EDITORIAL .................................................................................................................................................. 3

SELECTED CONTENT FROM GUTMICROBIOTAFORHEALTH.COM

Beyond gut bacteria: looking into the gut mycobiota and yeast probiotics for managing gastrointestinal diseases
• The role of the gut mycobiota in influencing the immune system and inflammation-related diseases ................................................................. 6
• Yeast probiotics for the management of gastrointestinal symptoms of IBS ........................................................................................................... 9

Probiotics and emerging postbiotics for digestive and inflammation-related diseases
• Probiotics with an anti-inflammatory effect may reduce abdominal pain and hours of hospitalization in adult patients with acute uncomplicated diverticulitis ........................................................................... 13
• Bacterial extracellular vesicles: future postbiotics? .................................. 17
• In which circumstances is intestinal permeability increased and what can be done to improve it? ................................................................. 20

Fecal transplants and microbial consortia for tackling Clostridioides difficile infection: present and future
• Clostridioides difficile infection remains an unfamiliar subject for clinicians: prevalence, risk factors and co-occurrence with COVID-19 ...... 23
• Fecal transplants and defined commensal consortia: the pros and cons of restoring the gut microbiome in recurrent Clostridioides difficile infection .............................................................. 28

Key advances in personalized nutrition and medicine through the gut microbiome
• Why microbiome tests are currently of limited value for your clinical practice ......................................................................................... 32
• The gut microbiome in personalized nutrition and medicine: takeaways from the 2022 GMFH Summit .......................................................... 36
• Where do we stand in the management of IBS? Highlights from “IBS days 2022” in Bologna ............................................................. 50
shown to be an effective and safe tool include infectious diarrhea, antibiotic-associated diarrhea and irritable bowel syndrome. More recently, scientists have started exploring yeast-based engineered probiotics in mouse models of colitis to suppress intestinal inflammation, reduce levels of intestinal fibrosis and promote microbiome recovery.

Current observations of the direct or indirect role of the gut mycobiota in the host immune system advocate further research into fungi to prevent and manage acute and chronic gastrointestinal disease.

Probiotics and emerging postbiotics for digestive and inflammation-related diseases

Inflammation and increased intestinal permeability are common hallmarks of a wide range of diseases and the increasing evidence to support probiotics’ effectiveness is partly explained by those mechanisms. That is the case of the probiotic strain *Limosilactobacillus reuteri* ATCC PTA 4659, which has been shown to be a potential therapeutic approach for acute diverticulitis due to its anti-inflammatory properties, its microbiota-supporting properties and its role in excluding gut pathogens.

Strengthening intestinal barrier function is also another way by which specific probiotic bacterial strains modulate human disease. Evidence is mounting that altered epithelial barrier integrity is involved in infections, obesity, irritable bowel syndrome and inflammatory bowel disease, among others. On the whole, a diet rich in nutrients, food staples and food supplements (e.g., prebiotic fibers, probiotics, polyphenols, glutamine, vitamin D and zinc) that regulate the intestinal tight junction’s barrier might have a beneficial effect for reducing gastrointestinal disease symptoms.

Beyond probiotics, postbiotics (i.e., inanimate microorganisms and/or their components that confer a health benefit on the host) emerge as an intervention with potential health benefits through mechanisms that may or may not directly target the microbiome. Scientists claim that non-viable cells may be functional components of probiotics and should be characterized in probiotic products. That, therefore, has implications...
for reporting inanimate microbes in products for use in intervention trials and for the marketplace. Of all the components of dead bacteria, membrane vesicles have recently attracted scientific interest in the field of postbiotics.

Fecal transplants and defined microbial consortia for restoring gut microbiome

Based on the assumption that some microbial species contribute to an unfavorable gut microbiota, fecal microbiota transplantation (FMT) has emerged as a therapeutic approach for replacing an altered resident gut microbiota with a favorable one from a healthy donor. The intervention has demonstrated clear efficacy in treating recurrent *C. difficile* infection. Beyond that indication, FMT is also being explored for irritable bowel syndrome, obesity, type 2 diabetes, inflammatory bowel disease and even neurological disorders.

On November 2022, the FDA approved the first fecal microbiota product for preventing recurring *C. difficile* infection in adults, although due to its microbiologically undefined nature, this is not a probiotic drug. While studies are beginning to better elucidate the underlying mechanisms of FMT, major challenges in the field include characterizing determinants of the efficacy of FMT, safety and the need for consensus before generalizing the treatment in clinical practice worldwide. Meanwhile, the field is moving toward a defined consortium of microbes that can restore an altered gut microbiome depleted from an antibiotic or disease state and overcome the time-consuming job of finding appropriate donors and safety concerns associated with FMT.

Toward personalized medicine: how the microbiome shapes patient response to diet

The microbiome is a potentially modifiable factor at the frontier of personalized medicine and nutrition. The makeup of our microbiome, which impacts how we respond to diet and drugs, was a hot topic at the 2022 GMFH World Summit. As the presence of specific strains may have the ability to modulate disease progression and therapeutics, the interest in using the microbiota for individualized treatments increases. However, the evidence does not yet suggest promoting or excluding entire food groups based on microbiome tests, which even in the absence of evidence are widely promoted as a means of determining the health of a person’s gut microbiome or for helping individuals lose weight.

As we learn more and more about the relevance of the microbiome for host health and disease, it becomes clear that classic, one-size-fits-all nutrition-based recommendations do not make sense, as was experienced with the generalized advice of restricting fermentable dietary substrates in patients (FODMAP diet) for patients with IBS. In contrast to the common belief that restrictive diets work best, emerging data indicate that consumption of dietary fibers induces an adaptive response by the gut microbiota toward fermentative pathways with lower gas production. Therefore, the findings question the common belief that restricting diet according to digestive tolerance is the desired goal in patients with digestive issues.

GMFH ecosystem evolution

*C. difficile* infection is a common public health threat, not only in the hospital setting but in the community. Together with the European Society of Neurogastroenterology & Motility (ESNM), GMFH prepared a comprehensive and practical seven-session webinar series to update health care professionals and scientists working in the gut microbiome on the major advances in the field. Taking place throughout 2022, we live-covered the sessions on Twitter using the hashtag #GMFHCoverage with 6.2M+ impressions and 130 participants from all over the world.

The GMFH digital community grew this year to exceed 150,500 members, including scientists, health care professionals and the general public. In 2022, the GMFH website had more than 1.1 million page views and that number continues to grow.

Last year’s edition of the Gut Microbiota for Health World Summit took place both in person and virtually. In 2023, the event’s 11th edition will take place in the traditional format on 11 and 12 March in Prague, with an
agaenda that includes one keynote lecture, 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 safe and gut-friendly 2023 and keep in touch for upcoming advances in the field!

References


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.

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 receptor expressed in innate immune cells such as dendritic cells.
Beyond gut bacteria: looking into the gut mycobiota and yeast probiotics for managing gastrointestinal diseases

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

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

while immunological mechanisms have not yet been fully described,” acknowledges Mathias L. Richard.

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.

References:


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
Beyond gut bacteria: looking into the gut mycobiota and yeast probiotics for managing gastrointestinal diseases

SELECTED CONTENT

Yeast probiotics for the management of gastrointestinal symptoms of IBS

Published on September 27th, 2022 by Andreu Prados

Bacteria and fungi in the human gut microbiota may contribute to the underlying mechanisms of IBS, which means the latter can be explored as a potential target for IBS. This article explores what is known about the role of the gut microbiome and yeast probiotics in irritable bowel syndrome.

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

Why the bacterial and fungal intestinal microbiome are relevant in the development of irritable bowel syndrome

Irritable bowel syndrome (IBS) is the most common disorder of gut-brain interaction seen by primary care physicians and diagnosed by gastroenterologists. Despite it being a heterogeneous disease, changes in the gut microbiome have recently been associated with IBS symptoms. There are three clinical scenarios that link IBS to the gut microbiome (also available for review elsewhere). First, while the majority of patients suffering from a bout of gastroenteritis recover, 10% will develop IBS symptoms. Second, the administration of systemic antibiotics may increase the risk of IBS by altering the gastrointestinal environment. Last, interventions that target the gut microbiome, such as probiotics and non-absorbable antibiotics, may lead to symptoms improvement.
Beyond gut bacteria: looking into the gut mycobiota and yeast probiotics for managing gastrointestinal diseases

Yeast probiotics for the management of gastrointestinal symptoms of IBS

While studies on the role of the gut microbiome in IBS have focused primarily on bacteria, intestinal fungi (known collectively as gut mycobiome) have been largely overlooked. Nevertheless, the fecal mycobiome may help with differentiating patients with IBS from healthy controls and may contribute to IBS-related visceral hypersensitivity.

