A novel treatment for patients with constipation: Dawn of a new age for translational microbiome research?

Ayesha Shah¹ · Mark Morrison² · Gerald Holtmann¹

Published online: 7 November 2018
© Indian Society of Gastroenterology 2018

In this issue of the Indian Journal of Gastroenterology, the group of Ghoshal et al. [1] present data of a randomized, placebo-controlled study targeting the gastrointestinal (GI) microbiome in patients with chronic constipation that demonstrates remarkable effects and at the same time has explored the potential mechanisms of action.

Enabled by breakthrough new sequencing technologies and innovative computational capabilities, there has been a whole new world of microbiome research. The large number of peer reviewed publications with the key word “gut microbiome” suggests that there is a tsunami of new knowledge related to the GI microbiome but thus far not much has translated into clinical practice. Beyond doubt, the unprecedented growth in research related to the human microbiome that has conquered virtually all areas of medicine is adding substantial knowledge in our understanding of many disease processes. The microbiome is believed to be key for the manifestation for many highly prevalent diseases including immune-mediated, metabolic and malignancies [2]. Treatments targeting the GI microbiome may be considered the holy grail of more effective treatments for many diseases. Indeed, three decades ago, the publication of a controlled trial that targeted a bacterium named *Campylobacter* (now *Helicobacter*) *pylori* in order to cure peptic ulcer disease [3] can be seen as the front runner of microbiome targeted interventions.

As of today, a Google search will return in excess of 7 million hits and PubMed will return nearly 50,000 publications with the search term “microbiome.” On the other hand, microbiome-related discoveries that have resulted in paradigm shifts in regard to evidence-based treatments are as yet, rare. Fecal microbiota transplantation (FMT) in chronic or relapsing *Clostridium difficile* infection (CDI) is such an example. Based upon a systematic review and meta-analysis [4], FMT from a healthy donor into an individual with CDI can resolve symptoms and seems efficacious and safe for the treatment of recurrent CDI. In addition, FMT with encapsulated stool preparations of healthy donors have been tested with success [5]. Other indications tested with thus far mixed results include, e.g. ulcerative colitis (UC), Crohn’s disease, irritable bowel syndrome, or constipation. Despite variation in processes, targeting the GI microbiome with FMT appears to be effective, e.g. for induction of remission in UC and the gain over placebo was approximately 20% [6, 7]. However, thus far with the exception of *H. pylori*-eradication treatments, therapies that target the microbiome in an individualized approach are not available and the emerging knowledge of the GI microbiome has not changed the management of highly prevalent GI diseases in the routine clinical setting.

Constipation is a highly prevalent condition in India [8] and other parts of the world [9] and better treatments are beyond doubt needed. Constipation can be defined as “unsatisfactory” defecation with infrequent stools, difficult passage, or both [10]. With regard to pathophysiology, the disorder is frequently categorized into primary and secondary. Primary causes are alterations of colonic or anorectal function, while secondary causes are related to extraintestinal or systemic disease or chronic adverse effects of medications [11]. In a population-based study in the USA, out of 10,000 respondents, 328 met the criteria for constipation predominant irritable bowel syndrome (IBS-C) and 552 for chronic

✉ Gerald Holtmann
g.holtmann@uq.edu.au

¹ Faculty of Medicine, Translational Research Institute, Department of Gastroenterology and Hepatology, Princess Alexandra Hospital, University of Queensland, Ipswich Road, Woolloongabba, Brisbane, QLD, Australia

² Diamantina Institute, Translational Research Institute, University of Queensland, Brisbane, QLD, Australia

constipation. It can be estimated that approximately one third of patients with symptoms of chronic constipation seek medical attention [12]. Chronic constipation can severely affect patients' life, reduce or impair work productivity and social activities of affected individuals. Constipation was reported to be extremely/very bothersome in 72% of IBS-C respondents and approximately 50% chronic constipation patients [13]. Overall, GI symptoms disrupted productivity, a mean of 4.9 days per month in IBS-C respondents, 3.2 in chronic constipation patients with abdominal symptoms [13]. Thus, these chronic conditions are not only highly prevalent, but have a substantial negative effect on the quality of life in affected patients. Unfortunately, current treatments for constipation are poor [14] and this might be reflected by the disease burden. In the USA, it is estimated that the financial burden to the health care system equals \$7 billion and more than \$500 million is spent on prescription and non-prescription medications [12]. There are many high-profile placebo-controlled studies exploring new treatment approaches in patients with constipation [15–17]. However, there is as yet no perfect treatment for constipation.

