted in adults and assessing its efficacy in IBS are available and randomized controlled studies with a long-term follow-up are needed to confirm the efficacy and safety of this type of treatment in a pathology without vital risk [9].

IS PEDIATRIC IBS DIFFERENT FROM ADULT IBS? [10]

- It is defined by abdominal pain at least 4 days per month associated with defecation and/or a change in stool consistency and/or frequency for at least 2 months (Rome IV criteria)
- It is the main cause of recurrent abdominal pain in children
- Dysbiosis, an increased prevalence of bacterial overgrowth in the small intestine and a risk of IBS after acute gastroenteritis have also been described in children
- A low-FODMAP diet and probiotics seem to be effective in children

DEFINITION

Prebiotic: ingested product that stimulates the growth of bacteria already present in the host and beneficial to the health of the individual

CONCLUSION

There are many arguments supporting the role of changes in gut flora composition and/or metabolic activities in the various pathophysiological mechanisms described in IBS. These results open new therapeutic perspectives, with the possibility of reducing patient symptoms through treatments with a direct or indirect effect on the gut microbiota

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COMMENTED ARTICLE
ADULTS' SECTION

By Prof. Harry Sokol
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Saint-Antoine Hospital, Paris, France

FECAL MICROBIOTA TRANSPLANTATION FROM PATIENTS WITH IRRITABLE BOWEL SYNDROME TO MICE RESULTS IN IMPAIRED INTESTINAL FUNCTIONS AND BEHAVIOR

From the original article by De Palma et al. (Sci Transl Med 2017) [1]

Irritable bowel syndrome (IBS) is a common disorder characterized by an impairment of intestinal functions often associated with anxiety. Although changes in gut microbiota composition have been documented, their relevance to the clinical symptomatology of IBS remains unknown. To assess the functional role of the commensal bacterial microbiota in IBS, the authors have colonized axenic mice (free of microbiota) with the fecal microbiota of healthy subjects or patients with diarrheal IBS (IBS-D), with or without anxiety, and have monitored intestinal functions and behavior in transplanted mice. In recipient mice, the microbiota profiles were grouped according to human donors. Mice that received a fecal microbiota from IBS-D patients had a taxonomic microbial composition similar to that of mice that received a fecal microbiota from healthy subjects. However, IBS-D mice had a different serum metabolomic profile. Mice with a IBS-D microbiota had an accelerated gastrointestinal transit, a dysfunction of the intestinal barrier, an activation of innate immunity and an anxious behavior. These results indicate that the gut microbiota could contribute to the intestinal and behavioral manifestations of IBS-D and suggest the potential benefit of microbiota-targeted treatments in IBS patients.

WHAT DO WE KNOW ABOUT THIS TOPIC?

The microbiota has an impact on the intestinal physiology, in particular by modulating the host intestinal motility and barrier and energy metabolism. Disturbances of the normal gut microbiota play a role in intestinal inflammation and visceral sensitivity. The influence of the gut microbiota extends well beyond the bowel, and its role has been shown in metabolic, liver and even neuropsychiatric disorders. The recent demonstrations of the ability of the gut microbiota to influence brain development, neurochemistry and cognitive and emotional functions have increased the interest in the gut microbiota-brain axis [2]. This axis has been involved in the pathogenesis of several bowel, neurological and psychiatric disorders, but the potential role of the microbiota has only been suggested by association studies between the phenotype and changes in microbiota composition.