Indeed, aside from bacteria, the gut mycobiome may participate to the known mechanisms of IBS, which include low-grade inflammation, fungal-bacterial interactions in the gut mucosa, visceral hypersensitivity, gut-brain interactions, intestinal barrier dysfunction and impaired gastrointestinal motility. These findings highlight the relevance of an altered microbiota-gut-brain axis in IBS development and suggest the potential of targeting not only bacteria, but the fungal component of the gut microbiome for diagnosing or managing IBS.

Can bacteria and yeast probiotics help patients with IBS?

A recent systematic review has reported that specific probiotics can benefit patients with IBS through alleviating abdominal pain and improving bowel movement frequency.

When choosing the right probiotic for IBS management, it should be remembered that within species strain differences may affect clinical outcomes. While core effects for probiotics have been described (e.g., a healthy gastrointestinal tract), strain-specific effects include immune modulation, anti-inflammatory properties and production of specific bioactives, which are worth considering when managing gastrointestinal disorders.

Particular species and strains of bacteria (belonging to the Lactobacillus, Bifidobacterium, Escherichia coli and Streptococcus genera) or yeast (i.e., Saccharomyces cerevisiae and S. boulardii) or a combination (i.e., Lactobacillus and Bifidobacterium strains) have been shown to be effective for improving overall IBS symptoms and abdominal pain.

Advantages of yeast probiotics versus bacterial probiotics

While yeast probiotics share health benefits with bacterial probiotics, important advantages of yeast probiotics are that:

• They are resistant against gastrointestinal enzymes, bile salts and variations in pH and temperature. That ensures yeast probiotics can reach the colon almost intact.

• They continue to work during antibiotic use due to yeast’s intrinsic resistance to antibiotics, which means yeast probiotics can be co-administered with antibiotics.

• The modification of the host immune response is considered an important mechanism of action that explains some of the positive health benefits of yeast probiotics.

Pierre Desreumaux, Professor of Gastroenterology at the University and Hospital of Lille France and founder of the European Charity Foundation DigestScience, explained to GMFH editors that yeast probiotics have several advantages compared to bacteria probiotics. “Yeast have higher natural resistance and robustness compared to bacteria particularly toward the aggressive environment encountered in the intestinal tract, but also against bacteriophages and antibiotics. Microbial driven world in the human intestinal flora is tempered by bacteriophages which are 10 times more numerous than bacteria and have the ability to kill bacteria and bacteria probiotics. With more than 44 million antibiotic prescriptions in 2020 in France having the ability to inactivate bacteria probiotics, the better robustness of yeast give a superiority of yeast probiotic compared to bacteria probiotic if we consider that the ability of the probiotic to remain alive in the digestive tract is important”, acknowledged Prof. Desreumaux.

Clinical evidence on the effect of probiotic yeasts on gastrointestinal symptoms in patients with IBS
Beyond gut bacteria: looking into the gut mycobiota and yeast probiotics for managing gastrointestinal diseases

Yeast probiotics for the management of gastrointestinal symptoms of IBS

“Modifying gut microbiota can be a potential strategy for treating IBS”, according to Professor Magnus Simrén. *Saccharomyces* has been the most widely studied genera as yeast probiotics for IBS management and more specifically the fungal strains *S. boulardii* and *S. cerevisiae*.

Three randomized clinical trials have shown the efficacy of *S. boulardii* in IBS. Since 2015, four prospective randomized placebo-controlled studies have shown that the *Saccharomyces cerevisiae* CNCM I-3856 strain can reduce abdominal pain—as demonstrated by the significant and clinically relevant response observed in 45 to 63% of volunteers—with a good level of tolerance in adult patients with IBS. In particular, it seems that *S. cerevisiae* CNCM I-3856 works better in patients who have IBS with constipation, compared to patients with IBS mixed or IBS with diarrhea.

The studied dose included one or two capsules (one capsule equals 500 mg, 8 x 10^9 colony forming units/g) for 8 to 12 weeks, which showed efficacy both when administered alone or when administered together with the standard treatment of IBS (i.e., antidiarrheal and/or antispasmodic). “The most recent study published in 2022 including a total of 456 subjects demonstrates also that *S. cerevisiae* CNCM I-3856 improves significantly the quality of life of patients restoring particularly their body image, health worry, food avoidance and dysphoria”, explains Prof. Desreumaux.

The putative mechanisms of action of *S. cerevisiae* CNCM I-3856 in IBS include immune-modulating properties and an interaction by the resident gut microbiota and a shift towards an increase in the production of short-chain fatty acids.

Regarding when probiotics fit within the patient with IBS’ journey, Prof. Desreumaux states that “The British Society of Gastroenterology Guidelines on the management of patients with IBS recommend in 2021 in first line therapy the practice of regular exercise, dietary and relaxation advice, and the use of probiotics. The use of probiotics therefore comes very early in the therapeutic arsenal offered to IBS patients, especially if these patients wish to have this type of treatment. Probiotic efficacy must be evaluated after 12 weeks and discontinues in absence of improvement. Depending on the activity of the disease, long-term or fractioned maintenance treatment may be proposed.”

Take-home messages

- While IBS is a heterogeneous disorder of the interaction between gut and brain, the bacterial and yeast components of the human gut microbiome are gaining attention as a potential therapeutic target.
- Particular species and strains of bacteria or yeast or a combination of the two have been shown to be effective for improving overall IBS symptoms and abdominal pain.
- Yeast probiotics have some advantages compared to bacterial probiotics, such as their resistance to the gastrointestinal tract’s harsh conditions and the possibility to be co-administered at the same time with antibiotics.
- The *cerevisiae* I-3856 strain has been shown to be effective and safe for reducing abdominal pain in patients with IBS, in particular for the subset of patients who have IBS with constipation.
Beyond gut bacteria: looking into the gut mycobiota and yeast probiotics for managing gastrointestinal diseases

References:


Probiotics with an anti-inflammatory effect may reduce abdominal pain and hours of hospitalization in adult patients with acute uncomplicated diverticulitis

Published on April 19th, 2022 by Andreu Prados

The involvement of the gut microbiota in diverticulitis is gaining interest. This article explores what we know so far about the role of the gut microbiota in diverticulitis and discusses two recent clinical trials on the role of probiotics in managing acute uncomplicated diverticulitis.

The link between the gut microbiota and acute diverticulitis has been underestimated

Diverticulitis is a type of diverticular disease in which an inflammation of one or more diverticulum in the colon occurs, which affects approximately 4% of patients with the presence of diverticula. Associated with the presence of severe and prolonged abdominal pain, fever and leukocytosis, a subset of patients with acute diverticulitis will be treated with antibiotics and rest without developing complications. However, about 15% of patients with acute diverticulitis may require hospitalization and even surgery if the diverticula ruptures.
Probiotics with an anti-inflammatory effect may reduce abdominal pain and hours of hospitalization in adult patients with acute uncomplicated diverticulitis

While the pathogenesis of diverticulitis is thought to have multiple origins, the role of fecal transplants, antibiotics and probiotics in reducing symptomatology by affecting inflammatory markers and changing the levels of gut bacteria suggests a link between the gut microbiota and diverticulitis that is largely underestimated.

On the involvement of the gut microbiota in acute diverticulitis, Veronica Ojetti from Università Cattolica del Sacro Cuore and Fondazione Policlinico Universitario A. Gemelli IRCCS in Rome (Italy) explained to GMFH editors via a phone interview that changes in gut microbiota composition observed in patients who develop acute diverticulitis consist with an increase of bacteria with inflammatory action and a decrease in bacteria with anti-inflammatory activity.

It seems that changes in the gut microbiota in patients with acute diverticulitis can fuel mucosal inflammation that, in turn, favor abdominal symptoms’ development.

Are probiotics helpful for diverticulitis?

The modulation of the gut microbiota through antibiotics has been used in patients with acute diverticulitis for managing systemic manifestations of infection. However, the side effects of antibiotics include a disruption to gut microbiota diversity, an increase in antibiotic-resistant bacteria and the flourishing of C. difficile infection. In addition, 2015 guidelines from the American Gastroenterological Association for treating acute uncomplicated diverticulitis recommend using antibiotics selectively, rather than routinely, in inpatients with uncomplicated diverticulitis (strength of recommendation: conditional; quality of evidence: low). That recommendation has its roots in the importance of inflammation over infection in acute diverticulitis, paired with the negative effects of overconsuming antibiotics.

