Human Microbiome Journal 13 (2019) 100061

Contents lists available at ScienceDirect

Human Microbiome Journal

journal homepage: www.elsevier.com/locate/humic

Original Article

A retrospective outcome study of 42 patients with Chronic Fatigue Syndrome, 30 of whom had Irritable Bowel Syndrome. Half were treated with oral approaches, and half were treated with Faecal Microbiome Transplantation

J.N. Kenyon[a,*], Shelly Coe[b], Hooshang Izadi[b]

[a] The Dove Clinic for Integrated Medicine, The Old Brewery, Twyford, Winchester, Hampshire SO21 1RG, United Kingdom
[b] Oxford Brookes University, United Kingdom

A B S T R A C T

The gut microbiome comprises the community of microorganisms in the intestinal tract. Research suggests that an altered microbiome may play a role in a wide range of disorders including myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

Methods: 42 participants with ME/CFS with Irritable Bowel Syndrome (IBS) were allocated into one of two groups, 21 were treated with standard oral approaches, which centred around various nutritional remedies, probiotics, prebiotics, dietary advice and lifestyle advice. The second group who had mostly failed using oral approaches, were treated with Faecal Microbiome Transplantation (FMT). Each patient received 10 Implants, each from a different screened donor, and the Implants were processed under anaerobic conditions. The transplant is delivered via a paediatric rectal catheter, which is inserted through the anus to reach the lower part of the sigmoid colon.

The results were assessed on a percentage basis before and after treatment, 0% being no improvement, 100% being maximum improvement. An exact non-parametric Mann-Whitney (one-tailed) test was used to compare medians from those on FMT compared with those receiving oral approaches only. On clinical experience over many years, the only way to judge improvement in Chronic Fatigue Syndrome as there is no test for Chronic Fatigue Syndrome, is my clinical assessment.

Results: The median for the FMT group was found to be significantly higher compared to the oral treatment group (Mann-Whitney U = 111.5, p = .003). Therefore, the FMT group improved to a greater extent (z = −2.761).

Conclusion: This study shows that FMT is a safe and a promising treatment for CFS associated with IBS. Adequately powered randomised controlled trials should be carried out to assess the effectiveness of FMT in patients with CFS and IBS.

1. Introduction

The gut microbiome comprises the community of microorganisms in the intestinal tract. Over the last five years, interest in the gut microbiome has grown considerably driven by new techniques in DNA sequencing allowing for characterisation of gut bacteria and the recognition of the potential impact the microbiome may have on health [1,2]. The large intestine has the highest number of microbial organisms, with less found in the more hostile low-pH environment of the small intestine. The large intestine is dominated by anaerobic bacteria which survive and thrive by anaerobically digesting our food [3–5]. The gut microbiome has coevolved with humans to match our modern lifestyles [6] and is beneficial for our health, supplying essential nutrients, synthetizing vitamins (i.e. vitamin K) and facilitating digestion of undigested carbohydrates [7–9]. Furthermore, bacteria also help maintain the integrity of the mucosal barrier by preventing antigens and pathogens entering the gut mucosa [10,11].

In healthy adults, 80% of the identified faecal microbiota can be classified into three dominant phyla: Bacteroides, Firmicutes and Actinobacteria. In general terms, the Firmicutes to Bacteroides ratio is regarded to be of significant relevance in the human gut microbiota composition. High Firmicutes and low Bacteroides usually correlates with a healthy diverse microbiome and reflects a largely plant-based diet. In unhealthy microbiomes the opposite is the case and may well be due to a more western type diet [12,13]. Alterations in the composition of the microbiome has the potential to significantly impact on our health and wellbeing. One of the side effects of antibiotic use is a change in gut microflora that allows overgrowth of harmful micro-organisms [14]. Clostridium Difficile-associated diarrhoea for example is a well-recognised infection linked to previous antibiotic use [15]. Furthermore, studies on young children with a developing microbiome have shown that antibiotics are especially likely to cause long lasting

* Corresponding author.
E-mail addresses: jnkenyon@doveclinic.com (J.N. Kenyon), scoe@brookes.ac.uk (S. Coe), hizadi@brookes.ac.uk (H. Izadi).

