GUT MICROBIOTA
RESEARCH & PRACTICE
edited by ESNM

YEAR AT A GLANCE

A selection of content from the
Gut Microbiota for Health 2023

February 2024

www.gutmicrobiotaforhealth.com

TABLE OF CONTENTS

EDITORIAL 3

SELECTED CONTENT FROM GUTMICROBIOTAFORHEALTH.COM

Diagnosing and targeting intestinal barrier dysfunction: from bench to bedside

- In which circumstances is intestinal permeability increased and what can be done to improve it? 7
- Learning about the gut barrier's essential role to our health 10

Gut mycobiota interactions with the host immune system and cancer

- The role of the gut mycobiota in influencing the immune system and inflammation-related diseases 11
- Cancer and microbiome: newsflash on epidemiology, fungi in etiology, and microbiome-derived markers for diagnosis 14
- The fascinating world of gut fungi and its relevance for health 17

Diet, probiotics and emerging therapeutic targets in IBD

- Which dietary components should be promoted, and which ones should be limited in inflammatory bowel disease? 20
- Is dietary fiber beneficial or deleterious for patients with IBD? 21
- What do we know about the role of probiotics for IBD? 24
- Study identifies a role for bacterial proteases in Crohn's disease 27

Probiotics and fecal microbiota transplantation: current status for gastrointestinal conditions, vaginal infections and weight loss

- Diagnosing IBS and targeting gut microbiota and metabolites to improve symptoms 30
- Can probiotics aid in treating bacterial vaginosis and vulvovaginal candidiasis? 34
- Are we ready to target the gut microbiota for obesity and weight management? A journey from bench to bedside 38
- Fecal microbiota transplantation: From clinical trials to market, where are we now? 41

EDITORIAL

Hervé Blottière
Year at a glance editorial head

Hervé Blottière is a Research Director at the French National Research Institute for Agriculture, Food and Environmental (INRAE). His areas of research focus on understanding the symbiosis between gut microbiota and its host in health and disease and decipher molecular mechanisms to develop therapeutic tools to restore symbiosis in chronic diseases.

Intestinal barrier dysfunction in gastrointestinal health and disease

The intestinal barrier acts as a dynamic interface between luminal food, commensal and pathogenic microorganisms, and the gastrointestinal tract. Its main function involves the selective regulation of the traffic of molecules across the gut to differentiate self from non self. An altered gut microbiome composition and function may lead to increased intestinal permeability, which is a major determinant of low-grade endotoxaemia that has been observed in patients with disorders of gut-brain interaction such as irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) and cardiovascular events[1,2].

While an altered intestinal permeability is involved in many pathological conditions, "leaky gut" is a buzz term used to refer to a fictitious syndrome that explain vague gastrointestinal and extraintestinal symptoms that has led to countless therapeutic approaches that lack a solid scientific basis. However, most tools to measure intestinal permeability have not been validated yet and it is unknown whether intestinal barrier dysfunction is a primary event or a bystander phenomenon in digestive and systemic diseases.

Dietary and pharmacological interventions might improve gut barrier dysfunction by upregulating junction proteins and thereby lower circulating lipopolysaccharide levels. Dietary patterns and components associated with potential to have positive effects on overall gut integrity include the Mediterranean diet, omega-3 fatty acids, fiber, prebiotics, polyphenols, some probiotics, microbial metabolites, glutamine, vitamin D and zinc. In contrast, saturated fats, emulsifiers, and alcohol increase the leakiness of intestinal barrier[3].

Commensal fungi in intestinal health, immunity, and cancer

While research into the role of gut microbiome in influencing the immune system has mainly focused on bacterial communities, recent studies have focused on how fungi (the mycobiome) is actively involved in shaping host digestive and immune homeostasis. What we know so far about the role of the gut mycobiome in host immune system and intestinal inflammation comes mainly from patients with IBD and IBS. For instance,

Debaryomyces, a fungus that is common in food, is more abundant in individuals with IBD and prevents mucosal healing[4]. Recent findings also suggest the gut mycobiome is involved in abdominal pain and visceral hypersensitivity seen in IBS, through mast cell recognition of intestinal fungi that may lead to histamine and tryptase release and subsequent barrier dysfunction and visceral hypersensitivity[5]. However, technical and biological challenges may limit full understanding of host-fungi interactions.

The role of the mycobiome on cancer phenotypes has also been explored. Two recent studies have found strong links between the prevalence of fungal DNA and a variety of human cancers. These findings reveal that fungi are ubiquitous across all major human cancers and that some mycobiome profiles can help predicting survival of cancer[6,7].

Considering the involvement of the mycobiome in intestinal and immune-related diseases, potential opportunities to target fungi emerge. Evidence of human interventional studies has shown that specific strains of *Saccharomyces boulardii* and *S. cerevisiae* may help managing antibiotic-associated diarrhea and IBS, preventing *Clostridioides difficile* (CDI) infection, and alleviating abdominal and improving quality of life in patients with IBS (global IBS symptoms and constipation-predominant IBS)[8].

Diet, probiotics, and emerging therapeutic targets in IBD

2023 has been a productive year for gut microbiome research in IBD. For the first time, researchers showed that changes in the gut microbiome precede Crohn's disease onset by up to five years, supporting a causal role of gut microbiome alterations in IBD[9]. Mice findings also revealed that proteases of bacterial origin are involved in Crohn's disease, like the microbial proteolytic imbalance previously involved in ulcerative colitis[10]. Beyond bacterial proteases, the immunomodulation of the colonic γδ T cell lymphocytes subset by intestinal epithelial cells could also lead to new therapies of IBD[11].

The role of diet in the onset and development of IBD has gained scientific interest in recent years, due to the role of some components of the diet with a proinflammatory potential in leading to changes in the gut microbiota and immunity, which can fuel mucosa IBD-related lesions. Observational studies suggest that in IBD it would be prudent to reduce the content of omega-6 polyunsaturated fatty acids in the diet and increase the omega-3 polyunsaturated fatty acids and olive oil along with promoting a diversity of fruit, vegetables and whole grains with some dairy intake may be protective for IBD[12]. While patients with IBD have been traditionally advised to follow a low-fiber diet to minimize symptoms, recent evidence suggest that the proinflammatory effect of fiber depends on the fiber type, individual immune status, and the fermentative capacity of the gut microbiota[13]. Regarding the role of probiotics in IBD, certain probiotics have shown to be effective and safe for the induction and maintenance of mild to moderately active ulcerative colitis, while the available evidence of probiotics for Crohn's disease is uncertain[14].

Probiotics and fecal microbiota transplantation for gastrointestinal conditions and beyond

The use of gut microbiome-modulating treatments, i.e. probiotics and fecal microbiota transplantation (FMT), is gaining interest in gastrointestinal conditions and other ailments that apparently are not connected to the gut. Some combinations of probiotics or strains may help managing IBS symptoms through targeting the gut microenvironment (microbiota and metabolites)[15]. Rather than using "one-size-fit all" approach, it is important to recommend the right probiotic strain that has been found to be effective for specific IBS-related gastrointestinal symptoms[16]. Beyond gut health, some clinical trials also support the use of specific probiotics, taken orally or vaginally, for restoring the vaginal microbiota and managing bacterial vaginosis and vulvovaginal candidiasis.

In 2023, the U.S. Food and Drug Administration approved the first fecal microbiota product administered orally for the prevention of recurrence of CDI in adults, following antibiotic treatment for this infection[17]. In addition to CDI, FMT has been tested in randomized controlled trials for the treatment of IBD and IBS with mixed results and for extra-gastrointestinal disorders such as metabolic syndrome, hepatic encephalopathy, and graft-versus-host disease. As a live biotherapeutic

product, the benefits of FMT should be balanced with its risks that include the transmission of infectious microorganisms from donor, an increased susceptibility to diseases associated to an altered gut microbiome composition and the transmission of antibiotic resistance genes present in commensal microorganisms[18]. Beyond these safety issues, one of the most important challenges that hinder FMT access to the market is understanding and predicting underlying ecological dynamics that drive the efficacy of FMT.

Apart that aforementioned gut microbiome-targeted interventions for IBS, the findings from the Atlantis trial showing the efficacy of amitriptyline for the management of IBS in primary care are worth highlighting[19]. Neuromodulators are used as a second-line treatment for IBS if dietary modifications, laxatives, anti-diarrheal drugs, or antispasmodics fail to improve symptoms. This is the first time that amitriptyline is tested in primary care.

GMFH digital ecosystem evolution

The GMFH digital community grew this year to reach 162,000 members, including scientists, health care professionals and the general public. In 2023, the GMFH website had 780,000 website visits and that number continues to grow.

Last year's edition of the Gut Microbiota for Health World Summit took place both in person in Prague and virtually. In 2024, the event's 12th edition will take place also in an hybrid format on 23 and 24 March in Washington, DC, with an agenda that includes two keynote lectures, four plenary sessions, and two workshops sessions.

Thank you for being part of the GMFH community over the last year. Don't forget to keep in touch with our website and social media to stay updated about what's going on with gut microbiome-targeted interventions in clinical practice.

Have a Happy New Year 2024 and we are looking forward to share with you upcoming relevant advances in the gut microbiome!

References

Dunleavy KA, Raffals LE, Camilleri M. Intestinal barrier dysfunction in inflammatory bowel disease: underpinning pathogenesis and therapeutics. *Dig Dis Sci*. 2023; 68(12):4306-4320. doi: 10.1007/s10620-023-08122-w.

Violi F, Cammisotto V, Bartimoccia S, et al. Gut-derived low-grade endotoxaemia, atherothrombosis and cardiovascular disease. *Nat Rev Cardiol*. 2023; 20(1):24-37. doi: 10.1038/s41569-022-00737-2.

Camilleri M, Vella A. What to do about the leaky gut. *Gut*. 2022; 71(2):424-435. doi: 10.1136/gutjnl-2021-325428.

Jain U, Ver Heul AM, Xiong S, et al. *Debaryomyces* is enriched in Crohn's disease intestinal tissue and impairs healing in mice. *Science*. 2021; 371(6534):1154-1159. doi: 10.1126/science.abd0919.

van Thiel I, de Jonge Wj, van den Wijngaard Rm. Fungal feelings in the irritable bowel syndrome: the intestinal mycobiome and abdominal pain. *Gut Microbes*. 2023; 15(1):2168992. doi: 10.1080/19490976.2023.2168992.

Narunsky-Haziza L, Sepich-Poore GD, Livyatan I, et al. Pan-cancer analyses reveal cancer-type-specific fungal ecologies and bacteriome interactions. *Cell*. 2022; 185(20):3789-3806.e17. doi: 10.1016/j.cell.2022.09.005.

Dohlman AB, Klug J, Mesko M, et al. A pan-cancer mycobiome analysis reveals fungal involvement in gastrointestinal and lung tumors. *Cell*. 2022; 185(20):3807-3822.e12. doi: 10.1016/j.cell.2022.09.015.

World Gastroenterology Organisation. Probiotics and prebiotics. February 2023. Available on: https://www.worldgastroenterology.org/guidelines/probiotics-and-prebiotics/probiotics-and-prebiotics-english

Raygoza Garay JA, Turpin W, Lee SH, et al. Gut microbiome composition is associated with future onset of Crohn's disease in healthy first-degree relatives. *Gastroenterology*. 2023; 165(3):670-681. doi: 10.1053/j.gastro.2023.05.032.

Santiago A, Hann A, Constante M, et al. Crohn's disease proteolytic microbiota enhances inflammation through PAR2 pathway in gnotobiotic mice. *Gut Microbes*. 2023; 15(1):2205425. doi: 10.1080/19490976.2023.2205425.

Dart RJ, Zlatareva I, Vantourout P, et al. Conserved γδT cell selection by BTNL proteins limits progression of human inflammatory bowel disease. *Science*. 2023; 381(6663):eadh0301. doi: 10.1126/science.adh0301.

Serrano-Moreno C, Brox-Torrecilla N, Arhip L, et al. Diets for inflammatory bowel disease: What do we know so far? *Eur J Clin Nutr*. 2022; 76(9):1222-1233. doi: 10.1038/s41430-021-01051-9.

Armstrong HK, Bording-Jorgensen M, Santer DM, et al. Unfermented β-fructan fibers fuel inflammation in select inflammatory bowel disease patients. *Gastroenterology*. 2023; 164(2):228-240. doi: 10.1053/j.gastro.2022.09.034.

Bischoff SC, Bager P, Escher J, et al. ESPEN guideline on clinical nutrition in inflammatory bowel disease. *Clin Nutr*. 2023; 42(3):352-379. doi: 10.1016/j.clnu.2022.12.004.

Goodoory VC, Khasawneh M, Black CJ, et al. Efficacy of probiotics in irritable bowel syndrome: systematic review and meta-analysis. *Gastroenterology*. 2023; 165(5):1206-1218. doi: 10.1053/j.gastro.2023.07.018.

Xie P, Luo M, Deng X, et al. Outcome-specific efficacy of different probiotic strains and mixtures in irritable bowel syndrome: a systematic review and network meta-analysis. *Nutrients*. 2023; 15(17):3856. doi: 10.3390/nu15173856.

FDA. FDA approves first orally administered fecal microbiota product for the prevention of recurrence of *Clostridioides difficile* infection. 26 April 2023. Available on:https://www.fda.gov/news-events/press-announcements/fda-approves-first-orally-administered-fecal-microbiota-product-prevention-recurrence-clostridioides

Hill C. Balancing the risks and rewards of live biotherapeutics. *Nat Rev Gastroenterol* Hepatol. 2020; 17(3):133-134. doi: 10.1038/s41575-019-0254-3.

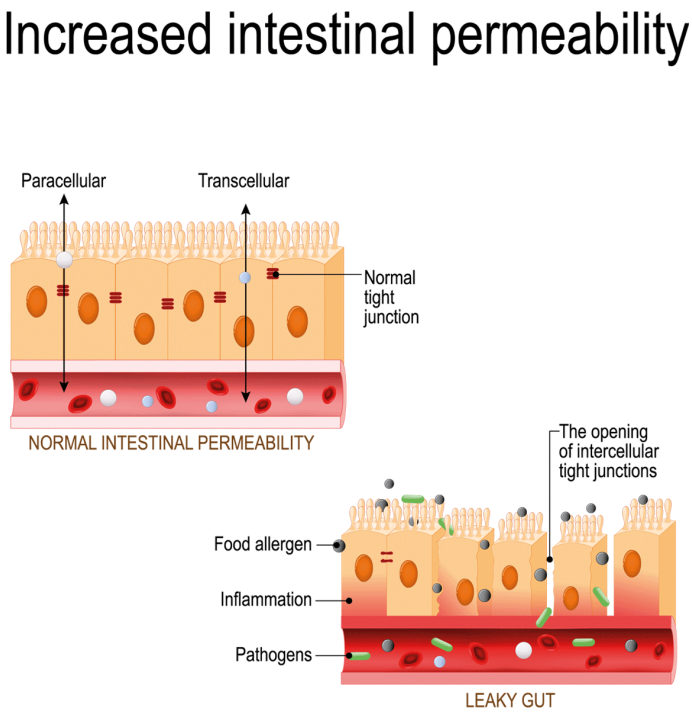
Ford AC, Wright-Hughes A, Alderson SL, et al. Amitriptyline at low-dose and titrated for irritable bowel syndrome as second-line treatment in primary care (ATLANTIS): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2023; 402(10414):1773-1785. doi: 10.1016/S0140-6736(23)01523-4.

SELECTED CONTENT

In which circumstances is intestinal permeability increased and what can be done to improve it?

Published on December 27th, 2022 by Andreu Prados

A wide range of diseases, from irritable bowel syndrome to depression, have been associated with increased intestinal permeability or 'leaky gut'. What does a leaky gut mean, how can it be diagnosed and what available dietary strategies work for managing it?



The educational content in this post, elaborated in collaboration with Bromatech, was independently developed and approved by the GMFH publishing team and editorial board.

What does increased intestinal permeability or 'leaky gut' mean?

The term 'leaky gut' is the simplistic concept used to reflect increased intestinal permeability due to a dysfunction in any of the gut barrier's components. Indeed, a leaky gut goes beyond an altered epithelial cell layer and can also affect the mucus layer and inner layer, including immune cells that are important components of the gut barrier.

Professor Giovanna Traina from the University of Perugia explained via email to GMFH editors that "a healthy intestinal barrier is essential for the maintenance of gastrointestinal health, but also for the systemic health of the host, as it is able to preserve the potential translocation of bacteria, food allergens, xenobiotics and inflammatory mediators in the systemic circulation, that may compromise the functionality of other organs."

SELECTED CONTENT

In which circumstances is intestinal permeability increased and what can be done to improve it?

Such a defect in the gut barrier may facilitate dietary and microbial antigen influx, leading to the chronic inflammation involved in the onset of modern diseases. Examples of diseases and disorders that have been linked to increased intestinal permeability include gastrointestinal disorders, enteric infections, obesity and metabolic syndrome, liver diseases, pancreatitis, autoimmune diseases and neuropsychiatric diseases. An altered intestinal barrier function can also be a result of host physiological factors (e.g., bile acids) and environmental factors (e.g., dietary components) and is not necessarily deleterious, leading to a disease phenotype.