IBS is a common bowel disorder characterized by chronic abdominal pain accompanied by impaired intestinal transit in the absence of identifiable structural anomaly. IBS patients with diarrhea are individualized in a recognized subgroup (IBS-D). IBS is

KEY POINTS

- Transferring the fecal microbiota from IBS-D patients to mice results in an accelerated intestinal transit and increased intestinal permeability compared to mice that received a microbiota from healthy subjects
- Transferring the fecal microbiota from IBS patients with anxiety to mice results in increased anxiety compared to control mice
- The microbiota is directly involved in the digestive and neuropsychiatric symptomatology of diarrheal IBS, at least in some patients

commonly accompanied by psychiatric comorbidities such as anxiety, and it is considered by some as a disorder of the gut-brain communication [3]. A large number of studies have reported changes in gut microbiota composition, stability and metabolic activity, at least in IBS subtypes compared to healthy subjects. A reduced abundance of Bacteroidetes, Actinobacteria and Faecalibacterium spp., along with an increase in Firmicutes, Lachnospiraceae, Enterobacteriaceae or Gammaproteobacteria is frequently reported, particularly in patients with IBS-D [4].

WHAT ARE THE MAIN RESULTS OF THIS STUDY?

The stools of 5 healthy subjects and 8 patients with IBS-D, including 4 with moderate anxiety, have been used to colonize axenic mice (10 recipient mice per donor). The gastrointestinal transit and behavior have been assessed 3 weeks later. The microbiota of patients and mice with IBS was overall slightly different from that of control subjects and mice. Nevertheless, several statistically significant differences were individualized with a strong association between the IBS status and bacteria belonging to the Lachnospiraceae and Bacteroidaceae families and between the "healthy" status and bacteria belonging to the Desulfovibrionaceae and Rikenellaceae families. Interestingly, the authors have shown an accelerated intestinal transit (Figure 1) and an impaired intestinal barrier (with increased permeability, Figure 2) in mice with an IBS-D microbiota compared to control mice. In addition, mice that received a microbiota from IBS-D patients with anxiety also showed signs of anxiety compared to the other mice (Figure 3). Finally, a metabolomic analysis of the serum showed significant differences between IBS-D and control mice. Seven metabolites were particularly discriminating: O-acetyl-L-carnitine and several types of lysophosphatidylcholine were increased in IBS-D mice, while phosphatidylserine metabolites were reduced compared to control mice.
These results therefore suggest that microbiota abnormalities are responsible, at least partially, for impairments of intestinal and neuropsychiatric functions observed in IBS patients.

WHAT ARE THE PRACTICAL CONSEQUENCES?

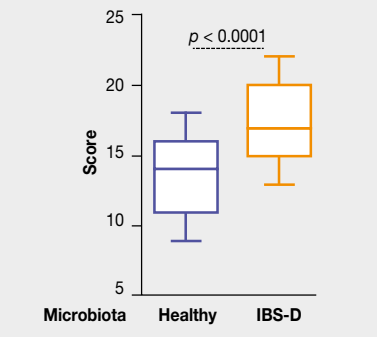
This study has shown that the microbiota is directly involved in the digestive and neuropsychiatric symptomatology of diarrheal IBS, at least in some patients. This suggests that the microbiota may be a therapeutic target in this disease and opens the possibility of a rational approach to explore this assumption. Furthermore, this publication also suggests that the gut microbiota could be used to stratify IBS patients into subgroups with potentially different therapeutic responses. This could contribute to the evolution towards personalized medicine.

CONCLUSION

The microbiota is directly involved in the digestive and neuropsychiatric symptomatology of diarrheal IBS, at least in some patients. In this disease, the microbiota could be a therapeutic target and could also be used to stratify patients for personalized medicine.

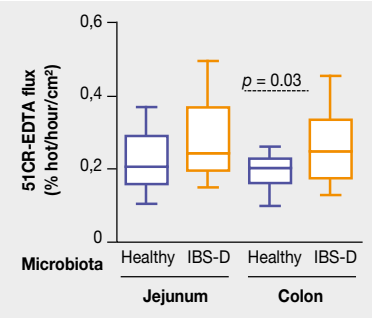
▼ FIGURE 1

Gastrointestinal transit in mice colonized with the fecal microbiota from healthy subjects (n = 53) and IBS-D patients (n = 88).



