

Recent findings:

Synbiotic may work for constipation

Nah Li Ching
Executive Editor

Recent study e-published in the August issue of the Clinical Nutrition revealed that dietary supplementation with a synbiotic composed of fructo-obligosaccharides (FOS) with *Lactobacillus* and *Bifidobacterium* helps relieve chronic constipation in women, without influencing abdominal symptoms.¹³

Following one week of non-interventional clinical observation, 100 constipated adult women (aged 18-75 years), diagnosed by ROME III criteria, were randomized to receive two daily doses (6 g) of synbiotic or maltodextrin (placebo group) for 30 days. The synbiotic is a product containing 6 g of FOS and 10⁸-10⁹ bacteria of the strains *Lactobacillus paracasei* (Lpc-37), *Lactobacillus rhamnosus* (HN001), *Lactobacillus acidophilus* (NCFM) and *Bifidobacterium lactis* (HN019). Treatment response was evaluated by patient's daily record of evacuation (stool frequency, consistency and shape, according to Bristol scale), abdominal symptoms (abdominal pain, bloating and flatulence) and constipation intensity (Constipation Scoring System AGACHAN).

Results of this prospective, randomized, double-blind, parallel study showed that patients treated with synbiotic had increased frequency of evacuation, as well as stool consistency and shape nearer normal parameters than patients in the placebo group. These benefits became more significant during the second and third weeks of treatment, respectively (interaction group/time, P <0.0001). There were no significant differences in abdominal symptoms, but AGACHAN score was better (lower) in the synbiotic than in the placebo group.

The study concluded that 30 days of supplementation with synbiotic combining FOS with *Lactobacillus paracasei* (Lpc-37), *Lactobacillus rhamnosus* (HN001), *Lactobacillus acidophilus* (NCFM) and *Bifidobacterium lactis* (HN019) improved clinical parameters relative to placebo in constipated women who met the ROME III criteria. These findings are in agreement with earlier studies showing that treatment with probiotics and synbiotics benefits patients with constipation, increasing stool frequency and consistency.

Quick Facts

In 622 short-term studies of probiotic administration, the incidence of adverse events in the probiotic groups was statistically similar to that of control groups.¹⁴



Constipation is a chronic disease estimated to affect about 16% of the worldwide general population. It is 2-3 times more prevalent and symptomatic in women than men, and the frequency appears to augment with increasing age, particularly after 65 years old. Large amounts of healthcare resources are expended on its diagnosis and treatment, and available therapies are unsatisfactory in one-third of patients.

Constipation can be a consequence of intestinal dysbiosis, with an increase of potentially pathogenic microorganisms and a decrease of potentially beneficial microorganisms. These alterations may affect large bowel motility and secretory functions by changing the metabolic environment of the colon and the amount of available physiologically active substances.

Many studies have demonstrated the positive association of prebiotic fibers such as inulin and FOS, and probiotic strains of lactobacilli and bifidobacteria with intestinal health. And combining the prebiotics and probiotics together (named synbiotics) have been shown to modify microbiota composition and restore intestinal microbial balance, providing synergism on the gastrointestinal functions. This information is further strengthened by the current study data showing that treatment with synbiotics improved evacuation parameters and constipation intensity of chronically constipated women. Further studies, however, in particular large, randomized controlled trials, are needed to confirm these results and to define the clinical role of synbiotic administration on constipated patients.



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Message from the Editor

Welcome to the 10th issue of The Probiotics News. Seemingly, it is easy to achieve the "perfect ten", but we must admit it is not. We are grateful to those doctors who have journeyed with us since the birth of the newsletter in 2008, our medical advisors and especially to our readers who have taken time to read our newsletters. We would not have made it this far without your support and heartening feedback.

The Probiotics News has always aimed to educate and update the community with the latest happenings on probiotics. Now, you are able to access all issues of The Probiotics News online from our newly revamped company website - www.mdpharm.com. Please feel free to contact us with any suggestion or thought you may have. We really do want to hear from you so that we can make the newsletter even more useful and informative down the road. And if you have any article you like to write, we would be delighted to hear from you.

