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Faecal microbiota transplantation in patients with *Clostridium difficile* and significant comorbidities as well as in patients with new indications: A case series

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Abstract

Faecal microbiota transplantation (FMT) is effective in recurrent *Clostridium difficile* infection (rCDI). Knowledge of the safety and efficacy of FMT treatment in immune deficient patients is scarce. FMT has been

suggested as a potential method for an increasing number of new indications besides rCDI. Among our FMT-treated rCDI patients, we reviewed those with major comorbidities: two human immunodeficiency virus patients, six haemodialysis patients, two kidney transplant patients, two liver transplant patients and a patient with chronic lymphatic leukaemia. We also reviewed those treated with FMT for indications other than rCDI: *Salmonella* carriage (two patients), trimethylaminuria (two patients), small intestinal bacterial overgrowth (SIBO; one patient), and lymphocytic colitis (one patient), as well as a common variable immunodeficiency patient with chronic norovirus infection and ESBL-producing *Escherichia coli* (*E. coli*) carriage. Of the thirteen rCDI patients treated with FMT, eleven cleared the CDI. The observed adverse events were not directly attributable to FMT. Concerning the special indications, both *Salmonellas* and ESBL-producing *E. coli* were eradicated. One trimethylaminuria patient and one SIBO-patient reported a reduction of symptoms. Three patients did not experience a benefit from FMT: chronic norovirus, lymphocytic colitis and the other fish malodour syndrome. There were no reported side effects in this group. FMT appeared to be safe and effective for immunocompromised patients with rCDI. FMT showed promise for the eradication of antibiotic-resistant bacteria, but further research is warranted.

Key words: Faecal microbiota transplantation; Antibiotic resistance; *Clostridium difficile* infection; Microbiota; Immunodeficiency; *Salmonella* infection

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Core tip: Knowledge of faecal microbiota transplantation (FMT) in immunocompromised patients and patients with conditions other than recurrent *Clostridium difficile* infection (rCDI) is scarce. We reviewed 13 FMT-treated patients with rCDI and major comorbidities as well as 8 patients with new indications. In our cohort, FMT appeared to be safe and effective for immunocompromised patients: dialysis patients, human immunodeficiency virus patients, solid organ transplant patients and a patient with chronic lymphatic leukaemia. Of the patients treated for indications other than rCDI, the most promising results were successful eradication of antibiotic-resistant bacteria. Eradication of chronic *Salmonella* carriage in two patients with FMT represents the first cases reported to date.

Lahtinen P, Mattila E, Anttila VJ, Tillonen J, Teittinen M, Nevalainen P, Salminen S, Satokari R, Arkkila P. Faecal microbiota transplantation in patients with *Clostridium difficile* and significant comorbidities as well as in patients with new indications: A case series. *World J Gastroenterol* 2017; 23(39): 7174-7184 Available from: URL: <http://www.wjgnet.com>

INTRODUCTION

The intestinal microbiota is an area of active research. Knowledge of the human microbiota has been accumulating rapidly in recent years. The gut bacteria was previously regarded as passive or harmful waste, but the intestinal microbiota is currently respected as a well-orchestrated organism with an active role in the development of immunity and maintenance of health^[1-4].

Microbial imbalance, dysbiosis, is suggested to play a role in many different diseases. The microbiota holds many expectations as a new treatment target. Faecal microbiota transplantation (FMT) is a straightforward way to change the microbial composition of the intestine^[1-4]. FMT has been shown to induce profound and long-lasting changes in the microbiota, offering a means to modify the gut microbiota relatively permanently for the treatment of microbiota-associated diseases^[5].

FMT has become a widely accepted treatment for recurrent *Clostridium difficile* infection (rCDI)^[6-9]. We, among others, have shown that FMT through colonoscopy is an effective treatment for rCDI^[5]. Experience in many centres has shown that FMT is also safe when performed to a high standard^[10-13].

The risk of adverse events of FMT is low in well performed studies^[6]. Rigorous screening of the donor is mandatory. Without proper screening, there is a possibility of transmitting infectious diseases and a possibility of transmitting conditions that FMT is suspected to ameliorate, such as obesity^[14].

All FMT should be performed at a health care unit by professionals who are familiar with the procedure^[15]. FMT is currently indicated only for rCDI^[15]. If FMT is used for other indications, then patients should be carefully evaluated, and the results, whether positive or negative, should be reported. Our group has treated a few patients with conditions other than rCDI and outside of on-going study programmes. Such cases have been evaluated carefully on an individual basis by a gastroenterologist, an infectious disease specialist and a microbiologist.

Although FMT has been effective and generally safe in published studies, data concerning FMT in certain special groups are scarce^[16]. More information is needed regarding the safety of FMT in immunosuppressed and other special groups such as patients undergoing haemodialysis^[12]. In our FMT-treated patients, we gathered information on patients with significant comorbidities, such as immune-deficient patients, patients with an organ transplant and hae-

modialysis patients.