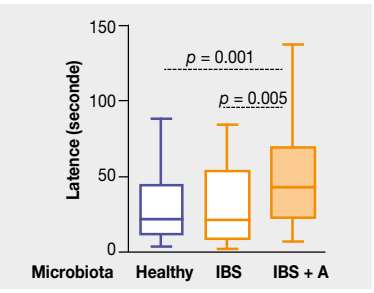
▼ FIGURE 2

The paracellular permeability was measured in the jejunum and colon in mice colonized with the fecal microbiota from healthy subjects (n = 10) and patients with irritable bowel syndrome (IBS) (n = 10).
The transport of macromolecules was assessed by adding a 51Cr-EDTA radioactive probe on the luminal side of a Ussing chamber, and the percentage detected on the serous side was measured.



▼ FIGURE 3

Anxiety was assessed using the step-down test in mice colonized with the fecal microbiota from healthy subjects (n = 53), IBS-D patients without anxiety (IBS; n = 48) and IBS-D patients with anxiety (IBS + A; n = 40).
Each mouse was placed at the center of a platform placed in height, and the latency time before the descent of the platform was measured.



IBS-D: Diarrheal Irritable Bowel Syndrome

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COMMENTED ARTICLE
CHILDREN' SECTION

NATURAL HISTORY OF THE GUT MICROBIOME IN INFANTS AND EFFECT OF ANTIBIOTIC TREATMENT ON BACTERIAL STRAIN DIVERSITY AND STABILITY

From the original article by Yassour et al. (Science Translational Medicine 2016) [1]

The gut microbial community is dynamic during the first 3 years of life, before stabilizing to an adult-like state. However, little is known about the impact of environmental factors on the developing human gut microbiome. The authors report a longitudinal study of the gut microbiome based on DNA sequence analysis of monthly stool samples and clinical information from 39 children, about half of whom received multiple courses of antibiotics during the first 3 years of life. Whereas the gut microbiome of most children born by vaginal delivery was dominated by Bacteroides species, the four children born by cesarean section and about 20% of vaginally born children lacked *Bacteroides* in the first 6 to 18 months of life. Longitudinal sampling, coupled with whole-genome shotgun sequencing, allowed detection of strain-level variation as well as the abundance of antibiotic resistance genes. The microbiota of antibiotic-treated children was less diverse in terms of both bacterial species and strains, with some species often dominated by single strains. In addition, M. Yassour *et al.* observed short-term composition changes between consecutive samples from children treated with antibiotics. Antibiotic resistance genes carried on microbial chromosomes showed a peak in abundance after antibiotic treatment followed by a sharp decline, whereas some genes carried on mobile elements persisted longer after antibiotic therapy ended. Those results highlight the value of high-density longitudinal sampling studies with high-resolution strain profiling for studying the establishment and response to perturbation of the infant gut microbiome.

By Prof. Emmanuel Mas
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WHAT DO WE KNOW ABOUT THIS TOPIC?

Gut microbiota composition takes place during the first years of life and reaches an "adult" profile around the age of 3. Different factors influence this composition, including the mode of delivery (cesarean section or vaginal delivery), the initial feeding (breastfeeding or infant milk formula) or the type of diet following diversification.
The use of antibiotics, especially during pregnancy or the first months of life, has an effect on the subsequent development of the child and on the occurrence of various diseases later in life.

