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SHORT REPORT

Faecal microbiota transplantation as a home therapy to frail older people

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Abstract

Background: *Clostridioides (Clostridium) difficile* infection (CDI) is a leading cause of antibiotics-associated diarrhoea. Faecal microbiota transplantation (FMT) is effective for recurrent CDI and may be provided as a home treatment to frail, older people.
Methods: We present four consecutive patients with recurrent CDI, treated at home using nasojejunal tube-delivered or encapsulated donor faeces. The primary outcome was combined clinical resolution and a negative CD toxin test 8 weeks post-treatment.
Results: All four patients had severe CDI and all improved clinically following one FMT. Sustained resolution following one FMT was observed in one patient. Two patients had recurrence and received a second FMT using capsules; both achieved resolution. One patient who had recurrence declined from further FMT due to fear of relapse and was established on long-term vancomycin. No adverse events related to FMT were observed.
Conclusion: Frail older people may benefit from FMT. Home treatment is a viable option and may be considered both for clinical cure and for palliation.

Keywords: faecal microbiota transplantation, *Clostridioides (Clostridium) difficile* infection, frailty, older people

Key points

- Frail older people with recurrent *C. difficile* infection have high morbidity and mortality.
- Faecal microbiota transplantation (FMT) may be administered in the patient's home.
- FMT which is offered to older people may be life-saving or palliative.

Introduction

Clostridioides (formerly *Clostridium) difficile* infection (CDI) is the leading cause of antibiotics-associated diarrhoea and a major health burden [1,2]. Disease severity ranges from mild persistent diarrhoea to life-threatening toxic megacolon and death [3]. From 2000 to 10, CDI incidence has doubled to 700,000 annual cases in Europe and the United States with a concurrent rise in hospitalizations, costs and deaths [2,4–6].

Older people are particularly prone to acquire CDI. Risk factors such as antibiotics exposure, high age and comorbidity are common in geriatric patients [1,2]. More than 90% of all CDI-attributable deaths occur among comorbid, frail older patients and their risk of severe CDI is increased 3-fold [2,7]. Recurrence develops in 20% following standard vancomycin treatment, and 12% suffer refractory disease, posing a therapeutic challenge [2,8].

Faecal microbiota transplantation (FMT) is a new and effective therapy for recurrent CDI with cure rates > 90% [9,10]. It is recommended for recurrent CDI and may be a rescue treatment for refractory or severe CDI [11]. In recent years, FMT has undergone drastic technical improvements, enabling widespread access to the treatment [12]. Thorough donor screening and application protocols have been implemented [13,14] and ensure safety and sustainability of the service. By convention, FMT requires hospital attendance. Frail older patients who are too weak to tolerate transportation for treatment may therefore be withheld treatment.

Specialised geriatric teams that provide patient-tailored geriatric care in the patients' homes have been implemented in most community settings to accommodate the needs of frail older patients. The implementation of acute geriatric teams has reduced admission rates and mortality [15], and it enables risk stratification of the patients. Geriatric teams may successfully handle home treatments such as FMT.

Here, we report our experience with providing FMT as a home treatment in a nursing home setting in four critically ill, geriatric patients with CDI.

Methods

This was a single-centre clinical collaboration between the specialised geriatric team and an established FMT programme [13] at a teaching university hospital.

The geriatric team comprised a geriatrician and a trained geriatric homecare nurse. All patients were assessed at the first home visit following discharge, using the Multidimensional Prognostic Index (MPI) as a cumulative frailty assessment [16]. We used the MPI to describe the patients' frailty level as low, moderate or severe. The MPI is based on subscores from eight domains, i.e. social status, medication, activities of daily living, mobility, cognitive status, risk of pressure sores, morbidity and nutritional risk. Each domain is assigned a score between 0 and 1 with different lowest and highest scores, leading to different domain weights. The MPI is calculated as the mean of the domain subscores. Three levels of MPI are identified according to validated cut-offs for the risk of mortality: values from 0 to 0.33 are considered as low, 0.34 to 0.66 as moderate and 0.67 to 1.0 as severe [17]. A Danish version of the MPI was translated and validated from the English version.

