Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Pharmacology

Fecal microbiota transfer for bowel disorders: efficacy or hype?

Max Schmulson[1] and Mohammad Bashashati[2]

Purpose of review: Dysbiosis has been related to the pathophysiology of disorders of – gut-brain interaction (DGBI) including irritable bowel syndrome (IBS) and functional constipation (FC). Accordingly, modulation of gut microbiota has been proposed as a potential treatment for these disorders. Gut microbiota modulation can be effected by probiotics, prebiotics, symbiotics, postbiotics, antibiotics and fecal transplantation (FMT) or bacteriotherapy. The latter is currently used for recurrent or severe *Clostridium difficile* colitis and has been the focus of recent research in IBS and FC. Recent findings: Several case series reported promising results for FMT in patients with IBS and FC, which prompted the conduction of randomized controlled trials (RCT) in these DGBI. Summary: Both case series and RCTs are herein discussed. To the best of our knowledge, as of yet, 5 RCTs have been published on IBS and one in FC with slow colonic transit. In IBS, the majority of studies have used the IBS severity scoring system (IBS-SSS) as an outcome measure; however, the selection criteria were different among the trials as well as the route and form of administration of the FMT. Therefore, the results are inconsistent and no conclusion can be drawn. Some studies suggest that the presence of post-infection (PI)-IBS and the baseline microbiota status in the donors could be predictor factors of successful FMT in IBS. In constipation with slow colonic transit, the FMT seems to be more effective, although the data is based on only one RCT. We believe that larger RCTs, controlled with true placebos and considering baseline intestinal microbiota of the study subjects as well as donors' microbiota are still needed before recommending FMT in IBS and/or FC. History of previous GI infection (e.g. PI-IBS) and IBS subtypes should also be taken into account.

Addresses
[1] Laboratorio de Hígado, Páncreas y Motilidad (HIPAM), Unidad de Investigación en Medicina Experimental, Facultad de Medicina, Universidad Nacional Autónoma de México (UNAM), Hospital General de México, Dr. Eduardo Liceaga, Mexico City, Mexico
[2] Division of Gastroenterology, Department of Medicine, Texas Tech University Health Sciences Center, El Paso, TX, United States

Corresponding author: Schmulson, Max (maxjulio@prodigy.net.mx)

Current Opinion in Pharmacology 2018, **43**:72–80

This review comes from a themed issue on **Gastrointestinal**

Edited by **Giovanni Sarnelli** and **Jan Tack**

https://doi.org/10.1016/j.coph.2018.08.012

Introduction

Functional gastrointestinal disorders (FGIDs) have traditionally been considered symptomatic disorders without structural alterations [1]. However, research has revealed the presence of abnormalities such as low grade inflammation, immune activation and/or dysbiosis [2–6]. Based on these data and studies showing an interaction of multiple pathophysiological factors in FGIDs, Rome IV created a new definition, now called Disorders of Gut–Brain Interaction (DGBI), defined as: "*a group of disorders classified by GI symptoms related to any combination of motility disturbances, visceral hypersensitivity, altered mucosal and immune function, gut microbiota, and/or central nervous system processing*" [1]. Irritable bowel syndrome (IBS) and functional constipation (FC) are the most common DGBIs in the lower gastrointestinal (GI) tract [7,8]. Considering that gut dysbiosis is one of the underlying mechanisms of these disorders [5,6], manipulation/modulation of gut microbiota represents a new strategy for the treatment of IBS and FC [9•,10,11,12]. Among the gut microbiota modulation options in IBS and FC, fecal microbiota transplantation (FMT), will be the focus of this review.

Modulation of gut microbiota in IBS and FC

Gut microbiota can be modulated by elimination diets, probiotics, prebiotics, symbiotics, antibiotics and FMT [12,13]. The majority of the trials in IBS and FC have focused on probiotics and prebiotics. In a systematic review and meta-analysis of RCTs, it was reported that the relative risk (RR) of IBS symptoms persisting with probiotics versus placebo was 0.79 (95%CI 0.70–0.89). Probiotics had beneficial effects on global IBS, abdominal pain, bloating, and flatulence scores. However, data for prebiotics and symbiotics were sparse. In FC, probiotics appeared to have beneficial effects in the mean number of stools, but these results were based on only two RCTs. Symbiotics also appeared beneficial in FC; and there were few studies with prebiotics to draw conclusions [14].

Postbiotics include bacterial components with the minimal structure that possess biological activity and devoid of side effects of live bacteria [15•,16]. Studies on postbiotics are majorly limited to animal and *ex vivo* models. A recent study showed that a *Lactobacillus casei* DG-derived postbiotic, decreases the proinflammatory cytokines mRNA and Toll like receptor 4 (TLR-4) protein expression in the intestinal biopsy samples of both healthy and PI-IBS

subjects stimulated with lipopolysaccharide (LPS), *in vitro* [17].