We would like to thank Prof Ducrotte and Dr Koh for their insightful write-ups this issue. We hope you will enjoy reading them as much as our editorial team has put together for you.

From all of us to all of you, have a happy and prosperous Lunar New Year!

God Bless!

Melvin Wong
Editor-in-chief

Lactobacillus plantarum 299v

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DECLARATION OF PERSONAL INTEREST

Philippe DUCROTTE has served as a speaker, a consultant and/or an advisory board member for Axcan Pharma, Cephalon, Danone, Janssen, Mayoly-Spindler and Rosell Lallemand.

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Irritable bowel syndrome (IBS) affects about 10 % of the adult population and is the most common functional digestive disorder. According to ROME III criteria, IBS is characterized by both chronic abdominal pain or discomfort and alterations in bowel habit which are not explained by structural or biochemical abnormalities. Several hypotheses attempt to account for the pathophysiology of IBS, but the aetiology still remains uncertain, and seems multifactorial¹. The pathophysiological role of the gut microbiota has been recently highlighted. Indeed, recent research has provided increasing data to support for the idea that disturbances of intestinal microbiota occur in patients with IBS, and that such abnormalities may contribute to IBS symptoms.

IBS remains a therapeutic challenge and the spectrum of drug and non-drug treatments is an additional argument for our poor knowledge about the exact cause of the condition. Imbalances in intestinal flora suggest that the modulation of the gut microbiota by probiotics could be a possible therapeutic option.

Probiotics are defined as "live microbial food ingredients that are beneficial for health". They have been studied and used in several gastrointestinal disease, including pouchitis, *Clostridium difficile* colitis and antibiotic-associated diarrhoea. The bacterial genera most often used as probiotics are lactobacilli and bifidobacteria. They mimic the effect of the commensal microbiota. Recent meta-analysis has concluded that probiotics is a promising therapeutic option in IBS². However, as with all bio-diverse communities, probiotics exhibit considerable inter-strain diversity and properties of one probiotic should not be extrapolated to another². Important differences exist between bacteria not only at the genus or species levels but also inside a single species at the strain level. In addition, it should not be assumed that probiotic actions in vitro reflect mechanisms of action in vivo.

Among the available strains, *Lactobacillus plantarum* 299v (Lp299v) DSM 9843 is an interesting one with true probiotic properties.

Lessons from experimental studies

The strain is able to survive within the gastrointestinal tract and to colonize the human ileal and colonic mucosa in vivo, because of a specific mechanism of mannose adhesion. Lp299v has shown antibacterial activity against several potential pathogenic agents, and its ability to inhibit the growth of *Listeria monocytogenes*, *Escherischia coli*, *Yersinia enterocolytica*, *Enterobacter cloacae* or *Enterococcus faecalis*. Lastly, Lp299v has beneficial immuno-modulatory activity, promoting an increased IL-10 synthesis and secretion in macrophages and T-cells derived from the inflamed colon. The strain decreases translocation, improves mucosal status and reduces

mucosal inflammation. Recently, an experimental study reported that Lp299v increased the transcription and excretion of the mucins MUC2 and MUC3 in goblet cells. All these properties are interesting for the relief of IBS symptoms.