CDI was identified by the geriatric team during post-discharge visits. Patients with unresolving diarrhoea, defined as three or more liquid stools per day, had stool samples taken for intestinal pathogens and a single-test algorithm polymerase chain reaction test for *C. difficile* toxin A, toxin B, or binary toxin. In patients with a positive *C. difficile* toxin test, antibiotic treatment was initiated. The CDI severity was evaluated according to clinical guidelines [3] and was considered refractory if the diarrhoea persisted or worsened beyond 6 days of antibiotic treatment.

At our institution, an FMT programme has been implemented since 2014 [13,18]. FMT was carried out using either nasojejunal tube delivery or glycerol-based enterocapsules with frozen-thawed, single donor faeces from thoroughly screened healthy blood donors [19]. FMT for nasojejunal tube delivery was processed as previously described [13] with ~50 g of crude donor faeces being processed into a 200 ml solution stored in a 500 ml cryobag (CryoMACS®, Miltenyi Biotec, Bergisch Gladbach, Germany). For the encapsulated FMT, ~21–25 g of crude donor faeces was diluted with sterile saline and glycerol, concentrated during a three-step centrifugation protocol and dispersed into double-coated, acid-resistant enterocapsules (Capsugel® VcapsTM size 0 og 00, Lonza Biopharmaceuticals, Colmar, France).

Delivery mode for each FMT was decided according to the clinical state of the patient. Patients deemed too frail to swallow capsules or with signs of gastroparesis were offered FMT by nasojejunal tube delivery, and encapsulated FMT was offered in all other cases. The nasojejunal tube delivery required tube insertion the day prior to the treatment, overnight fasting and radiologic imaging verification of intestinal position. Radiologic verification of intestinal tube placement was performed in the patient's home by an outgoing X-ray service. FMT required 6-hour fasting and cessation of proton pump inhibitors for 2 days. With nasojejunal delivery, the faecal solution was instilled at ambient temperature over 10 min. With encapsulated delivery, the 30 enterocapsules were ingested orally over 30 min with apple juice, acidic with a pH of 3 to prevent gastric capsule dissolution.

Patients were evaluated Week 1 and 8 following treatment, and the primary outcome was clinical resolution of diarrhoea with a negative *C. difficile* toxin test at Week 8. All patients were monitored closely the days following FMT, for clinical improvement and potential adverse reactions. All patients gave written informed consent to the treatment and to presentation of their treatment course. This study was carried out as a part of the observational cohort study, Fecal Microbiota Transplantation (FMT) for *Clostridium difficile* (CEFTA), registered at www.ClinicalTrials.gov (study identifier NCT03712722).

Results

Four consecutive older patients who were admitted to a nursery home and developed CDI received a patient-tailored home FMT regimen. All had severe comorbidities and were rated as severely frail (Table 1). In two patients, FMT was indicated by treatment-refractory primary CDI with rapid clinical deterioration. In the other two, the indication was recurrence of CDI with severe disease defined as abdominal pain, leukocytosis and hypoalbuminaemia. In all four, the joint evaluation by the geriatric team was that the infection was imminently life-threatening.

All patients experienced marked clinical improvements in the days following their FMT, with increased mobility and arousal and normalisation of bowel habits. Sustained

Table 1. Patient characteristics in four frail older patients who received FMT as a home treatment. The MPI is a cumulative frailty assessment tool validated in a Danish department of geriatrics, and individual scores were converted to low, moderate or severe degree of frailty