CASE REPORT

Study design

Of the patients treated with FMT in Helsinki University Hospital, we searched for those treated for rCDI and having major comorbidities and those treated for indications other than rCDI. We included dialysis patients and patients with known immune deficiencies in the rCDI group; human immunodeficiency virus (HIV), organ transplant or hematologic disease. We found 13 patients with rCDI and major comorbidities and 8 patients with conditions other than rCDI. We review the patient histories, the outcomes and adverse events of each patient.

Ethical aspects

Since FMT policy and legislation differ from country to country^[17,18], we consulted the Finnish Medicines Agency (Fimea), which is the national competent authority for regulating pharmaceuticals and blood and tissue products. Fimea noted that stool does not fall under the category of pharmaceuticals and did not consider it relevant to the establishment of new regulations specifically for FMT. In Finland, FMT studies do not require approval of the drug authority Fimea.

In Finland, FMT may be used by doctors based on their own judgement. We recommend that clinicians using FMT follow international guidelines^[15,19]. FMT is indicated for rCDI treatment; for other indications, it should be used only in a clinical trial setting.

FMT protocol

Some of the patients described in this article have been treated with stool from a donor familiar to them. Most of the described patients have been treated with stool from a universal donor - frozen and thawed stool from our local faecal bank. The faecal banking protocol is described in detail in our previous article^[10]. Briefly, faecal material from a healthy donor is mixed with saline and glycerol and frozen at -80 °C. In some cases, we used the faecal suspension stored at -20 °C, which did not seem to affect the results or safety of FMT. The frozen suspension is thawed a few hours before FMT and collected into two 100-mL syringes. When necessary, the suspension is passed through a pre-sterilized, stainless steel tea strainer to remove larger particles.

Donor screening was performed as described in detail by Mattila *et al.*^[6] and Satokari *et al.*^[10]. Briefly, the donors were screened for hepatitis C and B, HIV, *Treponema pallidum* and common enteric pathogens. The donor was required to lack antibiotics for the previous six months and to present no gastrointestinal symptoms.

The preferred route of administration of FMT

in our practice is colonoscopy. The suspension is administered into the cecum and ascending colon. Preceding the colonoscopy, the patients undergo bowel lavage by polyethylene glycol solution (between 3-5 L). The patients with rCDI underwent pre-treatment with vancomycin or metronidazole, and the treatment was stopped 36 h before the FMT. In some special cases, we administered FMT during gastroscopy, injecting the suspension into the duodenum as distally as possible.

Although FMT has become the routine treatment after two relapses for CDI in our hospital, the decision to assess FMT in immunosuppressed patients and in special indications is based on a very thorough consideration, especially of safety concerns, by gastroenterologist, specialist of infectious diseases and microbiologist with FMT experience.

Thirteen patients treated with FMT for rCDI and having significant comorbidities

In this article, we report the results of thirteen patients with major comorbidities who underwent rCDI and were treated with FMT (Table 1). Two of the patients had HIV, six were haemodialysis patients, two had a kidney transplant, two had a liver transplant and one had chronic lymphatic leukaemia (CLL).

Eleven of the thirteen rCDI patients (85%) treated with FMT successfully cleared the CDI. Six of the patients had major adverse events, of which two died at 2 and 5 mo post-FMT; however, these events were not directly attributable to FMT. A detailed description of each patient is published online as a supplement.

Eight patients treated with FMT and not having rCDI

Eight patients received FMT as an experimental form of treatment for various special indications. The patients and outcomes are compiled in Table 2 and described in detail below.

A carrier of salmonella #1

A 17-year-old male was found to be a carrier of *Salmonella* in a routine check-up on the 1st of September 2015. He had not had previous GI symptoms. According to Finnish health authority instructions, a *Salmonella*-positive person may not work in food processing. The patient was about to start his studies to become a cook and *Salmonella* was delaying his plans.

The *Salmonella* strain was resistant to doxycycline and ciprofloxacin. He had a mild knee symptom that was thought to be reactive arthritis. Ciprofloxacin was administered briefly and stopped as the sensitivity results of the *Salmonella* became apparent. He was receiving tetracycline for acne since the 18th of August, which was stopped on the 26th of October. In October, faecal salmonella was negative twice, but it was positive again on the 16th of November.