How can you diagnose a leaky gut in your clinical practice?

Several techniques involving biopsy and urine samples have been used to assess barrier function and intestinal permeability. **While none of the available tests is without its shortcomings, the lactulose/mannitol test is the most widely employed and focuses only on the permeability function.**

"The lactulose/mannitol ratio index is highly increased in intestinal inflammation and in pathologies characterized by an increased intestinal permeability, such as Crohn's disease," acknowledges Prof. Traina. When interpreting the test's results, it is important to keep in mind that both lactulose and mannitol are metabolized by the colonic microbiota, thus cannot be used in ulcerative colitis or irritable bowel syndrome, which mostly affect the colon.

Beyond the lactulose/mannitol test, Prof. Traina stated that **the levels of fecal calprotectin,** a protein released by the activation of neutrophils, **can be measured as a marker of intestinal permeability induced by intestinal inflammation.** On the apical area in close contact with the intestinal lumen, enterocytes are linked by tight junctions and impaired intestinal permeability may result from an increase in zonula occludens proteins. However, "data in literature are not yet entirely in favor of its use, as demonstrated by recent work in which **researchers advise to be careful in considering the measurement of serum zonulin as a marker of the integrity of the intestinal barrier,"** states Prof. Traina.

Other techniques measure barrier function in a broader sense, for instance bacterial translocation of lipopolysaccharide or epithelial cell damage with assays measuring fatty acid binding protein or citrulline. The measure of bacterial metabolites such as butyrate in serum or feces is another approach, due to its role in enhancing colonic barrier function. For the most part, the techniques have been applied in an experimental setting and their application in clinical practice remains to be seen.

Is there a role for dietary interventions in reducing the leakiness of intestinal permeability?

Prof. Traina explained that various factors can lead to perturbations in the structural dynamics of microbiota and to changes in the functional characteristics of the intestinal barrier. They are environmental factors, diet, genetic defects, stress and drugs.

Within that group, diet is one of the most important in its effect on barrier function. A diet high in saturated fats, fructose, emulsifiers and alcohol ingestion, along with vitamin A deficiency and changes in diet or the microbiota that lower butyrate levels can impair barrier function and increase permeability. **Prebiotic fibers** (especially derived short-chain fatty acids), **probiotics, polyphenols, glutamine, methionine, vitamin D and zinc can, in contrast, enhance barrier integrity.** All such nutrients and dietary interventions can be ingested through food staples and supplements.

Probiotic bacteria and yeasts are being increasingly studied due to their positive effects on overall gut integrity. That is the case of the multi-strain probiotic formulation consisting of ***Lactobacillus rhamnosus, Bifidobacterium lactis and B. longum***, which has been shown in two recent ***in vitro*** studies led by Prof. Traina

SELECTED CONTENT

In which circumstances is intestinal permeability increased and what can be done to improve it?

(here; here) to preserve the integrity and functioning of the intestinal barrier from the damage caused by the lipopolysaccharide inflammatory stimulus. The findings support the notion that specific probiotics are a plausible approach to enhancing epithelial barrier function in a specific manner, but that preliminary research should be confirmed in well-designed randomized clinical trials.

It is important to understand that while improving gut barrier function is increasingly used in the clinical setting as a therapeutic goal, the evidence is not yet there to support the efficacy of a single intervention in curing a disease by restoring or improving barrier function.

Take-home messages

- A reduced barrier function with increased permeability or 'leaky gut' has been associated with intestinal and extraintestinal diseases.
- A wide range of techniques are used for assessing barrier integrity and function but each one has its own limitations that should be kept in mind when interpreting their results.
- Probiotics are among the key dietary interventions being investigated due to their potential for producing positive effects on gut integrity and thus improving intestinal permeability, which is impaired in some conditions.
- Reversing an altered intestinal barrier function may be necessary but may not be sufficient to reverse disease pathogenesis, as other factors such as immune response play a role in perpetuating the disease.

Andreu Prados

Andreu Prados holds a Bachelor of Science Degree in Pharmacy & Human Nutrition and Dietetics. Science writer special... ised in gut microbiota and probiotics, working also as lecturer and consultant in nutrition and healthcare. Follow Andreu on Twitter @andreuprados

References:

Camilleri M, Vella A. What to do about the leaky gut. *Gut*. 2022; 71(2):424-435. doi: 10.1136/gutjnl-2021-325428.

Quigley EMM. Leaky gut – concept or clinical entity? *Curr Opin Gastroenterol*. 2016; 32(2):74-79. doi: 10.1097/MOG.0000000000000243.

Wyatt J, Vogelsang H, Hübl W, et al. Intestinal permeability and the prediction of relapse in Crohn's disease. *Lancet*. 1993; 341(8858):1437-1439. doi: 10.1016/0140-6736(93)90882-h.

Ikhtaire S, Sharif Shajib M, Reinisch W, et al. Fecal calprotectin: its scope and utility in the management of inflammatory bowel disease. *J Gastroenterol*. 2016; 51(5):434-446. doi: 10.1007/s00535-016-1182-4.

Ajamian M, Steer D, Rosella G, et al. Serum zonulin as a marker of intestinal mucosal barrier function: may not be what it seems. *PLOS ONE*. 2019; 14(1):e0210728.

Bron PA, Kleerebezem M, Brummer RJ, et al. Can probiotics modulate human disease by impacting intestinal barrier function? *Br J Nutr*. 2017; 117(1):93-107. doi: 10.1017/S0007114516004037.

Sichetti M, De Marco S, Pagiotti R, et al. Anti-inflammatory effect of multistrain probiotic formulation (*L. rhamnosus, B. lactis,* and *B. longum)*. Nutrition. 2018; 53:95-102. doi: 10.1016/j.nut.2018.02.005.

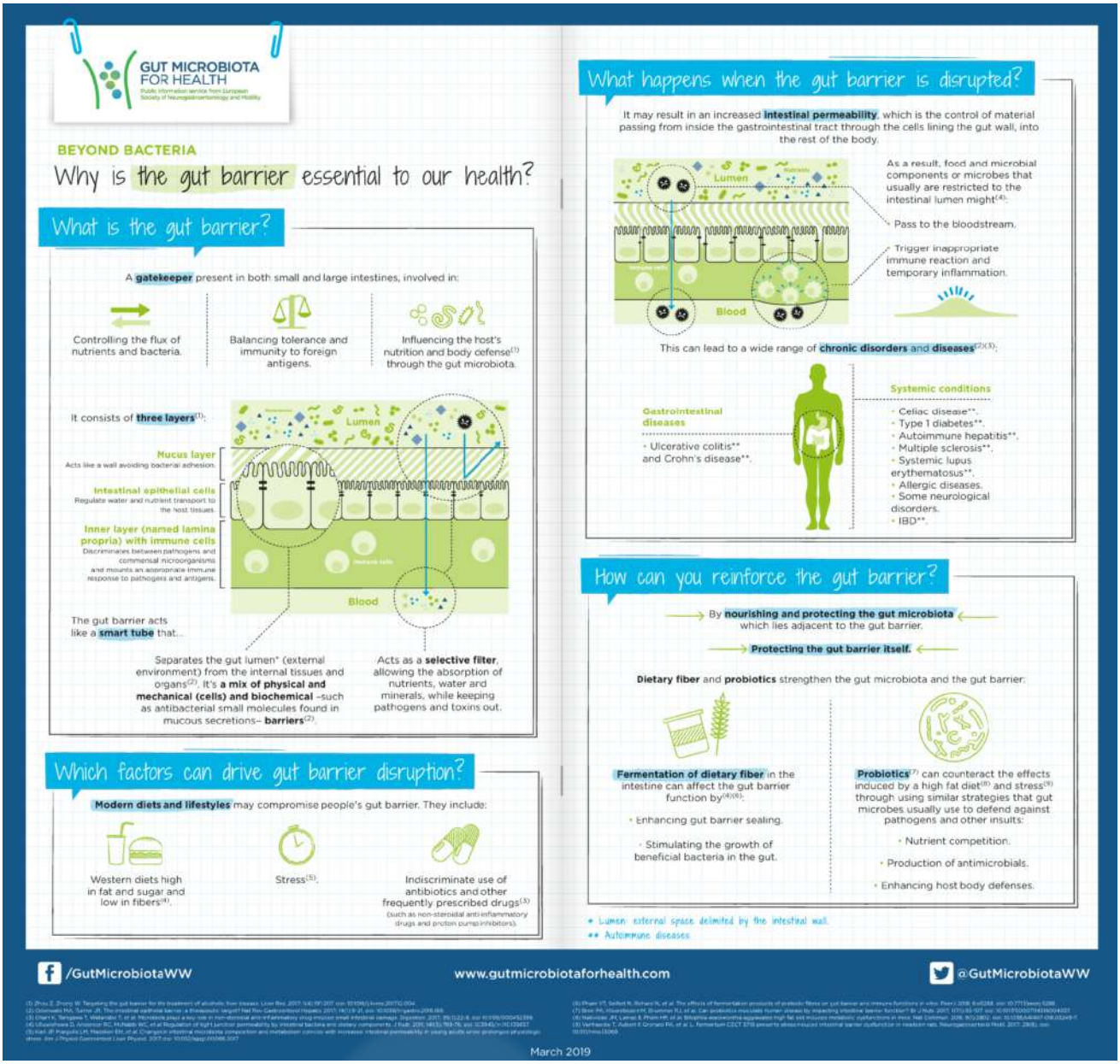
de Vito R, Conte C, Traina G. A multi-strain probiotic formulation improves intestinal barrier function by the modulation of tight and adherent junction proteins. *Cells*. 2022; 11(16):2617. doi: 10.3390/cells11162617.

SELECTED CONTENT

Learning about the gut barrier's essential role to our health

Published on March 27th, 2019 by GMFH Editing Team

The intestinal barrier is the first line of defense against pathogens and antigens in the gut, and it encompasses both physicial and chemical properties. Have a look at our infographic to learn how a dysfunctional intestinal barrier may play a role in the development of gastrointestinal diseases.



SELECTED CONTENT

The role of the gut mycobiota in influencing the immune system and inflammation-related diseases

Published on January 12th, 2023 by Andreu Prados

Gut fungi found in the lower gastrointestinal tract can influence the host immune system just like the bacterial microbiota. This article focuses on the role of the gut mycobiota in immune system homeostasis and its relevance for host health.

The educational content in this post, elaborated in collaboration with Lesaffre, was independently developed and approved by the GMFH publishing team and editorial board.

What evidence supports the importance of the gut mycobiota in immunity?

Initially, the resident mycobiota (fungal community) in the gastrointestinal tract was considered a passive component of the microbiome that could become pathogenic secondary to a disrupted intestinal milieu or a decreased immune response. However, recent research has shown that **the gut mycobiota is actively involved in shaping host digestive and immune homeostasis.**

The gut mycobiota may directly or indirectly interact with the host immune system through fungal-fungal, fungal-bacterial and fungal-host interactions. In a video interview with GMFH editors, Mathias L. Richard from the French National Institute for Agriculture, Food and Environment (INRAE) explained that the main pathway involved in gut fungi and immune system crosstalk is the C-type lectin pathway through Dectin-1, 2 and 3 receptors, among others. To a lesser extent, toll-like receptors, which are a type of pattern-recognition

SELECTED CONTENT

The role of the gut mycobiota in influencing the immune system and inflammation-related diseases

receptor expressed in innate immune cells such as dendritic cells and macrophages, are also involved in fungal detection by the immune system.

It may also be possible that metabolites or virulence factors produced by gut fungi themselves drive immune responses. For instance, that is the case of the toxin candidalysin produced by the gut commensal ***Candida albicans.*** While low levels of candidalysin are linked to a commensalism relationship between the host and ***C. albicans,*** increased candidalysin levels can lead to damage in host cells and tissues driving disease.

In the other direction, **the influence of host immunity on the gut mycobiota is also feasible.** For instance, a suppression of immune defense as a result of an immunosuppressive drug regimen or an immunocompromised status can favor the overgrowth of fungi such as ***Candida***, which otherwise remain peaceful members of the commensal gut microbiome.

The gut mycobiota emerges as a potential therapeutic target in inflammation-related diseases

Human gut mycobiota alterations and impaired immunity to intestinal fungi have been observed in patients with inflammatory diseases, which suggests that the gut mycobiota is an active player in immune-associated pathologies.

Preclinical findings in mice and observational data in humans have revealed a role for the mycobiota in gastrointestinal diseases. Indeed, **what we know so far about the role of the gut mycobiota in host immune systems and intestinal inflammation comes mainly from patients with inflammatory bowel diseases and** irritable bowel syndrome.

Active inflammation in patients with IBD promotes changes in the gut mycobiota composition, independent of the therapeutic regimen. Among the gut fungi involved, ***Candida*** species appear to be consistently associated with the progression and development of intestinal inflammation. In addition, strain-level variability rather than gut mycobiota composition alone may be an important driver of sensitivity in IBS.

The role of the gut mycobiota in inflammation-mediated diseases is also supported by the proven efficacy of yeast probiotics such as ***S. cerevisiae*** in intestinal inflammation. Despite the variability observed in mycobiota studies due to technical issues, mycobiota alterations in terms of diversity and composition have also been identified in type 2 diabetes, asthma and alcoholic liver diseases. According to Mathias L. Richard: "The main genera identified in these modifications of the gut mycobiota are ***Candida and Saccharomyces*** with, in many studies, an increase of ***Candida*** and a decrease of ***Saccharomyces.***"

Yeast probiotics for immune-related diseases

The abovementioned changes in the gut mycobiota, in the context of intestinal and extraintestinal diseases with a strengthened inflammatory response, suggest the possibility of restoring gut mycobiota as a potential target.

Yeast probiotics belonging to *Saccharomyces* genera have been widely studied as an efficacy and safety tool for managing gastrointestinal diseases, such as antibiotic-associated diarrhea and IBS, and preventing ***Clostridioides difficile*** infection. The two fungal species currently used as a probiotic in humans include very specific strains of ***S. boulardii*** and ***S. cerevisiae.***

Immune-mediated mechanisms may also be involved in the efficacy of yeast probiotics for managing gastrointestinal diseases. A resolution of inflammatory processes and gut microbiota modulation towards an increase in short-chain fatty acids such as butyrate, which have anti-inflammatory properties, have also been

SELECTED CONTENT

The role of the gut mycobiota in influencing the immune system and inflammation-related diseases

reported as putative mechanisms of action for yeast probiotics such as ***S. cerevisiae*** CNCM I-3856. "Data also show the reduction of inflammatory molecules like interleukin-8 using yeast probiotics or an improved epithelial healing, while immunological mechanisms have not yet been fully described," acknowledges Mathias L. Richard.

Watch the interview

Take-home messages

- The gut mycobiota might directly or indirectly communicate with the host immune system, shaping the development of gastrointestinal diseases such as IBD.
- Fungal dysbiosis is associated with immune-mediated diseases related to the gut (e.g., Crohn's disease and ulcerative colitis) and beyond (e.g., type 2 diabetes).
- The benefits of yeast probiotics in gastrointestinal diseases are partly mediated through immune mechanisms.

Andreu Prados

Andreu Prados holds a Bachelor of Science Degree in Pharmacy & Human Nutrition and Dietetics. Science writer special... ised in gut microbiota and probiotics, working also as lecturer and consultant in nutrition and healthcare. Follow Andreu on Twitter @andreuprados

References:

Mukherjee PK, Sendid B, Hoarau G, et al. Mycobiota in gastrointestinal diseases. *Nat Rev Gastroenterol Hepatol*. 2014; 12(2):77-87. doi: 10.1038/nrgastro.2014.188

Lapiere A, Richard ML. Bacterial-fungal metabolic interactions within the microbiota and their potential relevance in human health and disease: a short review. *Gut Microbes*. 2022; 14(1):2105610. doi: 10.1080/19490976.2022.2105610.

Naglik JR, Gaffen SL, Hube B. Candidalysin: discovery and function in *Candida albicans* infections. Curr Opin Microbiol. 2019; 52:100-109. doi: 10.1016/-j.mib.2019.06.002.

Jawhara S. How gut bacterial dysbiosis can promote *Candida albicans* overgrowth during colonic inflammation. *Microorganisms*. 2022; 10(5):1014. doi: 10.3390/microorganisms10051014.

Richard ML, Sokol H. The gut mycobiota: insights into analysis, environmental interactions and role in gastrointestinal diseases. *Nat Rev Gastroenterol Hepatol*. 2019; 16(6):331-345. doi: 10.1038/s41575-019-0121-2.

Van Thiel IAM, Stavrou AA, de Jong A, et al. Genetic and phenotypic diversity of fecal *Candida* albicans in irritable bowel syndrome. Sci Rep. 2022; 12(1):5391. doi: 10.1038/s41598-022-09436-x.

Sokol H, Leducq V, Aschard H, et al. Fungal microbiota dysbiosis in IBD. *Gut*. 2017; 66(6):1039-1048. doi: 10.1136/gutjnl-2015-310746.

