Clinical Case Report

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# Case series of successful treatment with fecal microbiota transplant (FMT) oral capsules mixed from multiple donors even in patients previously treated with FMT enemas for recurrent *Clostridium difficile* infection

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**Abstract**

**Rationale:** Studies have shown that fecal microbiota transplantation (FMT) is a safe and highly efficient treatment for recurrent Clostridium difficile infection (rCDI). However, it is still unknown if one versus multiple donors or enemas versus capsule FMT are most efficient.

**Patient concerns:** 10 patients with at least 3 previous episodes of CDI were offered treatment with FMT capsules. 9 patients decided to participate.

**Diagnoses:** In this study, we treated 9 patients (25–86 years) with rCDI.

**Interventions:** From October to November 2016, a total of 9 patients with recurrent CDI were treated with oral fecal microbiota capsules, with mixed donor feces from 4 donors with high microbiota diversity. All patients received treatment with vancomycin prior to the capsule regime.

**Outcome:** Patients had previous recurrences ranging from 2 to 10 recurrences. All 9 patients were successfully treated without recurrence after 180 days follow-up, even 2 patients previously treated with FMT enemas.

**Lessons:** FMT capsules based on multiple donors are highly efficient in patients with rCDI.

**Abbreviations:** CDI = *Clostridium difficile* infection, FMT = fecal microbiota transplantation, RBT = rectal bacteriotherapy, rCDI = recurrent CDI.

**Keywords:** capsules, donors, fecal microbiota transplant, recurrent *Clostridium difficile* infection

## 1. Introduction

*Clostridium difficile* infection (CDI) is a major public health concern and a common clinical challenge in hospitals in the Western world.[1] Antibiotic treatment, including metronidazole and vancomycin, facilitates a dysbiosis in the gut microbiota and due to this 20% to 60% of CDI patients have recurrent CDI (rCDI).[2,3] Therefore, trying to restore a normal composition of the gut microbiota in patients with rCDI may have the potential to eradicate CDI.

Multiple studies have shown that fecal microbiota transplantation (FMT) is a safe and highly efficient treatment for rCDI with a high cure rate compared to vancomycin treatment.[4,5] However, the administration of FMT is challenging. Whether FMT is administrated endoscopically or as an enema, these methods of administration are inconvenient for the patients as well as for the health care providers. A recent published study has shown that oral administrated encapsulated FMT is comparable to other FMT treatments in rCDI with a clinical success rate at 88% and nearly normalization of the gut microbiota 1 month after FMT treatment,[6] indicating that oral fecal microbiota capsules are emerging as an alternative and easier way of FMT administration. Aleris-Hamlet Hospitals, Copenhagen, are currently the only producer of oral FMT capsules in Denmark and in 2016 they offered 9 treatments for free for patients with rCDI at the Copenhagen University Hospital Hvidovre, Denmark. The aim of this case series is to describe our first experience with oral FMT capsules in Denmark.

## 2. Material and methods

### 2.1. Patients

From October to November 2016, a total of 10 consecutive patients were offered rectal bacteriotherapy (RBT),[7] FMT enema (from a single donor) or FMT-capsules (mixed from 4 donors), 9 patients chose to be treated with oral fecal microbiota capsules. Candidates for FMT or RBT treatment were patients

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with 2 or more recurrences of CDI who have received appropriate treatment with vancomycin, metronidazole, or fidaxomicin. Exclusion criteria were patients receiving chemotherapy, with life expectancy of < 3 months or ongoing antibacterial treatment (e.g., for endocarditis or tuberculosis). All patients were followed for 3 months through telephone interviews, and through searches in databases were stool sample results are registered.

### 2.2. Donor selection

Posters for recruitment were placed several places in Copenhagen with information on how to apply as a donor for FMT. A questionnaire similar to those for recruiting blood donors was used. Based on 200 applicants, 20 applicants were invited for an interview and a second questionnaire. The second questionnaire was specifically aimed for detecting possible conditions associated with disturbances in the gut microbiota within the applicant and the applicant's nearest family. These conditions included obesity, irritable bowel syndrome, inflammatory bowel diseases, neurological disorders, mental illnesses, and colorectal cancer among others. After the second screening procedure, 6 applicants were found qualified as donors. Fecal samples from these 6 persons were assessed for alfa-diversity using 16s rRNA gene amplicon sequencing. The 4 donors with the highest diversity were finally selected.

Once recruited, the donors were instructed to keep up a healthy lifestyle during the collection period.

### 2.3. Sample preparation

Donors were equipped with 500 mL bottles of oxygen reduced sterile saline (0.9% NaCl). Immediately after producing the sample, donors were instructed to cover the sample in the oxygen reduced saline to protect the sample from oxygen and to deliver it within one hour. Hereafter the sample was stored at 5°C and processed in the laboratory no > 3 hours later from the time of delivery. Sample and saline was homogenized, filtered, and centrifuged. The supernatant was discarded and the pellet mixed with glycerine as a cryoprotectant. Most of the process was done in an anaerobic environment using argon gas to protect the sample. Only when transferring the samples between containers they were shortly exposed to oxygen. Finally, the samples were frozen at −20°C.

