Fecal Microbiota Transplantation for Refractory Clostridioides Difficile Infection Is Effective and Well Tolerated Even in Very Old Subjects: A Real-Life Study

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Abstract

OBJECTIVES: Fecal microbiota transplantation (FMT) is an innovative therapy indicated for the treatment of recurrent Clostridioides difficile infections. Although CDI and its complications are more common in very old patients (≥80 years) due to their comorbidities, frailty and senescence of the immune system, limited data are available for this older patient population.
DESIGN: This was a single-center, real-life cohort study with retrospective outcome data registration, conducted at Toulouse, France.
SETTING AND PARTICIPANTS: Older people group was compared to the control group aged 18-79 years.
MEASUREMENTS: The primary outcome was overall survival at 52 weeks for ≥80 years patients compared to the control group after FMT. Recurrence-free survival at 52 weeks and, the occurrence of adverse events in the short and long term were the secondary endpoints.
RESULTS: A total of 58 patients were included, 19 were aged ≥80 years and 39 were aged 18-79 years. Overall survival at 52 weeks after FMT of the very old patients was not different from the control group (78.9% versus 89.7%, p= 0.29). Recurrence-free survival of CDI was not different between groups, with 94.3% in the 18–79-group versus 86.9% in the ≥80 group (p=0.44). The occurrence of short- or long-term adverse events was not statistically different between the two groups (36.8% vs 41%, p=0.45).
CONCLUSIONS: FMT is effective and well-tolerated in very old frail patients. This treatment brings a rapid benefit and limits the loss of functions. It also favors their maintenance at home or in a non-medical institution dedicated to dependent subjects and improves their quality of life.

Key words: Fecal microbiota transplantation, clostridioides difficile infection, frailty, older people.

Introduction

Fecal microbiota transplantation (FMT) is an innovative therapy indicated for the treatment of recurrent, severe or refractory Clostridioides difficile infections (CDI) (1, 2) and looks promising in other indications (3).

CDI is the most common cause of healthcare associated infection (1, 4). CDI is also found in the community and institutional wards. It is a major public health problem, responsible for an increase in hospitalizations, deaths and health care expenditure (5).

Many risk factors for infection have been identified and are more frequently found in the older people including hospitalisation, exposure to chemotherapy, antibiotic therapy and proton pump inhibitor (PPI) therapy (1). The majority of deaths attributable to Clostridium difficile occur in older people and, comorbid patients. The severity and recurrence of CDI are also more common in this population (5, 6). Recurrence of infection occurs in approximately 10-30% after appropriate antibiotic treatment, and increases after each recurrence, posing a real therapeutic challenge (7).

Older people are preferential candidates for FMT. Although very effective, this technique is still poorly understood by practitioners. Few studies have been conducted in the old population aged ≥65 years (8-10), showing the effectiveness and good tolerance of FMT. The frailty and comorbidities of an older patient may represent a barrier to the use of this treatment. Although CDI and its complications are more common in very old patients (≥80 years) due to their comorbidities, frailty and senescence of the immune system, limited data are available for this very old population (11).

The aim of this study was to evaluate the survival rate, efficacy and safety of FMT in very old frail patients.

Method

Study design

This was a single-center, cohort study with retrospective outcome data registration, real-life study conducted at the Toulouse University Hospital. The study protocol was approved by the French Regional Agency and by the research committee of the center (the Clinical Research Department of the Toulouse University Hospital) and registered in 2020. Individual information was provided to eligible persons and respects the « data processing and freedoms « rights according to articles 13 and 14 of the RGPD (registration number: RnIPH 2020-94). The objective of the study was to evaluate the efficacy and safety of FMT in very old patients (≥80 years) compared to the control group (18-79 years).

Study population

Patients were prospectively and consecutively included in the center's FMT register between 28/10/2015 and 12/03/2020. Inclusion criteria were age ≥18 years and having received FMT for recurrent CDI. Patients treated for another indication were not included. Exclusion criteria were a follow-up time of fewer than 6 months post-FMT and insufficient data collection. The cohort was separated into 2 age groups. A control group aged 18-79 years and a group of very old patients (≥80 years).