A 2-wk course of i.v. ceftriaxone was considered an

Table 1 The results of fecal microbiota transplantation treatments of thirteen patients with different comorbidities and *Clostridium difficile* infection

	Patient characteristics	Medical history	Post FMT situation	Adverse events in 1 mo
1	A patient with HIV, ulcerative colitis and rCDI	28-year-old male with HIV, antiviral medication and virus undetectable, previous suspicion of ulcerative colitis. Recurrent diarrhoea with <i>C. difficile</i> positivity, slow response to vancomycin.	No further relapses Two months after diarrhoea recurred at the same time with mild alcohol associated pancreatitis. In colonoscopy final diagnosis of ulcerative colitis was made. <i>C. difficile</i> remained negative.	No
2	A patient with HIV, alcoholism and rCDI	59-year-old female, depression, continuous heavy smoking and consumption of alcohol. HIV and antiviral therapy. rCDI after antibiotic treatment for respiratory infection.	No further relapses Diarrheal continued due to exocrine pancreatic insufficiency and excessive alcohol consumption 5 mo after FMT <i>C. difficile</i> reinfection treated with vancomycin and fidaxomicin	No
3	A Haemodialysis patient with rCDI #1	60-year-old female, rheumatoid arthritis and in haemodialysis due to amyloidosis. Chronic atrial fibrillation, polypectomies of rectum adenomas. Had <i>Enterococcus sepsis</i> 2012.	No further relapses. Half a year after FMT <i>Enterococcus faecalis</i> sepsis and an epidural abscess.	No
4	A Haemodialysis patient with rCDI #2	19-year-old female, haemodialysis due to Goodpasture syndrome complicated with pulmonary haemorrhage. Immunosuppressive therapy.	No further relapses.	No
5	A Haemodialysis patient with rCDI #3	77-year-old male, haemodialysis after renal carcinoma operation, diabetes II and COPD. <i>Pseudomonas septicaemia</i> followed by rCDI.	No further relapses. One week after FMT hospitalized due to generalized enema and possible cystitis. Two months after FMT hospitalized due to gastroenteritis, faecal clostridium was negative.	One week after hospitalized due to enema and cystitis
6	A Haemodialysis patient with rCDI #4	80-year-old male. Haemodialysis because of chronic glomerulonephritis, type II diabetes, hypertension, epilepsy, AV-block and a pace maker. <i>Staphylococcus aureus</i> septicaemia followed by rCDI.	No further relapses. <i>Staphylococcus aureus</i> sepsis 5 mo after the FMT.	No
7	A Haemodialysis patient with rCDI #5	66-year-old male, haemodialysis due to microscopic polyangiitis. Chronic atrial fibrillation.	No further relapses	No
8	A Haemodialysis patient with rCDI #6	79-year-old female. Hypertension, dyslipidaemia, atrophic gastritis. TIA 2004 and 2005, a pace maker due to bifascicular block. Coronary disease. Haemodialysis due to an episode of rhabdomyolysis.	2 wk after FMT reinfection after an antibiotic treatment of cystitis. No further FMT's due to poor general condition. Patient died 2 mo after FMT to underlying diseases	2 wk after <i>C. difficile</i> reinfection
9	A Kidney transplant patient with rCDI #1	78-year-old female. Kidney transplant due to polycystic renal disease. Polycystic liver, type II diabetes, hypertension and asthma. Operated for cholecystectomy and hysterectomy. <i>E. coli</i> sepsis and one month after another infectious episode treated with meropenem followed by severe rCDI.	No further relapses 3 d after FMT gastroenteritis, <i>Clostridium</i> was not tested. Restarted vancomycin for 2 d. 12 d after FMT the patient was hospitalized due to infection, CT scan did not reveal the aetiology.	Gastroenteritis 3 d after FMT Hospitalized 12 d after FMT
10	A Kidney transplant patient with rCDI #2	61-year-old female. A kidney transplant due to polycystic renal disease. rCDI after clindamycin for dental infection.	No further relapses	No
11	A Liver transplant patient with rCDI	56-year-old female. Liver transplant due to mushroom intoxication, a moderate renal failure.	No further relapses	No
12	A Patient with a liver transplant, renal insufficiency, haemodialysis and rCDI	69-year-old male. Liver transplantation due to alcohol cirrhosis, followed by renal insufficiency and haemodialysis.	No further relapses	No
13	A Patient with chronic lymphatic leukaemia, chronic norovirus infection and rCDI	65-year-old female. Chronic lymphatic leukaemia since 1996. Autologous stem cell transplantation in 2003. Cytostatic interventions from 2009-2011, after which she had prolonged pancytopenia, infections and hypogammaglobinaemia. In summer 2011, she had chronic norovirus infection and recurrent CDI, several vancomycin courses and gammaglobulin infusions. March 2012 FMT	No primary complications Hospitalized 2 wk after FMT due to diarrhoea. Both norovirus and <i>Clostridium difficile</i> stayed positive in stool samples. Patient died in August 2012, 5 mo after FMT for complications of her haematological disease.	CDI and norovirus related diarrhoea continued.

FMT: Fecal microbiota transplantation; HIV: Human immunodeficiency virus; rCDI: Recurrent *Clostridium difficile* infection; *C. difficile*: *Clostridium difficile*; *E. coli*: *Escherichia coli*.