Lessons from clinical trials

Four studies using Lp299v have been carried out. In a first study, Nobaek et al enrolled 60 IBS patients and compared Lp299v with placebo to determine whether endogenous colonic flora could be altered by probiotic consumption³. Moreover, several symptom-based endpoints were evaluated. The active treatment lasted 4 weeks after a 2-week observation period, then symptoms were reassessed 12 months after the end of the trial. A significant reduction of flatulence was identified while a decreased gas production was reported at 12 months. In a second study, Niedzelin et al⁴ randomized 40 IBS patients to receive over a period of 4 weeks, a liquid suspension of Lp299v or placebo. All patients treated with Lp299v reported a greater resolution of abdominal pain with a trend towards normalization of stools frequency in constipated IBS patients. With regards to all IBS symptoms, a greater percentage of patients (p <0.0001) described improvement. Recently, a large double-blind, placebo-controlled, parallel-designed study randomized a total of 214 Rome III IBS patients to daily receive either one capsule of Lp299v or one capsule of placebo for 4 weeks⁵. At the end of the treatment period, IBS symptoms in the *L. plantarum* 299v group were significantly improved when compared to both baseline and placebo (p <0.05). The global patient's assessment regarding treatment efficacy was significantly better in the *L. plantarum* 299v group when compared to the placebo group. Only one study gave negative results. In their trial, Sen et al⁶ randomized 12 patients in a cross-over manner and evaluated for changes in a composite score of global IBS symptoms. At 8 weeks, no significant difference was observed but the trial was clearly underpowered.

In these four trials, the safety of the strain was confirmed and no serious side-effect occurred.

To conclude, Lp299v appears an interesting candidate for a probiotic treatment in IBS patients.



Gut Microbiota: The 'unrecognized organ' in your body!

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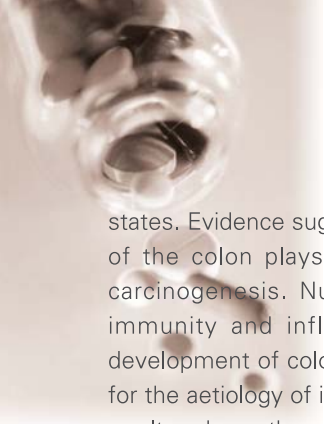


One common question that my patients ask when consulting for problems of the gut such as constipation or diarrhoea is: "Is it healthy to undergo colonic irrigation regularly?" Colonic irrigation is a procedure in which very large quantities of liquids (herbal preparations or even coffee!) are infused into the colon via the rectum through a tube, a few pints at a time, in an effort to flush out faecal contents. The common perception that the faecal material containing bacteria is 'bad' for heath is probably one of the oldest health misconceptions known to humankind.

The ancient Egyptians believed that faeces were associated with decay, and decay with death. They noted that bacterial putrefication occurs within the intestines after death and routinely removed the stomach and intestines as part of their embalming process. It was recorded in the papyrus that they used the reeds from the river Nile as a conduit by which they performed enemas to purge themselves of the faecal material as a way of restoring health, believing that it is from the food they eat that sicknesses arises. Even today, many patients believed that constipation must be eradicated and moving their bowels on a daily basis is a must to prevent "accumulation" of toxins in the gut. Some even believed that if constipation is not relieved, the faecal material will become permanently stuck on the walls of the bowel. None of these claims are supported by scientific evidence. Colonic irrigation done in unhygienic facilities by non-medical personnel actually put the patients at risk of introducing infections or even bowel perforation.^{7,8}

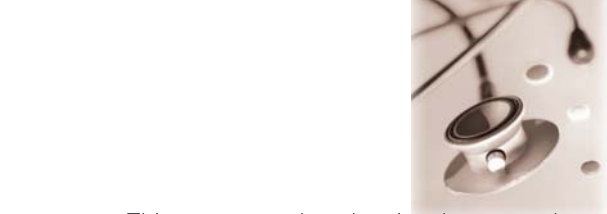
In fact, contrary to popular belief, increasing scientific evidence suggests that the complex microbial ecosystem of the human intestine actually plays a critical role in protecting the host against diseases or influence the susceptibility of the host in developing disease. The human intestinal microbiota is an ecosystem of more than 1000 species of bacteria residing within the intestine and normally participates in a symbiotic relationship with their human hosts. They play a critical role in the normal biological processes of the host by converting complex nutrients like mucins into simple sugars and short-chain fatty acids for absorption. They are also responsible for production of vitamins K and B12 as well as bile reabsorption. Indeed, rather than viewing the gut microbes as "toxins" to be flushed out of our system, they should be viewed as an additional "organ" in our body that is critical to our normal functioning through a complex interplay of human processes and digestive functions provided by these 1000 trillion bacterial cells. Their collective DNA material, defined as microbiome, is estimated to contain ≥150 times as many genes as the 2.85 billion base pairs in our human genome!