Processing of donor feces preparations

Fecal transplantation activity has been in place since 2015 in our center. Donor selection and donation preparation were performed under the responsibility of the in-house pharmacy. Donors were healthy anonymous adult volunteers carefully screened according to the recommendations of the French National Drug Safety Agency (ANSM) (13), the French Fecal Transplant Group (GFTF) (14), and from the end of 2019 the European recommendations (2). Briefly, all donors had a normal body mass index, no medical history, no use of medication in the preceding 6 months, no trip abroad in the previous 3 months, and a normal physical examination. In addition, the blood and the stools of all donors were examined for common biological tests and screened for pathogens according to guidelines (13, 14).

A fecal suspension was generated in isotonic saline solution with 10% of glycerol under aerobic conditions. Donation of feces was done on-site and approximately 50 gr of stool was required for each treatment. The definitive mixture was aliquoted with 200 mL of stool suspension and immediately frozen at – 80° C in individual samples. In some cases, we distributed the obtained preparation by concentrating it in 50 capsules frozen at – 80° C.

Patients were treated with vancomycin for at least 72 h and up to 48 h before the procedure. In case of administration by nasoduodenal tube or colonoscopy or capsules, they received an intestinal preparation with 1L of polyethylene glycol. The route of administration was left to the discretion of the clinician (nasoduodenal tube, enema, colonoscopy or capsules) taking into account the patient's condition.

Baseline and follow up

Demographic, CDI and FMT data were collected from paper and digital medical and paramedical records. Comorbidities (e.g., diabetes, neoplasia) were recorded by the Charlson score (15). Polypharmacy was defined as taking at least 5 drugs daily (16). Biological data at the time of FMT were collected. The history of Clostridium difficile infection (e.g., number of recurrences, contributing factors, treatment sequence, form of last episode), data on FMT (e.g., route of administration, donor-recipient compatibility) were reported. CDI were characterized according to the definitions given by IDSA (4) and ESCMID (1). The realization of a second FMT was noted. Frailty scores were assessed at the time of FMT to identify frail patients among the young older (aged ≥65 years) and the old older (aged ≥80 years). The Rockwood scale and the modified Rockwood index (7, 8) were used. These scores are based on medical-psycho-social assessments. The Rockwood scale is a clinical score ranging from 1 (very well) to 9 (terminally ill). The Rockwood frailty index quantifies deficits (presence of disease, ability in activities of daily living and clinical signs). The sum of the deficits present was added to the total number of deficits considered. 45 criteria were assessed for the calculation of the index. Motor assessment, family history, memory and psychiatric disorders were not recorded as they were often not detailed in the files. Follow-up and survival data were collected up to February 2021 by a call from the patient or their general practitioner at 52 weeks and supplemented by consultation of the hospital medical record and death register. The primary endpoint was overall survival at 52 weeks for the oldest patients compared to the control group after FMT. Overall survival included all-cause deaths within one year of FMT. Recurrence-free survival at 52 weeks, the occurrence of adverse events in the short term (within 72 hours post-procedure) and in the long term (within 52 weeks) were the secondary endpoints. Recurrence was defined as the presence of diarrhea (>3 stools per day) associated with a positive Clostridioides difficile toxin test. Patients lost to follow-up or who died before 52 weeks in the absence of the event were censored.

Other measurements

A secondary analysis comparing patients aged ≥75 years to 18-74 years was performed. The efficacy and safety of FMT were assessed in these two groups. An association between age and the occurrence of the primary and secondary endpoints was sought.

Statistics

Descriptive statistics were performed for each group. Categorical variables were assessed by percentages. Continuous variables were assessed by the median. Univariate analysis using the Wilcoxon rank sum test for continuous variables and the chi-square test or Fisher's exact test for categorical variables was used to search for an association between age and the occurrence of the endpoints. The search for an association was carried out by logistic regression analysis. A subgroup analysis was performed for the analysis of frailty scores (65-79 years versus ≥80 years). Overall and recurrence-free survival curves were analyzed by the log rank test. SAS version 9.4 software was used for univariate analyses and logistic regression, and PRISM 6 software for survival curves. A two-sided threshold of $p < 0.05$ was considered statistically significant.