Several therapeutic approaches exist for the management of chronic constipation that range from diet, over-the-counter stool softeners, bulking agents, classic laxatives, or recently developed pharmaceutical options [18] that provide some relief of constipation symptoms according to both objective and subjective measures [19]. Understandably though, fiber supplementation is the backbone of treatments in patients with chronic constipation or IBS-C [20]. These dietary fiber interventions, particularly those providing galacto-oligosaccharides, can lead to higher fecal abundance of *Bifidobacterium* and *Lactobacillus* spp. but do not change α -diversity [21]. However, this has been shown to improve GI symptoms [21]. On the other hand, following administration of fermentable sugars (with subsequent hydrogen and methane breath tests), GI symptoms frequently occurred and were associated with an increased hydrogen and methane gas production [22]. Indeed, a diet with reduced exposure to Fermentable Oligo-, Di-, Mono-saccharides and Polyols (FODMAP) may be effective in short-term management of selected patients with IBS-C but thus far, evidence is poor to fair based upon a recent systematic review [20].

Other data suggested that interventions targeting the GI microbiome with probiotics might be beneficial [23], with a recent meta-analysis of trials in elderly subjects showing *Bifidobacterium longum* was the most frequently used probiotic, and also suggesting that probiotics per se were effective [24]. However, there is substantial heterogeneity in relation to study designs, populations, and the risk of bias, which were also acknowledged. Therefore, data from more systematic and controlled studies are still required to determine the most efficient strains, doses, and the optimal treatment duration [24].

While many treatments for constipation appear to be efficacious and provide some gain over placebo in the short-term, it needs to be noted that for virtually all treatments, and in particular, novel pharmacologic therapeutic approaches including secretagogues [18], long-term data are lacking. This is important since it has been well demonstrated that significant numbers of patients are dissatisfied with the treatments available [25] even though they may have worked initially. Thus, while constipation might be seen by some as “trivial,” it is actually a “tricky” problem in the clinical setting and many patients seeking medical attention do not have long-term relief with available treatment options.

Previous studies have shown that the presence of methanogens is associated with chronic constipation and methane production after a carbohydrate challenge and its prevalence is higher in chronic constipation with slow colonic transit as compared to those with normal transit (even though stool characteristics were similar in both groups) [26]. Methane production correlated with colonic transit, suggesting an association with stool transport but not with stool characteristics.

The study by Ghoshal and colleagues [1] presented in this issue used a completely different approach by modulating the GI microbiome and more specifically methane-producing archaea with an antibiotic. These new data published by Ghoshal et al. must be seen against the background of microbiome data that suggest that the GI microbiome is “related” to numerous diseases including constipation [27]. Contrasting this, there are very limited data that provide insights about the mechanism of other interventions that target the GI microbiome.

There is now emerging evidence that specific microbes—and in particular methanogenic archaea—are associated with constipation and IBS-C [28]. A systematic review and meta-analysis of nine studies [29] showed breath methane positivity was more common in patients with functional constipation or IBS-C compared to non-constipated controls. Furthermore, there is experimental [30] and clinical evidence that methane is likely capable of slowing the intestinal transit [26, 29], implying that it may be responsible for the constipation. Other studies with human subjects have shown that slow intestinal transit may also facilitate growth of methanogenic bacteria [31, 32]. A prospective study [33], utilizing lactulose breath test found methane as a strong diagnostic test in predicting IBS-C, with a sensitivity of 91% and a specificity of 81.3%. In that context, Kim et al. [34] demonstrated that *Methanobrevibacter smithii* is the most prevalent and abundant methane-producing microbe in IBS-C subjects, whereas these same archaeal lineage is commonly depleted in Crohn's disease patients [35]. Thus, the cause-versus-consequence relationship(s) between methane production and constipation remain poorly defined, but once established, may lead to new options to personalize medicine targeting the GI

microbiome. For example, might the enrichment of the gut microbiome with specific anaerobic methanogens improve the symptoms of patients suffering from chronic (functional) diarrhea? Antibiotic therapy might have relatively nonspecific effects. In non-constipated IBS patients, treatment with rifaximin resulted in some changes of the overall composition of the stool microbiota by reducing abundance of *Clostridium* and increasing the presence of some species, such as *Fecalibacterium prausnitzii*. There was also a decrease in the Firmicutes/Bacteroidetes ratio and a higher biodiversity after treatment [36]. On the other hand, production of methane is not directly related to bacteria. Prokaryotes forming the domain of Archaea, comprise anaerobic methanogens such as *Methanobrevibacter smithii*, *Methanobrevibacter oralis*, *Methanobrevibacter massiliense*, *Methanosphaera stadtmanae*, *Methanobrevibacter arboriphilus*, *Methanobrevibacter millerae*, and *Methanomassiliicoccus luminyensis* [37]. Methanogens specifically metabolize hydrogen produced by anaerobic fermentation of carbohydrates into methane.