Probiotics are also a widely used gut microbiota-targeted intervention for preventing infectious diseases (e.g., antibiotic-associated diarrhea and upper respiratory tract infections) and avoiding many of the side effects of antibiotics. In particular, the probiotic properties that make them a potential therapeutic approach for acute diverticulitis include anti-inflammatory functions, their support for balancing the gut microbiota, their intestinal mucosa-strengthening function and their exclusion of pathogens in the gut.

Efficacy and safety of Limosilactobacillus reuteri ATCC PTA 4659 in acute uncomplicated diverticulitis

One of the most widely studied probiotics for managing gastrointestinal diseases is Lactobacillus reuteri. In particular, the Limosilactobacillus reuteri ATCC PTA 4659 strain (formerly known as Lactobacillus reuteri ATCC PTA 4659) has been shown in in vitro and animal findings to have anti-inflammatory effects in the intestine that are worth considering in the context of diverticulitis.

Two recent clinical trials showed L. reuteri ATCC PTA 4659 at a dose of 5 x 108 colony-forming units for 10 days might help manage acute uncomplicated diverticulitis and reduce...
Probiotics and emerging postbiotics for digestive and inflammation-related diseases

Probiotics with an anti-inflammatory effect may reduce abdominal pain and hours of hospitalization in adult patients with acute uncomplicated diverticulitis

hospitalization periods in adults admitted to the emergency department, either as an adjuvant to the standard antibiotic therapy or alone.

• The first randomized double-blind placebo study studied the supplementation with *reuteri* ATCC PTA 4659 as an adjuvant to the standard antibiotic treatment for diverticulitis (ciprofloxacin and metronidazole) in adult patients with acute uncomplicated diverticulitis. On day 10, the probiotic supplemented group showed an 8.1-point reduction in grade of abdominal pain from day 1, compared to a 6.7 reduction in the placebo group receiving only antibiotics. Although both groups showed a significant reduction in inflammatory marker C-reactive protein in the first 3 days of treatment, mean reduction in the probiotics group was markedly bigger. That translated into a 20-hour reduction in the hospitalization period of patients supplemented with the probiotic.

• In the second randomized double-blind placebo trial, adult patients with acute uncomplicated diverticulitis were supplemented with *reuteri* ATCC PTA 4659 or placebo, together with fluid replacement and bowel rest. Compared to placebo, C-reactive protein and calprotectin levels were significantly more decreased in the probiotics group at 72 hours from hospital admission. The probiotic group and the placebo group that only received fluid replacement and bowel rest reduced abdominal pain to the same extent. Yet, those receiving the probiotic showed, on average, an 8-hour reduction in hospitalization compared to the placebo group.

On the whole, the findings show supplementation with *L. reuteri* ATCC PTA 4659 strain might help adult patients with acute uncomplicated diverticulitis with managing abdominal pain and reducing hospitalization time by reducing inflammatory markers. The findings do not translate into other probiotic strains administered alone or in the synbiotics, highlighting the importance of recommending probiotics at strain level to patients to achieve health benefits.

While previous studies support the rationale of using probiotics to modulate the gut microbiota in patients with symptomatic uncomplicated diverticular disease, Veronica Ojetti, involved in both trials, acknowledges that these two randomized clinical trials are the first evidence on the use of probiotics during the acute phase of uncomplicated diverticulitis.

Veronica Ojetti explained to GMFH editors that in young patients (30-55 years old) with a mild acute diverticulitis, specific probiotics coupled with fasting, fluid therapy and an anti-inflammatory drug can help recovering patients with acute uncomplicated diverticulitis. On the other hand, old patients (more than 60 years old) with fever, high levels of C-reactive protein and comorbidities (e.g., diabetes and cardiovascular disease risk factors) might benefit from adding a probiotic to the mainstream antibiotic treatment.

**Take-home messages**

• The gut microbiota appears to be altered in diverticulitis and contributes to a state of inflammation and abdominal pain seen in patients with the condition.

• Probiotics emerge as a new gut microbiota-related intervention that might help manage acute uncomplicated diverticulitis by reducing inflammatory markers seen in patients with diverticulitis.

• Supplementation with probiotic strain *reuteri* ATCC 4659, whether with standard antibiotics for diverticulitis or alone, has been proven to be effective in reducing abdominal pain, inflammatory markers and accelerate recovery.
Probiotics with an anti-inflammatory effect may reduce abdominal pain and hours of hospitalization in adult patients with acute uncomplicated diverticulitis

References:


Research into microbial extracellular vesicles has progressed significantly over several decades. Following up on the 1989 breakthrough that bacterial extracellular vesicles contain genetic information, and the recent ISAPP definition on postbiotics, current research suggests bacterial extracellular vesicles derived from probiotic bacteria may be the postbiotics of the future with potential health benefits.
Bacterial extracellular vesicles: future postbiotics?

The GMFH editing team connected with Dr. Gabriel Vinderola, Associate Professor at Universidad Nacional del Litoral, Argentina, Principal Researcher from CONICET, and senior co-author of the ISAPP definition paper, to further discuss the matter. “Science is an evolving field and the first definition of any given concept is not necessarily the one that best represents science and follows scientific evolution,” explained Dr. Vinderola. “This happened with the definition of probiotics, first introduced in 1965, modified in 1989 and the latest one from 2002 still survives. For postbiotics, 6 definitions were proposed by different scientists from 2013 until 2021 when ISAPP proposed a new definition. The limitations of the previous definitions were discussed and clarified here.”

Separating the contribution to host health benefits made by postbiotics already present in probiotic products is not straightforward

ISAPP’s discussion around the definition focused especially on the starting material and the question: must a postbiotic be produced from a probiotic? As such a requirement would solely place capricious restrictions on a postbiotic, it was removed from the ISAPP definition. However, such a move does not necessarily exclude the presence of postbiotics in a probiotic formula sold over the counter. For instance, overfilling practices—loading a probiotic product with multiple times the expected number of live cells to ensure the amount reported on the package dosage is delivered by the end of the product’s shelf life—are barely reported or studied. Nevertheless, they are a strong indication of the presence of non-viable microorganisms alongside live cells in the initial probiotic formula.

Of all the cell fragments and components fragmenterived from inanimate bacterial cells, membrane vesicles have increasingly attracted scientific interest in the field of postbiotics. And while membrane vesicles may already be present and active in current probiotic products, what are bacterial vesicles and why do they offer potential as postbiotics?

“The contribution of non-viable microorganisms present in probiotic products may be really significant,” explains Dr. Vinderola, “but it is difficult to manage and to know what percentage of the benefit is due to non-viable microbes.” He further discusses the issue in this blog post.

Bacterial vesicles as a novel strategy to enhance the efficacy of probiotics

Extracellular vesicles (EVs) are non-viable elements, yet they are carriers of biological information produced in all domains of life. According to Dr. Vinderola, “EVs have a lot of potential and they fit the ISAPP definition of postbiotics as they are generated from the bacterial membrane. In fact, they will fit the definition when they are proven to have a health benefit.”

Bacterial EVs, in particular, contain various biomolecules derived from their progenitor bacteria, including proteins, lipids, nucleic acids, metabolites, and numerous surface molecules. And all that biological information represents the inanimate structures of their progenitor bacteria (i.e., Lactobacillus, Bifidobacterium, Akkermansia). In the case of probiotic bacteria, EVs may mediate interactions with immune cells and enterocytes, potentially conferring a health benefit on the host and therefore enlisting them as postbiotics. A representative example is the contribution of extracellular membrane vesicles in immune-dependent properties of Lactobacillus rhamnosus GG and L. reuteri DSM 17938.

Various research areas have put bacterial EVs increasingly in the spotlight, yet the underlying mechanisms and corresponding molecules driving their health effects remain poorly understood. In vitro findings show the involvement of Lactobacillus-derived extracellular vesicles in reducing pro-inflammatory responses mediated by monocytes. Other in vitro findings reveal that EVs produced from the probiotic Propionibacterium freudenreichii CIRM-BIA 129 mitigate inflammation by modulating the NF-κB pathway. Studies in mice indicate that Bifidobacterium longum-derived EVs alleviate food allergy...
Bacterial extracellular vesicles: future postbiotics?

through mast cell suppression, while *Akkermansia muciniphila*-derived EVs ameliorate obesity by reducing intestinal inflammation and permeability.