https://doi.org/10.1016/j.humic.2019.100061

Available online 25 July 2019

adverse changes [16–18]. Regulation of the gut flora has also been correlated with a host of inflammatory and immune conditions [19,20]. Recent changes in lifestyle including reduced exposure to pathogens in early life, dietary changes to a high intake of carbohydrates and fats from processed foods and reduced dietary fibre have been proposed to play a role in the rise of inflammatory conditions such as inflammatory bowel disease (IBS/D) and Crohn's disease [19,20]. The microbiome has been shown to have profound effects in the development of gut-associated lymphoid tissue, differentiation of gut immune cells and production of immune mediators such as IgA's and microbial defence peptides [21]. Recent research suggests that an altered microbiome may play a role in a wide range of disorders including Parkinson's disease [22,23] chronic liver disease [24,25], myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) [26,27] and also impact cancer patient recovery after treatments such as chemotherapy and radiotherapy [28].

In this study we randomly chose 21 patients from our sizeable population of Chronic Fatigue Syndrome patients. These patients were treated using oral approaches and also lifestyle and dietary advice. Then, 21 patients with Chronic Fatigue Syndrome who were treated with Faecal Microbiome Transplantation (FMT).

2. Materials and methods

All our Chronic Fatigue Syndrome patients were assessed using the agreed international consensus criteria for Chronic Fatigue Syndrome and Myalgic Encephalomyelitis [29].

Other possible diagnoses in all of these patients were ruled out with appropriate clinical examination and appropriate investigations by their General Practitioners prior to seeing us.

We divided the patients into two groups of 21 per group. 21 were treated with standard oral approaches, which centred around various nutritional remedies, probiotics, prebiotics, dietary advice and lifestyle advice. The second group were treated with FMT and the second group had mostly failed using oral approaches.

In the Faecal Microbiome Transplantation population in this study, each patient was implanted with 10 Implants, each from a different screened donor and we have found in clinical practice that 10 Implants is an optimal number, the Implants are processed under anaerobic conditions. The criteria for Chronic Fatigue Syndrome is as per Carruthers BM, van de Sande MI, et al. [29].

Donors are screened and undergo testing for many common communicable diseases to ensure that the procedure is done as safely as possible, but it is not possible to test donors for all possible organisms and some infections may be undetectable. To date there have not been any documented cases of an infection transmitted through FMT. The donor verifies that he/she has no history of:

1. Risky sexual behaviour
2. Use of illicit drugs
3. Tattoos or piercings in the last six months
4. Communicable disease
5. Metabolic syndrome (overweight, high blood pressure, fatty liver and/or Diabetes)
6. Any type of Cancer or active Autoimmune Disease
7. Risk factors for acquisition of HIV, Syphilis, Hepatitis B, Hepatitis C, Prion Infection or any Neurological Disease
8. Gastrointestinal comorbidities: e.g. Inflammatory Bowel Disease, Irritable Bowel Syndrome, Chronic Constipation or Diarrhoea
9. Receipt of Blood Transfusion in the preceding six months
10. Antibiotic use or any systemic immunosuppressive agent in the past three months prior to stool donation
11. Receipt of any type of Live Vaccine within three months prior to stool donation
12. Chemotherapy in the last three months.

The donor/donor blood sample is screened for:

Human Immunodeficiency Virus (HIV) 1/2, Hepatitis A. IgM, Hepatitis B (HBsAg), Hepatitis C antibody, Syphilis, IgG/IgM, Full Blood Count, Urea and Electrolytes, Ferritin, C-Reactive Protein, Tissue Transglutaminase, CMV, H-Pylori.

The Donor's Stool Sample has been tested for:

Campylobacter (Jejuni, Coli and Upsalliensis), Clostridium Difficile (A/B), Salmonella, Yersinia Enterocolitica, Vibrio (Parahaemolyticus Vulnificus and Cholera), Diarrhoea-causing E-Coli/Shigella, Enteroaggregative E-Coli (EAC), Enteropathogenic E-Coli (EPEC), Enterotoxigenic E-Coli (ETEC), Shiga-like toxin-producing E-Coli (STEC), E-Coli 0157, Shigella/Enteroinvasive E-Coli (EIEC), Cryptosporidium, Cyclospora Cayetanesis, Entamoeba Hystolitica, Giardiolambia, Adenovirus, Astrovirus, Norovirus GI/GLL, Rotavirusa, Sapovirus.