Ghoshal and co-workers demonstrated in their landmark study [1] that treatment with the antibiotic rifaximin reduced methane production and resulted in an improvement of colonic transit time and constipation symptoms. While it is possible that this is not due to a direct antibiotic effect (e.g. rifaximin impairs function of methanogens) but mediated by an overall change in the microbiome composition and metabolic functions. This needs to be kept in mind when the data are interpreted and conclusions drawn and future follow up studies designed. Considering the huge opportunities to develop novel and more effective treatments for constipation that target a root cause for slow transit, the study by Ghoshal et al. [1] paves the path for a paradigm shift in relation to the treatment of patients with constipation. This study provides evidence that the link between altered gut symptoms and the GI microbiome is not “just” an association and interventions targeting the microbiome can alter gut function and ultimately improve symptoms. We need to be aware that antibiotic therapy may come with some limitations; this however should not distract from the fact that this study is likely to change the way how we will treat constipation in the not too distant future in selected subgroups of patients. Thus, personalized medicine for a subgroup of patients with constipation targeting specifically GI methane production as the pathophysiological mechanism is just around the corner.

Compliance with ethical standards

Conflict of interest AS, MM, and GH declare that they have no conflict of interest.

Disclaimer The authors are solely responsible for the data and the content of the paper. In no way, the Honorary Editor-in-Chief, Editorial

Board Members, or the printer/publishers are responsible for the results/ findings and content of this article.

References

1. Ghosal UC, Srivastava D, Misra A. A randomized double-blind placebo-controlled trial showing rifaximin to improve constipation by reducing methane production and shortening colon transit time: a pilot study. *Indian J Gastroenterol*. 2018; 37: <https://doi.org/10.1007/s12664-018-0901-6>.
2. Lynch SV, Pedersen O. The human intestinal microbiome in health and disease. *N Engl J Med*. 2016;375:2369–79.
3. Marshall BJ, Goodwin CS, Warren JR, et al. Prospective double-blind trial of duodenal ulcer relapse after eradication of *Campylobacter pylori*. *Lancet*. 1988;2:1437–42.
4. Cammarota G, Ianiro G, Gasbarrini A. Fecal microbiota transplantation for the treatment of *Clostridium difficile* infection: a systematic review. *J Clin Gastroenterol*. 2014;48:693–702.
5. Youngster I, Russell GH, Pindar C, Ziv-Baran T, Sauk J, Hohmann EL. Oral, capsulized, frozen fecal microbiota transplantation for relapsing *Clostridium difficile* infection. *JAMA*. 2014;312:1772–8.
6. Costello SP, Soo W, Bryant RV, Jairath V, Hart AL, Andrews JM. Systematic review with meta-analysis: faecal microbiota transplantation for the induction of remission for active ulcerative colitis. *Aliment Pharmacol Ther*. 2017;46:213–24.
7. Moayyedi P, Surette MG, Kim PT, et al. Fecal microbiota transplantation induces remission in patients with active ulcerative colitis in a randomized controlled trial. *Gastroenterology*. 2015;149:102–9.e6.
8. Ghoshal UC, Abraham P, Bhatt C, et al. Epidemiological and clinical profile of irritable bowel syndrome in India: report of the Indian Society of Gastroenterology Task Force. *Indian J Gastroenterol*. 2008;27:22–8.
9. Mugie SM, Benninga MA, Di Lorenzo C. Epidemiology of constipation in children and adults: a systematic review. *Best Pract Res Clin Gastroenterol*. 2011;25:3–18.
10. Andresen V, Enck P, Frieling T, et al. S2k guideline for chronic constipation: definition, pathophysiology, diagnosis and therapy. *Z Gastroenterol*. 2013;51:651–72.
11. Wald A. Constipation: pathophysiology and management. *Curr Opin Gastroenterol*. 2015;31:45–9.
12. Sanchez MI, Bercik P. Epidemiology and burden of chronic constipation. *Can J Gastroenterol*. 2011;25 Suppl B:11b–5b.
13. Heidelbaugh JJ, Stelwagon M, Miller SA, Shea EP, Chey WD. The spectrum of constipation-predominant irritable bowel syndrome and chronic idiopathic constipation: US survey assessing symptoms, care seeking, and disease burden. *Am J Gastroenterol*. 2015;110:580–7.
14. Alsalmiy N, Madi L, Awaisu A. Efficacy and safety of laxatives for chronic constipation in long-term care settings: a systematic review. *J Clin Pharm Ther*. 2018;43:595–605.
15. Camilleri M, Kerstens R, Rykx A, Vandeplasse L. A placebo-controlled trial of prucalopride for severe chronic constipation. *N Engl J Med*. 2008;358:2344–54.
16. Chey WD, Webster L, Sostek M, Lappalainen J, Barker PN, Tack J. Naloxegol for opioid-induced constipation in patients with noncancer pain. *N Engl J Med*. 2014;370:2387–96.
17. Lembo AJ, Schneier HA, Shiff SJ, et al. Two randomized trials of linaclotide for chronic constipation. *N Engl J Med*. 2011;365:527–36.
18. Black CJ, Burr NE, Quigley EM, Moayyedi P, Houghton LA, Ford AC. Efficacy of secretagogues in patients with irritable bowel syndrome with constipation: systematic review and network meta-analysis. *Gastroenterology*. 2018. <https://doi.org/10.1053/j.gastro.2018.08.021>.