Roselletti E, Sabbatini S, Ballet N, et al. *Saccharomyces cerevisiae* CNCM I-3856 as a new therapeutic agent against oropharyngeal candidiasis. *Front Microbiol*. 2019; 10:1469. doi: 10.3389/f-micb.2019.01469.

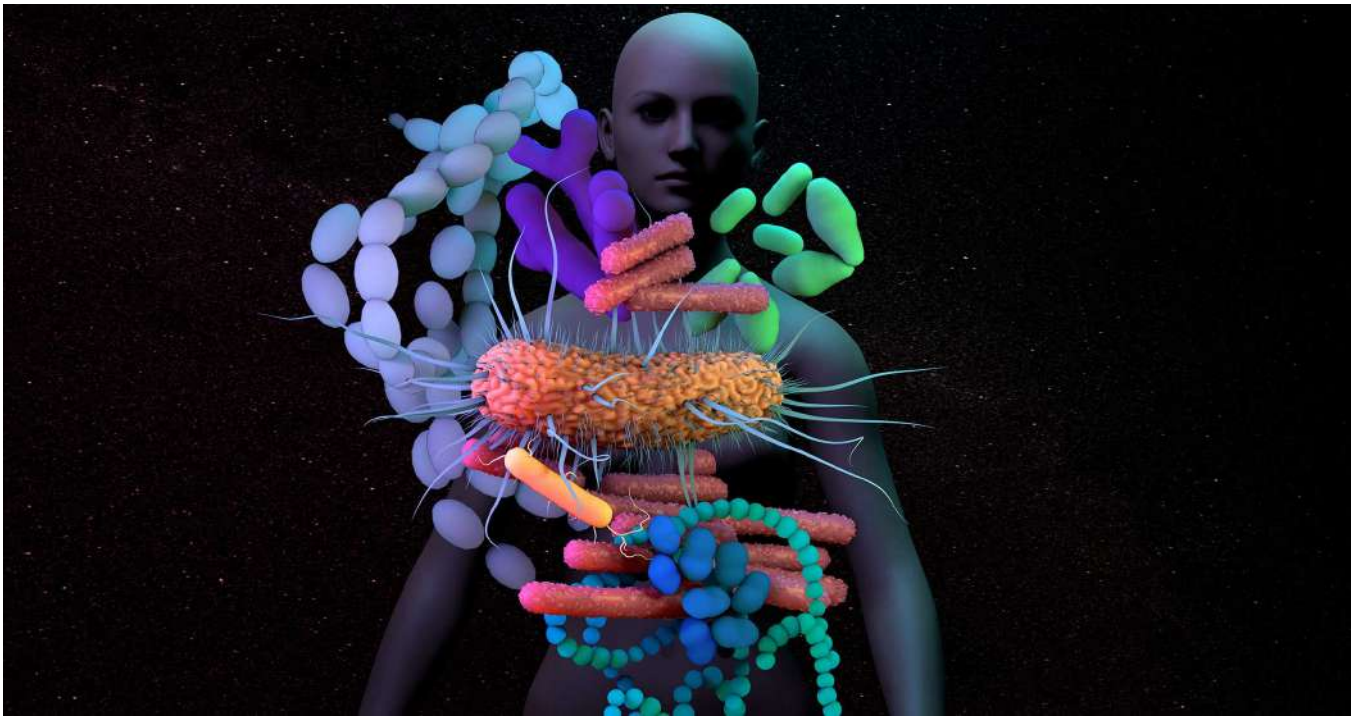
Mourey F, Decherf A, Jeanne JF, et al. *Saccharomyces cerevisiae* I-3856 in irritable bowel syndrome with predominant constipation. *World J Gastroenterol*. 2022; 28(22):2509-2522. doi: 10.3748/w-jg.v28.i22.2509.

SELECTED CONTENT

Cancer and microbiome: newsflash on epidemiology, fungi in etiology, and microbiome-derived markers for diagnosis

Published on March 22nd, 2023 by Konstantina Zafeiropoulou

Following the GMFH 2022 Year at a Glance report, it is time for a flashback in the latest research on cancer microbiome. This post ranges between the epidemiology, etiology and diagnosis of cancer, looking at the role of fungal and bacterial gut microbiome in all three health care branches.



Epidemiology: Is early-onset cancer an epidemic or "another" Provocative Question?

Cancer has been on the spot of public health for several decades, considering the significant increase of its prevalence and the augmenting cancer-associated death rates. Nevertheless, it is relatively recently that the sub-division into early-onset and later-onset cancers has been introduced, defined by the age of diagnosis. In a collaborative extensive review from researchers in Harvard Medical School and Harvard T.H. Chan School of Public Health, the cut-off of 50 years old was used to serve as the definition criterion, with patients younger than 50 years old at the time of diagnosis belonging in the early-onset cancer cohorts, while patients of or older than 50 years old belonging in the later-onset cohorts, respectively.

Ugai and colleagues evaluated trends in incidence of cancers in distinct organs of early-onset patients. They used cohorts from 44 countries around the world that provided age-standardized data on cancer incidence for the period 2002-2012. Among these, ten countries

SELECTED CONTENT

Cancer and microbiome: newsflash on epidemiology, fungi in etiology, and microbiome-derived markers for diagnosis

were selected for they were indicative of trends in the respective specific geographical regions. In these, incidence of **14 cancer types was reported to be increasing among 20-49-year-old adults:** breast, colorectal (CRC), endometrium, esophagus, extrahepatic bile duct, gallbladder, head and neck, kidney, liver, bone marrow, pancreas, prostate, stomach and thyroid.

Looking at the risk factors, the authors suggest a **strong etiological role for early life- (birth to 19 years of age) and young adulthood-exposome, as that is consisted by diet, lifestyle, environmental exposures, physical activity, and the microbiome.** Expectably, a thorough look at cancer risk factors easily reveals that most of them are also risk factors for other chronic diseases, i.e. diabetes and inflammatory bowel disease, which have been increasingly diagnosed over the past several decades. Therefore, the authors challenge whether **this early-onset cancer epidemic is the tip of the iceberg or -even worse- just "an example of increasing trend towards greater incidences of many chronic diseases in young and/or future generations".**

They answer suggesting large, prospective cohorts, collection of metadata with the means of electronic health records, and biospecimens throughout early life that will allow for detailed, multi-omics information. **They call for collaborations of researchers, healthcare providers, public health practitioners, policymakers and the public, shouting out for health literacy on early-onset cancers and beyond.**

Etiology: Current evidence on the role of mycobiome in cancer

The role of bacteria in tumorigenesis, progression of cancer and responses to cancer therapy has been greatly evaluated the past decades. **How much do we know about other microorganisms kingdoms in our body though? Recently, two in-depth, state-of-the-art, international studies, published in , reported comprehensive analyses of tumor-associated mycobiomes in a variety of human cancers.**

Narunsky-Haziza L. and colleagues generated the first so-called "Pan-Cancer Mycobiome Atlas". They characterized fungi in several sample types, including blood, plasma, and tumors, which they derived from four independent cohorts of patients with 35 distinct cancers. Using next generation sequencing techniques, the authors reported different compositions across the various cancer types, and therefore **indicated cancer type-specific fungal signatures**. Using intratumor fungal staining, they exhibited **cancer-specific fungal localization patterns, as well as spatial association with immune and cancer cells.** Lastly, using artificial intelligence and machine learning approaches, they prove that **fungi hold potential diagnostic and prognostic value,** and thus they highlighted once more the importance of the microbiome research (also) outside of the box of bacteria.

Dohlman A. and colleagues, followed a pan-cancer approach as well. They characterized fungi at multiple sites of the body of patients with cancer, and "confirmed" that human samples harbor tumor-associated mycobiota. Similar to Narunsky-Haziza et al., they could prove that the mycobiome is not only cancer specific, but cancer-type specific as well. **"In lung cancer, *Blastomyces* was associated with tumor tissues. In stomach cancers, high rates of *Candida* were linked to the expression of pro-inflammatory immune pathways, while in colon cancers *Candida* was predictive of metastatic disease and attenuated cellular adhesions."** Of significant note, *Candida* species were increased in tumors of the gastrointestinal tract and predictive of decreased survival.

SELECTED CONTENT

Cancer and microbiome: newsflash on epidemiology, fungi in etiology, and microbiome-derived markers for diagnosis

Diagnosis: Can we use microbiome-derived markers to succeed early diagnosis of colorectal cancer?

In both pan-cancer mycobiome studies mentioned above, the authors stressed the potential diagnostic and prognostic value of fungal signatures, but missed to mention the **diagnosis timeline.** Specifically for CRC, **diagnosis at early stages allows for treatment with a high overall survival.** Yet the current screening programs, which typically employ fecal biomarkers, followed by endoscopy, fail to provide diagnostic utility for early detection. Inclusion of microbiome-based biomarkers for screening and detection of CRC may proof beneficial.

Zwezerijnen-Jiwa and colleagues at Imperial College London and Amsterdam University Medical Centers recently reviewed all information available on microbiome-derived biomarkers for early detection of CRC. After screening 3,859 cancer-microbiome studies published until August 2022, the authors retrieved only 28 studies that reported the stage of colorectal cancer. They looked not only at the microbial composition, but the microbiome-derived metabolites, defined as co-metabolome, as well. All studies included in the systematic review evaluated solely the bacterial component of gut microbiome. Even studies that made use of the metagenomics approach, and could have evaluated non-bacterial signatures as well, tended to report only bacterial taxa as potential biomarkers. After looking at the confounding factors and large variations in study design and analytical precision, the authors suggested that **"Gut microbial-derived biomarkers could be leveraged to enhance current screening programs for CRC. However, significant barriers must be overcome before this can be achieved."** Following up the very recent studies on cancer mycobiome above, inclusion of fungal biomarkers may help achieve this goal.

References:

Ugai T., Sasamoto N., Lee H.Y., Ando M. et al. Is early-onset cancer an emerging global epidemic? Current evidence and future implications *Nat. Rev. Clin. Oncol.* 2022. doi: 10.1038 /s41571-022-00672-8

Mayer-Davis E., Lawrence J., Dabelea D., Divers J. et al. Incidence Trends of Type 1 and Type 2 Diabetes among Youths, 2002-2012 *N. Engl. J. Med*. 2017. doi: 10.1056/NEJMoa1610187

Kuenzing E., Fung S., Marderfeld L., Mak J., et al. Twenty-first Century Trends in the Global Epidemiology of Pediatric-Onset Inflammatory Bowel Disease: Systematic Review *Gastroenterology* 2022. doi: 10.1053/j.gastro.2021.12.282

Narunsky-Haziza L., Sepich-Poore G., Livyatan I., Asraf O., et al. Pan-cancer analyses reveal cancer-type-specific fungal ecologies and bacteriome interactions Cell 2022. doi: 10.1016/j.cell.2022.09.005

Dohlman A., Klug J., Mesko M., Gao I., et al. A pan-cancer mycobiome analysis reveals fungal involvement in gastrointestinal and lung tumors *Cell* 2022. doi: 10.1016/j.cell.2022.09.015

Siegel R., Miller K., Fuchs H., Jemal A. Cancer Statistics, 2021 *CA Cancer J. Clin*. 2021. doi: 10.3322/caac.21654

Zwezerijnen-Jiwa F., Sivov H., Paizs P., Zafeiropoulou K., et al. A systematic review of microbiome-derived biomarkers for early colorectal cancer detection *Neoplasia* 2022. doi: 10.1016/j.neo.2022.10086810.3389/fmicb.2019.02155

Konstantina Zafeiropoulou

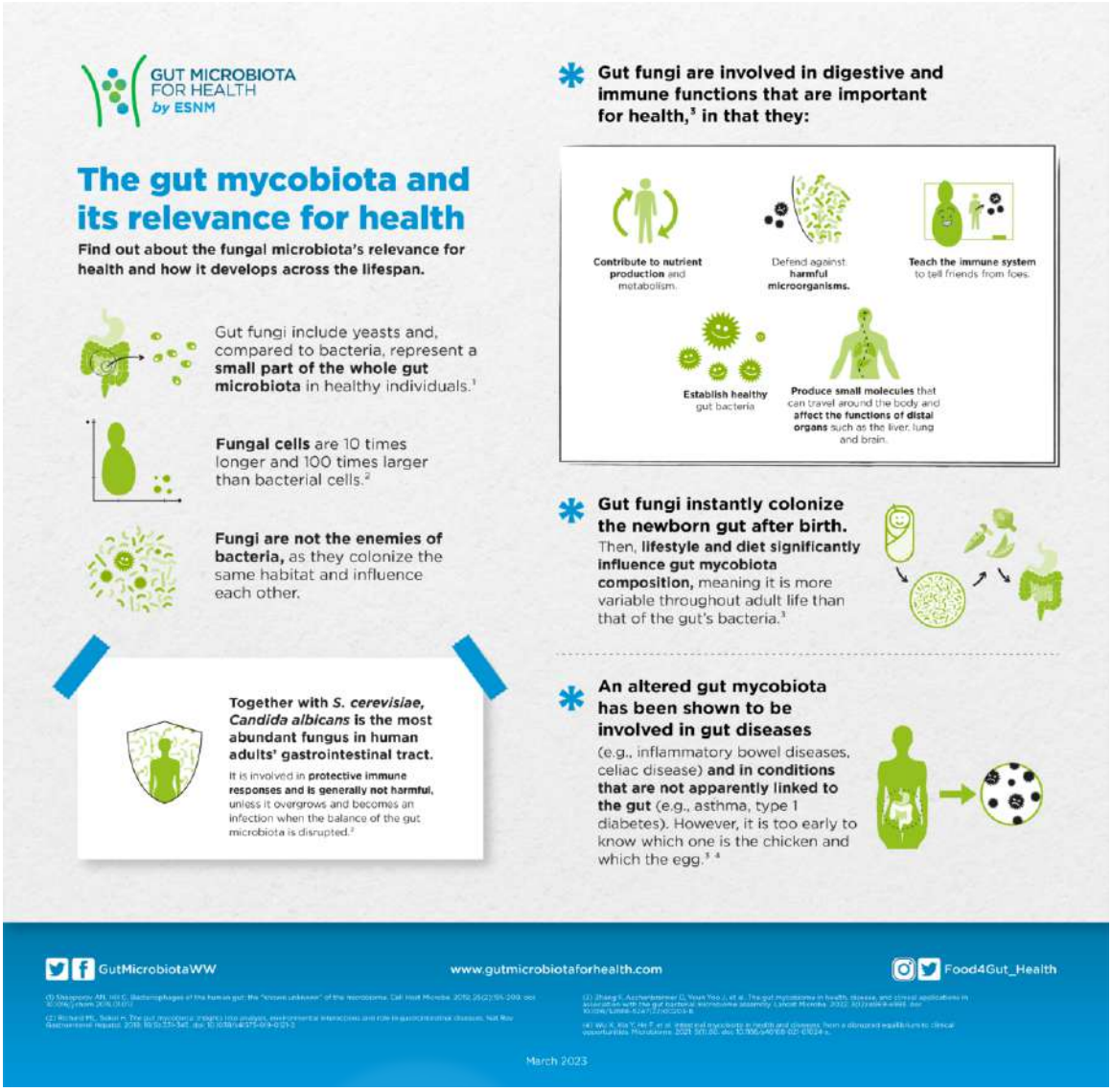
Konstantina Zafeiropoulou holds a Master of Science in Human Nutrition, and she is currently a PhD candidate at Amsterdam UMC unravelling the role of gut microbiota and long-term dietary patterns in the development of postoperative colorectal anastomotic leakage. Follow Konstantina on Twitter @zaf_kon

SELECTED CONTENT

The fascinating world of gut fungi and its relevance for health

Published on March 27th, 2023 by GMFH Editing Team

Discover the gut fungi world and their role in human health through our new infographic! Learn about their contribution to nutrient production, metabolism, defense against harmful microorganisms, and the establishment of healthy gut bacteria. The gut mycobiota is a dynamic and diverse community that coexists with other microorganisms in the gastrointestinal tract, such as bacteria, viruses, and archaea. While the bacterial microbiota has been extensively studied, the fungal community has only recently gained attention.



SELECTED CONTENT

Which dietary components should be promoted, and which ones should be limited in inflammatory bowel disease?

Published on May 19th, 2023 by GMFH Editing Team

What to eat or not to eat as a means of reducing IBD symptoms is one of the main queries a patient might have following diagnosis. Although there is no simple answer and dietary changes are not a substitute for medical therapy, to help consider this question, we have prepared a new infographic on the dietary components to promote and limit in patients with IBD.

The educational content in this post, elaborated in collaboration with Bromatech, was independently developed and approved by the GMFH publishing team and editorial board.