We used Implants supplied by The Taymount Laboratory https://taymount.com/.

The results were assessed on a percentage basis before and after treatment, 0% being no improvement, 100% being maximum improvement. In no case did we obtain more than a 95% response. This is a clinical judgement as there is no objective test for Chronic Fatigue Syndrome.

Essentially, FMT represents the transfer of the faecal microbiota from healthy donors to diseased recipients in order to restore a balanced gut microbial ecology, and in turn foster resolution of symptoms.

A liquid suspension of homogenised stool is instilled into the sigmoid colon using a paediatric catheter [Table 2]. Every patient in this study signed an Informed Consent allowing anonymous use of their data.

One patient reacted to several of the implants with diarrhoea, so we had to stop the implants. One other patient only managed to tolerate half of the implants. Other than that, there were no other adverse effects from the treatment.

3. Analysis

The data were tested for normality and an exact non-parametric Mann-Whitney (one-tailed) test was used to compare medians from those on FMT compared with those receiving oral approaches only.

4. Results

The results are attached in Tables 1 and 2.

The median for the FMT group was found to be significantly higher compared to the oral treatment group (Mann-Whitney $U = 111.5$, $p = .003$). Therefore, the FMT group improved to a greater extent ($z = -2.761$).

5. Discussion

Chronic Fatigue Syndrome is relatively common [30]. Chronic Fatigue Syndrome is often a co-morbid clinical condition with Irritable Bowel Syndrome [31,32].

We know that in the microbiome of Chronic Fatigue Syndrome patients the intestinal microbiome is abnormal [33,34]. Essentially, FMT represents the transfer of the faecal microbiota from healthy donors to diseased recipients in order to restore a balanced gut microbial ecology, and in turn foster resolution of symptoms [35]. FMT has been used for many years for the treatment of Clostridium Difficile (CDiff) and more recently for conditions such as Irritable Bowel Syndrome and Ulcerative Colitis with significant studies published to support these uses [36].

The notion of the faecal transplant as a therapeutic invention is not new, as this procedure was first performed almost two millennia ago by a Chinese Medical Scientist named Ge Hong [37].

Compared to Probiotics, which act temporarily, the satisfactory

Table 1
Chronic Fatigue Syndrome patients treated with FMT.

