CHAPTER 10

Fecal Microbiota Transplantation: Indications in Perspective


Adapted from:

Fecestransplantatie: wanneer wel en wanneer niet. Accepted for publication in Nederlands Tijdschrift voor Geneeskunde
CASE

A 48-year old woman was admitted to the hematology department for her second induction chemotherapy for Acute Myeloid Leukemia. The first induction treatment was complicated by a bacteremia with multi-resistant *Pseudomonas aeruginosa*. Early in the second induction treatment, again the patient developed a fever and bacteremia with this multi-resistant strain of *P. aeruginosa* for which she was treated with a combination of meropenem, colistin, and amikacin. Because the fever held, treatment was switched to ceftolozane/tazobactam (a last resort antibiotic), after which the patient recovered. As Fecal Microbiota Transplantation (FMT) has been described in literature as a successful treatment of multi-resistant organisms, we opted to treat this patient with FMT two weeks before the start of the third induction chemotherapy. After FMT, stool culture for *P. aeruginosa* was negative and during the third induction treatment the patient did not develop a bacteremia.

This case report illustrates one of the possible applications of FMT. Currently, the association between the intestinal microbiota and other gastrointestinal, but also non-gastrointestinal conditions, receives a lot of attention, and research in this field is rapidly expanding (Table 1). The number of conditions associated with a disrupted gut microbiota is extensive and by no means inclusive as of yet, but is FMT effective in all these conditions?
FECAL MICROBIOTA TRANSPLANTATION

Fecal Microbiota Transplantation (FMT) is defined as the transfer of diluted, filtered, feces obtained from a healthy donor into the gastrointestinal tract of a patient by nasogastric tube, duodenal tube, colonoscopy, enema or capsules.¹ It is suggested that FMT restores the function of the gut microbiota. Especially colonization resistance and diversity of the gut bacteria increase after FMT. At this moment, recurrent *Clostridium difficile* infection (CDI) is the only recognized indication for FMT, with cure rates around 85%.¹ Since 2016, it is possible to order ready-to-use donor feces suspensions from the Netherlands Donor Feces Bank (NDFB), for treatment of recurrent CDI. The NDFB makes it possible to treat every patient with recurrent CDI in their local hospital, which greatly simplifies logistics and allows for a degree of quality control in this, by design, non-standardized treatment. In the past few years, the potential use of FMT for other indications has been discussed (Table 1). Here, we present an overview of the conditions with the most treatment potential.

Table 1. Overview of conditions in which the gut microbiota seems to play a part in the pathogenesis

<table>
<thead>
<tr>
<th>Nature of the studies</th>
<th>Gastro-intestinal</th>
<th>Extra-intestinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized controlled trials</td>
<td>Recurrent <em>Clostridium difficile</em> infection, Ulcerative colitis</td>
<td>Metabolic syndrome</td>
</tr>
<tr>
<td>Case series</td>
<td>Crohn’s disease, Irritable bowel syndrome, Carriage multidrug-resistant organisms, Graft versus host disease</td>
<td>Idiopathic thrombocytopenic purpura, Chronic fatigue syndrome, Fibromyalgia</td>
</tr>
<tr>
<td>Case reports / clinical success stories</td>
<td>Hepatic encephalopathy, Refractory celiac disease</td>
<td>Multiple sclerosis, Parkinson’s disease</td>
</tr>
<tr>
<td>Mice-based studies</td>
<td></td>
<td>Parkinson’s disease, Autism, Depression, Non-alcoholic fatty liver disease, Rheumatoid arthritis</td>
</tr>
<tr>
<td>Studies on effect of FMT have not yet been performed</td>
<td>Cholelithiasis, Colon carcinoma</td>
<td>Allergy, Cardiovascular disorders, Hypercholesterolemia</td>
</tr>
</tbody>
</table>
SEARCH STRATEGY

PubMed was searched for publications about the effectiveness of FMT for different conditions (up to January 2017), using the search term ‘fecal microbiota transplantation[Medical Subject Heading (MeSH)]’, combined with the following search terms, both with and without MeSH: ‘gastrointestinal disorders’, ‘inflammatory bowel disease’, ‘irritable bowel disease’, ‘metabolic syndrome’, ‘insulin resistance’, ‘diabetes mellitus type 2’, ‘graft versus host disease’, ‘depression’, ‘autistic disorder’, ‘anxiety’ and ‘multiple drug resistant organism’. Also used were ‘gut-brain axis’ and ‘gastrointestinal microbiome[MeSH]’. Based on references in the yielded articles, additional articles were collected.