All donors were screened vigorously for pathogens in blood and feces before and after the collecting period and extensive laboratory analysis were performed to detect any signs of infection or inflammation in accordance with international guidelines.[8] Once donors had passed the second screening all fecal samples were mixed before being double encapsulated using Capsugel DR Caps size 0 and 00. We used 25 capsules per daily dose for 3 days, each capsule containing 0.6 mL of material hereof 0.4 mL fecal material and 0.2 mL glycerol. In this way, a daily dosage of 25 capsules provides approximately 10 g of concentrated fecal matter. Both patients previously treated with FMT enema received 85 g of fresh feces from unrelated donors once.

### 2.4. Ethics

Ethical approval was not necessary. Donors were recruited and patients were treated according to hospital guidelines, where FMT is a treatment option. The National Danish Health Authority has been informed and informed consent was given by patients for the FMT treatments.

## 3. Results

Patients with rCDI are referred to the Department of Infectious Diseases, Copenhagen University Hospital Hvidovre, for either FMT or rectal bacteriotherapy (RBT), a fixed mixture of intestinal bacterial strains. A total of 10 consecutive patients were offered RBT, FMT enema (from a single donor) or FMT-capsules (mixed from 4 donors), 9 patients chose to be treated with oral fecal microbiota capsules. The patients had at least 3 previous episodes of CDI (3–11 episodes) (Table 1). The majority of the patients were women (67.8%) and the mean age at the time of treatment was 63.8 years (25–86 years). All patients received treatment with vancomycin prior to the capsule regime. One patient had also previously been treated with one FMT administrated as an enema and 2 treatments with RBT. Another patient had previously received one FMT treatment as an enema.

All patients were treated once with 25 oral fecal microbiota capsules a day for 3 consecutive days. One patient (patient number 4, Table 1) was additionally given a second but prolonged treatment with 25 capsules a day for 5 days because of reccurrence of CDI after the first capsule treatment.

All patients were, hereafter, clinically and microbiologically cured with absence of CDI after 180 days follow-up. No adverse events were reported.

## 4. Discussion

The optimal mode of FMT delivery is still unknown but a few studies suggest that colonic delivery is superior to upper gastrointestinal FMT, especially in patients with severe CDI.[9–11] A recent observational prospective follow-up study comparing nasogastric tube delivery and lower endoscopic delivery supports this,[12] but randomized clinical trials comparing different delivery modalities is needed. In our 9 rCDI cases upper

**Table 1**

**Clinical characteristics of the 9 Danish patients treated with oral encapsulated FMT.**

| Patient number | Age, years | Sex | Numbers of CDI recurrences | Previous treatments with FMT and/or RBT |
|---|---|---|---|---|
| 1 | 75 | F | 4 | – |
| 2 | 64 | F | 3 | – |
| 3 | 26 | F | 2 | – |
| 4 | 25 | F | 10 | One FMT (enema) and 2 RBT (enema) |
| 5 | 84 | F | 4 | – |
| 6 | 81 | M | 5 | – |
| 7 | 78 | M | 4 | – |
| 8 | 86 | F | 5 | – |
| 9 | 55 | M | 4 | One FMT (enema) |

CDI = *Clostridium difficile* infection, FMT = fecal microbiota transplantation, RBT = rectal bacteriotherapy.

gastrointestinal delivery with capsules was efficient, easy and well tolerated, but none of our patients had severe CDI at the time of treatment. Although colonic delivery may be superior to upper gastrointestinal delivery, delivery by colonoscopy can cause fatal complications such as perforation of colon. These risks due to more invasive methods of administration are eliminated with the intake of oral encapsulated FMT which is a far gentler administration form. In our study, capsules were given instead of FMT enemas. Compared to enemas the capsules may cover a larger area of the intestines. Also, the capsules were administered for 3 consecutive days; the enema was typically given for 1 day only. Finally, the capsules were produced under great effort to reduce exposure to oxygen. The enema preparation was produced using a household blender and therefore exposed to oxygen to a much higher degree. Only few well-sized randomized clinical trials exist comparing delivery mode. In a meta-analysis frozen FMT preparations were found to be as efficacious as fresh material in one RCT, but the numbers of patients in the remaining RCTs were too small to allow definitive conclusions regarding delivery.[13]

The main focus, when selecting donors for FMT, is screening for infectious and metabolic diseases and "traditionally" there is a one-donor-for-one-patient approach. However molecular techniques have made it possible to characterize the gut microbiome and Aleris-Hamlet Hospitals, Copenhagen, used these techniques to design FMT capsules of pooled fecal material from donors with the most diverse fecal microbiome. It is still unknown if using multiple universal donors is superior to the one-donor-for-one-patient approach, but in the case of these 9 Danish patients it was effective. Even though it must be emphasized that our study is only a small nonrandomized observational study. Chang et al[14] showed that patients with rCDI had a significant decreased diversity of the gut microbiome compared with healthy controls and patients with an initial episode of CDI, and this could indicate that repopulating the altered gut microbiota of patients with rCDI with FMT material from multiple universal donors for a more diverse composition could be beneficial compared with using only one donor.

## 5. Conclusion

In this brief communication, we describe the use of FMT capsules based on donor material from multiple selected donors as treatment for rCDI. This method is easy to accept for the patient and easy to use for the hospitals. The treatment was safe and efficient in all of 9 Danish patients with rCDI.

## Author contributions

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