Patient		% Improved
(F) Age 36	Severe Chronic Fatigue Syndrome with Irritable Bowel Syndrome for three years, following multiple antibiotics for Quinsy. Severe debilitating Irritable Bowel, with lack of energy. She had FMT in February 2018, following this the Irritable Bowel cleared up, energy significantly better. Has always had many food sensitivities, they are gradually beginning to resolve. A further course of FMT is under consideration.	70%
(F) Age 40	Polycystic Ovary Syndrome, also Irritable Bowel and a Chronic Fatigue. She had FMT in October 2017, following the FMT her energy is much improved and is practically normal, has remained so ever since. Also, her mood is more stable.	90%
(F) Age 59	Severe Vaginal Thrush for five years, recurrent abdominal bloating, Irritable Bowel Syndrome and Chronic Fatigue Syndrome. Clostridium Difficile in 2013. She had FMT in May 2017, two months after FMT the Irritable Bowel cleared up completely, her skin is significantly better than it was prior to treatment, Vaginal Thrush is still something of a problem, but not as bad as it was. She finds she is no longer craving sweet foods.	90%
(F) Age 73	History over many years of Irritable Bowel Syndrome and Chronic Fatigue Syndrome, also overweight. We treated her with FMT in December 2017, the Irritable Bowel Syndrome cleared up during the two months following the FMT and has remained normal. She is still having difficulty in losing weight.	60%
(F) Age 43	Several years history of Chronic Fatigue Syndrome. Also, Irritable Bowel Syndrome. We carried out FMT in January 2017, since that time the IBS has cleared up, energy significantly improved and has remained so.	70%
(F) Age 42	8-year history of Chronic Fatigue Syndrome. Also, Irritable Bowel Syndrome. We treated her with FMT in November 2018, I first saw her in May 2018. Since the FMT her persistent Oral Thrush has cleared, her digestion has improved, and the Irritable Bowel has settled down. She is no longer constipated. Her energy improved almost to normal following the FMT but has had a bit of a relapse since significant family upset, which has been draining on her energy reserves.	95%
(F) Age 73	Insomnia, persistent Nausea, poor energy due to Chronic Fatigue Syndrome, lack of appetite. Has lost a great deal of weight over several years. Complains of bad body odour. We carried out FMT in February 2017. Since then the Nausea has disappeared, the appetite has returned, and she is now putting on weight.	95%
(F) Age 46	I first saw her in 2016 with a history of Chronic Fatigue Syndrome and Fibromyalgia for several years. We carried out FMT in January 2017, no significant response to the FMT. We are thinking of repeating the FMT.	0%
(F) Age 66	At the age of 26 this patient contracted amoebiasis in the Himalayas, then she had lots of antibiotics for various indications and has had Irritable Bowel Syndrome and Chronic Fatigue Syndrome since the age of 30. Also, she has been diagnosed with SIBO and had developed multiple food sensitivities. We carried out FMT in July 2017, her Irritable Bowel Syndrome normalised over the next four weeks, her energy improved and became normal, then she had exposure to contaminated water, probably containing parasites, then she relapsed to some extent and had to have a second course of FMT in December 2017. Since that time, she has been completely normal.	95%
(F) Age 47	This patient has had regular courses of antibiotics since the age of 12 for a range of reasons. She has had many years of Chronic Fatigue and Irritable Bowel Syndrome. We carried out FMT in August 2018, since then the Irritable Bowel has settled down and the Chronic Fatigue has resolved.	90%
(F) Age 73	This patient has had a history of recurrent Candidiasis over many years, including Oral Thrush. She has many years history of Irritable Bowel Syndrome and Chronic Fatigue Syndrome. We carried out FMT on her in November 2018. Since that time, she has had no more Candidiasis, the Irritable Bowel has settled down, and there is significant maintained improvement in her energy levels.	85%
(F) Age 70	This patient has had a history over many decades of a Chronic Fatigue Syndrome. We used FMT in April 2017, there was no improvement in her energy levels since the FMT.	0%
(F) Age 70	Chronic Fatigue Syndrome for 20 years, also Addison's Disease, Fibromyalgia and Irritable Bowel Syndrome. FMT carried out in August 2018. She reacted to several of the Implants with Diarrhoea, so we had to stop the Implants. Clinically, no change.	0%
(F) Age 61	20-year history of Chronic Fatigue Syndrome and Fibromyalgia, also Irritable Bowel Syndrome. Oral treatment did not work. FMT was carried out in April 2018. Following FMT her energy improved dramatically and has remained improved. The Irritable Bowel Syndrome has cleared up and she also lost one and a half stone in weight.	90%
(F) Age 41	Many years history of Chronic Fatigue Syndrome, multiple food sensitivities and Irritable Bowel Syndrome. FMT carried out in September 2018. She managed to tolerate half of the Implants and then temporarily had to stop. No clinical improvement yet.	0%
(F) Age 44	Eight-year history of Chronic Fatigue Syndrome getting significantly worse. Also, Irritable Bowel Syndrome. We carried out FMT on her in October 2018. Her Irritable Bowel Syndrome has cleared up completely, energy is beginning to recover.	75%
(F) Age 56	History of Chronic Fatigue Syndrome, Irritable Bowel Syndrome for many years. Resistant to oral approaches for treating both of these conditions. We carried out FMT in May 2018. Since that time her energy is significantly better, and remains better, bowel function is now normal.	80%
(F) Age 70	Chronic Fatigue Syndrome for many years, also Irritable Bowel Syndrome. We treated her with FMT in October 2017. Bowel habit is now normal, resistance to intercurrent infections has now returned to normal, energy was consistently improved and remains so.	95%
(M) Age 65	Chronic Fatigue Syndrome for many years. We treated him with FMT in November 2017. Energy has returned to normal.	95%
(F) Age 52	This patient has had Chronic Fatigue Syndrome for many years. Also, Irritable Bowel Syndrome. We treated her with FMT in July 2018. Since then, her energy has returned to normal and she has now been able to return to work, her gut has also returned to normal.	95%
(F) Age 48	History of Chronic Fatigue Syndrome and Irritable Bowel for many years. We carried out FMT on her in March 2018. Since then her Irritable Bowel Syndrome has cleared up completely and also her energy has returned to normal.	95%

outcome of treatment with FMT suggests that faeces contain a superior combination of intestinal bacterial strains and is more favourable for repairing disrupted native microbiota by introducing a complete, stable community of intestinal micro-organisms [38].