FECAL MICROBIOTA TRANSPLANTATION IN GASTROINTESTINAL DISORDERS

Inflammatory bowel diseases

Ulcerative colitis and Crohn’s disease are chronic inflammatory bowel diseases (IBD) with an average incidence of 29.2 cases per 100,000 inhabitants per year. In patients with IBD, the function of the bowel microbiota is disturbed. It is unknown, however, whether this disturbance is due to the inflammation or plays an active part in its pathogenesis. Therefore, the question is whether restoring the balance of the gut microbiota by FMT can reduce disease activity.

Until now, three randomized controlled trials have been published where patients with active ulcerative colitis were treated with FMT (Table 2). In a Canadian study (Moayyedi et al.), 75 patients received a weekly enema over a period of 6 weeks, with either donor feces or a placebo (water). In the group receiving donor feces, more patients reached clinical remission (9/38; 24%) than in the placebo group (2/37; 5%). In this study, feces was obtained from six different donors: the feces from two donors
was remarkably more effective than the feces of the other four. The feces of the two so-called ‘super donors’ contained many butyrate-producing bacteria. Butyrate is an essential source of nourishment for epithelial cells in the colon and has proven anti-inflammatory characteristics.\(^5\)

In a second, Dutch, study (Rossen et al.), patients received either donorfeces or autologous feces by duodenal tube, which was repeated after three weeks.\(^3\) In the intervention group, 7/23 (30%) reached the primary endpoint versus 5/25 (20%) in the placebo group. That the remission rate did not really differ between both groups can be largely explained by the effectiveness of autologous FMT (12-15% higher than after water as placebo); the question is whether or not autologous FMT should also be considered as an intervention. Microbiota analysis showed that in the donorfeces-responders, the composition of the intestinal microbiota had shifted to that of the donor; in the non-responders such a shift was not seen. In patients who reached the primary endpoint after autologous FMT, the composition of the intestinal microbiota had shifted towards an increase in abundance of *Bacteroidetes, Proteobacteria, and Bacilli*, which was not seen in the non-responders.

In the most recent, Australian, study (Paramsothy et al.), 85 patients with ulcerative colitis were randomized to either FMT or placebo (water) colonoscopic infusion, followed by donorfeces or placebo enemas five days per week for eight weeks.\(^4\) The fecal suspension used in this study contained a feces mix from three to seven different donors, aimed to increase bacterial diversity. In the intervention group, 11/42 (27%) patients reached the primary endpoint versus 3/43 (8%) in the placebo group. The clinical response to FMT proved to be associated with an increase in the diversity of the intestinal microbiota.

The results of these three randomized controlled trials are promising. However, in contrast to CDI, FMT in ulcerative colitis is clearly not ‘one size fits all’.\(^3\) Future trials
will build on these results, and it is expected that in the near future ‘super donors’ and distinct patient subgroups who can benefit from FMT will be identified. Until that time, FMT remains a strictly experimental treatment for ulcerative colitis, that can only be performed in a research context.

The use of FMT in Crohn’s disease is less well studied, and literature is limited to case-series. The effectiveness of FMT in these case-series varies from 0% to 89%.\textsuperscript{6,7} Randomized studies are warranted to assess the effectivity of FMT in Crohn’s disease.

| Table 2. Overview of the three randomized controlled trials of FMT in ulcerative colitis |
|-----------------------------------------|------------------------------------|----------------------------------|
| **Study design** | Moayyedi et al. 2015 | Rossen et al. 2015 | Paramsothy et al. 2017 |
| | Double blind, randomized, placebo controlled | Double blind, randomized, placebo controlled | Double blind, randomized, placebo controlled |
| **Number of inclusions** | 75 | 48 | 81 |
| **Population** | Adult patients with ulcerative colitis (Mayo score ≥ 4 with an endoscopic Mayo score ≥ 1) | Adult patients with ulcerative colitis (SCCAI ≥ 4 en ≤ 11) | Adult patients with ulcerative colitis (Mayo score 4-10) |
| **Primary endpoint** | Clinical remission at week 7* | Clinical remission at week 12** | Steroid free clinical remission and with endoscopic remission or response at week 8*** |
| **Route of delivery** | Enema | Duodenal tube | Colonoscopy and enema |
| **Number of donorfeces infusions** | 6 (6 weeks, 1 per week) | 2 (0 en 3 weeks) | 1x colonoscopy, 40x enema |
| **Donorfeces** | Fresh or thawed | Fresh | Thawed |
| **Donors** | 1 donor per patient | 1 donor per patient | Feces mix from 3-7 different donors |
| **Placebo** | Water | Autologous feces | Water |
| **Number of patients that achieved primary endpoint** | | | |
| FMT | 9/38 (24%) | 7/23 (30%) | 11/41 (27%) |
| Placebo | 2/37 (5%) | 5/25 (20%) | 3/40 (8%) |