What you eat matters for managing ulcerative colitis and Crohn's disease. Diet can affect the types and functions of the gut microbiota, as well as the gut's protective lining. **Although there is no specific food or diet that can prevent or cure ulcerative colitis and Crohn's disease, diet can help keep your gut healthy and prevent inflammation.**

The most widely studied diet therapy for IBD is an all-liquid, formula-based meal-replacement diet (called exclusive enteral nutrition or EEN). EEN provides all the essential nutrients from the formula, while excluding all other foods. EEN has been shown to have several benefits, including inducing remission (children), reducing inflammation, promoting mucosal healing and improving nutritional status. Ultimately, EEN is to be used for a defined period of time, then food is gradually re-introduced.

While there is no perfect diet that works for everyone with IBD, **Natasha Haskey**, PhD, who is a trained registered dietitian with a focus on IBD, explained to GMFH editors via email that a Mediterranean-like diet is recommended for individuals with IBD looking to eat a more healthy balanced diet and reduce inflammation.

High levels of consumption of vegetables, fruit, nuts, legumes, olive oil and lean protein sources have been shown to have a protective effect against developing IBD as well as contribute to a healthy gut microbiota. In contrast, Western dietary patterns, high in omega-6 polyunsaturated fatty acids, alcohol, red meat and food additives (excessive salt, emulsifiers and artificial sweeteners) promote intestinal inflammation and can worsen symptoms, and thus should be limited.

Fats are an important nutrient to pay attention to in IBD. Natasha's PhD research focused on studying the impact of dietary fats in a rodent model with chronic colitis. According to Natasha: "We saw that a diet rich in omega-6 polyunsaturated fatty acids (commonly found in corn, soybean, safflower and sunflower oils) promoted inflammation. In contrast, a diet that was rich in olive oil and contained omega-3 polyunsaturated fatty acids (from fish) and some saturated fat (milk fat) promoted immune homeostasis in ulcerative colitis." Based on those findings, in IBD it would be prudent to reduce the content of omega-6 polyunsaturated fatty acids in the diet and increase the omega-3 polyunsaturated fatty acids and olive oil along with a diet rich in fruit, vegetables, whole grains with some dairy intake.

As for when diet can help the most, Haskey acknowledges that diet can help manage symptoms and inflammation in both active disease and remission. However, given that each patient has their own microbial and genetic makeup, the most appropriate diet should be personalized. According to Natasha: "The diet needs to be personalized to each individual, considering their disease and what works within their lifestyle. Consulting

SELECTED CONTENT

Which dietary components should be promoted, and which ones should be limited in inflammatory bowel disease?

with a dietitian with expertise in managing IBD is essential to develop an individualized plan."

As our knowledge regarding the impact of diet on managing IBD improves, there are more opportunities to use diet as a supplementary therapy to control inflammation and alleviate symptoms. Before choosing one of the fad diets promoted for IBD online, speak to your healthcare provider so they can recommend a personalized eating plan that works for you.

References:

Sasson AN, Ananthakrishnan AN, Raman M. Diet in treatment of inflammatory bowel diseases. *Clin Gastroenterol Hepatol.* 2021; 19(3):425-435.e3. doi: 10.1016/j.cgh.2019.11.054.

Haskey N, Gold SL, Faith JJ, et al. To fiber or not to fiber: the swinging pendulum of fiber supplementation in patients with inflammatory bowel disease. *Nutrients*. 2023; 15(5):1080. doi: 10.3390/nu15051080.

Bischoff SC, Bager P, Escher J, et al. ESPEN guideline on clinical nutrition in inflammatory bowel disease. *Clin Nutr.* 2023; 42(3):352-379. doi: 10.1016/j.clnu.2022.12.004.

Liu X, Wu Y, Li F, et al. Dietary fiber intake reduces risk of inflammatory bowel disease: result from a meta-analysis. *Nutr Res.* 2015; 35(9):753-758. doi: 10.1016/j.nutres.2015.05.021.

Armstrong HK, Bording-Jorgensen M, Santer DM, et al. Unfermented b-fructan fibers fuel inflammation in select inflammatory bowel disease patients. *Gastroenterology.* 2023; 164(2):228-240. doi: 10.1053/j.gastro.2022.09.034.

World Gastroenterology Organisation. Probiotics and prebiotics. February 2023. Available on: https://www.worldgastroenterology.org/guidelines/probiotics-and-prebiotics/probiotics-and-prebiotics-english

Olendzki B, Bucci V, Cawley C, et al. Dietary manipulation of the gut microbiome in inflammatory bowel disease patients: pilot study. *Gut Microbes*. 2022; 14(1):2046244. doi: 10.1080/19490976.2022.2046244.

Galipeau HJ, Caminero A, Turpin W, et al. Novel fecal biomarkers that precede clinical diagnosis of ulcerative colitis. *Gastroenterology.* 2021; 160(5):1532-1545. doi: 10.1053/j.gastro.2020.12.004.

Wolters M, Ahrens J, Romaní-Pérez M, et al. Dietary fat, the gut microbiota, and metabolic health – A systematic review conducted within the MyNewGut project. *Clin Nutr.* 2019; 38(6):2504-2520. doi: 10.1016/j.clnu.2018.12.024.

Haskey N, Gibson DL. An examination of diet for the maintenance of remission in inflammatory bowel disease. *Nutrients.* 2017; 9(3):259. doi: 10.3390/nu9030259.

Carreras-Torres R, Ibáñez-Sanz G, Obón-Santacana M, et al. Identifying environmental risk factors for inflammatory bowel diseases: a Mendelian randomization study. *Sci Rep.* 2020; 10(1):19273. doi: 10.1038/s41598-020-76361-2.

Narula N, Chang NH, Mohammad D, et al. Food processing and risk of inflammatory bowel disease: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol.* 2023. doi: 10.1016/j.cgh.2023.01.012.

Camilleri M, Vella A. What to do about the leaky gut. *Gut.* 2022; 71(2):424-435. doi: 10.1136/gutjnl-2021-325428.

SELECTED CONTENT

Which dietary components should be promoted, and which ones should be limited in inflammatory bowel disease?

GUT MICROBIOTA FOR HEALTH *by* ESNM

Living better with inflammatory bowel disease

Following diagnosis, one of the main questions patients ask is what they should eat to help manage their inflammatory bowel disease (IBD).

Diet can affect the types and functions of the bacteria that live in your gut, as well as the protective lining of the gut. Choosing a healthy diet can help keep your gut healthy and prevent inflammation[1].

Nutrients and food sources to promote, as they have the potential to reduce inflammation in the gut

*** Dietary fiber[2 3 4]**

- Soluble fiber: sweet potatoes, carrots, pears, apples, oranges, legumes, oats, barley, flax seeds, chia seeds.
- Insoluble fiber: wheat bran, dark green leafy vegetables, whole grains, nuts, seeds, brown rice.

Fiber restriction is no longer recommended in IBD. A diet rich in a variety of fiber sources is important in maintaining a healthy gut.

*** Resistant starch[2]**

- Green banana, lentils, cooked and cooled legumes, plantains, cashews, barley, rye, cooked and cooled rice, potatoes or pasta.

Resistant starch may help reduce gut inflammation and help with symptoms in IBD.

*** Some probiotic bacteria and fermented milks[3 6]**

- Fermented milks: yogurt, kefir, labneh, amasi, ayran.
- Supplements (capsules, powders).

Specific single- or multi-strain probiotic bacteria may be helpful in the management of ulcerative colitis. The available evidence is uncertain about the efficacy of probiotics for Crohn's disease.

*** Omega-3 Polyunsaturated Fatty Acids (PUFAs)[9 10 11]**

- Fatty fish: salmon, tuna, herring, sardines, trout.
- Seafood: oysters, mussels, shrimp.
- Flaxseeds, chia seeds, walnuts, algae
- Omega-3 eggs.

Increasing the omega-3 PUFAs in the diet may help balance the immune system, reduce inflammation and improve the function of the gut lining.

*** Vitamin D[10]**

- Fatty fish (salmon, tuna mackerel), egg yolks, fortified dairy products, mushrooms.
- Sunlight exposure.

Vitamin D levels should be monitored in IBD, additional supplementation may be required to ensure adequacy.

*** Some prebiotics[2 3]**

- Foods that contain prebiotics: onions, garlic, chicory root, artichokes and agave.
- Supplements: psyllium, inulin, fructoologosaccharides, xylooligosaccarides.

There is some evidence to suggest that prebiotics may have a beneficial effect in IBD. Some people may have difficulty tolerating certain types of prebiotic fiber, which depends on the bacteria present in their gut[5].

*** Polyphenols[2]**

- Berries, green tea, whole grains (oats, barley and brown rice), nuts (almonds, walnuts and pecans), vegetables (dark green), fruits (apples, grapes, citrus fruit).

Polyphenols are a large group of compounds found in plant-based foods that can enhance the microbiome. They have been shown to promote the growth of beneficial bacteria and maintain the health of the gut lining in IBD.

*** Lean protein sources[7]**

- Fish, eggs, skinless chicken, turkey, legumes, tofu, soy-based products.

Lean protein sources are essential for growth and repair of body tissues, and they support muscle mass and immune function. Additionally, lean protein sources provide an important source of iron. People with IBD are at increased risk of low iron, so it is important to have your iron levels checked by your healthcare professional.

To enhance iron absorption, consume foods that are rich in vitamin C (citrus fruits, tomatoes, peppers) with foods that are high in iron[8].

*** Monounsaturated Fatty Acids[9 10]**

- Olive oil, avocados, nuts (almonds, cashews, pecans), pumpkin seeds, olives.

Monounsaturated fatty acids are a healthy fat and have been shown to have a positive effect on the microbiome.

Nutrients and food sources to limit in IBD, as they are associated with increased gut inflammation

*** Omega-6 Polyunsaturated Fatty Acids (PUFAs)[9 10]**

- Vegetable oils: corn, soybean, safflower, sunflower.
- Meat: meat from animals fed a corn-based diet.
- Processed foods: baked goods, snack foods, fried foods.

An excess intake of omega-6 PUFAs is associated with increased inflammation in IBD.

*** Alcohol[13]**

Any type of alcoholic beverage (beer, wine, spirits, cocktails).

Alcohol consumption is not recommended in IBD.

*** Red meat**

Beef, pork, lamb, veal.

A high intake of red meat has been associated with an increased risk of developing Crohn's disease and increased risk of relapse. Red meat intake should be limited to 4 ounces/week.

*** Foods with food additives (excessive salt, emulsifiers and artificial sweeteners)[12]**

- Limit intake of ultra-processed foods that contain emulsifiers (polysorbate 80, carboxymethyllcellulose), refined carbohydrates, trans fatty acids, palm oil.

- Foods such as pastries, snack foods (chips, crisps), fast foods, processed meats, soda pop and sweetened beverages should be limited.

Increased ultra-processed food intake is associated with higher risk of CD. Choose whole, unprocessed foods such as whole grains, fruit, vegetables, lean protein and healthy fats instead.

There are different dietary options that can be used to help manage IBD. Before trying any of them, always seek the advice of a physician or another qualified healthcare provider who will recommend a tailored diet that fits your medical condition.

GutMicrobiotaWW www.gutmicrobiotaforhealth.com Food4Gut_Health

1. Sasson AN, Ananthakrishnan AN, Raman M. Diet in treatment of inflammatory bowel diseases. *Clin Gastroenterol Hepatol.* 2021; 19(3):425-435.e3. doi: 10.1016/j.cgh.2019.11.054.

2. Haskey N, Gold SL, Faith JJ, et al. To fiber or not to fiber: the swinging pendulum of fiber supplementation in patients with inflammatory bowel disease. *Nutrients.* 2023; 15(5):1080. doi: 10.3390/nu15051080.

3. Bischoff SC, Bager P, Escher J, et al. ESPEN guideline on clinical nutrition in inflammatory bowel disease. *Clin Nutr.* 2023; 42(3):352-379. doi: 10.1016/j.clnu.2022.12.004.

4. Liu X, Wu Y, Li F, et al. Dietary fiber intake reduces risk of inflammatory bowel disease: result from a meta-analysis. Nutr Res. 2015; 35(9):753-758. doi: 10.1016/j.nutres.2015.05.021.

5. Armstrong HK, Bording-Jorgensen M, Santer DM, et al. Unfermented ß-fructan fibers fuel inflammation in select inflammatory bowel disease patients. *Gastroenterology.* 2023; 164(2):228-240. doi: 10.1053/j.gastro.2022.09.034.

6. World Gastroenterology Organisation, Probiotics and prebiotics. February 2023. Available on: https://www.worldgastroenterology.org/guidelines/probiotics-and-prebiotics/probiotics-and-prebiotics-english

7. Olendzki B, Bucci V, Cawley C, et al. Dietary manipulation of the gut microbiome in inflammatory bowel disease patients: pilot study. *Gut Microbes.* 2022; 14(1):2046244. doi: 10.1080/19490976.2022.2046244.
8. Gallpseu HJ, Caminero A, Turpin W, et al. Novel fecal biomarkers that precede clinical diagnosis of ulcerative colitis. *Gastroenterology.* 2021; 160(5):1532-1545. doi: 10.1053/j.gastro.2020.12.004.

9. Wolters M, Ahrens J, Romani-Pérez M, et al. Dietary fat, the gut microbiota, and metabolic health – A systematic review conducted within the MyNewGut project. *Clin Nutr.* 2019; 38(6):2504-2520. doi: 10.1016/j.clnu.2018.12.024.

10. Haskey N, Gibson DL. An examination of diet for the maintenance of remission in inflammatory bowel disease. *Nutrients.* 2017; 9(3):259. doi: 10.3390/nu9030259.

11. Carreras-Torres R, Ibáñez-Sanz G, Obón-Santacana M, et al. Identifying environmental risk factors for inflammatory bowel diseases: a Mendelian randomization study. *Sci Rep.* 2020; 10(1):19273. doi: 10.1038/s41598-020-76361-2.

12. Narula N, Chang NH, Mohammad D, et al. Food processing and risk of inflammatory bowel disease: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol.* 2023. doi: 10.1016/j.cgh.2023.01.012.

13. Camilleri M, Valla A. What to do about the leaky gut. *Gut.* 2022; 71(2):434-435. doi: 10.1136/gutjnl-2021-325428.

Additional references on gut microbiota and IBD:

Ramos, G. P., and Papadakis, K. A. (2019). Mechanisms of disease: inflammatory bowel diseases. Mayo Clin. Proc. 94, 155–165.

Ma, Y., Xu, X., Li, M., Cai, J., Wei, Q., and Niu, H. (2019). Gut microbiota promote the inflammatory response in the pathogenesis of systemic lupus erythematosus. Mol. Med. 25:35.

O'Donnell, S., Borowski, K., Espin-Garcia, O., Milgrom, R., Kabakchiev, B., Stempak, J., et al. (2019). The unsolved link of genetic markers and crohn's disease progression: a north american cohort experience. Inflamm. Bowel Dis. 25, 1541–1549.

Pang, J. X. Q., Kheirkhahvahidabadi, H., Bindra, S., Bindra, G., Panaccione, R., Ekstoen, B., et al. (2021). Differential effect of genetic burden on disease phenotypes in Crohn's disease and ulcerative colitis in a Canadian cohort. J. Can. Assoc. Gastroenterol. 4, 65–72.

Zhang, D., Liwinski, T., and Elinav, E. (2020). Interaction between microbiota and immunity in health and disease. Cell Res. 30, 482–506.

Andoh, A., Kuzuoka, H., Tsujikawa, T., Nakamura, S., Hirai, F., Suzuki, Y., et al. (2012). Multicenter analysis of fecal microbiota profiles in Japanese patients with Crohn's disease. J. Gastroenterol. 47, 1298–1307.

Joossens, M., Huys, G., Cnockaert, M., De Preter, V., Verbeke, K., Rutgeerts, P., et al. (2011). Dysbiosis of the faecal microbiota in patients with Crohn's disease and their unaffected relatives. Gut 60, 631–637.

Darfeuille-Michaud, A., Boudeau, J., Bulois, P., Neut, C., Glasser, A. L., Barnich, N., et al. (2004). High prevalence of adherent-invasive Escherichia coli associated with ileal mucosa in Crohn's disease. Gastroenterology 127, 412–421.

Liu, S., Zhao, W., Lan, P., and Mou, X. (2020). The microbiome in inflammatory bowel diseases: from pathogenesis to therapy. Protein Cell 15, 331–345.

Iliev, I. D., and Leonardi, I. (2017). Fungal dysbiosis: immunity and interactions at mucosal barriers. Nat. Rev. Immunol. 17, 635–646.

Behshti-Maal, A., Shahrokh, S., Ansari, S., Mirsamadi, E. S., Yadegar, A., Mirjalali, H., et al. (2021). Gut mycobiome: The probable determinative role of fungi in IBD patients. Mycoses 64, 468–476.

Sokol, H., Leducq, V., Aschard, H., Pham, H. P., Jegou, S., Landman, C., et al. (2017). Fungal microbiota dysbiosis in IBD. Gut 66, 1039–1048.

Qiu, X., Ma, J., Jiao, C., Mao, X., Zhao, X., Lu, M., et al. (2017). Alterations in the mucosa-associated fungal microbiota in patients with ulcerative colitis. Oncotarget 8, 107577–107588.