Likewise, faeces contain other factors, proteins, vitamins and bile acids, which may enhance gut recovery [39].

A recent very interesting study shows that in patients with Irritable Bowel and Chronic Fatigue Syndrome, there is an authentic blood microbiome in non-communicable diseases. The chief origin of these microbes is the gut microbiome (especially when it shifts composition to a pathogenic state known as (Dysbiosis').

This study has significant limitations as it is a retrospective Observational Outcomes Study, it is not a Randomised Control Trial. The aim is to encourage proper Randomised Control Studies to be carried out in this area, because our Observational Outcomes Study here showed benefits amongst many patients, so this area is worth investigating further.

From our current study and from the effectiveness of Faecal Microbiome Transplantation, it would appear that this hypothesis is the first event that can result in Chronic Fatigue Syndrome associated with Irritable Bowel Syndrome [40].

6. Conclusion

Faecal Microbiome Transplantation is a safe, and from this study, an encouraging treatment for Chronic Fatigue Syndrome associated with Irritable Bowel Syndrome. This study argues for carrying out a Randomised Controlled Study of Chronic Fatigue Syndrome and Irritable Bowel Syndrome patients.

Table 2
Chronic Fatigue Syndrome treated with oral approaches.

Patient		% Improved
(F) Age 67	Chronic Fatigue Syndrome since 2007, associated with Insomnia, we have been treating her since 2010 and the response has been modest, but we have managed to maintain that modest degree of response.	35%
(F) Age 31	This patient has had Chronic Fatigue Syndrome since childhood, we have been treating her since the early 1990s. We have had modest improvement and we have managed to maintain that, but nothing further than that and her energy remains well below that of her peers.	40%
(F) Age 71	Chronic Fatigue Syndrome and Irritable Bowel Syndrome for 30 years. We have been treating her since 2000. We have had modest but maintained improvement in the Irritable Bowel Syndrome and Chronic Fatigue Syndrome.	35%
(F) Age 75	This patient has had Chronic Fatigue Syndrome since 1986. We have been treating her using various approaches over these years and have had marginal improvement only	10%
(F) Age 49	30-year history of Chronic Fatigue Syndrome, moderate improvement only. I have been seeing her for 20 years.	30%
(M) Age 40	25-year history of Chronic Fatigue Syndrome, using oral approaches. Also, Irritable Bowel Syndrome for the same period of time. Moderate improvement only. I have been seeing him for 15 years.	30%
(F) Age 64	40-year history of Chronic Fatigue Syndrome, I have been seeing her for 20 years, modest improvement only in her Chronic Fatigue symptoms.	35%
(F) Age 49	Chronic Fatigue Syndrome and Irritable Bowel Syndrome for 20 years, I have been treating her since June of this year. She has more or less complete improvement with oral approach.	90%
(M) Age 68	40-year history of Chronic Fatigue Syndrome. I have been treating him for 10 years with little improvement.	10%
(F) Age 27	Chronic Fatigue Syndrome since 2002. We treated her for a year when I saw her initially in 2012, no significant improvement.	0%
(F) Age 70	Chronic Fatigue Syndrome for 30 years, Irritable Bowel Syndrome for the same time. We have been treating her for nine months. She has had modest improvement.	35%
(M) Age 44	10-year history of Chronic Fatigue Syndrome and Irritable Bowel Syndrome. We have been treating him for 18 months. We have had modest improvement only.	35%
(F)Age 71	Irritable Bowel Syndrome and Chronic Fatigue Syndrome for over 40 years. We have been treating her for 20 years with modest improvement only.	40%
(F) Age 30	10-year history of Irritable Bowel Syndrome and Chronic Fatigue Syndrome. We have been treating her for 2 years with modest improvement only.	20%
(F) Age 60	She has had Chronic Fatigue Syndrome and Irritable Bowel Syndrome for 20 years, we have been treating her intermittently since 2010. We have obtained modest improvement only.	30%
(F) Age 75	Chronic Fatigue Syndrome, Irritable Bowel syndrome for 20 years. Some significant improvement, by about 50%.	50%
(M) Age 42	Chronic Fatigue Syndrome for over 20 years as well as Irritable Bowel Syndrome. Marginal improvement only obtained.	10%
(F) Age 34	Chronic Fatigue Syndrome and Irritable Bowel Syndrome for 15 years. We have been treating her since 2013 and she has had significant improvement.	75%
(F) Age 54	Chronic Fatigue Syndrome and Irritable Bowel Syndrome for 20 years, we have been treating her for five years and she has obtained significant improvement by 70%.	70%
(F) Age 25	10 -year history of Chronic Fatigue Syndrome. We have been treating her since 2014, she has obtained very good improvement, up to 90%.	90%
(F) Age 35	Chronic Fatigue Syndrome and Irritable Bowel Syndrome for 6 years, we have been treating her for three years and she has obtained 90% improvement.	90%