*Total Mayo score ≤2 with an endoscopic Mayo score of 0. **SCCAI score ≤ 2 combined with ≥ 1 point decrease in the Mayo endoscopic score. ***Total Mayo score ≤ 2, all sub-scores ≤ 1, and ≥ 1 point reduction in endoscopic sub-score. Abbreviations: SCCAI: simple clinical activity index.
**Irritable Bowel Syndrome**

Irritable Bowel Syndrome (IBS) occurs in 10-15% of the population and is characterized by abdominal pain, bloating, flatulence, and changes in bowel movement pattern without evidence of any underlying causes. The recently increased knowledge on the microbiota composition in IBS patients strengthens the hypothesis that a disruption in gut microbiota plays a role in the pathogenesis of IBS.

To date, publications on the use of FMT in IBS are limited to case-reports and case-series. A recent case-series describes 13 IBS patients (9 IBS-diarrhea, 3 IBS-obstipation, 1 IBS-mix) receiving FMT: 9/13 patients experienced resolution or improvement of symptoms, and 6/13 patients reported an improvement of overall well-being after FMT. In a second, recent case-series, 12 patients with IBS with intermittent diarrhea and severe bloating, were treated with FMT. Nine patients (75%) reached the primary endpoint being ‘adequate relief of global IBS symptoms and abdominal bloating’ 12 weeks after FMT. The results of FMT in IBS seem promising, but randomized studies (currently underway worldwide) will have to prove whether FMT deserves a role in IBS treatment. Because the etiology of IBS is also related to nutrition and lifestyle, research into using a combination of FMT, lifestyle and nutritional changes seems indicated.

---

**FECAL MICROBIOTA TRANSPLANTATION IN EXTRA-INTESTINAL DISORDERS**

**Metabolic syndrome**

In addition to genetics and lifestyle, the composition of gut microbiota also seems to play a part in our metabolism, as the gut microbiota influences, among other things, our energy metabolism, and the uptake of cholesterol and glucose (Figure 1).
Figure 1. Possible links between the gut microbiota and metabolism. Continuous lines: likely pathway; dotted lines: putative pathways.⁵


The transfer of feces from obese human donors to germ-free mice, resulted in increased weight and insulin resistance, compared to germ-free mice who received feces from non-obese human donors.¹² In a randomized controlled trial, 18 men with a body mass index (BMI) > 30 km/m² and concomitant insulin resistance were treated with feces from lean donors or autologous feces.¹¹ Six weeks after FMT, the insulin sensitivity had improved slightly in the intervention group. Also, the gut microbiota diversity and the number of butyrate-producing bacteria had increased. However, no effect on BMI or energy metabolism was found. These findings are in agreement with results from earlier observational studies which reported less butyrate-producing
bacteria in the intestinal microbiota of patients with Diabetes Mellitus type II compared to healthy controls.\textsuperscript{13,14}

**Graft versus host disease**

Patients who undergo a stem cell transplantation receive chemotherapy, immunosuppressive medication and many antibiotics; this influences the composition of the gut microbiota. Because infections and Graft versus Host disease (GVHD) are the two most important complications after stem cell transplantations, the association between the composition of the intestinal microbiota, and morbidity and mortality in these patients are popular areas of research.\textsuperscript{15}

Recently, two small case series were published where patients who suffered from GVHD were treated with FMT. In the first case series\textsuperscript{16} (N = 4), three patients showed a complete recovery of GVHD after FMT, and subsequently the steroids dosage could be reduced. Initially, the fourth patient also responded to FMT. However, diarrhea reoccurred after his steroids dosage was lowered. In the second case series\textsuperscript{17} (N = 3) two patients showed a complete recovery from GVHD after respectively six and two FMTs. The third patient also showed an initial response but experienced a quick return of diarrhea. In this patient FMT was not repeated.