Most information so far comes from laboratory and mice experiments, and ongoing clinical trials have only recently been investigating the role of postbiotics for obesity, type 2 diabetes and IBS. To our knowledge, there are no clinical trials to date examining probiotic-derived EVs’ health benefits against infectious or auto-inflammatory diseases. Therefore, it is essential we use the current information cautiously. Findings in mice have been promising, yet there is an unmet need for clinical proof before we move to microbial EV technology and its potential in innovative diagnostic and therapeutic solutions in precision medicine.

Vesicles’ very small size means they can penetrate the gut barrier, reach host tissues and interact with distinct cell types that the original whole bacterial cell could not otherwise reach, and that may have a potentially negative systemic effect on the host. In other words, there is a long way to go before that possibility can be excluded and the move to clinical application of EVs can be made.

“EVs may be another tool that medical doctors may use to modulate the gut immune system and the microbiome,” proposes Dr. Vinderola, “maybe, with the possible plus that, as they are not living microbes, the safety issue concerning translocation in immunocompromised patients may be lower. In any case, safety cannot be presumed, but properly demonstrated.”

References:


Fiore W., Arioli S., Guglielmetti S. The neglected microbial components of commercial probiotic formulations Microorganisms 2020. doi: 10.3390/microorganisms8081077


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.”
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 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.

**References:**


**Selected Content**

Clostridioides difficile infection remains an unfamiliar subject for clinicians: prevalence, risk factors and co-occurrence with COVID-19

Published on February 25th, 2022 by Andreu Prados

*Clostridioides difficile* infection is the most frequent cause of antibiotic-associated diarrhea in the hospital setting that has increased in severity. This article looks at the risk factors for developing *C. difficile*-associated disease, the spectrum of manifestations and the impact of the COVID-19 pandemic on the occurrence of *C. difficile* infection.

*Clostridioides difficile* infection remains an unfamiliar subject for clinicians: prevalence, risk factors and co-occurrence with COVID-19

Published on February 25th, 2022 by Andreu Prados

*Clostridioides difficile* infection is the most frequent cause of antibiotic-associated diarrhea in the hospital setting that has increased in severity. This article looks at the risk factors for developing *C. difficile*-associated disease, the spectrum of manifestations and the impact of the COVID-19 pandemic on the occurrence of *C. difficile* infection.
Fecal transplants and microbial consortia for tackling *Clostridioides difficile* infection: present and future

**SELECTED CONTENT**

*Clostridioides difficile* infection remains an unfamiliar subject for clinicians: prevalence, risk factors and co-occurrence with COVID-19

To prevent expansion of potential pathogens. However, disruption to the microbiota’s abundance and diversity may prompt *C. difficile* to multiply and cause gastrointestinal infection.

**This opportunistic pathogen is the leading identified cause of hospital diarrhea associated with antibiotic therapy worldwide and is considered an urgent public health threat** by the Centers for Disease Control and Prevention in the United States. In fact, in 2020, 113,451 *C. difficile* infections were reported in the US among hospitalized patients, including community-onset and hospital-onset infections. More worrisome, *C. difficile* infection has increased in severity, supported by CDC data showing that 1 out of every 11 patients aged 65 or older with a healthcare-associated *C. difficile* infection die within 1 month of diagnosis.

CDI incidence is also increasing in the EU, accounting for a total of 7,711 cases in 2016, of which over 75% were acquired in the healthcare setting, according to the Annual Report from the European Centre for Disease Prevention and Control. *C. difficile* infection is among the six healthcare-associated infections that have a huge impact on the cumulative number of years lost due to ill-health, disability or early death, exceeding the burden of other infections, including influenza and tuberculosis. The emerging burden of *C. difficile* is also apparent in other parts of the world, including the Western Pacific and Asia.

*C. difficile* infection has a profound impact on both the healthcare system and patients’ quality of life and that can continue even after infection clearance. Indeed, it is worth noting that the burden is underestimated due to limited EU data and the small number of hospitals that report any data on the condition.

While CDI is often comorbid with other diseases, the reported mortality rate ranges from 6% to 30% and its annual costs range from $8,911 to $30,049 for hospitalized patients.

More worrisome is that CDI often heralds the beginning of a vicious cycle of recurrence, defined as CDI that relapses after the successful treatment of the first episode. It is estimated that nearly one in six patients with CDI will experience recurrent infection within 2 to 8 weeks of their first episode. In addition, up to 65% patients with recurrent CDI often experience two or more additional episodes. The possible return of infection several weeks after patients receive initial antibiotic treatment can both impact their well-being and pose a treatment challenge. Furthermore, it is associated with an annual cost of approximately $2.8 billion.

**Risk factors for developing *C. difficile*-associated disease**

The pathogenesis of *C. difficile* involves multiple factors, with debilitating diseases and comorbidities (e.g., gastrointestinal disorders, cancer or kidney disease) combined with antibiotic treatment leading to an alteration of the colonic microbiota, thus favoring the proliferation of *C. difficile*.

Exposure to antibiotics is the main risk factor for developing *C. difficile* infection. Antibiotics reduce overall gut microbiota diversity and cause metabolic shifts in important taxa, favoring the subsequent increased susceptibility to colonization and development of bacterial antibiotic resistance. Although antibiotics are the primary recommended treatment against *C. difficile*, they may perpetuate the loss of colonization resistance and worsen further disruptions to the gut microbiome, which in turn favors recurrences.

Recent and long-term hospitalization, advanced age (>65 years old), impaired immune response, use of multiple antibiotics for long periods of time, proton pump inhibitors, chemotherapy and feeding tubes also increase the risk of CDI.
The disease spectrum varies from asymptomatic carriage and mild diarrhea to severe and life-threatening CDI, particularly in older patients. The transition from asymptomatic \textit{C. difficile} colonization to CDI is prevented by adequate gastric acid production, the production of bacteriocins by a healthy gut microbiota, bile acid composition and host immune status.

\begin{itemize}
  \item Asymptomatic colonization with \textit{difficile} is particularly common in infants and adults who have contact with the health system (e.g., older adults in long-term care facilities or nursing homes, healthcare workers and patients in rehabilitation centers), which favors exposure to \textit{C. difficile} spores. Although asymptomatic colonized individuals do not show clinical manifestations, they serve as potential disease carriers and transmit \textit{C. difficile}.

  \item Symptomatic infection with \textit{difficile} ranges from mild diarrhea to potentially life-threatening conditions including pseudomembranous colitis, toxic megacolon and death. Several markers of disease severity have been studied and include: age (>70 years), cardiorespiratory failure, ongoing treatment with systemic antibiotics, leukocyte counts and serum creatinine, among others.
\end{itemize}

It is also worth noting that disease severity has been related to hypervirulent strains that share microbial characteristics and the gut microbiome changes they induce. For instance, the hypervirulent ribotype 027 strain has been the most prevalent strain identified in community-acquired \textit{C. difficile} infection. The main mechanisms explaining its high hypervirulence include antibiotic resistance, hyperproduction of toxins, improved toxin binding to the host intestinal epithelium and increased sporulation. That situation highlights the need for personalized treatments for infection control and better health outcomes among patients treated with antibiotics.

\textbf{Clinicians should be aware of \textit{C. difficile} co-infection with COVID-19}

Some evidence has suggested that hospitalized patients with COVID-19 can show an altered gut microbiome, which is related to disease severity. In the current situation, therefore, co-infection with \textit{C. difficile} and COVID-19 may lead to poor outcomes and add to the complexity of CDI diagnosis. That might be explained by risk factors for CDI also being factors that increase the likelihood of COVID-19, causing an overlap between the two conditions. For instance, consumption of non-steroidal anti-inflammatory drugs, antibiotic therapy and older age are among the key factors that explain \textit{C. difficile} co-infection during COVID-19.

It is also important to bear in mind that some patients with \textit{C. difficile} infection usually present with several comorbid conditions, including irritable bowel syndrome and inflammatory bowel diseases. Patients with \textit{C. difficile} infection have a high risk for developing post-infectious IBS. \textit{C. difficile} infection is also the most common infectious complication associated with IBD explained by alterations in the gut microbiome led by this common diarrheal illness.

Scientists have also speculated about the persistence of SARS-CoV-2 viral particles in the feces of patients with CDI, despite COVID-19 rapid antigen tests turning negative. It is also important to keep in mind that CDI can worsen the health outcomes of patients with COVID-19, especially in cases with risk factors associated with CDI.