Inczefi, O.; Bacsur, P.; Rasal, T.; Karresztes, C.; Molnar, T. The Influence of Nutrition on Intestinal Permeability and the Microbiome in Health and Disease. Front. Nutr. 2022, 9, 718710.

Lo Sasso, G.; Khachatryan, L.; Kondylis, A.; Battey, J.N.D.; Sierro, N.; Danilova, N.A.; Grigoryeva, T.V.; Markelova, M.I.; Khusnutdinova, D.R.; Laikov, A.V.; et al. Inflammatory Bowel Disease-Associated Changes in the Gut: Focus on Kazan Patients. Inflamm. Bowel Dis. 2021, 27, 418–433.

May 2023

SELECTED CONTENT

Is dietary fiber beneficial or deleterious for patients with IBD?

Published on August 7th, 2023 by Manon Oliero

Dietary fibers, known to regulate intestinal inflammation and gut barrier functions, have been avoided by patients with inflammatory bowel diseases (IBD) to avoid flare-ups. However, recent findings suggest that if fiber type, patient immunological condition, and the fermentative ability of the gut microbiota are taken into account, they could be beneficial and prevent relapses.

The prevalence of inflammatory bowel diseases (IBD), which include ulcerative colitis (UC) and Crohn's disease (CD), has increased over recent decades in Western countries. While the lack of **dietary fiber from these populations could therefore be one factor to blame, dietary fibers are often overlooked by IBD patients who fear that following a high-fiber diet will worsen their symptoms.** Such exclusion diets can improve symptoms but may deprive patients of the benefits of fibers. However, recently, scientists are **moving away from the concept that dietary fiber should be avoided in patients with IBD.** Indeed, from fermentation, the gut microbiota releases short-chain fatty acids (SCFAs), that regulate metabolism, cell turnover, and the immune system.

In a new research article published in Gastroenterology, Armstrong et al. investigated the effects of different

SELECTED CONTENT

Is dietary fiber beneficial or deleterious for patients with IBD?

β-fructans on barrier function and inflammation using colonic biopsies from pediatric patients with IBD and healthy controls. They based their hypothesis on the fact that some patients with IBD are sensitive to high-fiber diet and that they have a dysbiotic gut microbiota with fewer fiber-fermenting microorganisms, meaning that fibers are not fully fermented and remain in the gut where they could trigger inflammation.

The authors first tested the effect of β-fructans on inflammation response from monocytes, peripheral blood mononuclear cells (PBMCs) and ex-vivo colonic biopsy culture, as well as the fermentation capacity of gut microbiota. **Unfermented β-fructans lead to an inflammatory response, gut barrier changes and pro-inflammatory cytokines**, whereas when these fibers are fermented by gut microbes, they reduce inflammation by releasing SCFAs.

Unfermented dietary fructooligosaccharides (FOS) and inulin, but not barley, maltodextrin or dextrin, increased the release of the pro-inflammatory cytokine IL-1β by human monocytes, PBMCs, and in some patient biopsy tissues cultured ex vivo. More particularly, **biopsy samples from UC and CD patients in flare-up phase showed an increased pro-inflammatory profile** (IL-1 β, IL-5, IL-23) compared with CD and UC in remission and non-IBD patient biopsies, in which a decrease in IL-1β secretion was observed with FOS supplementation. The authors also found higher levels of CD45+ cells in biopsies from patients with UC and CD. Altogether, these findings suggest that the fiber type, immune status and the fermentative capacity of their gut microbiota influence the proinflammatory role of dietary fibers.

To validate their hypothesis the authors cultured anaerobically fecal samples with FOS and applied the resulting supernatant of these fecal cultures onto monocytes and measured their inflammatory response. In order to down regulate inflammation, a decreased concentration of FOS and increased concentration of SCFAs by fermentation were required. The authors found that the **fermentative capacity of the gut microbiota** as reflected by decreased FOS levels and increased SCFAs, **was lower in UC and CD patients in flare-up** compared with IBD patients in remission and non-IBD patients.

To validate their findings, in a randomized controlled trial cohort, they **supplemented UC patients in remission with β-fructans (15 g/d over 6 months) or placebo**. In UC patients in remission, β-fructans **significantly reduced the risk of flare** as indicated by the lower level of fecal calprotectin (a marker of intestinal inflammation) compared with placebo. **Nevertheless, 31% of UC patients in the β-fructans group experienced a flare-up at the study endpoint** with increased pro-inflammatory cytokines in response to β-fructans supplementation. Armstrong et al found a low FODMAP diet among IBD patients correlated with a pro-inflammatory response to FOS. This finding raises the possibility that FOS consumption during remission may lessen the degree of inflammation thereafter.

The study of Armstrong et al highlights the intricacy of the variables influencing everyone's response to fiber. Indeed, when fiber-fermenting microbes are present in an uninflamed gut, fermentation strengthens the intestinal barrier and reduces the inflammatory response. In contrast, **when the capacity of the gut microbiota to ferment fiber is reduced and the gut environment is inflammatory, β-fructans stimulate inflammation.** In the future, dietary fiber advice should be tailored to each patient's pathological condition.

SELECTED CONTENT

Is dietary fiber beneficial or deleterious for patients with IBD?

References:
Wang R, Li Z, Liu S, *et al.* Global, regional and national burden of inflammatory bowel disease in 204 countries and territories from 1990 to 2019: a systematic analysis based on the Global Burden of Disease Study 2019. *BMJ Open.* 2023;13:e065186.

Haskey N, Gold SL, Faith JJ, et al. To Fiber or Not to Fiber: The Swinging Pendulum of Fiber Supplementation in Patients with Inflammatory Bowel Disease. *Nutrients.* 2023;15:1080.

Armstrong HK, Bording-Jorgensen M, Santer DM, et al. Unfermented β-fructan Fibers Fuel Inflammation in Select Inflammatory Bowel Disease Patients. *Gastroenterology.* 2023;164(2):228-240.

Shin A et Kashyap PC. Promote or Prevent? Gut Microbial Function and Immune Status May Determine the Effect of Fiber in Inflammatory Bowel Disease. *Gastroenterology.* 2023; 164(2):182-184.

Manon Oliero

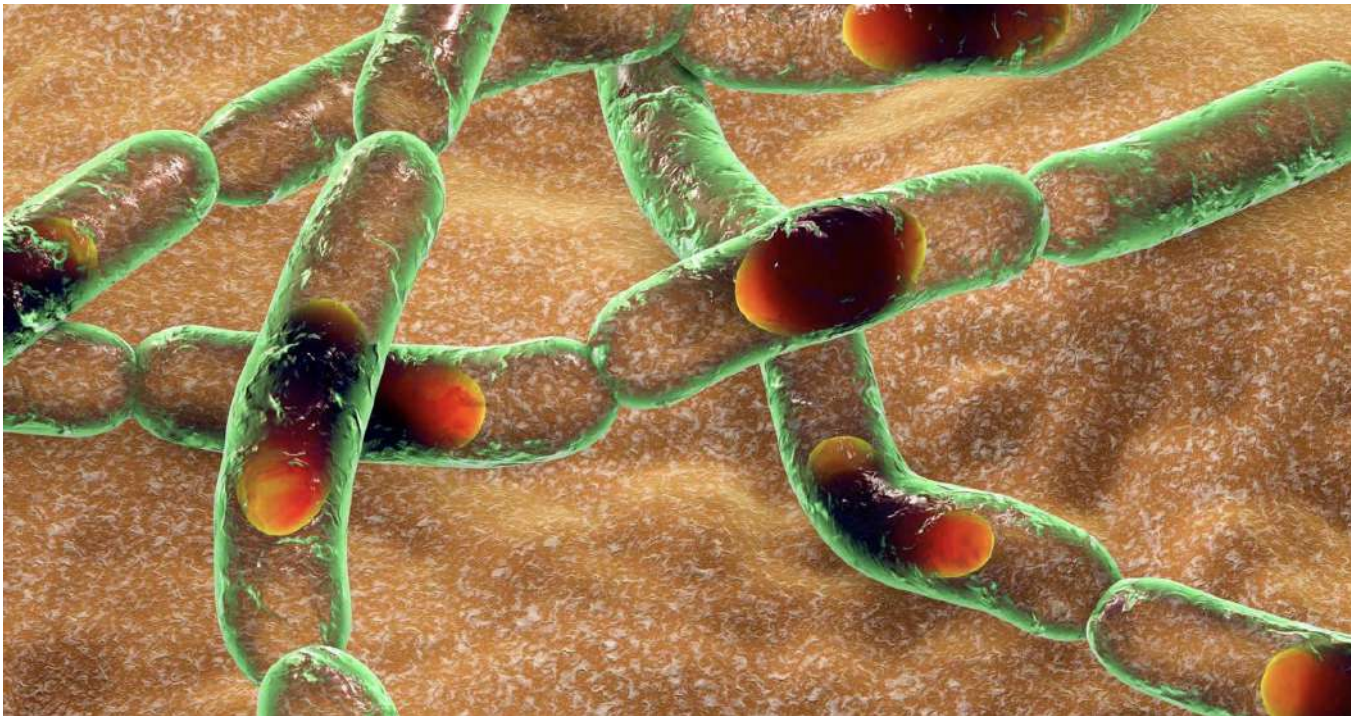
Manon Oliero is starting her PhD about gut microbiota, nutrition and cancer at the CRCHUM of Montreal. Before, she speci... alized in the gut microbiota and nutrition field by obtaining a master's degree in Paris in microbiology and a food and health engineer degree in Beauvais. She first meets the scientific communication world in Barcelona after her work on gut microbiota and diet at the VHIR. She is really concern about health of the population and believe that with a better diet and lifestyle we can all make ourselves healthier.

SELECTED CONTENT

What do we know about the role of probiotics for IBD?

Published on July 10th, 2023 by Andreu Prados

Differences in the gut microbiota in patients with IBD compared to healthy controls suggest that probiotics may be of help. This article takes an in-depth look into the rationale of using probiotics for IBD and summarizes the evidence from recent clinical guidelines for the use of probiotics in Crohn's disease, ulcerative colitis and pouchitis.



The educational content in this post, elaborated in collaboration with Bromatech, was independently developed and approved by the GMFH publishing team and editorial board.

What is the rationale for using probiotics in IBD?

A single cause of inflammatory bowel diseases (IBDs), and particularly of ulcerative colitis (UC) and Crohn's disease (CD), has yet to be identified. However, contributory elements to the pathogenesis of IBD include host genetic susceptibility, the environment and host immune response. Within them, alterations in both the composition and functions of the gut microbiota have been involved in IBD pathogenesis and it is therefore feasible to think that gut microbiota is both the chicken and the egg in IBD.

Robust alterations in the composition and function of the gut microbiota in IBD have suggested that targeting that area with fecal microbiota transplantation, probiotics and phage therapy might be beneficial in IBD.

SELECTED CONTENT

What do we know the role of probiotics for IBD?

The rationale of using probiotics in IBD in particular is based on their anti-inflammatory properties (i.e., reducing calprotectin levels), their role in modulating gut microbiota composition (i.e., overcoming the lack of beneficial *Lactobacillus* and Bifidobacterium seen in patients with IBD), the production of short-chain fatty acids and the strengthening of intestinal barrier integrity.

Other mechanisms are also plausible and include correcting the altered tryptophan metabolism observed in IBD and modulating the expression of heat shock proteins (chaperones). For instance, the levels of heat shock proteins 60 and 10 are increased in colon mucosa of patients with CD and UC in relapse supporting the hypothesis that this is a potential mechanism involved in the development and maintenance of IBD.

That has led to some studies exploring the role of probiotics in shaping the expression of mucosal heat shock proteins in patients with IBD. Some probiotics have shown efficacy in decreasing the levels of heat shock proteins. Other mechanisms of action by which some probiotics may work in UC is by boosting the expression of cytoprotective heat shock proteins 70 and 25, which are decreased in the mucosa by colitis.

Probiotics in ulcerative colitis and pouchitis

The latest clinical guidelines from the European Society for Clinical Nutrition and Metabolism (ESPEN) and the World Gastroenterology Organisation agreed that **certain bacteria and yeast probiotics are effective and safe for the induction and maintenance of mild to moderately active UC in pediatric and adult populations, but not in the case of severe disease.**

Moreover, some probiotic blends with *Bifidobacterium* and *Lactobacillus* species coupled with anti-inflammatory drugs may represent an effective approach in mild-to-moderate UC, with beneficial effects that persist after two years of treatment. Specific probiotics can also be as effective as an alternative to conventional therapy (namely, aminosalicylates) and the ESPEN guidelines conclude that "selected probiotics can be used as an alternative to 5-aminosalicylic acid (5-ASA) standard therapy if 5-ASA is not tolerated for the treatment of mild or moderate active disease."

While the evidence for using probiotics to prevent pouchitis is contradictory, some data suggest **certain probiotics may prevent further relapse after the induction of remission with antibiotics and may be used as maintenance treatment for children and adults in remission.**

Commensal strains selected for their anti-inflammatory properties such as *Faecalibacterium prausnitzii*, purified microbial metabolites (i.e., butyrate and tryptophan metabolites) and phage therapy are also promising treatments targeting the microbiota, which could be used in parallel with available treatments that target host inflammatory response.

Probiotics in Crohn's disease

The available evidence is uncertain about the efficacy of probiotics for Crohn's disease. Currently, the ESPEN clinical guidelines state that "probiotics should not be recommended for treatment of CD, neither for treatment of active disease nor for prevention of relapse in the remission phase or postoperative recurrence of disease."

Probiotics in the form of foods or food supplements: pros and cons

While some studies assessed the efficacy of fermented milks enriched with bifidobacteria in UC, it is not possible to ensure that fermented milks (and other fermented foods) contain the right strains and in an adequate amount with scientific evidence to improve IBD symp-

SELECTED CONTENT

What do we know the role of probiotics for IBD?

toms, and the maintenance of cold temperatures from production to consumption cannot be ensured either. Moreover, while including fermented foods as part of a well-balanced diet makes sense, the available evidence does not allow for their recommendation in gastrointestinal conditions such as IBD. This is mainly because the microorganisms, byproducts or nutrients responsible for their health benefits are not completely understood.

Take-home messages

The gut microbiota is a driver of mucosal inflammation in IBD and contributes with genes and host immune response to the pathogenesis of this gastrointestinal condition.

The latest clinical guidelines from the European Society for Clinical Nutrition and Metabolism and the World Gastroenterology Organisation agreed that certain bacteria and yeast probiotics are effective and safe for the induction and maintenance of mild to moderately active UC.

The available evidence, meanwhile, is uncertain about the efficacy of probiotics for Crohn's disease.

Andreu Prados

Andreu Prados holds a Bachelor of Science Degree in Pharmacy & Human Nutrition and Dietetics. Science writer special... ised in gut microbiota and probiotics, working also as lecturer and consultant in nutrition and healthcare. Follow Andreu on Twitter @andreuprados

References:

Benech N, Sokol H. Targeting the gut microbiota in inflammatory bowel diseases: where are we? Curr Opin Microbiol. 2023; 74:102319. doi: 10.1016/j.mib.2023.102319.

Naseer M, Poola S, Ali S, et al. Prebiotics and probiotics in inflammatory bowel disease: where are we now and where are we going? Curr Clin Pharmacol. 2020; 15(3):216-233. doi: 10.2174/1574884715666200312100237.

Agus A, Planchais J, Sokol H. Gut microbiota regulation of tryptophan metabolism in health and disease. Cell Host Microbe. 2018; 23(6):716-724. doi: 10.1016/j.chom.2018.05.003.

Bellavia M, Tomasello G, Romeo M, et al. Gut microbiota imbalance and chaperoning system malfunction are central to ulcerative colitis pathogenesis and can be counteracted with specifically designed probiotics: a working hypothesis. Med Microbiol Immunol. 2013; 202(6):393-406. doi: 10.1007/s00430-013-0305-2.

Rodolico V, Tomasello G, Zerilli M, et al. Hsp60 and Hsp10 increase in colon mucosa of Crohn's disease and ulcerative colitis. Cell Stress Chaperones. 2010; 15(6):877-884. doi: 10.1007/s12192-010-0196-8.

Tomasello G, Sciumè C, Rappa F, et al. Hsp10, Hsp70, and Hsp90 immunohistochemical levels change in ulcerative colitis after therapy. Eur J Histochem. 2011; 55(4):e38. doi: 10.4081/ejh.2011.e38.

Liu HY, Gu F, Zhu C, et al. Epithelial heat shock proteins mediate the protective effects of Limosilactobacillus reuteri in dextran sulfate sodium-induced colitis. Front Immunol. 2022; 13:865982. doi: 10.3389/fimmu.2022.865982.

Bischoff SC, Bager P, Escher J, et al. ESPEN guideline on clinical nutrition in inflammatory bowel disease. Clin Nutr. 2023; 42(3):352-379. doi: 10.1016/j.clnu.2022.12.004.