Table 2 The results of fecal microbiota transplantation treatments of eight patients with different new indications

Patient and diagnosis	Age at 1 st FMT and gender	Route of administration	Outcome	FMT related complications
1 A carrier of <i>Salmonella</i> #1	17-year-old male	Colonoscopy	Successful eradication of <i>Salmonella</i>	No
2 A carrier of <i>Salmonella</i> #2	52-year-old female	Colonoscopy	Successful eradication of <i>Salmonella</i>	No
3 A patient with TMAU #1	24-year-old male	Gastroscopy	Moderate self-reported benefit up to 6 mo, at 12 mo symptoms had recurred to former severity	No
4 A patient with TMAU #2	49-year-old female	Gastroscopy	No change in self-reported symptom severity	No
5 A patient with SIBO	66-year-old male	Gastroscopy (treated 3 times using 2 donors)	Self-reported decrease in symptom severity	No
6 A patient with lymphocytic colitis	21-year-old female	Colonoscopy	Two week decrease in self-reported symptoms, then recurrence of symptoms to former severity	No
7 A carrier of norovirus	32-year-old female	Colonoscopy	No change in self-reported symptom severity, no success in virus eradication	No
8 A carrier of ESBL-producing	31-year-old female	Colonoscopy	Successful eradication of ESBL-producing <i>E. coli</i>	No

FMT: Fecal microbiota transplantation; TMAU: Trimethylaminuria; SIBO: Small intestinal bacterial overgrowth; *E. coli*: *Escherichia coli*.

option, but the patient did not accept this treatment due to his needle phobia. A two-week course of trimethoprim -sulfadiazine 160 mg/500 mg 1 × 2 per orally was started on the 26th of November since the *Salmonella* strain was found to be sensitive. Unfortunately, the faecal *Salmonella* test was still positive after this treatment.

On the 29th of January 2016, the patient was given FMT as described in detail in the FMT protocol section. Preceding the FMT, he received a 5-d course of ceftriaxone 2 g × 1 i.m. The colonoscopy findings were normal, as well as the histology of routine biopsies. There were no complications during the procedure, but the patient fainted soon afterward, which might have been caused in part by the pain and anxiety-relieving medications used during the colonoscopy. He recovered rapidly.

An upper abdomen ultrasound was performed and did not reveal any gallstones. Gallstones are a known risk factor for resistant *Salmonella*.

On the 9th of February - less than two weeks after FMT - the stool test was salmonella-positive and the treatment was considered a failure at first. However, the subsequent three tests (the 2nd, the 8th and the 11th of May) were all negative. According to the instructions of Finnish health authorities, the patient is considered free from *Salmonella* after having three negative samples in a row, and our patient could continue his studies.

There were no reported side effects of the FMT treatment. We consider it likely that the transplanted new gut microbiota played a role in the eradication of *Salmonella*, although we cannot exclude the possibility that the *Salmonella* would have been eradicated spontaneously.

A carrier of salmonella #2

A 52-year-old woman had *Salmonella* enteritis in

March 2016. Her symptoms ceased, but she remained a chronic carrier. She had been treated with courses of trimethoprim-sulphadiazine and amoxicillin. She had also undergone a two-week course of intravenous ceftriaxone, but the *Salmonella* culture remained positive. The bacterial strain was resistant to ciprofloxacin. She was on sick leave during this time because of her work in food production. FMT treatment was administered through colonoscopy on the 17th of November 2016. Prior to FMT, a course of ceftriaxone 2 g 1 × 1 i.v. was administered for six days. The three subsequent faecal tests after FMT (the 2nd, 12th and 19th of December 2016) for *Salmonella* were all negative, and she could return to work. No side effects were observed.

The rationale for treating salmonella carriage with FMT

The prevalence of chronic *Salmonella* carriage is estimated to be 2%-5% in endemic areas. Symptomless carriage of *Salmonella*, especially of individuals working in food production, is considered to be the main route of distribution of the disease among people. Furthermore, persistent carriage of *Salmonella* is associated with gallstones. Fluoroquinolones are the drug of choice for the treatment of chronic carriage of *Salmonella*^[20], but strains that are resistant to ciprofloxacin pose a special challenge.

In animal models, *Salmonella* carriage is associated with changes in the intestinal microbiota^[21]. It is not known whether people with *Salmonella* carriage possess alterations of the gut microbiota. To the best of our knowledge, there are no reported cases of eradication of *Salmonella* with FMT. FMT has been shown to reduce antibiotic resistance genes in the gut microbiota^[22,23]. FMT has shown potential in eradicating faecal carriage of different multidrug-resistant bacteria in case reports^[24]. Therefore, changing or diversifying the intestinal microbiota through FMT is a promising

new option to eradicate chronic *Salmonella* in cases where antibiotics have failed.