No.	Gender, age	Previous history	Incident	Frailty level	Antibiotics before CDI	Initial CDI presentation	Clinical course following FMT
1	Female 85 years	Atrial fibrillation, hypothyroidism, upper gastrointestinal bleeding	Chest pain and fever, cholangitis	Severe	Piperacillin-tazobactam, ciprofloxacin, cefuroxim, pivmecillinam	Severe, *C. difficile* toxin A/B, initial resolution. Recurrence within 1 week, severe CDI with abdominal pain, refractory to vancomycin	Tube-delivered FMT with complete recovery and negative *C. difficile* test
2	Female 93 years	Hypertension, atrial fibrillation, recent stroke	Fall with rhabdomyolysis	Severe	Cefuroxim, pivmecillinam	Severe, *C. difficile* toxin A/B, refractory to metronidazole and vancomycin, with general deterioration. Severe bradycardia, but pacemaker implantation not possible due to CDI	Tube-delivered FMT with instant improvement. Pacemaker inserted. Recurrence following prophylactic antibiotics. Second FMT delivered by capsules, complete recovery
3	Male 88 years	Atrial fibrillation, biological aortic valve, ischaemic heart disease	Fall and wound infection	Severe	Dicloxacillin, penicillin, cefuroxim, meropenem, trimopan	Severe, *C. difficile* toxin A/B, initial resolution with metronidazole. Recurrence after 2 weeks, rapid decline despite vancomycin	Tube-delivered FMT with clinical resolution. Recurrence after 2 months, vancomycin no effect. Capsule FMT for refractory CDI with complete recovery
4	Female 92 years	Hypertension, diabetes mellitus, polymyalgia, renal failure	Fall with rhabdomyolysis, hip fracture	Severe	Piperacillin-tazobactam	Severe, *C. difficile* toxin A/B, no effect of vancomycin, deterioration with immobilisaiton, anorexia, confusion, leukocytosis	Tube-delivered FMT, complete recovery. Recurrence following pivmecillinam for UTI, improvement with vancomycin. Feared further recurrences, established on long-term vancomycin

resolution at Week 8 following one FMT was observed in one of four patients. Two patients received antibiotics and had CDI recurrence. They both received a second FMT using capsules and achieved resolution. One patient with recurrence declined further FMT due to fear of another relapse, and because she tolerated vancomycin she was prescribed long-term vancomycin treatment. No adverse events related to FMT were observed during follow-up.

The clinical courses of the four patients are summarised in Table 1.

Discussion

In this study, we present four cases of severely ill, older patients who were successfully treated with FMT in their homes as a life-saving therapy for refractory or recurrent CDI. All four patients were weakened to a degree where they could not tolerate hospitalisation. Our results provide the proof of principle how current FMT programmes may collaborate with specialised geriatric teams to extend their reach to those most in need.

Older patients are particularly vulnerable to CDI. As illustrated here, older people with CDI rapidly and progressively lose function with affection of multiple organs. CDI should be suspected on broad indications, and vancomycin treatment should be started promptly and according to published guidelines [11]. Our results are in accordance with a previous study demonstrating that the high effect of FMT also applies to the geriatric population with recurrent CDI [7]. Importantly, the present paradigm only to use FMT for patients with their third or fourth recurrence is problematic in this population because not all older patients survive their first recurrence or even their initial CDI. All patients in the present study showed a marked and immediate clinical improvement following their first FMT. A crude evaluation of bowel habits and *C. difficile* toxin tests may be insufficient to identify the overall effect of providing FMT to this population. The results and the limited number of patients call for further clinical trials, and we suggest that future studies in older people include validated indices of general performance and function, such as the MPI and muscle strength parameters such as hand grip strength.

In the present study, we used FMT delivered by capsules or tube. Both methods have pros and cons. Although tube delivery requires tube insertion and X-ray control, capsule

ingestion requires intact gastric emptying. Treatment effects are similar with the two methods [20], but a higher load of donor faeces may be applied using tube delivery. This may be relevant in patients with a high risk of relapse, e.g. those with liver cirrhosis or anaemia [10,21]. In each patient, a risk-benefit balance should guide a joint treatment decision. Particular attention should be paid to patients with refractory disease, i.e. those who do not improve clinically with vancomycin. The optimal treatment regimen for these patients remains to be determined, but it may include early FMT [14]. It also underpins that only patients who respond well to vancomycin should be considered for long-term maintenance treatment.

In conclusion, home treatment with FMT may successfully be provided to frail older patients with CDI who cannot tolerate hospital admission. Patient assessment and monitoring from a specialised geriatric team and collaboration with an FMT centre enable a balanced treatment approach that may be both life-saving and cost-effective.

Declaration of Conflicts of Interest: None.

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