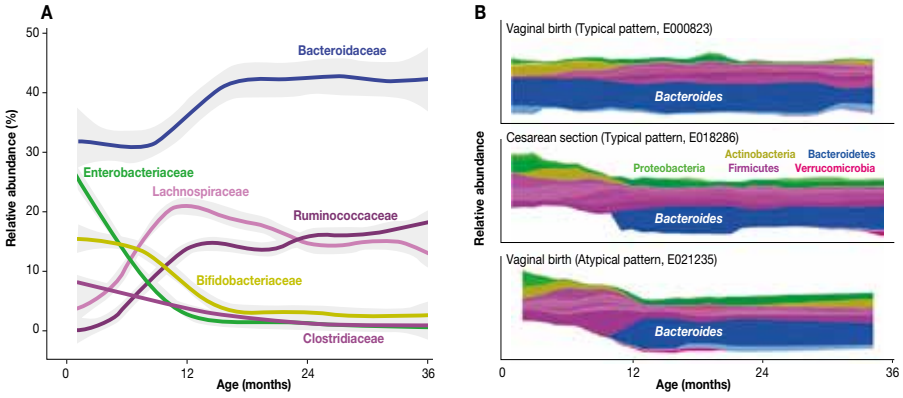
WHAT ARE THE MAIN RESULTS OF THIS STUDY?

This is a longitudinal study in which the stools of 39 Finnish infants aged 2-36 months were collected. The authors analyzed gut microbiota composition according to different parameters (mode of delivery, type of feeding, use of antibiotics).
The authors have thus determined the relative abundance of the main bacterial families during these 3 years (Figure 1A). Some families are present at the age of 2 months such as Enterobacteriaceae (25%), Bifidobacteriaceae (15%) and Clostridiaceae (8%) and then decrease while others are almost

▼ FIGURE 1

Characteristics of the gut microbiota in infants.

A. Evolution of bacterial families in 39 infants during the first 36 months of life (shadows correspond to 95% confidence intervals).
B. Profiles representative of 3 children according to the mode of delivery.



absent such as Lachnospiraceae (4%) and Ruminococcaceae (0%) and then increase. The gut microbiota of an infant develops continuously; its compositions are closer for a given individual at two successive times than between different individuals of the same age.

The members of the Bacteroides genus are absent from the gut microbiota of the 4 newborns born by cesarean section but also of 7 out of 35 infants born vaginally (Figure 1B). The species of the Bifidobacterium genus are more abundant in these infants with low amounts of Bacteroides, even in those born by cesarean section.

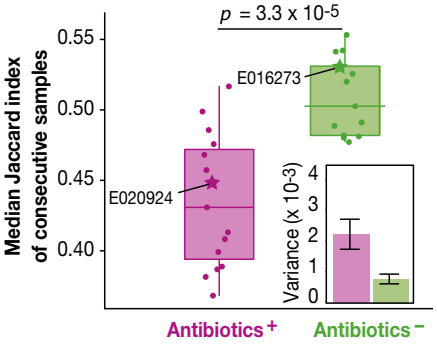
Infants treated with antibiotics have a less wealthy gut microbiota, with many species dominated by a single strain ($p = 1.38 \times 10^{-9}$). Antibiotics have an effect on the diversity of some strains (Bifidobacterium fragilis) and not on others (Bifidobacterium vulgatus). The short-term stability of the gut microbiota is decreased in children treated with antibiotics and with a greater variability (Figure 2). The study of antibiotic resistance genes has shown a rapid effect (increase and then decrease) during antibiotic treatments for genes encoded by chromosomes and a more lasting effect for genes encoded by episomes, probably due to an easier interspecies spreading of episomes. It should be noted that 11 out of 39 children were carriers of antibiotic resistance genes, before any antibiotic treatment, from the age of 2 months.

KEY POINT

The species of the Bacteroides genus are absent in the first 6-18 months of life in children born by cesarean section but also in 20% of children born vaginally; gut microbiota diversity is decreased in these children

▼ FIGURE 2

Stability of the gut microbiota in infants.
Stability (Jaccard index) has been calculated between all consecutive and separated samples according to the antibiotic treatment (median, 25th and 75th percentiles). The insert corresponds to the variance in the two groups.



WHAT ARE THE PRACTICAL CONSEQUENCES?