Table 1. Clinical and biological characteristics of patients at the time of FMT

	18-79	≥80	p
n	39	19	
Women (%)	26 (66.7)	13 (68.4)	0.89
Age	62 [49; 71]	84 [83; 90]	<0.001
Comorbidities			
Charlson score	4 [2; 8]	7 [6; 9]	0.005
High blood pressure	13 (33.3)	12 (63.2)	0.05
Neoplasia	14 (35.9)	3 (15.8)	0.11
Renal failure	7 (17.9)	11 (57.9)	0.002
Irritable bowel Syndrome	3 (7.7)	0	0.54
Intestinal bowel disease	4 (10.3)	0	0.29
Hemopathy	3 (7.7)	3 (15.8)	0.38
Chemotherapy	5 (13.2)	0	0.16
HIV	2 (5.1)	0	1
Organ transplant	4 (10.3)	0	0.29
Immunosuppressive agent	6 (15.4)	0	0.16
Cirrhosis	2 (5.1)	1 (5.3)	1
Diabetes	2 (5.1)	5 (26.3)	0.03
Therapy			
Polypharmacy	24 (61.5)	17 (89.5)	0.03
Proton pump inhibitor	12 (30.8)	6 (31.6)	0.95
ATB before CDI	24 (63.2)	14 (77.8)	0.27
Biology before FMT			
CRP (mg/L) [a]	2.6 [1; 13.6]	23.5 [3.25; 40.7]	0.01
WBC (G/L) [b]	6.66 [5.41; 8.34]	8.19 [5.82; 9.72]	0.29
Alb (g/L) [c]	33 [31; 40]	29.1 [24; 32]	0.04
Creatinine (μg/L) [d]	68.4 [56; 82]	85 [62; 119]	0.11
Hb (g/dL) [e]	11.7 [10.8; 13.1]	11 [9.7;12.9]	0.18

a. 11 missing data (3 for ≥ 80 years); b. 8 missing data (1 for ≥80 years); c. 30 missing data (10 for ≥80 years); d. 10 missing data (2 for ≥80 years); e. 7 missing data (1 for ≥80 years)

Results

Population

A total of 58 patients were included in this study 19 were ≥80 years old and 39 were 18-79 years old. Table 1 shows the clinical and biological characteristics of the 2 groups at the time of FMT. The median age of the oldest patients was 84 years. The oldest patients were aged 95 years. The median age in the control group (18-79 years) was 62 years. The oldest patients had more comorbidities than the control group, with a median Charlson score of 7 versus 4 (p= 0.003). Frailty scores for patients aged ≥80 years were twice as high at the time of FMT as those aged 65-79 years. The median Rockwood scale score was 6 [4 ;6] versus 3 [3 ; 4] respectively (p=0.007) and the median Rockwood index was 0.311 [0.178; 0.489] versus 0.156 [0.111; 0.178] respectively (p=0.02). Polypharmacy was higher in the oldest group (89.4% versus 61.5%, p=0.03). Risk factors for CDI were reported. Just under a third of patients were

taking PPI in both groups before FMT. About 37% of patients aged 18-79 years and 23% of those ≥80 years had not taken an antibiotic before CDI. An immunosuppressive factor (organ transplantation, chemotherapy and IBD in particular) was more often found in the younger age groups for 18-79 years, without reaching the significance threshold. This difference was significant when comparing the 18-74 years group to the ≥75 years group. At the time of the first episode of CDI, antibiotic therapy was reported evenly between the 2 groups (77.8% and 63.2%, p=0.27). CRP measured <72h before FMT was higher in the ≥80 group compared to the 18-79 years group (23.5mg/L versus <5mg/L, p= 0.01) while WBC count was not significantly different between the 2 groups.

CDI characteristics and treatments received

The median number of recurrences before FMT was 3 in both groups (Table 2). The lines of treatment received were comparable between the 2 groups. Fidaxomicin was more often

Table 2. CDI and FMT characteristics

CDI characteristics	18-79	≥80	p-value
IPP	12 (30)	6 (33)	1
ATB before CDI	25 (64)	13 (76)	0.36
Number of relapses before FMT	3 [2; 3]	3[3; 4]	0.21
Prior treatments			
Number of treatment lines [a]	4 [3 ;4]	4[3 ;4]	0.21
Metronidazole	31 (83.8)	17 (89.5)	0.70
Fidaxomicin	25 (67.6)	10 (52.6)	0.27
Vancomycin	35 (94.6)	18 (94.7)	1
Pulsed vancomycin	10 (27)	6 (31.6)	0.72
CDI severity [b]			
Simple	33 (86.8)	18 (94.7)	0.65
Severe	5 (13.2)	1 (5.3)	0.65
FMT characteristics Serocompatibility			
Cytomegalovirus[c]	37 (97.4)	17 (89.5)	0.25
Toxoplasmosise[d]	35 (100)	17 (100)	1
Epstein Barr virus[e]	36 (97.3)	16 (100)	1
FMT route			
Naso-duodenal	36 (92.3)	10 (52.6)	0.001
Coloscopy	0	1 (5.3)	0.33
Rectoscopy	2 (5.1)	5 (26.3)	0.03
Enema	0	3 (15.8)	0.03
Capsule	1 (2.6)	0	1
Length of stay in days[f]	4[3 ;8]	5[3 ;13]	0.13