This previously unrecognized "organ" in our body profoundly impact intestinal homeostasis and disease



states. Evidence suggests that the bacterial population of the colon plays an important role in colorectal carcinogenesis. Numerous studies show that gut immunity and inflammation have impact on the development of colorectal cancer.^{9,10} One hypothesis for the aetiology of inflammatory bowel disease is that an altered or pathogenic microbiota causes inflammation in a genetically predisposed individual. In this aspect, probiotics have some efficacy in the treatment of ulcerative colitis (UC) and pouchitis. "Faecal Transplantation" or more elegantly called Faecal Microbiota Therapy (FMT) has demonstrated efficacy in treating refractory *Clostridium difficile* infection, and there are case reports of FMT successfully treating UC.¹¹ This has further strengthened the idea that our gut microbiome are not just passive bystanders to be ignored in our search for better health but may in fact play an active role and be a target for therapeutic manipulation.

Recent technological advances such as metagenomics and next-generation sequencing have allowed us to study in greater details the various microbiota residing within the human body. The work by Arumugam et al has shed some really interesting insights on this aspect.¹² Based upon the analysis of high-throughput meta-omics data, it appears that the healthy human gut flora can be classified into three major types ("enterotypes") that are independent from host nationality, age, body mass index and gender. By combining 22 newly sequenced faecal metagenomes of individuals from four countries (from Denmark, France, Italy and Spain) with previously published data sets, they were able to classify them into three robust clusters (which they call edenterotypes) that are not nation or continent specific. These bacterial communities dominated by a distinct genus - *Bacteroides*, *Prevotella* or *Ruminococcus*. People with type 1, for example, had high levels of *Bacteroides*. In type 2, *Bacteroides* were relatively rare, while *Prevotella* was unusually common. Each of these genera has different nutrient-processing preferences - *Bacteroides* to carbohydrates, *Prevotella* to mucins, and *Ruminococcus* to mucins and sugars. Such differences in their biological behaviour and their differing abilities to influence biological processes could conceivably affect an individual's ability to metabolize certain drugs or affect one's risks of developing diseases, although much more research needs to be done to clearly establish a causal relationship. It seems that Enterotype 1 produces more enzymes for making vitamin B7 (biotin) and Enterotype 2 more enzymes for vitamin B1 (thiamine). Arumugam et al also confirmed these enterotypes in two other published, larger cohorts, indicating that intestinal microbiota variation is generally fairly distinctly stratified, not a continuous



spectrum. This suggests that despite the more than 1000 species of bacteria residing in our colon, there are a limited number of well-balanced host-microbial symbiotic states that might influence our response to different dietary or drug intake. Indeed, these distinct intestinal bacterial profiles in each person can be likened to each of us having a distinct and well defined blood type. It is quite possible that each of us acquired a distinct enterotype during our infancy and that this unique host-microbial symbiotic relationship remains fairly stable over our lifetime.

Patients with IBS-like symptoms after a bout of infective gastroenteritis could possibly have an "imbalance" of their usual bacterial flora leading to disequilibrium in their enterotype makeup. Anecdotally, I have found that prescribing a course of probiotics after bowel cleansing and colonoscopy for symptom evaluation often helps to restore a more regular bowel habit in these patients. Presumably the bowel cleansing done as part of the colonoscopic evaluation process serves as a form of "hard reset" for our system and wipes out the "defective software". Ingesting a good probiotic thereafter with a cleansed colon is akin to re-installing good software into the hard disk and allows our gut system to resume normal functioning again! Let's continue to use good 'software' to keep our system in good working order!