Guarner F, Sanders ME, Szajewska H, et al. World Gastroenterology Organisation Global Guidelines. Probiotics and prebiotics. February 2023. Available on: https://www.worldgastroenterology.org/guidelines/probiotics-and-prebiotics/probiotics-and-prebiotics-english

Davide Palumbo V, Romeo M, Marino Gammazza AM, et al. The long-term effects of probiotics in the therapy of ulcerative colitis: a clinical study. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2016; 160(3):372-377. doi: 10.5507/bp.2016.044.

Staudacher HM, Nevin AN. Fermented foods: fad or favourable addition to the diet? Lancet Gastroenterol Hepatol. 2019; 4(1):19. doi: 10.1016/S2468-1253(18)30392-3.

SELECTED CONTENT

Study identifies a role for bacterial proteases in Crohn's disease

Published on June 26th, 2023 by Amber Hann and Heather Galipeau

Inflammatory bowel disease is a chronic remitting and relapsing condition that causes severe inflammation of the intestines and disabling bowel symptoms. It affects millions of lives globally, and although alterations in the gut microbiome have been associated with IBD, precise mechanisms remain incompletely understood. New research from McMaster University now implicates bacterial proteases in Crohn's disease.

Proteases are enzymes that break down proteins. Past studies have linked excessive production of human proteases with inflammation. However, the gut microbiome is an important source of proteases, which bacteria use to provide energy for themselves or as virulence mechanisms. Indeed, increased bacterial protease activity associated with gut microbiota changes was recently demonstrated in patients at risk for IBD before the onset of ulcerative colitis (UC).

A new study, conducted at the Farncombe Institute, in McMaster University, investigated whether bacterial proteolytic activity is also involved in Crohn's disease (CD). The study, recently published in Gut Microbes, **measured proteolytic activity in stool samples from patients with CD and then used these fecal microbial communities to colonize germ-free mice.**

Mice colonized with stool that had high proteolytic activity developed high fecal proteolytic activity themselves, compared with mice colonized with low proteolytic microbiota or microbiota from healthy controls. The higher proteolytic activity was paralleled by increased proteinase activated receptor-2 (PAR2), but not PAR1, cleavage by the microbiota in vitro.

SELECTED CONTENT

Study identifies a role for bacterial proteases in Crohn's disease

"Proteases with elastolytic activity, meaning they degrade elastin substrates, are pro-inflammatory. They cleave protease-activated receptor-2 (PAR2), expressed on the surface of many cell types including the gut epithelium and immune cells, activating downstream proinflammatory signalling pathways," said first author Amber Hann, a PhD student in the Verdu lab at McMaster University.

Next researchers were interested in the microbiota differences observed between the fecal samples with low and high proteolytic activity. They found **mice colonized with CD high proteolytic microbiota had an increased abundance of pathogenic taxa (e.g., *Hungatella [formerly Clostridioides] hathewayi*** and ***Romboutsia ilealis)*** **and a decreased abundance of beneficial taxa (e.g., *Akkermansia muciniphila, Alistipes putredinis, and Ruminococcus bromii).***

Unsurprisingly, the two CD microbiotas also had distinct predicted functional profiles. Several serine proteases were differentially expressed. Specifically, **the protease K04772 was observed to be increased in the high proteolytic CD microbiota.** Using analyses of functional predictions of microbial communities, the researchers demonstrated that mRNA transcripts of the protease K04772 positively correlated with increased mRNA transcripts of H. hathewayi. Thus, they concluded **one source of the proinflammatory protease activity seen in this CD cohort studied is from *H. hathewayi.***

Investigators then colonized additional germ-free mice with high or low proteolytic CD microbiota and subjected them to intestinal injury. Having high proteolytic CD microbiota made the mice more susceptible to intestinal injury and colitis. To investigate mechanisms, germ-free mice lacking ***Nod2*** (a common polymorphism in CD involved in bacterial sensing; ***Nod2***-/-) and mice lacking cleavable PAR2 were colonized with high proteolytic CD microbiota. ***Nod2***-/-developed severe colitis, but mice lacking cleavable PAR2 were protected from colitis, indicating this is a key event by which proteolytic CD microbiota mediates inflammation.

Overall studies that support a role of bacterial protease activity in the pathogenesis of CD and UC are mounting. *"Proteases are important for bacteria to survive but can also drive inflammation, especially if present in high abundance"* explains Amber, who is currently investigating the factors that drive the high bacterial protease activity, so that this proinflammatory activity of the microbiome can be prevented.

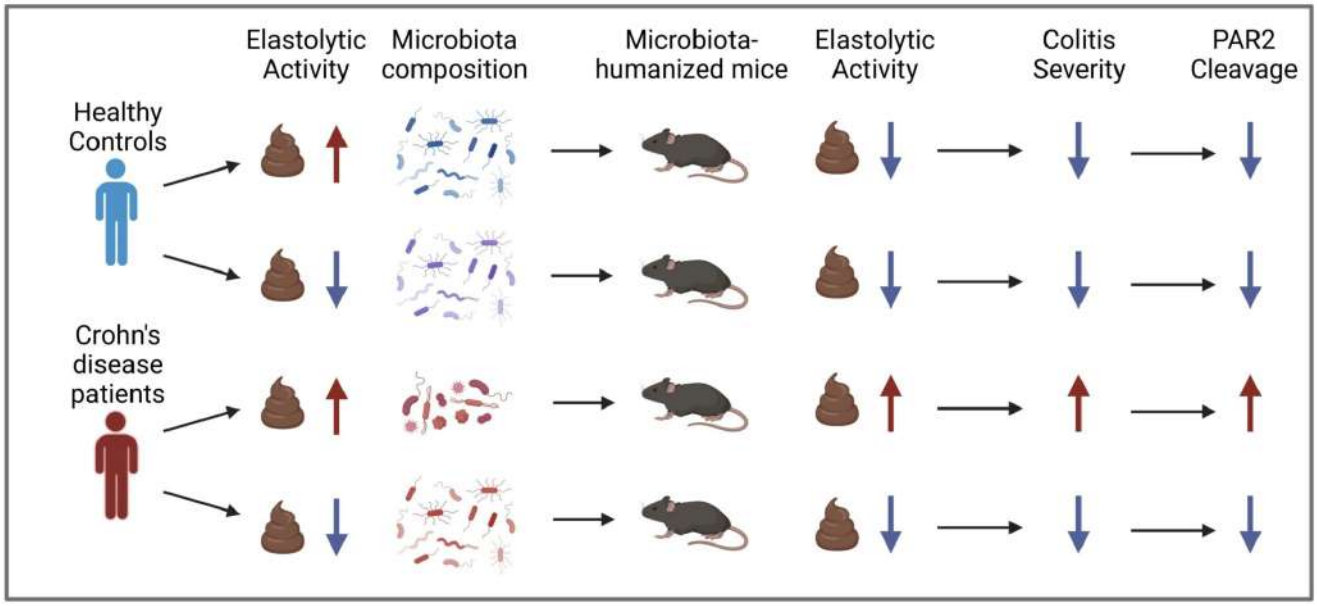
Although these findings cannot rule out the involvement of host proteolytic enzymes, they support that specific microbial proteolytic signatures can be targeted for interventions in patients with CD, preferably at an early stage of the disease. **Establishing a role for microbial proteolytic activity in IBD could lead the development of anti-proteolytic therapies directed at the bacterial taxa involved or the factors that drive this proinflammatory activity.**

Heather Galipeau

Heather Galipeau is an Assistant Professor at McMaster University (Canada) where she is researching dietary and microbia... l interactions in celiac disease and inflammatory bowel disease. She obtained her PhD in 2015 from McMaster University in Elena Verdu's lab, during which she found that the small intestinal microbial background influences the degree of immuno-pathology triggered by dietary antigens, such as gluten.

SELECTED CONTENT

Study identifies a role for bacterial proteases in Crohn's disease



Adapted from: Galipeau HJ, Caminero A, Turpin W, Bermudez-Brito M, et al. Gastroenterology 2021.

Amber Hann

Amber Hann is a PhD student (Medical Sciences) in the Verdu lab at McMaster University. She is currently investigating d... ietary drivers if microbial proteolytic activity in inflammatory bowel disease using patient samples and preclinical animal models.

References:

Galipeau, H. J. et al. Novel Fecal Biomarkers That Precede Clinical Diagnosis of Ulcerative Colitis. *Gastroenterology* **160**, 1532–1545 (2021).

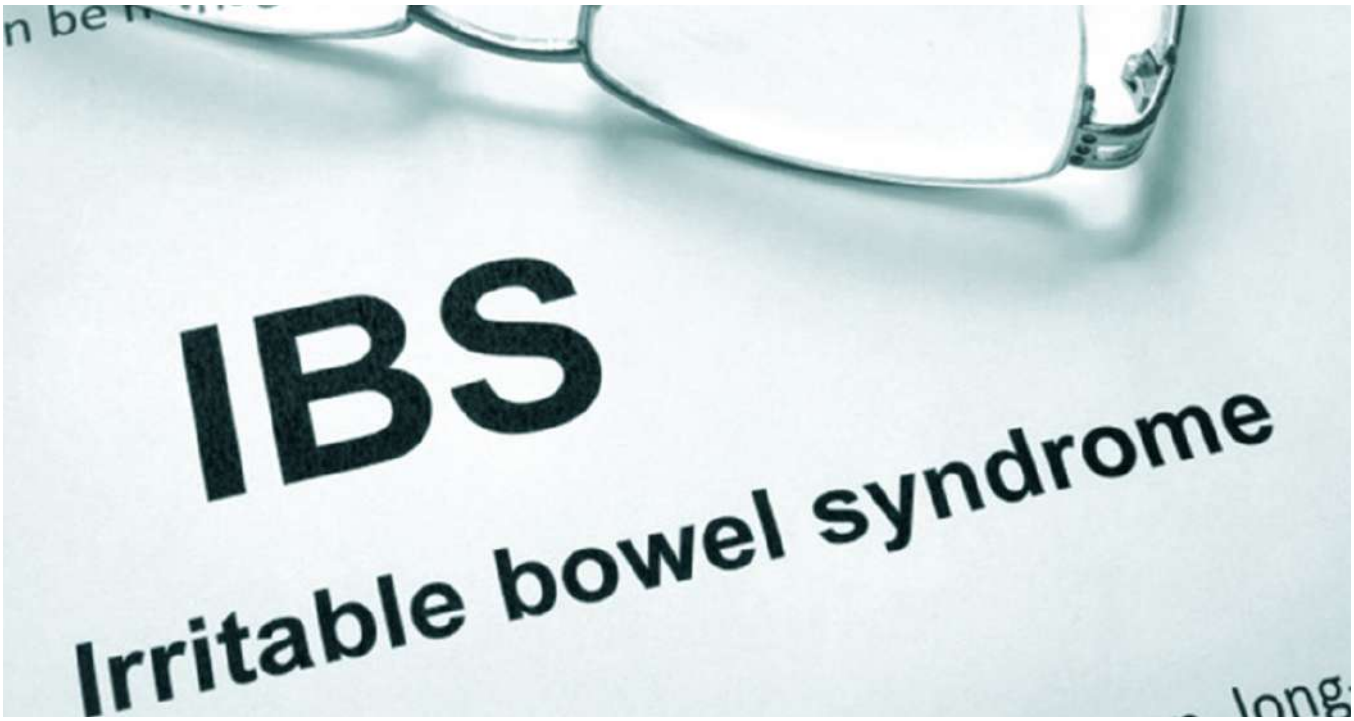
Santiago, A. & Hann, A. et al. Crohn's disease proteolytic microbiota enhances inflammation through PAR2 pathway in gnotobiotic mice. *Gut Microbes* **15**, 2205425 (2023).

SELECTED CONTENT

Diagnosing IBS and targeting gut microbiota and metabolites to improve symptoms

Published on October 18th, 2023 by Andrea Costantino

Chronic abdominal pain, diarrhea, constipation, and bloating are common gastrointestinal symptoms. While a structural or an organic disease can be suspected because of the symptoms and is often easy to be diagnosed by endoscopy or imaging methods, sometimes gastrointestinal symptoms are not related to any alteration that may be seen through diagnostic techniques, and consequently have been classified under the umbrella of "disorders of gut-brain interaction".



The educational content in this post, elaborated in collaboration with Bromatech, was independently developed and approved by the GMFH publishing team and editorial board.

Getting diagnosed with IBS

The use of symptom-based criteria for the diagnosis of gastrointestinal functional disorders may help physicians to diagnose and legitimize s uch disorders, and not be seen only as a combination of symptoms. A major improvement toward the understanding of these disorders was introduced by the criteria of the Rome Foundation. Many criteria have been adopted and the last ones are related to the Rome IV criteria (2016). Rome IV changed the terminology from functional disorders to disorders of gut-brain interaction (DGBI) since the term "functional" implied illegitimacy and stigmatized the patients1.

Diagnosing IBS and targeting gut microbiota and metabolites to improve symptoms

Even though a diagnosis could be made with the mentioned criteria, **certain examinations may be helpful to exclude not only inflammatory bowel diseases and celiac disease, but also bile acid diarrhea, congenital sucrose-isomaltase deficiency, histamine mediated disorders, systemic nickel allergy and high stool burden related to pelvic floor dysfunction**[3]. It has also been described that post-infective IBS and may occur in approximately 11% of people suffering an acute infection[4]. Recent studies also showed that COVID-19 might increase the risk of developing chronic intestinal symptoms and IBS[5,6].

Many patients diagnosed with IBS may also look for further diagnosis. However, when physicians identify patients' complaints as factual and can make a diagnosis based on these criteria, **providing empathy, engaging the patient in patient-centered interaction by describing the mechanisms of the disorder and by finding possible solutions to improve the physiological condition, those patients are more likely to accept the diagnosis.**

When the illness becomes easier to understand, it is also treated more appropriately! The good news is that the positive diagnosis of IBS by using symptom-based criteria and limited investigation is durable and safe, and it highlights that IBS is not associated with the development of organic gastrointestinal disease[2].

IBS subtypes and overlapping symptoms influence their management in clinical practice

IBS is classified into 4 subtypes based on predominant bowel habits:

- IBS with predominant constipation
- IBS with predominant diarrhea
- IBS with mixed bowel habits
- IBS unclassified

Moreover, there is functional diarrhea and constipation when these symptoms are not associated to pain. Functional abdominal bloating and distension are diagnosed only if these are the predominant symptoms and neither is required to make the diagnosis of IBS.

To meet the diagnostic criteria of IBS according to Rome IV, the following symptoms need to be present: **abdominal pain, on average at least 1 day a week in the past 3 months** (with the first onset at least 6 months before diagnosis), **associated with two of the following symptoms: pain related to defecation, change in frequency of stool or change in form (appearance) of stool**[1].

Targeting the gut microbiota to improve IBS symptoms

Although the etiology of IBS remains in part unknown, understanding the potential mechanisms has progressed rapidly over the years involving the gut microbiota, the gut-brain axis, the altered intestinal motility, the epithelial barrier, the immune system, the enteric nervous system, certain food antigens, and psychological and genetic factors[7].

The post-infective IBS model shows the central role of an alteration of gut microbiota as a leading mechanism for IBS. Other clinical scenarios linking IBS to gut microbiota include the increased risk of IBS induced by systemic antibiotics and IBS symptom improvement after taking probiotics or non-absorbable antibiotics.

Microbiota dysbiosis in IBS has been recognized by the Rome Foundation as a plausible factor contributing to the disorder[8]. Experiments with animal models, aimed to indicate the importance and possible etiological role of the microbiota in IBS, have proven that the colonization of germ-free animals with microbiota from IBS patients can induce visceral hypersensitivity, impair intestinal permeability, and altered gastrointestinal transit time[9].

SELECTED CONTENT

Diagnosing IBS and targeting gut microbiota and metabolites to improve symptoms

Specific bacteria (e.g., a decrease in *Bifidobacterium* and *Faecalibacterium* genus and an increase in *Lactobacillaceae* family, *Bacteroides* genus and *Enterobacteriaceae* family) **have been associated with the gut microbiomes of patients with IBS,** although it is too early to determine if these microbes are a product or cause of IBS[10]. It is also interesting to note that IBS symptoms severity is related to specific traits of gut microbiota composition (i.e., low microbial richness and Bacteroides enterotype enriched) and function (i.e., low methane exhaled), which highlights the potential of modulating gut microbiota as means to improve IBS symptoms and the quality of life of these patients.

The involvement of the gut microenvironment in IBS symptoms has led to the publication of a range of studies that suggest antibiotics, prebiotics and probiotics may exert their therapeutic activity through their impact at the level of gut microbiota composition, microbial metabolism products (e.g., short-chain fatty acids) and gut barrier integrity. However, the use of these gut microbiome-based treatments is not always universally approved. This is the case of rifaximin as non-absorbable antibiotic for IBS as its use is based on a potential capacity of changing an altered gut microbiota but more clinical studies are needed to better establish our understanding on the therapeutic role of antibiotics in IBS[11].

Future microbiome therapeutics in the pipeline for IBS include fecal microbiota transplants, microbial consortia, phages and engineered bacteria, while these strategies are still under study to translate their physiological effects into a possible clinical practice. For instance, Quigley and colleagues recently found the next generation probiotic *Blautia hydrogenotrophica* (MRx1234) is a new potential safe therapeutic option for patients with IBS-constipation, IBS-D or those who have mixed symptoms[12].