a. 2 missing data; b. 1 missing data; c. 1 missing data; d. 6 missing data; e. 4 missing data; f. 1 missing data in the 18-79 years group.

prescribed in younger patients, with a significant difference when comparing ≥ 75 years to 18-74 years (77.4% versus 44%, p= 0.01). There were few severe infections, only 1 in the very old patients, with no statistical difference between the groups.

Donor-recipient serocompatibility for CMV, toxoplasmosis and EBV was similar between the 2 groups. Transplantation was administered by the lower route (rectoscopy, enema, colonoscopy) in 47.4% in ≥80 years-old patients, compared with 5.1% in younger patients. The nasogastric tube was the most frequently used route, 52.6% in the ≥ 80-year-olds versus 92.3% with a significant difference between the 2 groups (p=0.001). Only one patient in the cohort received capsule FMT, this technique being available at the end of the study in our center. The choice of technique was adapted at the time of FMT for some patients. One very old patient had a pyloric stenosis discovered during the nasogastric tube placement. The administration could be done by enema. The average length of stay in hospital for FMT was not different between the two groups.

Figure 1. Overall survival at 52 weeks of patients aged ≥80 years compared to 18-79 years


Number at risk	0 weeks	12 weeks	24 weeks	52 weeks
18-79	39	39	36	34*
≥ 80	19	19	19	14
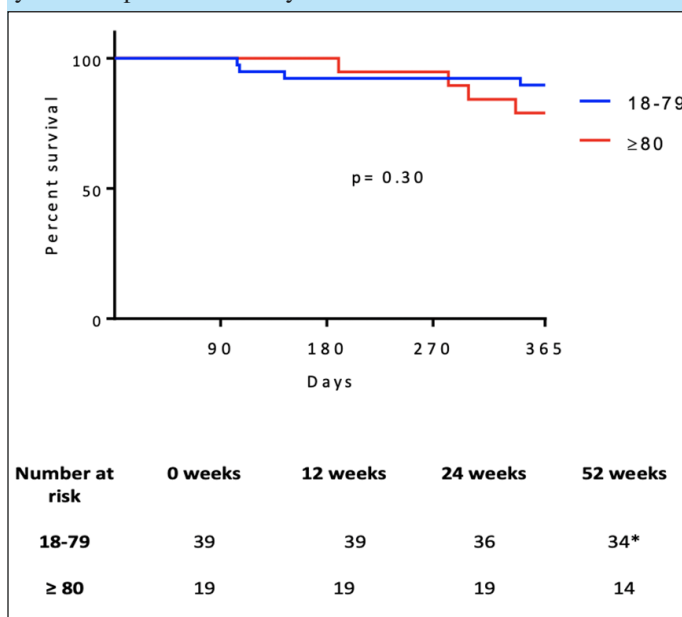
* Censored (n=1): Event not occurring at 314 days follow up.

Table 3. Occurrence of secondary endpoints

	18-79	≥80	p-value
ICD relapse	5 (14.3)	4 (23.5)	0.45
Second FMT	2 (40)	0	0.46
Second FMT Cure	2 (100)	0	N/A
Any adverse event	16 (41)	7 (36.8)	0.76
Early ardverse event	7 (17.9)	6 (31.6)	0.32
Diarrhea	3 (7.7)	3 (15.8)	1
Vomiting	2 (5.1)	0	1
Abdominal pain	4 (10.3)	0	0.29
Sepsis	0	1 (5.3)	0.33
Psychiatric collapse	0	1 (5.3)	0.33
Late adverse event	11(28.2)	1 (10.5)	0.19
Diarrhea	4 (10.3)	0	0.29
Abdominal pain	3 (7.7)	1 (5.3)	1
Constipation	3 (7.7)	0	0.54
Intestinal bowel disease	0	1 (5.3)	0.33
Sepsis	1 (2.6)	0	1
Psychiatric collapse	2 (5.1)	0	1
Serious adverse event	2 (5.1)	2 (10.5)	0.59
Sepsis	1	1	0.33
Severe psychiatric collapse	1	0	1
Intestinal bowel disease	0	1	0.33