\textbf{Take-home messages}

\begin{itemize}
  \item \textit{Clostridioides difficile} infection is the most frequent cause of antibiotic-associated diarrhea in the hospital setting, appearing after the gut microbiota is disturbed.
\end{itemize}
**SELECTED CONTENT**

**Clostridioides difficile** infection remains an unfamiliar subject for clinicians: prevalence, risk factors and co-occurrence with COVID-19

- **Difficile** infection is more challenging that just a hospital diarrhea as one in 11 people over age 65 diagnosed with a healthcare-associated *C. difficile* infection die within one month.

- Nearly one in six patients with CDI will experience recurrent infection in the following 2 to 8 weeks, highlighting the public threat that recurrent **difficile** poses worldwide.

- The transition from asymptomatic **difficile** colonization to CDI is prevented by adequate gastric acid production, bacteriocin production by a healthy gut microbiota, bile acid composition and host immune status.

- Hypervirulent strains have been identified in community-acquired CDI and are related to increased severity of infection, increased mortality rates and increased recurrence.

- IBDs may make patients more susceptible to **difficile** infection and new-onset IBS is common after *C. difficile* infection.

- The gut microbiome is vulnerable to infection with COVID-19 and clinicians should be aware that both conditions can occur at the same time.

---

**References:**


---

**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
**Clostridioides difficile** infection remains an unfamiliar subject for clinicians: prevalence, risk factors and co-occurrence with COVID-19


Fecal transplants and defined commensal consortia: the pros and cons of restoring the gut microbiome in recurrent *Clostridioides difficile* infection

Published on September 19th, 2022 by Andreu Prados

Correcting the altered gut microbiome is an important goal in *Clostridioides difficile* management, but the matter is not addressed by mainstream treatments with antibiotics. This article focuses on where fecal microbiota transplantation and investigational microbiota-based therapeutics stand for *C. difficile* infection (Part 3).

Why are antibiotics for primary and recurrent *C. difficile* infection insufficient?

While antibiotics are the current mainstream treatment for *C. difficile* infection, they do not induce a durable response in some patients and their efficacy declines in patients with multiple recurrences. Such recurrences usually happen within 8 weeks of completing antibiotic treatment, while delayed recurrences are also common. In addition, antibiotics do not address the underlying mechanisms involved in recurrence, which include a persistent altered gut microbiome with reduced diversity.
Fecal transplants and defined commensal consortia: the pros and cons of restoring the gut microbiome in recurrent *Clostridioides difficile* infection

Further complicating *C. difficile* management in the clinical setting is the fact that other species co-exist with the bacterium and can induce *C. difficile*-like symptoms that are age-dependent, according to preliminary findings under peer review.

“Patients with *C. difficile* infection have very few limited options in terms of really good therapy,” says Dina Kao, professor of medicine and director of the FMT program at the University of Alberta in Canada.

Due to high recurrent *C. difficile* infection and failure rates for antibiotic therapy, fecal microbiota transplantation (FMT) or investigational microbiota-based biotherapeutics, if available, can be considered for patients with multiple *C. difficile* infection recurrence, either alone or following a course of antibiotics.

Fecal microbiota transplantation for recurrent *C. difficile*: the pros and cons

*C. difficile* guidelines suggest using FMT for second recurrence. FMT consisting of donated stool being homogenized, filtered and then administered via colonoscopy, enema or oral capsules has shown a success rate for treating recurrent *C. difficile* infection that is greater than 85% after one or more treatments, compared to the 40%-to-50% success rate of antibiotics, and survival benefit, compared to antibiotics alone. While FMT appears to be effective in treating medically refractory severe or fulminant *C. difficile* infection, a recent systematic review concludes that multiple treatments are required and a subset of patients require additional courses of antibiotics to achieve resolution. In addition, the best route of FMT delivery is still unknown.

For now, the U.S. Food and Drug Administration (FDA) allows fecal transplants for patients with *C. difficile* who have not responded to standard therapies, in an approach known as enforcement discretion. However, several limitations mean clinicians cannot use FMT as the standard of care for treating recurrent CDI.

First, *FMT is heterogeneous and has serious risks*, including the death of two patients caused by an *Escherichia coli* infection.

Second, although some studies have suggested that FMT success relies on the composition of the stool donor, the microbiome profile that better predicts FMT response is still a long way from being known. Prof. Sahil Khanna, a gastroenterologist at Mayo Clinic, acknowledged at the 2022 GMFH World Summit that donors with microbiome-related diseases (e.g., obesity, IBS, IBD and neuropsychiatric conditions, among others), stool infections (either by enteric pathogens or multi-drug resistant organisms), blood infections (HIV, viral hepatitis, syphilis and others) and emerging pathogens (i.e., SARS-CoV-2) should be excluded from acting as fecal transplant donors.

It is also important to keep in mind that beyond bacteria, fecal samples are reported to contain viruses (mainly bacteriophages), fungi and many small molecules, such as bile acids and short chain fatty acids, which may contribute to or perpetuate the altered gut microbiome seen in patients with *C. difficile* infection. This suggests it is time to move away from fecal transplant towards targeted, refined microbiome therapies, according to this opinion article led by Kao and colleagues.

Last, beyond safety-related concerns, and crucially, quality control, the difficulty of setting up and managing a stool bank in a hospital and the cost of fecal transplants hinder the generalized use of fecal microbiota transplants in clinical practice. On the whole, the variable nature of FMT makes documenting a relationship between fecal strain colonization, impact on the structure and functions of the gut microbiome and
Fecal transplants and defined commensal consortia: the pros and cons of restoring the gut microbiome in recurrent Clostridioides difficile infection

clinical efficacy challenging. “There’s just so many unanswered questions when it comes to fecal transplant,” says Kao.

**Defined consortia of bacteria as an alternative therapeutic to fecal transplants**

Specific and carefully characterized stool-derived or synthetic fractions are currently being studied as safer treatments than FMT for recurrent *C. difficile*.

**Phase I, II and III clinical trials report efficacy and safety results of several investigational microbiota-based therapeutics for reducing CDI recurrence and normalizing gut microbiome composition following standard-of-care antibiotic treatment.** A sustained clinical response has been shown in a high number of patients receiving live biotherapeutics, highlighting the involvement of microbiome repair, with a safety profile similar to placebo. For instance, some live biotherapeutic products have achieved treatment success rates of up to 80% and most responders remained free of *C. difficile* occurrence up to 24 months after treatment, thus highlighting both efficacy and durability.

Despite the clinical success of some standardized microbiota-based therapies, no defined microbiome restoration therapies have been approved by regulatory organizations. Indeed, the FDA has yet to regulate them, given they are not a drug, a biologic or a tissue.

Moreover, stool-derived consortia do not contain a defined population of microbes, which may pose regulatory risks compared to products with defined populations of microorganisms. In the latter case, populations cannot vary from lot to lot as the starting material is defined and it seems the stool-derived consortia field is moving in the same direction.

Beyond *C. difficile* infection, researchers have also been exploring the use of microbiome-based therapies for conditions including inflammatory bowel diseases, hepatic encephalopathy, urinary tract infections by multidrug resistant organisms, food allergies and cancer.

**Take-home messages**

- Multiple recurrences are common in patients with *difficile* infection and failure rates for antibiotic therapy are high.
- While fecal microbiota transplantation has shown a success rate of more than 85% for treating recurrent difficile infection, serious risks remain.
- Several clinical trials support the investigational use of stool-derived or defined consortia of microbes for treating recurrent difficile infection.

**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
Fecal transplants and defined commensal consortia: the pros and cons of restoring the gut microbiome in recurrent Clostridioides difficile infection

References:


Why microbiome tests are currently of limited value for your clinical practice

Published on July 4th, 2022 by Andreu Prados

Patients usually ask for microbiome tests to manage gut-related issues, to find out what type of diet or food supplement fits best and to get information about the risk of developing chronic diseases. But what kind of information do microbiome tests provide and how reliable are their results for clinical practice?

Scientists have not yet been able to define a single healthy gut microbiome profile

The current interest shown by patients suffering from gut ailments in testing their stool samples is rooted in the changes in gut microbiome composition or functions linked to almost every chronic disease.

But while a shared common gut microbiome signature has been found across unrelated diseases (i.e., cancer, cardiovascular diseases, gastrointestinal diseases, neuropsychiatric conditions and other conditions such as skin problems and autoimmune disorders), causation remains mostly unresolved.