Recent studies also support other novel targets of potential interest for managing IBS symptoms. Histamine produced by specific gut bacteria has been involved in abdominal pain, which suggests the role of targeting bacterial histamine for managing abdominal pain in IBS. Also, following a low FODMAP diet was superior to the spasmolytic agent otilonium bromide in improving symptoms in patients with IBS in primary care. Sequestering harmful molecules in the gut environment through an intestinal adsorbent has also shown promising in improving stool consistency, abdominal pain, stool frequency and urgency in patients with IBS-predominant diarrhea. Overall, these findings suggest the potential of impacting gut microbiota and metabolites as means of improving IBS symptoms[13].

Take-home messages

- The use of symptom-based criteria for IBS helps physicians to make a diagnosis with limited investigations.
- Certain examinations may be helpful as a support to exclude less common organic diseases.
- IBS can have a slow-onset or a rapid-onset which is often related to infections (post-infective IBS).
- An altered gut microbiota composition and function appears to be involved in IBS onset and development, with specific gut microbiota profiles related to the severity of IBS symptoms.
- Future microbiome therapeutics in the pipeline for IBS include fecal microbiota transplants, microbial consortia, phages and engineered bacteria, while are not ready yet to use in the clinical practice.

Diagnosing IBS and targeting gut microbiota and metabolites to improve symptoms

References:

Drossman DA. Functional Gastrointestinal Disorders: History, Pathophysiology, Clinical Features and Rome IV. *Gastroenterology*. 2016 Feb 19:S0016-5085(16)00223-7. doi: 10.1053/j.gastro.2016.02.032. Epub ahead of print.

Khasawneh M, Craig OF, Gracie DJ, et al. A diagnosis of irritable bowel syndrome using Rome IV criteria and limited investigations is durable in secondary care. *Clin Gastroenterol Hepatol.* 2023 Jun 9:S1542-3565(23)00444-5. doi: 10.1016/j.cgh.2023.05.022. Online ahead of print.

Camilleri M, Boeckxstaens G. Irritable bowel syndrome: treatment based on pathophysiology and biomarkers. *Gut*. 2023 Mar;72(3):590-599. doi: 10.1136/gutjnl-2022-328515.

Barbara G, Grover M, Bercik P, et al. Rome Foundation Working Team Report on Post-Infection Irritable Bowel Syndrome. *Gastroenterology*. 2019 Jan;156(1):46-58.e7. doi: 10.1053/j.gastro.2018.07.011.

Marasco G, Cremon C, Barbaro MR, et al.; GI-COVID19 study group. Post COVID-19 irritable bowel syndrome. *Gut.* 2022 Dec 9:gutjnl-2022-328483. doi: 10.1136/gutjnl-2022-328483. Epub ahead of print.

Noviello D, Costantino A, Muscatello A, et al. Functional gastrointestinal and somatoform symptoms five months after SARS-CoV-2 infection: A controlled cohort study. *Neurogastroenterol Motil*. 2022 Feb;34(2):e14187. doi: 10.1111/nmo.14187.

Chey WD, Kurlander J, Eswaran S. Irritable bowel syndrome: a clinical review. *JAMA*. 2015 Mar 3;313(9):949-58. doi: 10.1001/jama.2015.0954.

Simrén M, Barbara G, Flint HJ, et al.; Rome Foundation Committee. Intestinal microbiota in functional bowel disorders: a Rome foundation report. *Gut.* 2013 Jan;62(1):159-76. doi: 10.1136/gutjnl-2012-302167.

Crouzet L, Gaultier E, Del'Homme C, Cartier C, Delmas E, Dapoigny M, Fioramonti J, Bernalier-Donadille A. The hypersensitivity to colonic distension of IBS patients can be transferred to rats through their fecal microbiota. *Neurogastroenterol Motil.* 2013 Apr;25(4):e272-82. doi: 10.1111/nmo.12103.

Pittayanon R, Lau JT, Yuan Y, et al. Gut Microbiota in Patients With Irritable Bowel Syndrome-A Systematic Review. *Gastroenterology.* 2019 Jul;157(1):97-108. doi: 10.1053/j.gastro.2019.03.049.

Iribarren C, Maasfeh L, Öhman L, et al. Modulating the gut microenvironment as a treatment strategy for irritable bowel syndrome: a narrative review. *Gut Microbiome.* 2022; 3:e7. doi: 10.1017/gmb.2022.6.

Quigley EMM, Markinson L, Stevenson A, et al. Randomised clinical trial: efficacy and safety of the live biotherapeutic product MRx1234 in patients with irritable bowel syndrome. *Aliment Pharmacol Ther.* 2023; 57(1):81-93. doi: 10.1111/apt.17310.

Simrén M. Targeting the gut microenvironment in IBS to improve symptoms. *Nat Rev Gastroenterol Hepatol.* 2023; 20(2):69-70. doi: 10.1038/s41575-022-00718-3.

Andrea Costantino

Andrea Costantino is a medical doctor, specialist in Gastroenterology. He is currently a PhD student at the University o... f Milan. Since 2016 he has been working at the Department of Gastroenterology and Endoscopy of the Ospedale Maggiore Policlinico of Milan. He has always been interested in the treatment of patients with disorders of the gut-brain interaction.

SELECTED CONTENT

Can probiotics aid in treating bacterial vaginosis and vulvovaginal candidiasis?

Published on June 14th, 2023 by Andreu Prados

Probiotics are commonly used in clinical practice for digestive ailments. Some clinical trials also support the use of specific probiotics, taken orally or vaginally, for restoring the vaginal microbiota and managing bacterial vaginosis and vulvovaginal candidiasis. Here's what we know.

The educational content in this post, elaborated in collaboration with Lesaffre, was independently developed and approved by the GMFH publishing team and editorial board.

What common situations can disrupt the vaginal microbiota?

Just like all other body mucosae, the vaginal mucosa is colonized by a microbiota that protects it against pathogenic insults. **The vaginal microbiota varies between women and has a low diversity because it is dominated by different species of *Lactobacilli*** (Lactobacillus crispatus, L. gasseri, L. iners and L. jensenii).

In addition to a varied microbiota profile between women, it is common for an individual woman's vaginal microbiota composition to fluctuate over time without showing signs of an unhealthy vaginal state. Also, a vaginal bacterial community with low *Lactobacilli* content and a high proportion of strictly anaerobic organisms that produce lactic acid has been described in reproductive-age Hispanic and black women and is linked to an unbalanced and asymptomatic state.

SELECTED CONTENT

Can probiotics aid in treating bacterial vaginosis and vulvovaginal candidiasis?

Factors that can change vaginal mucosa pH and lead to an imbalance of vaginal microbiota include:

- ethnic origin
- hormone fluctuations, typical in pregnancy, lactation and menopause or induced by contraceptives
- sexual behavior (i.e., having new sexual partners, frequent change of sexual partners)
- aggressive or incorrect hygiene (e.g., vaginal douching)
- antibiotics
- a decrease in immunity (e.g., HIV infection)
- some drugs (e.g., chemotherapy or corticosteroids)
- stress
- and some diseases (e.g., diabetes)

When *Lactobacilli* numbers fall, other bacteria or yeast normally present in the vagina can overgrow, causing various types of imbalance, including bacterial vaginosis (BV) and vulvovaginal candidiasis (VVC).

Can probiotics balance the vaginal microbiome and help manage BV?

BV is a common dysbiosis of the vaginal microbiota characterized by diverse, predominantly anaerobic bacteria, such as *Gardnerella vaginalis*, *Prevotella* species and *Mobiluncus* species, and relatively low numbers of *Lactobacillus* species.

BV is common in women and up to 50% of cases are asymptomatic. In women with symptomatology, the main signs of BV include itchiness around the vulva, a thin gray-white discharge and a "fishy" odor. BV can also increase the risk of sexual transmitted infections and has been associated with preterm birth.

While antibiotics are currently the recommended treatment for BV, they come with side effects, including an imbalance of the vaginal microbiota that can lead to recurrent infections. However, according to recent systematic reviews and meta-analysis (here; here; here), **bacteria and yeast probiotics have shown evidence of being potential prophylactic agents or adjuvant treatments for BV alongside conventional antibiotics.**

Some *Lactobacillus*-containing probiotics have shown benefits in preventing and treating bacterial vaginosis with a variable degree of efficacy.

The orally administered yeast probiotic **Saccharomyces cerevisiae CNCM I-3856** migrates from intestine to vagina, where it may exert its benefits against bacteria involved in BV (here; here; here).

It is important to highlight that the efficacy of probiotics varies with administration route and dosage. For instance, oral administration of probiotics seems to be more effective than vaginal application in treating BV because oral probiotics (bacteria or yeast) are able to migrate from intestine to vagina and eliminate the intestinal pathogens that may be responsible for vaginal infection recurrence. In addition, the oral route for administering probiotics is also the easiest and more convenient way of giving a treatment, which may improve treatment compliance and efficacy. Some probiotics have also been shown to reduce BV recurrences 11 months after treatment.

Some of the mechanisms of action that explain the rationale of using probiotics for BV include direct interference with pathogens' adherence to vaginal tissues, inhibition of sialidase activity and reduction of vaginal epithelial exfoliation.

Beyond probiotics, combining probiotics with antibiotics and performing vaginal microbiome transplants are both ongoing approaches currently being researched with the aim of strengthening vaginal health and preventing BV recurrence.

Are probiotics useful for improving antifungal treatment of VVC?

VVC is the most prevalent vaginal infection in the

Can probiotics aid in treating bacterial vaginosis and vulvovaginal candidiasis?

world, which affects about 75% of reproductive age women, with the main causative agent being *Candida albicans.* Recurrences are common, with 50% of women with VVC having two or more episodes. In contrast to BV, yeast infection is characterized by a white discharge with the consistency of cottage cheese, no vaginal odor, and redness and inflammation of the vulva.

Some evidence suggests some probiotics used as adjuvant therapy to antifungal drugs could be effective for treating VVC.

- Some studies support the benefits of *Lactobacillus* species for VVC together with antifungal treatments (e.g., reuteri RC-14®, *L. rhamnosus* GR-1®, *L. rhamnosus* Lcr35®). However, a 2017 Cochrane review concluded that, overall, **low and very low quality evidence shows that probiotics containing Lactobacillus species as an adjuvant therapy did not change the clinical cure rate**, as compared to conventional treatment.
- However, the aforementioned 2017 Cochrane systematic review did not include yeast probiotics. **The efficacy of yeast probiotics for treating VVC is supported by recent data in animal models and small intervention studies,** such as the case of cerevisiae CNCM I-3856 as a potential agent for managing VVC based on its immuno-modulatory and anti-inflammatory properties (here; here; here; here).

Based on mouse studies, probiotics' mechanisms of action against vaginal candidiasis include the ability to interfere with the expression of some virulence traits of *Candida albicans* in the vaginal cavity and to suppress the host inflammatory response mediated by the influx of neutrophils caused by the fungus into the vagina.

Concluding remarks

Bacterial vaginosis and vulvovaginal candidiasis are common dysbiosis of the vaginal microbiota characterized by relatively low numbers of *Lactobacillus* species.

The evidence for probiotic (bacteria or yeast) treatment of bacterial vaginosis is more compelling compared to vulvovaginal candidiasis. While some yeast probiotics have shown promising benefits for vulvovaginal candidiasis, more research is needed before broad conclusions could be drawn.

Furthermore, increasing evidence suggests that oral consumption of probiotics may be preferred over vaginal administration for vaginal health.

References:

Ravel J, Gajer P, Abdo Z, et al. Vaginal microbiome of reproductive-age women. *PNAS*. 2011; 108 (Suppl 1):4680-7. doi: 10.1073/pnas.1002611107.

Auriemma RS, Scairati R, del Vecchio G, et al. The vaginal microbiome: a long urogenital colonization throughout woman life. *Front Cell Infect Microbiol*. 2021; 11:686167. doi: 10.3389/fcimb.2021.686167.

Wilton L, Kollarova M, Heeley E, et al. Relative risk of vaginal candidiasis after use of antibiotics compared with antidepressants in women: postmarketing surveillance data in England. *Drug Saf.* 2003; 26(8):589-97. doi: 10.2165/00002018-200326080-00005.

Amabebe E, Anumba DOC. The vaginal microenvironment: the physiologic role of Lactobacilli. *Front Med.* 2018; 5:181. doi: 10.3389/fmed.2018.00181.

Centers for Disease Control and Prevention. Bacterial vaginosis. Available on: https://www.cdc.gov/std/treatment-guidelines/bv.htm

Mitchell H. Vaginal discharge—causes, diagnosis, and treatment. *BMJ.* 2004; 328(7451):1306-8. doi: 10.1136/bmj.328.7451.1306.

Kenyon C, Colebunders R, Crucitti T. The global epidemiology of bacterial vaginosis: a systematic review. *Am J Obstet Gynecol.* 2013; 209(6):505-23. doi: 10.1016/j.ajog.2013.05.006.

Klebanoff MA, Brotman RM. Treatment of bacterial vaginosis to prevent preterm birth. *Lancet.* 2018; 392(10160):2141-2. doi: 10.1016/S0140-6736(18)32115-9.

SELECTED CONTENT

Can probiotics aid in treating bacterial vaginosis and vulvovaginal candidiasis?

Chen R, Li R, Qing W, et al. Probiotics are a good choice for the treatment of bacterial vaginosis: a meta-analysis of randomized controlled trial. *Reprod Health.* 2022; 19(1):137. doi: 10.1186/s12978-022-01449-z.

Liu H-F, Yi N. A systematic review and meta-analysis on the efficacy of probiotics for bacterial vaginosis. *Eur Rev Med Pharmacol Sci.* 2022; 26(1):90-8. doi: 10.26355/eurrev_202201_27752.

Wang Z, He Y, Zheng Y. Probiotics for the treatment of bacterial vaginosis: a meta-analysis. *Int J Environ Res Public Health.* 2019; 16(20):3859. doi: 10.3390/ijerph16203859.

Cayzeele-Decherf A, Pélerin F, Jüsten P. Saccharomyces cerevisiae CNCM I-3856 as a natural breakthrough for vaginal health: a clinical study. *Med J Obstet Gynecol.* 2017; 5(4):1112.

Decherf A, Dehay E, Boyer M, et al. Recovery of Saccharomyces cerevisiae CNCM I-3856 in vaginal samples of healthy women after oral administration. *Nutrients.* 2020; 12(8):2211. doi: 10.3390/nu12082211.

Sabbatini S, Monari C, Ballet N, et al. Saccharomyces cerevisiae-based probiotic as novel anti-microbial agent for therapy of bacterial vaginosis. *Virulence*. 2018; 9(1):954-66. doi: 10.1080/21505594.2018.1464362.

Sabbatini S, Monari C, Ballet N, et al. Anti-biofilm properties of Saccharomyces cerevisiae CNCM I-3856 and Lacticaseibacillus rhamnosus ATCC 53103 probiotics against G. vaginalis. *Microorganisms*. 2020; 8(9):1294. doi: 10.3390/microorganisms8091294.

Ouwehand A, Lehtoranta L. Probiotics for vaginal health; oral consumption vs. local application. 2021.

Ya W, Reifer C, Miller LE. Efficacy of vaginal probiotic capsules for recurrent bacterial vaginosis: a double-blind, randomized, placebo-controlled study. *Am J Obstet Gynecol.* 2010; 203(2):120.e1-6. doi: 10.1016/-j.ajog.2010.05.023.

Xie HY, Feng D, Mei Wei D, et al. Probiotics for vulvovaginal candidiasis in non-pregnant women. *Cochrane Database Syst Rev.* 2017; 11:CD010496. doi: 10.1002/14651858.CD010496.pub2.

Gabrielli E, Pericolini E, Ballet N, et al. Saccharomyces cerevisiae-based probiotic as novel anti-fungal and anti-inflammatory agent for therapy of vaginal candidiasis. *Benef Microbes.* 2018; 9(2):219-30. doi: 10.3920/BM2017.0099.

Pericolini E, Gabrielli E, Ballet N, et al. Therapeutic activity of a Saccharomyces cerevisiae-based probiotic and inactivated whole yeast on vaginal candidiasis. *Virulence.* 2017; 8(1):74-90. doi: 10.1080/21505594.2016.1213937.

Cohen CR, Wierzbicki MR, French AL, et al. Randomized trial of Lactin-V to prevent recurrence of bacterial vaginosis. *N Engl J Med*. 2020; 382(20):1906-15. doi: 10.1056/NEJMoa1915254.

Andreu Prados

Andreu Prados holds a Bachelor of Science Degree in Pharmacy & Human Nutrition and Dietetics. Science writer special... ised in gut microbiota and probiotics, working also as lecturer and consultant in nutrition and healthcare. Follow Andreu on Twitter @andreuprados

SELECTED CONTENT

Are we ready to target the gut microbiota for obesity and weight management? A journey from bench to bedside

Published on May 24th, 2023 by Andreu Prados, Patrice D. Cani

Studies over the last decade have brought new hope that gut microbiome-targeted therapeutics might offer novel treatments for obesity. In this post, we ask whether dietary interventions, prebiotics, probiotics and medication that target the microbiome are useful for weight management.