This prospective study provides interesting information on the implementation of the gut microbiota during the first 3 years of life. It shows the importance, in the first 6 months of life, of the "low Bacteroides" profile present in all children born by cesarean section but also in 20% of children born vaginally. In this group, the bacterial diversity is lower, even at the age of 36 months, regardless of the mode of delivery.
Gut microbiota diversity is decreased in children treated with antibiotics. Although the gut microbiota returns to its balanced state within the following month, longer-term effects cannot be excluded, in particular via some antibiotic resistance genes. However, the effects of antibiotics were not reproducible, even after analysis of each class of antibiotics.

KEY POINT

Antibiotics modify the gut microbiota

Antibiotic resistance genes may be present before treatment and persist for longer or shorter periods

CONCLUSION

This study shows the interest of studying longitudinally the development of the gut microbiota and the factors that may influence it. Children treated with antibiotics have a less diversified and less stable gut microbiota than those who were not

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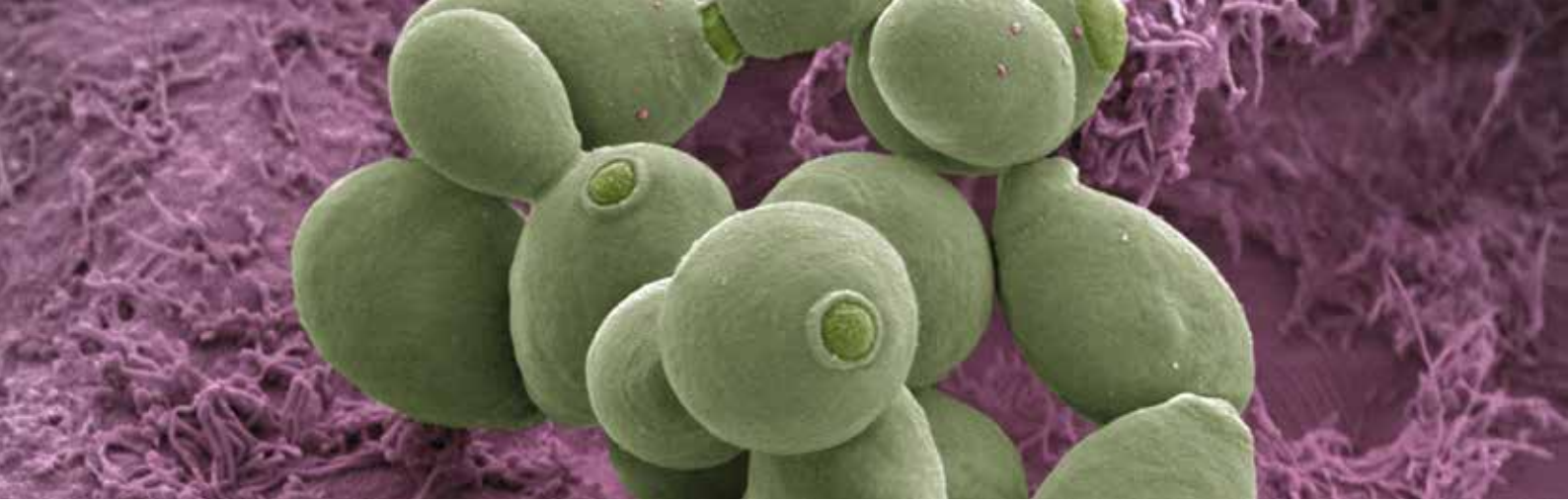

LITERATURE SELECTION

A NEW MECHANISM OF ACTION FOR THE PREVENTION OF ANTIBIOTIC ASSOCIATED DIARRHEA WITH SACCHAROMYCES BOULARDII CNCM I-745: INTESTINAL MICROBIOTA RESTORATION

By Prof. Ener Cagri DINLEYICI
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Since their discovery, millions of doses of antibiotics have been used in the world both in children and adults. Antibiotic Associated gastrointestinal symptoms, mainly Diarrhea (AAD), are well-described clinical conditions associated with antibiotic use.