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Guinane CM, Cotter PD. Role of the gut microbiota in health and chronic gastrointestinal disease: understanding a hidden metabolic organ. Therap Adv Gastroenterol 2013;6(4):295–308.
[2] Marchesi JR, et al. The gut microbiota and host health: a new clinical frontier. Gut 2016;65(2):330–9.
[3] Qin J, et al. A human gut microbial gene catalogue established by metagenomic sequencing. Nature 2010;464(7285):59–65.
[4] Miquel S, et al. Faecalibacterium prausnitzii and human intestinal health. Curr Opin Microbiol 2013;16(3):255–61.
[5] Human Microbiome Project C. Structure, function and diversity of the healthy human microbiome. Nature 2012;486(7402):207–14.
[6] Ley RE, et al. Evolution of mammals and their gut microbes. Science 2008;320(5883):1647–51.
[7] Murota K, Nakamura Y, Uehara M. Flavonoid metabolism: the interaction of metabolites and gut microbiota. Biosci Biotechnol Biochem 2018:1–11.
[8] Jennis M, et al. Microbiota-derived tryptophan indoles increase after gastric bypass surgery and reduce intestinal permeability in vitro and in vivo. Neurogastroenterol Motil 2018;30(2).
[9] Nicholson JK, et al. Host-gut microbiota metabolic interactions. Science 2012;336(6086):1262–7.
[10] Gagnon M, et al. Study of the ability of bifidobacteria of human origin to prevent and treat rotavirus infection using colonic cell and mouse models. PLoS ONE 2016;11(10):e0164512.
[11] Rangan KJ, et al. A secreted bacterial peptidoglycan hydrolase enhances tolerance to enteric pathogens. Science 2016;353(6306):1434–7.
[12] Turnbaugh PJ, et al. A core gut microbiome in obese and lean twins. Nature 2009;457(7228):480–4.
[13] Verdam FJ, et al. Human intestinal microbiota composition is associated with local and systemic inflammation in obesity. Obesity (Silver Spring) 2013;21(12):E607–15.
[14] Malik U, et al. Association between prior antibiotic therapy and subsequent risk of community-acquired infections: a systematic review. J Antimicrob Chemother 2018;73(2):287–96.
[15] Brown KA, et al. Meta-analysis of antibiotics and the risk of community-associated Clostridium difficile infection. Antimicrob Agents Chemother 2013;57(5):2326–32.
[16] De La Cochetiere MF, et al. Resilience of the dominant human fecal microbiota upon short-course antibiotic challenge. J Clin Microbiol 2005;43(11):5588–92.
[17] Sullivan A, Edlund C, Nord CE. Effect of antimicrobial agents on the ecological balance of human microflora. Lancet Infect Dis 2001;1(2):101–14.
[18] Jakobsson HE, et al. Short-term antibiotic treatment has differing long-term impacts on the human throat and gut microbiome. PLoS ONE 2010;5(3):e9836.
[19] Quigley EM. Gut bacteria in health and disease. Gastroenterol Hepatol (N Y) 2013;9(9):560–9.
[20] Shen S, Wong CH. Bugging inflammation: role of the gut microbiota. Clin Transl Immunol 2016;5(4):e72.
[21] Sommer F, Backhed F. The gut microbiota–masters of host development and physiology. Nat Rev Microbiol 2013;11(4):227–38.
[22] Minato T, et al. Progression of Parkinson's disease is associated with gut dysbiosis: two-year follow-up study. PLoS ONE 2017;12(11):e0187307.
[23] Fasano A, et al. Gastrointestinal dysfunction in Parkinson's disease. Lancet Neurol 2015;14(6):625–39.
[24] Da Silva HE, et al. Nonalcoholic fatty liver disease is associated with dysbiosis independent of body mass index and insulin resistance. Sci Rep 2018;8(1):1466.
[25] Woodhouse CA, et al. Review article: the gut microbiome as a therapeutic target in the pathogenesis and treatment of chronic liver disease. Aliment Pharmacol Ther 2018;47(2):192–202.
[26] Giloteaux L, et al. Reduced diversity and altered composition of the gut microbiome in individuals with myalgic encephalomyelitis/chronic fatigue syndrome. Microbiome 2016;4(1):30.
[27] Nagy-Szakal D, et al. Fecal metagenomic profiles in subgroups of patients with myalgic encephalomyelitis/chronic fatigue syndrome. Microbiome 2017;5(1):44.
[28] Roy S, Trinchieri G. Microbiota: a key orchestrator of cancer therapy. Nat Rev Cancer 2017;17(5):271–85.
[29] Carruthers BM, van de Sande MI, et al. Myalgic encephalitis: international consensus criteria. J Intern Med 2011;270:327–38. https://doi.org/10.1111/j.1365-2796.2011.02428.x.
[30] Nacul LC, Lacerda EM, et al. Prevelance of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) in three regions of England: a repeated cross-sectional study in primary café. BMC Mes 2011;9:91. https://doi.org/10.1186/1741-7015-9-91.
[31] Aaron LA, Herrel R, et al. Comorbid clinical conditions in chronic fatigue: a co-trin control study. J Intern Med 2001;16:24–31. https://doi.org/10.1111/j.1525-1497.2001.03419.x.
[32] Hausteiner-Wiehle C, Henningses P. Irritable bowel syndrome: relations with functional, mental, and somatoform disorders. World J Gastroenterol 2014;20:6024–30.