The educational content in this post, elaborated in collaboration with Biocodex Microbiota Institute, was independently developed and approved by the GMFH publishing team and editorial board.
Key advances in personalized nutrition and medicine through the gut microbiome

SELECTED CONTENT

Why microbiome tests are currently of limited value for your clinical practice

In a course recently launched by Xpeer, with an unrestricted grant from the Biocodex Microbiota Institute, on detection, prevention and treatment of gut microbiome dysbiosis in the clinical setting, consultant in gastroenterology and member of the GMFH World Summit’s Scientific Committee Francisco Guarner has updated some features of an altered gut microbiome, which include:

- Low microbial richness or diversity,
- Depletion of short chain fatty acid-producing bacteria, and
- Instability in composition over time.

However, decreased gut microbe diversity does not always mean an unhealthy gut microbiome. For instance, a patient following a mostly plant-based diet can temporarily show a decrease in gut microbiome diversity. That is caused by an enrichment of microbes specifically involved in degrading plant carbohydrates but is not a negative health hallmark. The same happens with the low diversity shown by the gut microbiome of breastfed infants as a result of specific bacteria being selected for degrading human milk oligosaccharides in breast milk, which is known to be beneficial for infant health.

As Colin Hill from APC Microbiome Ireland and the School of Microbiology at University College Cork (Ireland) recently stated in a perspective: “You have the microbiome you deserve”. Simply put, the gut microbiome is unique to each person and is relatively stable and resilient, so it is difficult to predict if someone would benefit from a specific gut microbiome composition or from changing their current gut microbiome to a new composition.

The different types of microbiome tests currently available, based on methods for studying gut microbes

Today analysis of the gut microbiome is based on microbe isolation through culture-dependent characterization and DNA extraction through culture-independent characterization.

If a microbe grows easily in a test setting, that does not necessarily mean it is the most abundant or important in the fecal sample. In that regard, culture-based tests are inaccurate as they favor oxygen-loving bacteria, most of which are pathogens, while missing bacteria that grow without oxygen, which include the vast majority of gut commensals. To overcome that limitation, emerging technologies such as culturomics (high-throughput cell culture of bacteria) are being developed in an effort to isolate anaerobic microbes from the human gut.

The second major type of microbiome test is molecular-based stool tests using DNA based methods, such as next generation sequencing of 16S ribosomal RNA genes or whole genome shotgun sequencing, with the latter allowing inference of gut microbiota functions.

It is also feasible to measure metabolic products of the microbiome either in stool or serum using metabolomic methods, although that approach is mostly used for research purposes. However, the vast majority of metabolites measured in human blood and feces remain unknown. Although they are widely used in the research setting when moving beyond studying composition to focus on gut microbial activity, they offer little value for the healthcare provider today.

Francisco Guarner summarized the current status of microbiome tests as follows: “Existing microbiome tests today use different techniques and focus on taxonomy. Most of them provide little information for diagnostic or prognostic purposes.”

There is a long way to go before microbiome tests are used as an indicator of the evolution of patients’ gastrointestinal symptoms

Microbiome testing is still in its infancy. Here is a summary of some clinical takeaways that you can explain to your patients the next time they ask about the utility of microbiome tests:
Why microbiome tests are currently of limited value for your clinical practice

• Scientists have not yet defined a healthy or normal gut microbiome that can reliably predict whether a person will develop a particular disease.

• Relying on stool samples for studying the gut microbiome is inaccurate as the microbiome in stool does not faithfully reflect the microbiome at the intestinal mucosa. The stool microbiome is stable over time and different from the luminal microbiome, which varies depending on each part of the gastrointestinal tract.

• Some commercial microbiome test reports describe the patient’s gut microbiome profile in terms of “good” and “bad” bacteria. The behavior of a particular gut microbe depends on the environment in which it lives and interactions with other commensal species. For instance, some people are asymptomatic colonizers of the potential pathogens Clostridioides difficile.

• That a commercial microbiome test provides a large amount of information is not an indicator of its reliability. Approximately 20% of bacterial gene sequences have not been identified and over 40% of the 10 million microbial genes have uncharacterized functions, which means the science on how to use diet or food supplements to correct specific levels of microbial metabolites is just not there yet.

• Currently, fecal microbiome analyses have limited value in guiding treatment decisions as they provide little important information on gastrointestinal symptom severity, which are ultimately the beacon that guide your clinical decisions.

Some potential applications of microbiome tests that are emerging but not ready to use as routine practice in the clinic as yet include the use of specific fecal microbial signatures to predict which patients will respond better to interventions.

For instance, some research has shown that the gut microbiome might help discriminate between responders and non-responders to dietary interventions in patients with irritable bowel syndrome or obesity. Other pilot studies have shown the potential of fecal microbial signatures to predict the response to biological treatment in patients with inflammatory bowel diseases or for colorectal cancer screening.

Experts agree it is too soon to know what the information provided by microbiome tests means. “While interesting, microbiome stool testing is a bit ahead of its time to be marketed to consumers presently,” says Kate Scarlata. She adds: “Some stool microbiome tests offer information beyond the microbes in the stool such as stool fat (to assess if fat malabsorption is present) or stool elastase (a marker for adequate pancreatic enzyme production) but these specific tests can be easily run by a health care provider and are often covered by insurance, unlike these ‘full-service’ stool microbiome tests which can cost the consumer a lot of cash.”
Why microbiome tests are currently of limited value for your clinical practice

References:


The gut microbiome in personalized nutrition and medicine: takeaways from the 2022 GMFH Summit

Published on May 5th, 2022 by Joël Doré, Andreu Prados

The 10th Gut Microbiota for Health World Summit took place on March 12th and 13th 2022, focusing on the role of gut microbiome-related interventions as part of individualized nutrition and medicine. This post highlights the major learnings from the conference and how they might impact clinical practice in the foreseeable future.

Purna Kashyap from Mayo Clinic (USA) kicked off the GMFH World Summit with a summary of current evidence on using the gut microbiome for precision medicine.

While the one-size-fits-all approach in medicine has ceased to be efficient, precision medicine is a model focused on tailoring treatments to subgroups of patients by using an integrated multidisciplinary approach combining different kinds of genomic and environmental data. Precision medicine requires considering both the microbiome as an integral component of our hologenome and the exposome (i.e., drugs, pathogens and diet).
The gut microbiome in personalized nutrition and medicine: takeaways from the 2022 GMFH Summit

Microbiome as a potentially modifiable factor at the frontier of personalized medicine.

Source: Purna Kashyap's presentation at the GMFH World Summit 2022.

One example of the gut microbiome's relevance in personalized nutrition and medicine is the prediction of postprandial blood glucose responses to diet using an unbiased machine learning approach. It highlights a strong microbiome impact as driver of interindividual variability. While the microbiome is an integral component of precision medicine, Kashyap suggested that the future work needed to incorporate the microbiome as a tool for individualized interventions includes identifying clinically actionable microbiome-driven mechanisms that will enable more effective subtyping of patients and improving the comparability of microbiome data worldwide. In that regard, a checklist has recently been published for guiding scientists and encouraging reproducibility in reporting the results of human microbiome research.

Nicola Segata from the University of Trento presented large-scale studies showing links between some microbes, favorable metabolic traits and dietary patterns, which were especially driven by the presence and diversity of healthy and plant-based foods. While we are far from predicting what a person should eat based on their gut microbiome, Segata highlighted that machine learning algorithms allow us to better predict how each individual may respond to dietary patterns, foods and nutrients.

As it becomes possible to identify the microbes most associated with specific foods, the challenges in unraveling nutrition-microbiome links that need to be solved to move the field forward include: strain-level resolution in microbiome studies; unraveling the unknowns in the human microbiome; using large integrative cohorts; considering the transmission
Key advances in personalized nutrition and medicine through the gut microbiome

SELECTED CONTENT

The gut microbiome in personalized nutrition and medicine: takeaways from the 2022 GMFH Summit

Dirk Haller from the Technical University of Munich shared recent data on arrhythmic bacterial signatures that enable classification and prediction of type 2 diabetes across different cohorts, supporting the hypothesis that daily oscillation of microbial profiles is functionally linked to metabolic health. Up to 15% of identified operational taxonomic units were rhythmic, some of them peaking during the day and others peaking at night. The findings also show the importance of considering time of defecation in microbiome research and highlights that collecting a single daily fecal sample when studying the gut microbiome may not be enough to achieve an overall picture.