AAD is defined as a diarrhea associated with antibiotic exposure, either while on antibiotics or for up to 8 weeks after antibiotic discontinuation [1]. Recent reports show that probiotics have beneficial effects on the prevention of AAD. Saccharomyces boulardii CNCM I-745 is one of the recommended probiotic for the prevention of AAD by the Yale and Harvard Working Group, (Recommendations for Probiotic Use in 2015 [2]). Some mechanisms of action are described (interference with bacterial adhesion, inactivation of toxins and other virulence factors, and enhancement of mucosal immune function) for the prevention of AAD; however, there is limited information about the probiotic use with antibiotics on intestinal microbiota composition [3]. Kabbani et al. [3] published their recent study about the comparison of intestinal microbiota composition comparing amoxicillin-clavulanate alone and amoxicillin-clavulanate with Saccharomyces boulardii CNCM I-745 among healthy adults. Regarding to their study results, antibiotic use reduced Roseburia and increased Escherichia, Parabacteroides, and Enterobacter.

Microbiota alterations reverted toward baseline but were still not completely resolved two weeks after completion of antibiotic administration. With the addition of Saccharomyces boulardii CNCM I-745 to the antibiotic treatment, they observed less pronounced microbiota shifts and less overgrowth of Escherichia. Gastrointestinal symptom rating scale (GSRS) scores was significantly lower (mainly diarrhea-GSRS subscore) in participants receiving antibiotics with Saccharomyces boulardii CNCM I-745 than in participants receiving antibiotics alone. The concomitant use of Saccharomyces boulardii CNCM I-745 with amoxicillin-clavulanate microbiota is accompanied by less microbiota modifications and by a decrease of AAD rate.

The potential beneficial effects of probiotics on intestinal microbiota composition during antibiotic treatment might result with the reduced long term complications associated with antibiotic use as well as prevention of AAD. Further studies should explore the precise mechanisms of action of probiotics on intestinal microbiota composition and function.

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NEW HOPES FOR OBESITY AND TYPE 2 DIABETES

NEXT GENERATION PROBIOTIC RESEARCH IN MICROBIOTA TARGETED THERAPY ERA

Obesity and type 2 diabetes are important health problems worldwide. Recent evidence indicates that the gut microbiota plays a key role in the pathophysiology of obesity and type 2 diabetes. Both are characterized by low-grade inflammation, gut barrier disruption and specific changes in the gut microbiota composition. Patrice Cani and colleagues had previously isolated a mucin-degrading bacterium (Akkermansia muciniphila), which is an important microorganism in metabolic health [1-3].

The presence of A. muciniphila inversely correlates with body weight in humans and regulates the cross-talk between the host and the gut microbiota Experimental studies showed that treatment with A. muciniphila reversed high-fat diet-induced metabolic disorders, including fat-mass gain, metabolic endotoxemia, adipose tissue inflammation, and insulin resistance [1-3]. Cani and de Vos group [4] recently showed that a pasteurized version (this formulation increased the effectiveness) of A. muciniphila could reduce fat mass development, insulin resistance, and dyslipidemia in mice. Moreover, the pasteurized bacterium modulated both the host urinary metabolome and intestinal energy absorption. These effects are related with Amuc_1100 protein that is isolated from the outer membrane of A. muciniphila.

The Amuc_1100 protein blocks the passage of toxins into the blood, reinforces the immune defenses of the intestine, and ameliorates leaky gut syndrome, for instance. This report also showed the results of live or pasteurized A. muciniphila use in human population with obesity and metabolic syndrome; it seems safe in individuals with excess body weight.

Obesity and type 2 diabetes are multifactorial diseases and it is difficult to resolve these problems with single bacteria formulation; however, A. muciniphila seems to have beneficial effects on metabolic dysfunction.

Further human studies in the near future will show the potential benefits of this bacteria and the Amuc_1100 protein in patients with metabolic syndrome.