[33] Morten KJ, Staines-Urias E, Kenyon J. Potential clinical usefulness of gut microbiome testing in a variety of clinical conditions. Hum Microb J 2018;10:6–10. https://doi.org/10.1016/j.humic.2018.08.003.
[34] Navaneetharaja N, Griffiths V, et al. A role for the intestinal microbiota and virome in myalgic encephamyoletis/chronic fatigue syndrome (ME/CFS)? J Clin Med 2016;5:1–22. https://doi.org/10.3390/jcm5060055.
[35] Cammarota G, Ianaro G, Gasbarrini A. Faecal microbioto transplantation for the treatment of clostridium difficile infection: a systemic review. J Clin Gastroenterol 2014;48(8):693–720.
[36] The use of faecal microbiota transplant as treatment for recurrent or refractory Clostridium difficile infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines Benjamin H Mullish, et al Gut 2018;0:1–22. doi: 10.1136/gutjnl-2018-316818.
[37] Zhang F, et al. Should we standardise the 1,700 year old fecal microbiota transplantation? Am J Gastroenterol 2012;107:1755.
[38] Xu M-Q, et al. Faecal microbiota transplantation broadening its application beyond intestinal disorders. World J Gastroenterol 2015;21(1):102–11. https://doi.org/10.3748/WJG.V.21.I1.102.
[39] van Nood E, et al. Faecal microbiota transplantation: facts and controversies. Curr Opin Gastroenterol 2014;30:34–9.
[40] Potgieter M, Bester J, et al. FEMS Microbiol Rev 2015;39:567–91. https://doi.org/10.1093/femsre/fuv013.