A patient with trimethylaminuria (fish malodour syndrome, TMAU) #1

A 24-year-old male had been diagnosed with fish malodour syndrome (trimethylaminuria, TMAU) two years earlier, but the symptoms had started at the age of 16 years. Choline loading resulted in a TMA/TMA-n-oxide-ratio of 0.43 mg/mmol creatinine (reference range 0.05-0.21). He had a severe odour problem, especially when sweating. He had been treated with riboflavin and activated charcoal without effect. A choline restricted diet and occasional two-week courses of metronidazole followed by lactobacilli treatment had a slight positive effect. Copper chlorophyllin was prescribed, but he did not initiate the treatment. After metronidazole pre-treatment, he was given experimental FMT through gastroscopy on the first of December 2015. Six weeks after FMT, he reported a slight reduction of the odour. Six months after the treatment, he reported fewer odour problems, but after one year, the malodour had returned to its former severity. He did not report any side effects.

A patient with TMAU #2

A 49-year-old female with TMAU. Odour problems started at the age of 12 when menstruation began. The odour problem was at its worst 7-10 d post-ovulation. The diagnosis was confirmed based on the urine TMA-oxide and TMA ratio. TMA-oxide was 59.1 mg/mmol creatinine (reference 17-147), and TMA was 16.5 mg/mmol creatinine (reference 2.5-10.8) ratio 0.28 (reference 0.05-0.21).

She was in the perimenopausal phase with hot flashes and excess paroxysmal sweating, causing the odour problem to worsen, but it was partly in control with hormonal treatment. Two-week metronidazole courses only helped temporarily. She had used a strict choline-restricted diet, vitamin B2 and high doses of lactobacilli. Copper chlorophyllin and activated charcoal had been ineffective. She had previously subjectively felt less of an odour problem for a few weeks after bowel cleansing for colonoscopy. FMT was given as an experimental therapy through colonoscopy. As a pre-treatment, the patient was prescribed metronidazole 400 mg three times per day for 7 d to facilitate engraftment of the donor's microbiota. Metronidazole was stopped 36 h prior to FMT. No relief of the malodour was achieved after FMT.

The rationale for treating fish malodour syndrome with FMT

Trimethylaminuria (TMAU) is a condition in which body odour resembles that of a dead fish. In TMAU, trimethylamine (TMA) accumulates in the body. Primary trimethylaminuria is genetic and caused by an inability to convert the fish smelling TMA into non-odorous

trimethylamine-N-oxide (TMAO) in the liver due to a deficiency of the hepatic microsomal flavin-containing monooxygenase (FMO3). Secondary TMAU is defined as an accumulation of TMA without inherited FMO3 deficiency. The aetiology of secondary TMAU is not fully known. One causal factor may be the gut microbiota, which can produce TMA through the metabolism of certain food compounds such as TMAO and choline^[25]. Thus, altering TMA metabolism may be possible through manipulating the intestinal microbiota. To our knowledge, there are no previous reported cases of TMAU treated with FMT.

A choline-restricted diet and copper chlorophyllin are the recommended treatments for TMAU^[26]. Some patients experience partial relief for symptoms by using antibiotics followed by high doses of lactobacilli, riboflavin or charcoal tablets. Our hypothesis is that TMAU can be ameliorated by manipulating the gut microbiota through FMT. Some short-term positive effects were achieved in one patient, but the bacterial spectrum of the present single FMT did not seem to be effective for the treatment of TMAU. More data concerning the effect of FMT on TMAU are needed.

A patient with small intestinal bacterial overgrowth

The patient was 66 years old in January 2015 when he received his first FMT. He had colectomy and ileal pouch-anal anastomosis (IPAA) surgery in 2008 for ulcerative colitis and adenocarcinoma of the caecum. He had experienced bloating and flatulence during his adult life, but it had become worse since IPAA. He had bowel movements on average 6 times per day.

Endoscopic examination of the pouch showed no inflammation. On the small bowel passage X-ray, there was a small bowel dilatation of 10 cm on the left side of the abdomen. Small bowel MRI did not show an indication for surgery.

Before FMT, the patient underwent several treatments with inadequate results. He was treated with dietary changes and dimethicone to decrease bloating and flatulence. A probiotic - *Escherichia coli* (*E. coli*) Nissle up to 2 × 2 capsules (2.5 × 10⁹-25 × 10⁹ CFU/capsule) was administered to remediate dysbiosis. Antibiotics were given to decrease small intestinal bacterial overgrowth (SIBO). He received a course of metronidazole and two courses of rifaximin 200 mg 1 × 4, with one course lasting two weeks and the other four weeks with a tapering dosage. He reported a slight benefit from all of these treatments, but continued to suffer from flatulence and bloating.

On the 20th of January 2015, the patient received FMT *via* gastroscopy as an experimental treatment. For this treatment, 200 mL of the frozen and thawed faecal material was infused through a gastroscope deep into the descending duodenum. Biopsies were obtained *via* gastroscopy and revealed *Helicobacter*-negative atrophic gastritis.