Rifaximin, a luminal antibiotic, has proven to be efficacious for the treatment of diarrhea predominant IBS (IBS-D). The composition and diversity of the gut microbiota using 4 hypervariable region 16S ribosomal RNA gene sequencing, were assessed in the clinical trial to evaluate the efficacy of rifaximin retreatments in patients responding to a first treatment (Target 3). The results suggested that rifaximin had a modest and transient effect across a broad range of stool microbes. Future research may determine whether the taxa affected by rifaximin are causally linked to IBS-D [18•].

FMT is the process of replacing or reinforcing the gut microbiota of a patient with a condition related to dysbiosis, with the microbiota from a healthy donor [19••,20]. The European Consensus Conference on FMT in Clinical Practice, strongly recommended the implementation of FMT centers for the treatment of refractory or recurrent *Clostridium difficile* infection, as well as in severe or fulminant *C. difficile* induced colitis [21]. In addition, they concluded that there was no strong evidence based recommendation for the use of FMT in other clinical conditions, such as inflammatory bowel disease, IBS and metabolic disorders. However, it was recommended that the experience resulting from the FMT approach to *C. difficile* could be translated in terms of scientific information, technical know-how and knowledge dissemination platforms to other clinical conditions within research protocols [21]. With this background, we will review and discuss the available studies on FMT in IBS and FC.

FMT in irritable bowel syndrome (IBS)

Several case series have been reported in IBS. In 1989, Borody *et al.* reported FMT by rectal enemas in patients with IBS and IBD [22•]. Another study reported two pilot studies in Post Giardia-IBS, one with antibiotics and one with FMT. Compared with the pre-treatment phase, symptom scores were barely reduced after antibiotics, but were significantly reduced after FMT. Symptom improvement did not persist one year later and both treatments were considered to be ineffective [23]. Since then, several other case series from different parts of the world, showed positive results [22,24,25,26,27,28,29••,30••,31]. These series used different diagnostic criteria for IBS, form of FMT, route of administration and outcome variables. Table 1 summarizes the results of the case series using FMT in IBS and FC.

The first RCT on FMT in IBS was published in abstract form in 2017 [32]. Eight patients with IBS were allocated to donors feces and 8 to their own feces. The IBS-SSS scores significantly decreased at four and eight weeks after treatment, compared to baseline in IBS patients receiving donors-FMT, but not in controls, and there were no differences between the groups. The Gastrointestinal Symptom Rating Scale (GSRS)-IBS scores significantly decreased in both groups at two and four weeks, again without differences between the groups. The IBS-Quality of Life (IBS-QoL) and SF-36 significantly increased at 8 weeks in the donors-FMT but not in controls. RCT on FMT in IBS are summarized in Table 2.

Another RCT study in moderate to severe Rome III IBS-D or IBS-M patients was recently conducted in Norway [33]. Patients were allocated to 50–80 g of fresh-FMT (same day use) or frozen-FMT ($n = 60$) versus patients own feces as control ($n = 30$). The transplant was administered through colonoscopy. The primary endpoint of symptom relief of more than 75 points assessed by IBS-SSS three months after FMT, was achieved by 65% of those receiving FMT versus 43% of controls ($p = 0.049$). Participants who received frozen-FMT had lower IBS-SSS scores throughout the follow-up than did those who received fresh-FMT despite a higher mean baseline. Also, patients who received fresh-FMT showed no response compared to controls. In this study, a large long-lasting placebo effect was observed. Adjusting for other functional comorbidities, both active FMT-formulations had similar effects on the IBS-SSS scores. Two patients had soiling of transplant on their way home from treatment (one in each group) and three experienced self-limiting intermittent abdominal pain (one in the active and two in the control group), but no serious adverse events with FMT [33].

Holvoet *et al.* recently published an abstract, this time on a RCT in 64 Rome III-IBS patients with severe bloating, without constipation. Patients were assigned to fresh-FMT from two donors or patients' own frozen stool. Donors were selected based on having a high microbial richness and yielding good clinical results in their preliminary pilot trial. Transplants were administered through an electromagnetically guided nasojejunal tube. At week 12, the primary endpoint of self-reported adequate relief of both general IBS symptoms and bloating was reported by 49% in the donor-FMT recipients compared to 29% in controls ($p = 0.004$). There was a significant difference in the secondary endpoints, including a reduction of abdominal discomfort, number of stools, urgency, abdominal pain and flatulence in the FMT but not in controls. The IBS-related quality of life also improved in the donor-FMT recipients. There were no significant differences in the efficacy according to individual donors [34].

Aroniadis *et al.* reported the results of a multicenter, double-blind, randomized, placebo-controlled trial in moderate to severe IBS-D patients. Patients were randomized to 25 FMT-capsules followed by 25 placebo-capsules or the same number of placebo-capsules