**Gut-brain axis**

Multiple studies suggest a relation between the gut microbiota and the brain, the so-called ‘gut-brain axis’. By neuro-endocrine, neuro-immune, neural and hormonal pathways, the products metabolized or produced by the gut microbiota, can influence our brain activity and vice versa (Figure 2).\textsuperscript{18}

In 2011 it has been observed that feces of anxious mice, when transferred to normal mice, leads to anxious behavior and the other way around.\textsuperscript{18} Additionally, transfer of feces of a depressed patient to germ-free mice and rats, induced depressed and nervous behavior as well.\textsuperscript{19,20}
A study in patients with autism showed an increased prevalence of IBD and other gastrointestinal disorders.\textsuperscript{21} Also, their intestinal permeability seems to be increased, and the composition of the gut microbiota seems to differ from healthy controls.\textsuperscript{22} A study in mice showed that treatment with \textit{Bacteroides fragilis}, one of the most important bacterial species in the healthy intestinal microbiota, leads to a change in autistic behavior.\textsuperscript{22} Until now, studies on the effect of FMT in the treatment of depression, autism or other neurological or psychiatric disorders have not yet been performed in humans.

\textbf{Figure 2.} The neural, immunological, endocrine, and metabolic pathways of gut-brain axis. Putative mechanisms by which bacteria access the brain, and influence behaviour include bacterial products that gain access to the brain via the bloodstream, via cytokine release from mucosal immune cells, via the release of gut hormones, or via afferent neural pathways, including the vagus nerve. Stress and emotions can influence the microbial composition of the gut through the release of stress hormones or sympathetic neurotransmitters that influence gut physiology and alter the habitat of the microbiota. Alternatively, host stress hormones such as noradrenaline might influence bacterial gene expression or signalling between bacteria, and this might change the microbial composition and activity of the microbiota.\textsuperscript{18}

\textit{Adapted from:} Collins SM, Surette M, Bercik P. The interplay between the intestinal microbiota and the brain. Nat Rev Microbiol 2012; 10: 735-42
Fecal Microbiota Transplantation for Elimination of Multidrug Resistant Bacteria

The worldwide increase in bacterial resistance to antibiotics hinders treatment of bacterial infections, and reduces the success rate. Multidrug-resistant Gram-negative bacteria are especially prone to colonize the colon and become part of the normal intestinal microbiota. In some individuals, these colonizing bacteria will disappear naturally, in others they can persist for extended periods of time. Colonization with multidrug-resistant organisms (MDRO) usually happens in patients with multiple comorbidities or patients who need more antibiotics.

Data on FMT used for the eradication of the MDRO carriage are limited to case reports and one case series (N = 5). In these instances, carriage with vancomycin-resistant enterococci, meticillin-resistant Staphylococcus aureus (MRSA), ‘Extended Spectrum β-Lactamase’ (ESBL) and carbapenems producing Enterobacteriaceae were successfully treated with FMT. Most of these patients were critically ill, had many comorbidities and/or an underlying CDI. Some patients were immunocompromised. In the case series, five patients with MRSA enteritis were successfully treated with FMT. During a three month follow up after FMT, their stool remained negative for MRSA. These reported findings remain very promising, despite a recent report of FMT failure for this indication. At this moment several clinical studies on the effect of FMT for the elimination of MDRO carriage are underway.

Conclusion

At the time of writing the only recognized indication for FMT is (recurrent) infection with Clostridium difficile. However, research in the past few years has shown that FMT has also treatment potential in several other disorders. Although the number of
studies and respective sample sizes are limited, in patients with ulcerative colitis FMT seems to lead to clinical remission and endoscopic disease improvement in 24-30% of patients. In patients with metabolic syndrome, the insulin sensitivity increases slightly after FMT. Case reports and case series suggest a positive effect of FMT in IBS, GVHD, and eradication of MDRO carriage. Currently, there are over 100 clinical studies underway (www.clinicaltrials.gov) looking into the possible effects of FMT in different diseases including, but not limited to, ulcerative colitis, Crohn’s disease, IBS, metabolic syndrome, primary sclerosing cholangitis, epilepsy, Parkinson’s disease, acute pancreatitis and non-alcoholic steatotic hepatitis.

As long as these studies have not yet been completed, for now, FMT remains a strict experimental but promising treatment for all (except for CDI) discussed disorders.
REFERENCES