Figure 2. CDI recurrence-free survival of groups at 52 weeks

Number at risk	0 weeks	12 weeks	24 weeks	52 weeks
18-79	39	36	32*	31**
≥ 80	19	18	17***	15****
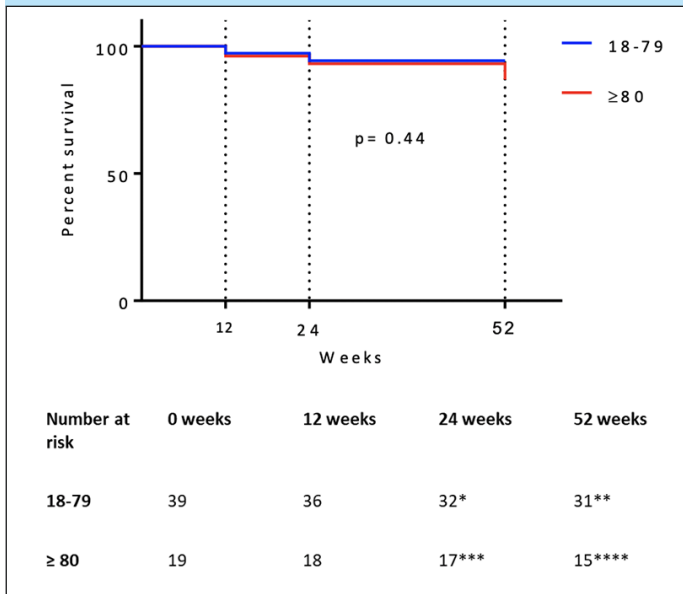
* 2 deaths ; **1 death ; ***1 death ; **** 1 death

Primary efficacy endpoint

Overall survival at 52 weeks after FMT of the oldest patients was not different from the control group (Figure 1). It was 78.9% in the ≥80 years group versus 89.7% in the 18-79 years group (p= 0.29). Four deaths were reported in each group during follow-up. None were related to FMT.

Secondary efficacy endpoint

Recurrence-free survival (Figure 2) of CDI was not different between groups, 94.3% in the 18-79 years group versus 86.9% in the ≥80 years group (p=0.44). At 52 weeks (Table 3), 23.5% of patients ≥80 years had relapsed versus 11.8% of younger patients (p= 0.45). The occurrence of short or long-term adverse events was not statistically different between the 2 groups (36.8% vs 41%, p=0.45). The majority of events were mild to moderate (diarrhea, abdominal pain, vomiting, constipation).

Two severe events were reported in both groups. An 83-years-old diabetic man with polyvascular disease treated with Imatinib for chronic lymphocytic leukemia developed undocumented sepsis within 24 hours of FMT, resulting in a 15-day extension of hospital stay. This event was linked to the procedure by a probable translocation mechanism. Among the late events, a 59-years-old female patient presented a severe psychiatric decompensation with a suicide attempt following FMT. A Clostridiodes difficile septic shock leading to death was reported in a 66-years-old patient, 104 days after FMT. This event was related to a failure of FMT not to the procedure. Inflammatory bowel disease (IBD) was diagnosed 3 months after transplantation in an 85-years-old patient. He had pre-existing abdominal disorders associated with myelodysplastic

syndrome. FMT was ruled out as a cause. An extra-hematological manifestation of the myelodysplastic syndrome was retained. This patient died at age 89, 4 years after FMT.

There was no association between age and the occurrence of primary and secondary endpoints in logistic regression.

Discussion

FMT is a major therapy in the management of CDI recognized by all international guidelines. Very old patients are particularly at risk of CDI but are under-represented in studies. To our knowledge, there have been no targeted analyses of the safety and efficacy of FMT among the ≥80 years age group. In clinical practice, this innovative therapy is not yet sufficiently proposed to the oldest patients, due to lack of knowledge but also to fear of invasive procedures. In this real-life cohort study with retrospective outcome data registration, we analyzed the efficacy and tolerance of FMT in very old (≥80 years), comorbid (mean Charlson score 7) and frail (mean 6 on the Rockwood scale) patients.