Six weeks after FMT, the patient reported that his

symptoms and bowel movements decreased 50% and that the scent of his flatus was milder. The patient was considered to have reached a partial response and was scheduled for a new FMT.

The second FMT *via* gastroscopy was performed on the 2nd of October using the stool of the same donor as in the first FMT. This time, macrogol bowel preparation was used. The patient reported some benefit from the second treatment, but since disturbing flatulence continued, a third FMT was scheduled with a one-week course of per oral penicillin pre-treatment because the patient had previously experienced relief of his symptoms when using penicillin for a dental infection.

The third FMT *via* gastroscopy was performed on the 29th of January 2016. The transplant was from another donor who was an unfamiliar, tested and generally healthy person, whose stool was frozen and thawed on the day of the transplantation. The last contact with the patient was on the 21th of June 2016, *i.e.*, five months after the third FMT. He reported having fewer symptoms, but some flatulence persisted, though with a milder scent than previously.

The patient was considered to have gained a partial response to his SIBO symptoms from these three FMT treatments.

The rationale for treating SIBO with FMT

A SIBO is defined as an increase in the number or alterations of the type of bacteria in the small bowel. It may be associated with several features, such as alterations of the small bowel anatomy, motility, and immunity, among others. Alterations of the gut microbiota are associated with SIBO by definition. SIBO causes bloating and diarrhoea. Malabsorption, malnutrition and weight loss may also be present. SIBO can most accurately be diagnosed with jejunal aspirate, but this is not widely used due to the invasiveness of the procedure^[27]. Hydrogen or methane breath tests are used more widely, but in many centres, including our own, these tests are not in clinical use. We diagnose SIBO clinically based on symptoms and signs. Our SIBO patient had an altered GI anatomy due to a J-pouch and altered immunity due to ulcerative colitis. He received three FMTs through gastroscopy and reported reduced symptoms. For a more objective evaluation of the FMT effect on SIBO, hydrogen breath tests before and after the treatments would have been valuable. More research on the effect of FMT on SIBO is warranted.

A patient with lymphocytic colitis

A female patient who was diagnosed with microscopic colitis in 2013 at the age of 18 had diarrhoea up to 20 times per day. Faecal calprotectin was constantly negative. She had an inadequate response to medications - mesalamine 2.4 mg/d, budesonide 9 mg/d for two months, loperamide or fibres. She had

tried various diets to relieve the symptoms. The patient wished to be treated with FMT. For her case, there were no on-going scientific study protocols to follow.

After repeated requests from the patient and with no other rational treatment options available, FMT through colonoscopy was administered as an experimental treatment on the 21st of June 2016.

In the follow-up telephone conversation on the 7th of July, the patient reported to have gained a benefit from the procedure for two weeks, after which the diarrhoea recurred as before. The outcome was considered negative and no further transplants were given.

The rationale for treating lymphocytic colitis with FMT

Lymphocytic colitis is a subtype of microscopic colitis. It is a cause of diarrhoea that is more common in elderly people, but it may even affect children. Microscopic colitis may be associated with an altered gut microbiota. In a small study, patients with microscopic colitis had a decrease in *Akkermansia* species compared with the healthy controls. *Akkermansia* is considered to have a protective effect on the intestinal epithelium^[28,29]. Our patient with lymphocytic colitis was treated once with FMT through colonoscopy. She experienced short-term (two weeks) relief of her symptoms, after which the symptoms recurred. The outcome was considered negative. In possible future studies, it might be worth considering a recurrent treatment-protocol with FMT, which has shown some promising results in IBD patients^[30,31] and in a single case of collagenous colitis^[32], as well as pre-treatment with antibiotics prior to FMT, which may facilitate engraftment of the donor's microbiota^[5].

A carrier of norovirus

A 32-year-old woman was treated with FMT for being a chronic carrier of norovirus. As a long-term diagnosis, she had common variable immunodeficiency (CVI), coeliac disease and osteoporosis. She had chronic diarrhoea since 2009, malabsorption since 2012 and partial parenteral nutrition since March 2015. Her norovirus infection was diagnosed in September 2013. Previously, she did not have acute gastroenteritis. Several medications for her norovirus infection had been attempted without success: interferon alfa, interferon with ribavirin and nitazoxanide.

FMT was administered in March 2016 through gastroscopy. She was susceptible to bacterial infections due to CVI and bronchiectasis. She had received trimethoprim-sulfamethoxazole as a long-term prophylactic treatment, which was ceased 36 h before FMT. Bowel lavage was not administered prior to FMT. Routine biopsies of the gastroscopy revealed partial villus atrophy.

After FMT, the symptoms of the patient remained unchanged, with four to six bowel movements per day.

Faecal norovirus remained positive. Thus, the patient did not benefit from the experimental FMT treatment. No side effects related to the FMT were observed.