Emeran Mayer from University of California Los Angeles shared epidemiological and clinical studies that support the hypothesis that irritable bowel syndrome (IBS) symptoms and anxiety/depression are indeed two closely linked manifestations of the brain-gut-microbiome system. While a causal role for the gut microbiome in IBS is yet to be confirmed, multiomics analyses have established significant differences in the composition and function of the gut.
The gut microbiome in personalized nutrition and medicine: takeaways from the 2022 GMFH Summit

Microbiome between IBS and healthy controls and between IBS subgroups based on bowel habits. As such, it seems that multomic microbiome classifiers for IBS perform better than those only focused on composition, metagenome, metatranscriptome and metabolome.

Furthermore, IBS-diarrhea and IBS-constipation can be differentiated through diverse microbiome functional shifts. When it comes to clinical translation of targeting the gut-brain system, a randomized controlled trial found that cognitive behavioral therapy reduced IBS severity through involving changes in the gut microbiome composition and increased levels of microbiome-derived serotonin levels in fecal samples.

How human migration and diet drive an altered gut microbiome

Dan Knights from the University of Minnesota covered the effects of immigration and diet on microbiome variation. In that regard, moving to an industrialized country increases the risk of metabolic disorders such as obesity within just a few years of residence. That is partly explained by the loss of ancestral gut microbes related to many diseases, as reported by the Immigrant Microbiome Project. The gut microbiome diversity decreased with each generation of residence in the United States. After two generations, the microbiomes of residents that immigrated from Thailand were no longer distinguishable to US residents.

Knights also presented data showing that food intake is highly individualized and diet alone only explains up to 10% of microbiome variation. Indeed, he noted in his presentation that “Our gut microbes care about actual foods and see a lot more than what’s on food labels”. That explains some links between gut microbes and foods but not at the nutrient level, with the current understanding of how diet affects health limited to nutritional components tracked by available databases and not including untracked biochemicals in food.

Why thinking in terms of foods rather than isolated nutrients is more important for gut microbes. Source: Dan Knights’s presentation at the GMFH World Summit 2022.
Diet composition can also impact the metabolic products that are ultimately present in the gut lumen and plasma, as suggested by data presented by Gary Wu from the University of Pennsylvania. By following individuals with a vegan, omnivore or synthetic enteral nutrition diet lacking in fiber, Wu and colleagues showed the dramatic reduction in gut microbiome recovery seen with a fiber-free diet, which was also accompanied by an alteration of carbohydrate and amino acid-derived bacterial metabolites. Thus, depriving the human gut microbiome of a dietary component such as fiber can affect metabolites related to other dietary substrates involving the induction of specific gut bacterial taxa.

Rachel Carmody from Harvard University focused on how not only diet but also food processing shapes gut microbiome structure and function, highlighting the plasticity of the gut microbiome to adapt to food availability in the environment. Low-digestibility starch (raw sweet potato) and high-digestibility starch (cooked sweet potato) led to profound changes in gut microbiome composition and function within hours, and that was also seen in humans who ate plant-based diets served raw or cooked. The key impact of starch digestibility was confirmed when it was found that the effects of cooking on the gut microbiome were most profound for starch-rich foods (sweet and white potato) compared with nonstarchy foods (beet and carrot).

In addition, cooking foods led to an inactivation of antimicrobial compounds that plants use to defend themselves, while raw plant diets increased xenobiotic metabolism and led to a fall in susceptible gut microbes. Finally, transplanting gut microbes from mice fed raw-versus-cooked plant foods into germ-free mice showed that recipients of the raw plant diet gained more body mass and fat. On a raw diet, less energy was gained directly by the host and more nutrients reached the colon and led to increased microbiota-driven energy gain.

Potential applications of microbiome-based therapies for pathogen infection and modulation of cancer therapy

While fecal microbiota transplantation has been widely used for recurrent Clostridioides difficile infection (CDI), limitations such as heterogeneity and safety issues prompted scientists to supplant the technique with rationally designed microbial therapeutics consisting of a well-characterized mixture of effector bacterial strains.

Sahil Khanna from Mayo Clinic gave an overview of available standardized microbiome-based therapies, including available standardized microbial replacement therapies proven to be a safe and effective in treating recurrent CDI. For use after a first, second or third episode of C. difficile, they potentially reduce the heterogeneity of fecal microbiota transplants while correcting the disrupted microbiome that antibiotics do not address.
The gut microbiome in personalized nutrition and medicine: takeaways from the 2022 GMFH Summit

Current standardized microbiome-based therapies in the pipeline, tested in phase I, II and III clinical trials.
Source: Sahil Khanna’s presentation at the GMFH World Summit 2022.

Other conditions in which standardized therapies are being investigated in preclinical and phase I clinical trials are ulcerative colitis, urinary tract infections, hepatic encephalopathy, solid tumors, gram negative infections and food allergy.

Kenya Honda from Keio University and RIKEN Center for Integrative Medical Sciences in Tokyo explained a reductionist approach focused on identifying a minimal effector species or consortium that acts on a specific phenotype for therapeutic purposes. The research has identified different effector bacteria consortia with immunomodulatory properties, of interest for IBD and cancer treatment, for managing pathogen infection and improving metabolic health. Honda focused his talk on the role of Klebsiella decolonization and trypsin-degrading bacteria as targets for managing IBD, multidrug-resistant bacterial microorganisms and viral infections. Honda’s research group is now working on translating the findings into the clinical setting for managing multidrug-resistant bacterial microorganisms, viral infections and inflammatory bowel disease.

Jennifer Wargo from MD Anderson Cancer Center updated microbiome-related interventions studied in the context of improving responses to cancer therapy and limiting toxicity in patients with established cancer. Wargo shared recent
Dietary fiber is linked to cancer immunotherapy response. Source: Jennifer Wargo’s presentation at the GMFH World Summit 2022.

The gut microbiome in personalized nutrition and medicine: takeaways from the 2022 GMFH Summit

findings on the impact of intra tumoral microbes and gut microbes in response to cancer immunotherapy. She also discussed how the gut microbiome can be modulated to enhance responses to immunotherapy and abrogate toxicity. For instance, gut microbiome modulation via fecal microbiota transplants has been shown to improve responses to treatment in patients with metastatic melanoma and in treating immunotherapy toxicity.

In addition, diet can affect response to immune checkpoint blockade, with patients who consume at least 20 grams of dietary fiber a day with no probiotic use living longer without their cancer progressing than those who consumed less dietary fiber.

Dietary fiber is linked to cancer immunotherapy response.
Source: Jennifer Wargo’s presentation at the GMFH World Summit 2022.
The gut microbiome in personalized nutrition and medicine: takeaways from the 2022 GMFH Summit

The future outlook for probiotics

The last plenary session focused on how the field of probiotics can approach rational selection of microbes and genetically engineered and synthetic bacteria. Eric Alm from Massachusetts Institute of Technology focused on designing microbiome-based therapeutics through a rationally designed cocktail of probiotics. Alm presented research showing the potential of specific bacterial clades from the gut, including Faecalibacterium prausnitzii levels within Ruminococcaceae, as a means of predicting risk of antibiotic-associated diarrhea (study in 30 healthy subjects). In addition, Alm is trying to cultivate and isolate a broad diversity of bacteria from the fecal samples derived from human communities across the planet coupled with genome sequences and multi-omics data with the final goal to develop a library of gut bacteria before they disappear and explore mechanistic microbiome research. One of the challenges is the fact that gut bacteria continuously acquire new functionalities based on host lifestyle secondary to industrialization.

Philippe Langella from INRAE focused on genetically modified lactic acid bacteria to deliver proteins of therapeutic interest for inducing both mucosal and systemic immune responses. For instance, Lactococcus lactis and Lactobacillus casei can deliver proteins such as elafin and secretory leukocyte peptidase inhibitor to counterbalance protease-antiprotease imbalance and restore membrane permeability in patients with IBD. Likewise, lactic acid bacteria can also be used to deliver cDNA plasmid with microbial anti-inflammatory molecules from F. prausnitzii to reduce colitis.

The GM LAB can deliver several types of molecules

Food-grade lactic acid bacteria are good candidates for mucosal delivery strategies for therapeutic proteins and DNA vaccines. Source: Philip Langella’s presentation at the GMFH World Summit 2022.
Gut microbiota-derived bile acids metabolites exhibit anti-inflammatory properties with therapeutic potential in the context of inflammatory bowel diseases.