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QUALITY CONTROL

AN IMPORTANT "ADDITIONAL" CRITERIA FOR PROBIOTIC DEFINITION

Probiotics are generally defined as follows: "Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit to the host".
There are some criteria for the definition of probiotics, including being present in a sufficient number by the end of the shelf-life, resisting to acid and bile, colonizing the gut, or having clinical trials which show the clinical benefits on specific conditions.

Numerous probiotic products are available worldwide (food, drug, food supplement, medical food); however, the identification of the product label strains is a problematic issue.
In April 2017, the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN), Working Group for Probiotics and Prebiotics, published their recommendations on "quality control" of probiotics per the published results on quality assessment of the probiotic products from different countries [1].

ESPGHAN reports showed common inconsistencies and deviations from product label, misidentified/ misclassified strains, containing non-claimed strains, diminished number of viable colonies and/or decreased functional properties, and the presence of contamination.

KEY POINT

ESPGHAN working group summarized its recommendations for probiotic products:

- precise identification of microorganisms to the strain level
- differentiation of probiotic products intended to improve otherwise normal diet in the healthy population from drug-like probiotic preparations prescribed for specific clinical situations/indications which approved by clinical trials
- systematic quality controls and publication of the results by the authorities for viability and strain-level identification
- performing quality control in certified laboratories utilizing validated and standardized methodology under the auspices of the respective regulatory agencies
- mandatory evaluations for probiotics used in vulnerable populations such as neonates, infants and children
- reporting adverse events which are potentially related to probiotic products

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A NEW "THROW A CURVE" STUDY

DELIVERY MODE'S EFFECTS ON INTESTINAL MICROBIOTA COMPOSITION DURING THE EARLY LIFE PERIOD

The composition of intestinal microbiota is influenced by various factors and delivery mode is a well-defined one. Previous studies have shown a lower diversity and lower abundance of intestinal microbiota composition during early life in infants born by cesarean section. Dominguez-Bello and colleagues [1] showed Lactobacillus, Prevotella and Sneathia species are dominant in the intestinal microbiota of infants delivered vaginally while Staphylococcus species have been identified as the main gut microbiota in infants born by cesarean section.
A recent study of Hill and colleagues [2] published in 2017, confirms previous results and shows that delivery mode and gestational age have both significant effects on early neonatal microbiota composition.

Contrary to all previous findings, in March 2017, Chu et al. [3] published their studies in Nature Medicine and mentioned that within the first 6 weeks of life, the infant microbiota undergoes substantial reorganization, which is not primarily driven by the mode of delivery.
They enrolled 81 pregnant women for longitudinal sampling though 6 weeks after delivery, and recruited second matched cross sectional cohort including 81 pregnant women for sampling once at the time of delivery. Stool, oral gingiva, nares, skin and vagina samples were evaluated with whole-genome shotgun sequencing for the composition and function of the neonatal and maternal microbiota.
They showed minor variations in oral gingiva, nares and skin microbiota composition that are related with C/S delivery.
However, the delivery mode has no effect on the meconium microbiota composition and intestinal microbiota composition at 6 weeks of life. Also, there are no functional differences for intestinal microbiota related with delivery mode. This is the largest clinical trial that is shown; there are no differences between newborns delivered vaginally or by cesarean section. Difference between the results of previous studies and recent ones should be extensively evaluated for other potential factors.

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CONGRESS REVIEW

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FOCUS ON THE GUT SUMMIT 2017

GUT MICROBIOTA FOR HEALTH WORLD SUMMIT

MARCH 2017

PARIS, FRANCE

GUT-BRAIN AXIS: FROM MURINE MODELS TO CLINICAL TRIALS

A workshop has allowed summarizing recent developments on the physiological bases and clinical perspectives related to the gut microbiota-brain interactions. In particular, it has been shown that transferring the gut microbiota from patients with irritable bowel syndrome (IBS) to mice results in equivalent symptoms and a pro-inflammatory state [1]. Therapeutically, an unpublished clinical study by Pinto Sanchez et al. has suggested that the administration of Bifidobacterium longum improves depression scores and digestive symptoms of IBS patients by activating the brain regions controlling emotions.
A first therapeutic hope to be confirmed!