Initial findings linking gut microbiota and obesity: insights from animal models

Even though obesity is the result of a long-term imbalance between energy intake and energy expenditure, lifestyle interventions aimed at restoring that imbalance do not work for everybody. In recent years, increasing evidence has linked obesity to the gut microbiota.

Initial findings in rats two decades ago showed that changes in the gut microbiota caused by fermentable fiber such as inulin-type fructans (e.g., inulin or oligofructose) reduced body weight and adipose mass in rats by involving gut peptides that regulate appetite. Additional findings showed that slim germ-free mice colonized with a normal gut microbiota gained more body fat by 60% and increased their insulin resistance, even though they reduced their food intake. When using a humanized mouse model, researchers showed

Are we ready to target the gut microbiota for obesity and weight management? A journey from bench to bedside

that mice receiving the microbiota from obese human donors gained more weight as compared to their counterparts receiving the microbiota from a genetically-identical twin pair but which was lean. However, the germ-free model widely used in elucidating the causal role of the microbiota during obesity also has its caveats, as the housing conditions of mice can lead to contradictory results in the context of obesity (see here and here).

The difficulty of translating mouse results into the human context

When data across different human studies were analyzed, the connection between obesity and gut microbiota composition was less strong. While gut microbiota composition is an important contributor of weight gain in mouse models, it may not be the most important factor driving human weight changes. This can be explained by the fact that different factors that should be considered as confounding variables in human microbiome studies (e.g., social environment and social pressure, multiple dietary factors, specific drugs and bariatric surgery) can affect both the composition and diversity of the gut microbiota. So far, there is no clear hallmark of obesity based on the gut microbiota composition and the so called ***"Firmicutes/Bacteroidetes ratio"*** is one of the example that should no longer be used.

Weight-loss interventions that affect the gut microbiota

The most widely studied weight-loss interventions that shape the gut microbiota and host hormones include dietary patterns (e.g., Mediterranean diet, fiber-enriched diet and ketogenic diet), fasting, physical activity, some medications (e.g., anti-obesity drugs such as Orlistat and glucose lowering drugs such as Metformin), fecal microbiota transplantation and bariatric surgery.

Diet is the intervention with the strongest impact on the gut microbiota and a Mediterranean diet rich in fiber is the dietary pattern supported by human data with the most evidence to support its use for improving cardiometabolic health. In contrast, the benefits of the ketogenic diet for promoting weight loss that come mostly from mice data are not conclusive. While intermittent fasting is another popular diet used for losing weight, available studies are limited and most of the time of short duration, which limits making general recommendations for weight loss. Therefore, the best method for losing weight is probably based on personalizing dietary advice with the help of a registered dietitian, while the science remains limited on the use of the results of what kind of microbes live in our gut as means of helping with losing weight.

Targeting the human gut microbiota with specific bacteria linked to beneficial effects in the context of obesity such as on insulin resistance and pre-diabetes is also another feasible option. The case of Akkermansia muciniphila is a key example. This bacterium is a normal inhabitant of the human gut. It has been shown that both live bacteria and pasteurized A. muciniphila (i.e., heat-inactivated form) may improve insulin sensitivity, total cholesterol and liver dysfunction and decrease blood inflammatory markers when supplemented for three months to people who met the criteria for metabolic syndrome. Although, no specific effects on body weight were observed in this study.

Instead of administering a few bacteria in low doses in form of a probiotic, consortia of bacteria also offer a potential new treatment for weight management. However, while a few randomized placebo-controlled studies have explored the administration of fecal microbiota transplants in

SELECTED CONTENT

Are we ready to target the gut microbiota for obesity and weight management? A journey from bench to bedside

patients with obesity and metabolic syndrome, their efficacy is limited and relies largely not only on donors' diet and gut microbiota composition, but on the recipient gut microbiota.

The mechanisms by which microbiota-targeted interventions impact host metabolism involve many potential factors such as the production of short-chain fatty acids, endocannabinoids, tryptophan metabolites and bile acids. For instance, both butyrate and propionate stimulate the secretion of gut peptides such as glucagon-like peptide 1 (GLP1), peptide tyrosine tyrosine (PYY) and GLP2. These effects can contribute to reduce food intake, improve glucose metabolism, maintain inflammation at bay and keep anaerobic conditions in the gut lumen. These changes can also prevent the metabolic endotoxemia that accompanies obesity by preventing lipopolysaccharide (LPS) leakage into the bloodstream. Strikingly, specific microbial profiles have been found in the liver, adipose tissue and plasma in people with morbid obesity and diabetes, whereas their relevance to host metabolism remains to be seen.

Take-home messages

To sum up, while the first treatment for cardiometabolic disorders is a healthy diet and sufficient exercise, gut microbiota-related interventions have brought new hope despite being a new field of research. One challenge that should be overcome is to move away from simple associations between shifts in the gut microbiota at the taxonomic level and the features of obesity. Instead, also exploring the metabolic capacity of the intestinal microbiota and metabolites produced seems to be more relevant in terms of health outcomes. Trying to avoid the classification of gut microorganisms as "friend" or "foe" can also help in advancing the field, as can measuring confounders that can impact the effects of the gut microbiota on the host metabolism.

References:
Van Hul M, Cani PD. The gut microbiota in obesity and weight management: microbes as friends or foe? *Nat Rev Endocrinol.* 2023; 19(5):258-71. doi: 10.1038/s41574-022-00794-0.

Andreu Prados
Andreu Prados holds a Bachelor of Science Degree in Pharmacy & Human Nutrition and Dietetics. Science writer special... ised in gut microbiota and probiotics, working also as lecturer and consultant in nutrition and healthcare. Follow Andreu on Twitter @andreuprados

SELECTED CONTENT

Fecal microbiota transplantation: From clinical trials to market, where are we now?

Published on February 7th, 2023 by Andreu Prados

While fecal microbiota transplants are recommended for multiple recurrent Clostridioides difficile infection, their use in clinical practice is hindered by a lack of regulation and understanding of the underlying ecological dynamics. This article covers major challenges for the treatment in transitioning from bench to bedside, from the scientific, clinical and regulatory perspectives (Part 6).

Ferring Pharmaceuticals has had editorial planning involvement, including suggestions of content and topics, as well as proposal of experts for articles. The final educational content was independently developed and approved by the GMFH publishing team and editorial board.

This is the sixth article in a special collection that focuses on the epidemiology, diagnosis and management of C. difficile infection, which is of relevance to gastroenterologists. See the first article on *C. difficile* infection prevalence and risk factors here, the second article on diagnosing and managing primary and recurrent *C. difficile* infection here, the third article on the pros and cons of fecal transplants and defined commensal consortia for recurrent *C. difficile* infection here, the fourth article on *C. difficile* infection from clinicians' and patients' perspectives here and the fifth article on *C. difficile* complications here.

SELECTED CONTENT

Fecal microbiota transplantation: From clinical trials to market, where are we now?

The evolution of fecal microbiota transplants, one of the most advanced microbiome-based treatments

While fecal microbiota transplants (FMTs) have been practiced since the 1950s, it was not until recently that they were re-discovered as a therapeutic approach for restoring an altered gut microbiota composition and function. Current European and American guidelines recommend FMTs for treating patients with recurrent *Clostridioides difficile* infections.

Initially, FMT was performed after little processing of the original fecal material. Yet as key microbes or functions involved in its efficacy have been characterized, companies have developed products consisting of defined consortia of microorganisms (namely investigational microbiome biotherapeutics).

The approval of other therapeutic candidates for the microbiome is also expected in early 2023 and will open the door to future biologics license applications (a formal documentation required by the FDA to commercialize a new drug).

Challenges that hinder fecal microbiota transplants' access to market

While establishing stool banks has enabled a centralization of ready-to-use feces suspensions to meet the needs of patients, some challenges still hinder access to the treatment for severely ill patients. A definition of quality standards for FMT is of utmost importance due to safety concerns around the transmission of multi-drug resistant organisms through FMT. Standardization of preparation processes best suited to preserve functionalities of the intestinal ecosystem, development of appropriate tools to finely assess engraftment and documentation of compatibility between FMT drug and the recipient are major scientific challenges that this treatment modality needs to overcome in order to move from the bench to the bedside according to Joël Doré, a trained gut microbial ecologist with 40 years' experience in both basic and translational developments in microbiome-based therapies. In the current post-COVID-19 era, screening donors and recipients to ensure the efficacy and safety of FMT is also relevant.
Despite products based on FMT being among the most advanced microbiome-based treatments, **the lack of consistency in regulatory standards and scientific guidelines derived from those standards hinders its ready-to-use application for patients.** The United States has the longest history in taking the lead in the microbiome field. In 2013, the FDA positioned FMT for recurrent CDI as a therapeutic intervention that only needs the informed consent of the patient, while for other indications it is considered a drug and thus requires an investigational new drug application to be made. In November 2022, a product composed of a defined consortium of microorganisms was the first-ever microbiome therapeutic approved by the FDA for preventing the recurrence of *C. difficile* infection in adults after standard-of-care antibiotic treatment.

When making FMT readily available to severely ill patients, Doré states that: "Production of the drugs should not be a limiting factor, but it still is in many countries. The false perception that the academic/hospital structures will be able to fulfill the need is probably at stake. It has to become the routine job of pharma companies to condition the FMT drugs and make them readily available."

Australia has facilitated access to fecal transplants for treating not only *C. difficile* but other digestive conditions. Last November, it became the first country in the world to receive regulatory approval for fecal transplants as a biological drug for restoring the gut microbiota in the management of gastrointestinal disorders.

In Europe, there is a long way to go before marketing authorizations of FMT are granted. And even though the

SELECTED CONTENT

Fecal microbiota transplantation: From clinical trials to market, where are we now?

EU Innovation Network published a recent report with an update of the regulatory situation of FMT in Europe, the quality and safety requirements of FMT is defined by individual countries.

Most EU countries have regulated FMT as a drug, while Finland regulates it as a therapeutic intervention and Italy as tissue. The United Kingdom also regulates FMT as a drug and Canada classifies it as a biological drug. When FMT is classified as a pharmaceutical drug or biological product, it is subject to more stringent requirements and legislation. In addition, the degree of processing of the fecal material or its indication also determines how FMT is regulated. Despite FMT being a widespread treatment in Europe, there is a significant underuse of FMTs (covering only 10% of patients with recurrent CDI).

Raising clinical awareness, adjusting regulatory frameworks for FMT and collaboration between scientists, clinicians and regulatory agencies are suggested as steps that will help move the field forward.

According to Doré: "By far the general consensus in Europe is to consider FMT products as drugs, which is probably the best for the patients. A harmonized regulation for all countries considering FMT products as drugs could be promoted. *C. difficile infection* it is the only ecological disease for which FMT as an ecological treatment does not seem extremely demanding: the barrier function that eliminates the pathogen can be restored with a preparation that does not attempt to preserve all functionalities of the intestinal ecosystem."

Beyond regulatory issues, another challenge is FMT application in vulnerable populations, such as children. The pediatric population will be less likely to benefit from the treatment given the lack of clinical trials in children and the limitations of available tests to differentiate infection from colonization in children, which obstructs clinical decisions on the best time to start FMT therapy. As for any other drug, FMT may not be recommended for specific vulnerable populations, until proven safe.

The future of fecal microbiota transplants

While infectious diseases are the field in which applications of FMT are most widely researched, scientists have also started exploring its role for preserving the gut microbiome damaged after cancer treatments and also for inflammatory bowel diseases, due to its immune-modulating properties. Examples of diseases in which FMT could become an accepted treatment option in the future are irritable bowel syndrome, liver disorders, decolonization of multidrug-resistant bacteria, metabolic disorders, some neurological disorders and even as add-on to cancer therapy.

According to Doré: "The current scientific literature indicates that fecal microbiota transfer will be much more potent than most if not any of the single strain or small consortia tested in line with the probiotic concept. It will nevertheless most likely be add-on therapies in the many contexts for which standard of care is not providing a cure but also is only efficient in a fraction of patients. Scientific evidence has been building for ulcerative colitis, for cancer therapy with immune checkpoint inhibitors or possibly chimeric antigen receptor (CAR) T-cells, and possibly for therapeutic dead-ends such as steroid-resistant acute graft versus host disease, acute-on-chronic liver failure or amyotrophic lateral sclerosis."

Take-home messages

- While fecal microbiota transplants are commonly used for medically refractory or recurrent difficile infections, questions remain about its effectiveness, safety, regulation and best practice.
- The US and Australia have approved FMT for recurrent difficile infection, while in Europe, regulation of the procedure hinders its widespread use, especially among high-risk patients for whom the treatment might be lifesaving.

SELECTED CONTENT

Fecal microbiota transplantation: From clinical trials to market, where are we now?

- Beyond gastrointestinal conditions, immune-mediated diseases and oncology are areas of potential interest for fecal microbiota transplants and their application in those contexts may take place in the near future.

References:

Kelly CP. Fecal microbiota transplantation – an old therapy comes of age. *N Engl J Med.* 2013; 368(5):474-475. doi: 10.1056/NEJMe1214816.

Gosálbez L. Microbiome Drug Development: 2022 in review. Microbiome Times. December 30, 2022. Available in: https://www.microbiometimes.com/microbiome-drug-development-2022-in-review/

Gut Microbiota for Health. A new study illustrates the risks of administering fecal microbiota transplants to compromised patients. Schneider S. April 6, 2020. Available in: https://www.gutmicrobiotaforhealth.com/a-new-study-illustrates-the-risks-of-administering-fecal-microbiota-transplants-to-compromised-patients/

Kazemian N, Kao D, Pakpour S. Fecal microbiota transplantation during and post-COVID-19 pandemic. *Int J Mol Sci.* 2021; 22(6):3004. doi: 10.3390/ijms22063004.

U.S. Food & Drug Administration. Science and regulation of live microbiome-based products used to prevent, treat, or cure diseases in humans. September 17, 2018. Available in: https://www.fda.gov/vaccines-blood-biologics/workshops-meetings-conferences-biologics/science-and-regulation-live-microbiomeprevent-treat-or-cure-diseases-humans#event-materials

BiomeBank. BiomeBank announces world first regulatory approval for donor derived microbiome drug. November 9, 2022. Available: https://www.biomebank.com/news/media-release/biomebank-announces-world-first-regulatory-approval-for-donor-derived-microbiome-drug/

European Medicines Agency. Faecal Microbiota Transplantation. June 2022. Available in: https://www.ema.europa.eu/en/documents/report/faecal-microbiota-transplantation-eu-horizon-scanning-report_en.pdf

Hocking L, Ianiro G, Leong RW, et al. Faecal microbiota transplantation for recurrent C. difficile infections: challenges and improvement opportunities for clinical practice and healthcare systems. *Aliment Pharmacol Ther.* 2022. doi: 10.1111/apt.17309.
Merrick B, Allen L, M Zain NM, et al. Regulation, risk and safety of faecal microbiota transplant. *Infect Prev Pract.* 2020; 2(3):100069. doi: 10.1016/j.infpip.2020.100069.

Hourigan SK, Nicholson MR, Kahn SA, et al. Updates and challenges in fecal microbiota transplantation for Clostridioides difficile infection in children. *J Pediatr Gastroenterol Nutr.* 2021; 73(4):430-432. doi: 10.1097/MPG.0000000000003229.

Ransom EM, Burnham CAD, Jones L, et al. Fecal microbiota transplantations: where are we, where are we going, and what is the role of the clinical laboratory? *Clin Chem.* 2020; 66(4):512-517. doi: 10.1093/clinchem/hvaa021.

National Institute for Health and Care Excellence (NICE). Fecal microbiota transplant for recurrent *Clostridioides difficile infection.* 31 August 2022. Available: https://www.nice.org.uk/guidance/mtg71

Ianiro G, Segal JP, Mullish BH, et al. Fecal microbiota transplantation in gastrointestinal and extraintestinal disorders. *Future Microbiol.* 2020; 15:1173-1183. doi: 10.2217/fmb-2020-0061.-based-products-used-

Andreu Prados

Andreu Prados holds a Bachelor of Science Degree in Pharmacy & Human Nutrition and Dietetics. Science writer special... ised in gut microbiota and probiotics, working also as lecturer and consultant in nutrition and healthcare. Follow Andreu on Twitter @andreuprados

JOIN OUR COMMUNITY TODAY AND STAY TUNED

with the most relevant scientific developments about gut microbiota.

With more than 165,000 members around the globe!

Gut Microbiota for Health

@GMFHx

Gut Microbiota News Watch

Monthly newsletter

YEAR AT A GLANCE

February 2023

www.gutmicrobiotaforhealth.com

ESNM European Society of Neurogastroenterology & Motility

www.esnm.eu

Alser Strasse 4, 1090 Vienna, Austria

Gut Microbiota & Health