Source: Sloan Devlin’s presentation at the GMFH World Summit 2022.
COVID-19, the gastrointestinal tract and the microbiome

COVID-19 is not only a respiratory disease and Siew Ng from The Chinese University of Hong Kong closed the GMFH World Summit with an update on what we have learned so far about the connection between COVID-19 and the microbiome.

The gut may act as a SARS-CoV-2 reservoir and the gut microbiome can shape COVID-19 risk and severity. That is supported by findings that show how several immunomodulatory species, depleted in COVID-19, persist for more than 30 days after clearance of the virus, together with an excessive inflammatory response and an altered gut microbiome composition that persisted for more than 6 months.
There are 14 interventional trials taking place on gut microbiota modulation in COVID-19. Some recent data exploring microbiota modulation as potential therapeutics in COVID-19 presented by Ng include a recent observational study involving more than 7,300 subjects (with SIM01 Microbiome Immunity Formula), in which well-controlled blood glucose correlated with improved outcomes in COVID-19, suggesting the potential of a low glycemic index diet rich in vegetables and fruits for improving outcomes in hospitalized patients. Proof-of-concept research has also shown the benefits of cocktail formulas with probiotics and prebiotic fibers as adjuvant therapy in immunological responses and changes in the gut microbiome of hospitalized patients with COVID-19. Finally, there was mention of preliminary evidence in mice and humans on the role of gut microbiome composition as a predictor of immune response to COVID-19 vaccines and vaccine-related adverse events.
Key advances in personalized nutrition and medicine through the gut microbiome

SELECTED CONTENT

The gut microbiome in personalized nutrition and medicine: takeaways from the 2022 GMFH Summit


2. The impact of immigration and diet on the gut microbiome


The gut microbiome in personalized nutrition and medicine: takeaways from the 2022 GMFH Summit

3. Microbiome-based therapies for pathogen infection and modulation of cancer therapy


4. The future outlook for probiotics


The gut microbiome in personalized nutrition and medicine: takeaways from the 2022 GMFH Summit


5. COVID-19, gut microbiome and probiotics


Online COVID-19 gastroenterology collection published by Gut, Frontline Gastroenterology and BMJ Open Gastroenterology: https://gut.bmj.com/pages/covid-19/
Where do we stand in the management of IBS? Highlights from “IBS days 2022” in Bologna

Published on July 18th, 2022 by Giada De Palma

The third edition of IBS DAYS 2022 provided current advances and a look to future therapeutic approaches on the rapidly advancing field of irritable bowel syndrome. This article summarizes major highlights on diet and gut microbiome interactions of relevance for IBS.

The bi-annual meeting “IBS days 2022”, organized by Dr. Giovanni Barbara and Dr. Vincenzo Stanghellini (University of Bologna) took place June 20-22nd. Leading experts of one of the most common and elusive disorders of the gastrointestinal tract, the Irritable Bowel Syndrome (IBS), got together under the scorching sun of Bologna. Within the beauty of the frescoed walls at the medieval Palazzo Re Enzo, we forgot about the last two years of pandemic, and fully immersed into the latest clinical diagnostic tools, therapeutic algorithms, and discovery research on Disorders of Gut-Brain Interaction (DGBI), including IBS.

From emphasizing proper patient-physician communication (Dr. Douglas Drossman, University of North Carolina, USA), reviewing the available and potential future biomarkers (Dr. Giovanni Barbara), to raising the intriguing hypothesis of a continuum between functional and organic disease (Dr. Eamon Quigley, Houston Methodist Hospital and Weill Cornell Medical College, USA), this meeting was packed with concepts useful to both the researcher and the clinician. Here are some of the topics discussed in this interesting meeting.

Food for thought on the underlying mechanisms of gut pain

Emerging evidence has started to elucidate the underlying drivers of gut pain. For instance, recent findings in mice and in humans revealed that a bacterial gut infection can change local immune responses in the gut, leading to certain foods being perceived as harmful and causing persistent gut pain driven by histamine release by mast cells. But there could also be a role for microbial histamine in inducing visceral hyperalgesia seen in IBS patients. I had the pleasure to present our
Key advances in personalized nutrition and medicine through the gut microbiome

**SELECTED CONTENT**

Where do we stand in the management of IBS? Highlights from “IBS days 2022” in Bologna

Work performed at McMaster University which discovered a novel interaction of microbes with fermentable carbohydrates leading to bacterial production of a key pain mediator, histamine. The findings may open the way to microbiome-directed therapies, either through a direct specific probiotic therapy or indirectly through dietary modifications, for this subset of IBS patients.

The role of **intestinal and non-intestinal infections** as triggers of IBS, had a prominent role in the discussions. Post-infectious IBS (PI-IBS) was described decades ago as a very defined subset of IBS occurring after a gastrointestinal infection. Dr. Stephen Collins (McMaster University, Canada) presented data on *Clostridioides difficile* infection and onset of severe constipation. Dr. Giovanni Marasco (University of Bologna, Italy) showed extensive data on persistent gastrointestinal symptoms after COVID-19 infection and a potential rise of DGBI after the COVID-19 pandemic.

**Extraintestinal comorbidities of IBS**

Another central theme in the meeting was that of **comorbidities and symptoms beyond the gastrointestinal tract** in DGBI. Dr. Magnus Simren (University of Gothenburg, Sweden) reminded us of the significant impact that anxiety, depression, and somatic symptoms have in DGBI. Dr. Javier Santos (Vall d’Hebron University Hospital, Barcelona) explained the ambitious goals of the DISCOvERIE project: to study the link between anxiety and depression and IBS while identifying biomarkers for accurate and earlier diagnosis, prognosis, and management of patients. Dr. Premysl Bercik (McMaster University) presented novel data demonstrating that the initial gut microbiota-brain signalling is mediated by the innate immune system. Dr. Barbara reported that psychological and abdominal symptoms correlate with increased gut permeability in IBS patients with diarrhea (IBS-D), suggesting the lactulose/mannitol ratio could help discriminate between IBS-D patients and asymptomatic controls.

**Diet and other available interventions for managing IBS-related symptoms**

Dr. Elena Verdu (McMaster University, Canada) alerted about the widespread use of restrictive diets, such as the low FODMAP diet and the gluten-free diet, raising the importance of biomarker discovery for a more tailored use of these diets. To this end, she presented data on the use of non-specific IgG anti-gliadin antibodies which, after ruling out celiac disease and wheat allergy, could identify IBS patients that preferentially benefit from a **reduction** of gluten containing foods.

Dr. Robin Spiller (NIHR, Nottingham, UK) guided us through the impact of dietary fibers and fermentable carbohydrates on the gut microbiota, proposing that changes in microbial fermentation pathways to reduce gas production could potentially help patients with IBS.

**Fecal microbiota transplantation (FMT)** seems to be a topic of great interest in many meetings and given the importance of the microbiome and of infections in IBS, we heard an update on the many trials performed to date by Dr. Colleen Kelly (Alpert Medical School of Brown University, USA). While for *C. difficile* infections FMT does not seem to require donor selection or specific mode of delivery, for IBS, the data are not so clear. Moreover, long-COVID and the recent report that the virus can linger in our gut for longer than expected, remind us that donor screening is essential.

**Why the traditional advice of “restricting diet according to digestive tolerance” needs to be revisited**

One of the central themes was the role of diet, as a driver of symptoms in DGBI but also as part of its management. Dr. Francisco Guarner (Teknon Medical Center, Barcelona) cautioned that strict exclusion diets can destabilize our microbiome. For instance, a recent randomised cross-over small study showed that the
Where do we stand in the management of IBS? Highlights from “IBS days 2022” in Bologna

number of anal gas evacuations and sensation of flatulence secondary to following the Mediterranean diet were less evident in individuals with a robust gut microbiome (higher stability). These findings suggest that the traditional advice of “restricting diet according to digestive tolerance” does not always work for everybody, as a more stable gut microbiome driven by a diet that usually includes plant-based foods leads to a better tolerance of digestive symptoms.

After two intense days of learning and deliberation, we return renewed to our laboratories and clinical practice with an increased knowledge and awareness of this debilitating condition, with the hope to make a difference for our patients. We look forward to the updates in next edition of the IBS days!

References for further reading:


Giada De Palma

Dr. Giada De Palma is currently an assistant professor and research associate at McMaster University in the laboratory of Dr. Bercik and Dr. Collins. She obtained her PhD in Spain with Dr. Yolanda Sanz, and later trained as postdoctoral fellow at McMaster, studying the role of microbiota in the gut-brain axis. Her research interests include the microbial-diet-host interactions and their impact on gut function and behavior.