Rationale for treating chronic norovirus infection with FMT

Approximately 5% of CVI patients have enteropathy. In some case reports, chronic norovirus infection has been the cause of CVI-associated enteropathy, and eradication of the virus has cured the symptoms. It has even been hypothesized that chronic norovirus could be a key player in most of these cases^[33].

It is suspected that the gut microbiota plays a role in regulating norovirus infection and its pathogenesis^[34], and the relationship between the gut bacteria and norovirus infection is undergoing active analysis using murine models. We did not find any published cases of chronic norovirus or CVI enteropathy treated with FMT, and to our knowledge, the patient presented herein is the first reported case.

A carrier of ESBL-producing *E. coli*

A 31-year-old female patient with asthma was a carrier of the multidrug-resistant *E. coli*-extended spectrum beta-lactamase producing strain (ESBL). She had received pyelophritis caused by ESBL-producing *E. coli* two times, in October 2015 and June 2016. Both episodes of pyelonephritis had been treated with intravenous ertapenem. The duration of the second ertapenem treatment was ten days.

She had studied scientific literature concerning ESBL and *E. coli* virulence factors. After her second pyelonephritis, a consultant infectious disease specialist recommended ESBL eradication with FMT. Prior to FMT, faecal cultures for ESBL-producing *E. coli* were collected five times between August 2016 and February 2017. All the cultures were positive with ESBL-producing *E. coli*.

The *E. coli* strain was resistant to amoxicillin-clavulanic acid, ampicillin, cephalexin, ceftriaxone, cefuroxime, levofloxacin and trimethoprim-sulfamethoxazole, susceptible to ertapenem, meropenem, tobramycin, fosfomycin and nitrofurantoin and showed intermediate susceptibility to ceftazidime and piperacillin-tazobactam.

The patient was hospitalized for meningitis in November 2016. She was treated with ceftriaxone and acyclovir. The meningitis was shown to be caused by an enterovirus. She recovered fully, but the episode delayed her FMT treatment.

FMT was performed *via* colonoscopy on the 31st of January 2017. The endoscopic finding was normal, as were the routine biopsies. Six weeks later, on the 20th of March, the faecal culture of ESBL-producing *E. coli* was negative. The patient had symptoms of cystitis, and the urine test showed elevated leukocytes and *E. coli*, but this time they were susceptible to all the

tested antibiotics. She was treated with a two and a half day course of nitrofurantoin 75 mg twice a day.

The rationale for treating ESBL-producing *E. coli* carriage with FMT

Antibiotic resistance is an emerging global health problem. One of the most common and clinically relevant types of antibiotic-resistant bacteria are the ESBL-producing enterobacteria, especially *E. coli*, which occurs worldwide^[35]. Antibiotic resistance is largely caused by excessive use of wide spectrum antibiotics. We, among other authors, have reported the reduction of antibiotic resistance genes in the intestinal microbiome of patients with rCDI after FMT^[22,23].

FMT has been successfully used for the eradication of ESBL-producing *E. coli* and other multidrug-resistant bacteria in a small number of published case reports^[36-38]. Clinical use of FMT for eradicating resistant bacteria requires further study in larger groups of patients.

DISCUSSION

We report the results obtained for 21 FMT-treated patients; thirteen of the patients had rCDI with a significant underlying comorbidity, and eight of the patients had a condition other than rCDI. The 21 reviewed patients consisted of a heterogeneous group with many comorbidities. This establishes a limitation to our study; definitive conclusions cannot be drawn for the patients as a group. The strength of our study is that we review real life patients who are often excluded from studies due to their comorbidities.

There remains a paucity of data about FMT treatments of patients with different comorbidities. In particular, immunocompromised patients have been excluded from many studies due to the suspected risk of infectious complications. Published data from case series to date suggest that FMT is acceptably safe and effective, even for immunocompromised patients^[11,12,39].

Of our thirteen patients with rCDI, *Clostridium difficile* (*C. difficile*) was successfully eradicated from eleven patients. Of those eleven, a patient with HIV and alcoholism experienced reinfection four months after FMT. One patient had gastroenteritis symptoms three days after the FMT and took vancomycin for two days without consulting a doctor. Faecal *C. difficile* was not tested. Her CDI relapses before FMT had been severe. There were no relapses of CDI documented over 8 mo of follow-up, and thus the outcome was considered positive. Two patients experienced a relapse, of which one had received antibiotics less than a week after FMT.

At one month of follow-up after FMT, two of the thirteen rCDI patients had relapsed. Two of the patients were hospitalized due to infections that were

not related to FMT. Two dialysis patients had sepsis in the months following FMT. One dialysis patient died two months after FMT. A patient with CLL and chronic norovirus did not clear the CDI or norovirus; she died due to complications of CLL five months after FMT. The HIV patient resolved the *C. difficile* infection through FMT but experienced an activation of underlying ulcerative colitis two months after FMT. The patient group had many comorbidities, and all the adverse events were considered likely to be unrelated to the FMT.