MICROBIOTA, CHINESE MEDICINE AND TYPE 2 DIABETES

Dr. Liping Zhao in Shanghai has investigated whether the Gegen qinlian decoction (GQD) that is used in traditional Chinese medicine for more than 2,000 years in many diseases, including type 2 diabetes, could influence the gut microbiota [2]. In a randomized, controlled, double-blind clinical trial, his team has shown that the GQD modifies the gut microbiota in a dose-dependent manner, in particular with an enrichment of Faecalibacterium prausnitzii. These microbiota changes occur before patient clinical improvement and are associated with improved glucose tolerance and glycated hemoglobin (HbA1c).
The "experience-based medicine" thus begins to reveal its secrets!

GUT MICROBIOTA AND CELIAC DISEASE: TOWARDS NEW THERAPEUTIC PERSPECTIVES

Celiac disease is typically a condition in which the genetic susceptibility (HLA D2 and DQ8) and environmental factors (exposure to gluten) act in synergy. However, these two factors do not

explain everything because the major part of the population is exposed to gluten and 30% of the population have this genetic susceptibility.

Other environmental factors should therefore be investigated to explain why some individuals get sick and others do not. In an interesting study, Caminero et al. have shown that the bacteria present in the small intestine play an important role. Indeed, Pseudomonas aeruginosa, a bacterium, present in the "dysbiotic" duodenum of patients, has proteolytic properties that hydrolyze gluten in "toxic" peptides to the intestinal mucosa, while some lactobacilli degrade these peptides produced by P. aeruginosa by "detoxifying" them [3].

Thus, the modulation of the gut microbiota could represent an adjuvant to the strict gluten-free diet that is difficult to follow by patients in the long term.

MODULATION OF THE GUT MICROBIOTA: INCREASINGLY PRECISE

Bernd Schnabl, San Diego, United States, studies (alcoholic or non-alcoholic) hepatic steatosis in which intestinal dysbiosis is well documented and for which many modulatory treatments of the gut microbiota have been proposed (in animal models but also in humans) based on prebiotics, probiotics, antibiotics and fecal microbiota transplantation. But when looking more carefully the metabolic consequences of dysbiosis caused by alcohol ingestion such as the reduced production of short-chain fatty acids (butyrate and propionate) or the increased secretion of bile acids, more precise therapeutic approaches are proposed: For example, by using butyrate-producing probiotics [4] or by modifying bile acid composition through administration of FXR (Farnesoid X receptor) agonist [5]. As observed, the therapeutic approaches of the microbiota become clearer…

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NEWS

RELEASED

REFERENCE BOOK ON THE MICROBIOTA

The knowledge around the gut microbiota is exponentially booming, conferring the status of a complete virtual organ to the microbiota.
The book Gut microbiota: A full-fledged organ, coordinated by Philippe Marteau (Hepatology, Gastroenterology and Nutrition department, APHP, Saint-Antoine Hospital, Paris) and Joël Doré (Research Director, Scientific Head of the MétaGénoPolis service unit, INRA, Jouy-en-Josas) and published in June 2017 by John Libbey Eurotext, invites you to discover the current state of this knowledge. This is the fourth book on the topic whose edition is sponsored by BIOCODEX, with the first published more than 30 years ago, in 1984!
BIOCODEX thus confirms its key role as a referring laboratory in spreading the knowledge on the gut microbiota.

The book is available in English and French.
For further information: www.biocodexmicrobiotainstitute.com

Gut microbiota:
A full-fledged organ
352 pages - 33 chapters - 45 authors
John Libbey Eurotext, 2017

MEETINGS

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