19. Pare P, Fedorak RN. Systematic review of stimulant and nonstimulant laxatives for the treatment of functional constipation. *Can J Gastroenterol Hepatol*. 2014;28:549–57.
20. Rao SS, Yu S, Fedewa A. Systematic review: dietary fibre and FODMAP-restricted diet in the management of constipation and irritable bowel syndrome. *Aliment Pharmacol Ther*. 2015;41:1256–70.
21. So D, Whelan K, Rossi M, et al. Dietary fiber intervention on gut microbiota composition in healthy adults: a systematic review and meta-analysis. *Am J Clin Nutr*. 2018;107:965–83.
22. Wilder-Smith CH, Olesen SS, Materna A, et al. Fermentable sugar ingestion, gas production, and gastrointestinal and central nervous system symptoms in patients with functional disorders. *Gastroenterology*. 2018;155:1034–44.e6.
23. Dimidi E, Christodoulides S, Fragkos KC, Scott SM, Whelan K. The effect of probiotics on functional constipation in adults: a systematic review and meta-analysis of randomized controlled trials. *Am J Clin Nutr*. 2014;100:1075–84.
24. Martinez-Martinez MI, Calabuig-Tolsa R, Cauli O. The effect of probiotics as a treatment for constipation in elderly people: a systematic review. *Arch Gerontol Geriatr*. 2017;71:142–9.
25. Muller-Lissner S, Tack J, Feng Y, et al. Levels of satisfaction with current chronic constipation treatment options in Europe - an internet survey. *Aliment Pharmacol Ther*. 2013;37:137–45.
26. Attaluri A, Jackson M, Valestin J, Rao SSC. Methanogenic flora is associated with altered colonic transit but not stool characteristics in constipation without IBS. *Am J Gastroenterol*. 2010;105:1407–11.
27. Parthasarathy G, Chen J, Chen X, et al. Relationship between microbiota of the colonic mucosa vs feces and symptoms, colonic transit, and methane production in female patients with chronic constipation. *Gastroenterology*. 2016;150:367–79.e1.
28. Ghoshal U, Shukla R, Srivastava D, Ghoshal UC. Irritable bowel syndrome, particularly the constipation-predominant form, involves an increase in methanobrevibacter smithii, which is associated with higher methane production. *Gut Liver*. 2016;10:932–8.
29. Kunkel D, Basseri RJ, Makhani MD, Chong K, Chang C, Pimentel M. Methane on breath testing is associated with constipation: a systematic review and meta-analysis. *Dig Dis Sci*. 2011;56:1612–8.
30. Pimentel M, Lin HC, Enayati P, et al. Methane, a gas produced by enteric bacteria, slows intestinal transit and augments small intestinal contractile activity. *Am J Physiol Gastrointest Liver Physiol*. 2006;290:G1089–95.
31. Fiedorek SC, Pumphrey CL, Casteel HB. Breath methane production in children with constipation and encopresis. *J Pediatr Gastroenterol Nutr*. 1990;10:473–7.
32. Peled Y, Weinberg D, Hallak A, Gilat T. Factors affecting methane production in humans. *Gastrointestinal diseases and alterations of colonic flora*. *Dig Dis Sci*. 1987;32:267–71.
33. Hwang L, Low K, Khoshini R, et al. Evaluating breath methane as a diagnostic test for constipation-predominant IBS. *Dig Dis Sci*. 2010;55:398–403.
34. Kim G, Deepinder F, Morales W, et al. Methanobrevibacter smithii is the predominant methanogen in patients with constipation-predominant IBS and methane on breath. *Dig Dis Sci*. 2012;57:3213–8.
35. Pascal V, Pozuelo M, Borruel N, et al. A microbial signature for Crohn's disease. *Gut*. 2017;66:813–22.
36. Soldi S, Vasileiadis S, Uggeri F, et al. Modulation of the gut microbiota composition by rifaximin in non-constipated irritable bowel syndrome patients: a molecular approach. *Clin Exp Gastroenterol*. 2015;8:309–25.
37. Nkamga VD, Henrissat B, Drancourt M. Archaea: essential inhabitants of the human digestive microbiota. *Hum Microbiome J*. 2017;3:1–8.