We also report eight cases of patients treated with FMT for a reason other than rCDI. These patients had prolonged *Salmonella* infection (two cases), ESBL-producing *E. coli* carriage, fish malodour syndrome (two cases), chronic norovirus infection, small bowel bacterial overgrowth and lymphocytic colitis. The acknowledged indication for FMT is recurrent *C. difficile* infection. When performed outside of this indication, FMT should preferably be conducted in a clinical trial setting^[19]. However, experimental treatment in carefully considered cases is justified when other treatment options are limited. Such cases also provide preliminary results regarding the use of a specific treatment for new indications.

In the past few years, an increasing number of diseases have been shown to be associated with alterations of the gut microbiota, yet the causality is in most cases undefined. FMT has been suggested to be investigated in many of these diseases^[1-4]. Although promising data about FMT in new indications such as autism^[40], constipation^[41] and epilepsy^[42] have been reported, careful consideration of the associated risks is necessary.

The eight patients treated for causes other than rCDI all had a condition in which disruption of the gut microbiota was a possible etiological factor. All eight patients expressed a strong wish to try FMT for their condition, for which other treatments had previously failed. The patients were informed of the experimental nature of the procedure. The justification of each treatment was considered by at least three specialists, including the performing gastroenterologist, the referring physician and the head of the Gastroenterology Department.

The carriers of *Salmonella* and ESBL-producing *E. coli*, and the SIBO patient seemed to have benefitted from FMT. One of the fish malodour syndrome patients received only short-term relief for malodour, and the other did not gain any benefit. The patient suffering from lymphocytic colitis and the CVI patient with chronic norovirus infection did not gain a benefit from FMT. The positive outcome of the carriers of *Salmonella* and ESBL-producing *E. coli* was objectively defined with a laboratory test, as was the negative outcome for the norovirus patient. The outcomes of the other three patients was based on self-reported symptoms

and thus were less objective. None of these patients reported any side effects.

The eradication of antibiotic resistant bacteria with FMT has been studied by many research groups, and the results to date are promising. Successful eradications have been described with several multidrug-resistant bacteria, such as ESBL-producing and carbapenemase-producing *Enterobacteriaceae*, vancomycin-resistant *Enterococci*, or methicillin-resistant *Staphylococcus aureus*^[36-38]. To the best of our knowledge, the two eradications of *Salmonella* carriage are the first reported cases. The efficacy of FMT for chronic norovirus infection and fish malodour syndrome has also not been reported previously. The treatment options for multidrug-resistant organisms are scarce - eradication and increasing colonization resistance by FMT may offer a new means to counter the problem.

We think it necessary to further study the effect of FMT in conditions where other treatment options are limited. Placebo-controlled trials should be preferred due to the high risk of a placebo effect in conditions in which the diagnosis relies mostly on symptoms, although randomized controlled trials may not be an option for infrequent conditions due to the small number of patients. Thus, case series provide valuable guidance for clinical practice and future clinical trials.

In conclusion, in our cohort, FMT appeared to be a safe and effective treatment for rCDI for patients with significant comorbidities, although further conclusions cannot be drawn due to the small sample size. FMT also shows promise for the eradication of antibiotic-resistant bacteria, for which further research is warranted. FMT is only indicated for rCDI; for other indications, FMT should still be performed only in a clinical trial setting.

COMMENTS

Case characteristics

The authors reviewed 21 fecal microbiota transplantation (FMT)-treated patients, of which 13 had recurrent *Clostridium difficile* infection (rCDI) and major comorbidities: two human immunodeficiency virus patients, six haemodialysis patients, two kidney transplant patients, two liver transplant patients and a patient with chronic lymphatic leukaemia. In addition, the authors reviewed 8 patients treated with FMT for new indications: *Salmonella* carriage (two patients), trimethylaminuria (two patients), small intestinal bacterial overgrowth, lymphocytic colitis, ESBL-producing *Escherichia coli* carriage and a common variable immunodeficiency-patient with chronic norovirus infection.

Treatment

The patients were treated with FMT. Most of the patients received FMT via colonoscopy, and stool from a universal donor was mainly used. In a minority of cases, FMT was administered through gastroscopy.

Related reports

Immunocompromised patients have been excluded from the majority of FMT studies, but case reports and series have started to emerge. The number of case reports of patients treated with FMT for indications other than *Clostridium*

difficile is growing. To our knowledge, eradication of *Salmonella* carriage with FMT has not been reported previously.

Experiences and lessons

FMT is acceptably safe for the treatment of rCDI in immunocompromised patients. FMT is promising as a treatment for the eradication of antibiotic-resistant bacteria. There is a great demand for further research on FMT for many new indications.

Peer-review

This article gives a clear description of 21 cases and reasonable discussion, and it can provide a good reference in the daily performance of FMT. The case description in the article is very detailed, the analysis is also very thorough. The article has a good clinical significance.

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