Nearly 89% of the oldest patients had been treated with metronidazole at the time of the initial episode, whereas vancomycin is more commonly recommended (1). Despite its particular benefits to this population at risk of recurrence, access to this treatment remains an obstacle to its use due to the need for pharmacists to prepare capsules, or use of the intravenous oral formulation. CDI impairs quality of life and leads to loss of function in frail older people. In our study, FMT intervened on average after a 3rd recurrence in those aged ≥80 years, with no significant difference from the control group. Early treatment with FMT in this population could limit their loss of function.

The recurrence-free survival reported in our study agree with the literature. However, studies conducted in the older people have a shorter follow-up time than our cohort. Girotra et al. (8), reported efficacy of 93.1% in an old population with fewer comorbidities and less frailty than in our cohort. Friedman-Korn et al (10) in a small cohort of comorbid old patients reported an early recovery rate of 86%. This rate is similar to our long-term follow-up results (52 weeks).

The overall survival of the oldest patients at 52 weeks was close to 79% and was not significantly different from younger patients. The advanced age and frailty of a patient should not rule out treatment with FMT. Quality of life and performance after FMT was not quantified during follow-up but improvement was frequently reported. Of the 4 patients aged ≥90 years, one 92-year-old woman died 1.5 years after FMT and had been maintained at home. A 90-years-old patient died 190 days after FMT. Another patient aged 95 who had a late failure of FMT, was alive at 52 weeks. A 95-years-old man died of acute myeloid leukemia 340 days after transplantation. This patient had an early failure at 1 week after a technically difficult FMT (failure of SNG placement and impassable rectal ampulla). Despite the early recurrence of CDI, clinical improvement was noted in this patient.

CDI is a major problem in nursing homes. Of the 293,300 cases of nosocomial CDI reported in a large US study in 2011,

104,400 were acquired in nursing homes (6). When it occurs in a nursing home, CDI is responsible for social isolation and may lead to exclusion from the nursing home due to hygiene constraints or the extent of diarrhea. Faced with distraught families, this possibility of exclusion has sometimes motivated the performance of FMT in old and frail patients.

Short-term adverse events were few and similar to those described in the literature (17). Only one severe event related to the procedure was reported in an 83-years-old immunocompromised patient with polyvascular disease. He presented with fever and elevated inflammatory markers. This undocumented septic episode resolved spontaneously. This is a rare event reported in immunocompromised patients like our patient (18).

There were no more events in patients ≥80 years of age. In the long term, only one patient aged ≥80 years reported fluctuating abdominal pain without frank alteration of her quality of life. One 84-years-oldpatient presented with a brief confusional episode after nasogastric tube placement and before transplant administration. She was treated by enema. The transplant can be administered by nasogastric tube, colonoscopy, enema, freeze-dried or frozen capsule. These different methods of administration have all been shown to be effective. The ideal route is the one adapted to the patient and mastered by the local team (19). The possibility of adaptation is essential in older people who more often have swallowing disorders and cognitive problems.

In recent years, FMT has undergone drastic technical improvements. The conditioning of transplants with donations stored at -80°C allows FMT to be performed in any hospital and even at home as shown by Jørgensen et al (11). It is not essential to perform FMT in an FMT center in all cases. The latest European consensus is in line with this. Stool banks are being developed throughout Europe and will allow widespread access to this treatment. The administration of donor feces suspension is simple and can be performed by any qualified health professional. This effective and well-tolerated therapy in frail patients aged ≥80 years should be offered and accessible to this population. Covid-19 has led to new expert recommendations (20) to ensure the safety of FMT. This reorganization has limited the increase in transplants stocks and thus temporarily the accessibility of this treatment.

Limitations of this study include the small number of patients aged ≥80 years, the monocentric and retrospective outcome data registration nature inducing a recall bias for late adverse events and a measurement bias related to the collection in the records.

In summary, FMT is effective and well-tolerated in very old frail patients. This treatment brings a rapid benefit and limits the loss of functions. Also, it favors their maintenance at home or in a non-medical institution dedicated to dependent subjects and improves their quality of life. An evaluation of the performance of older patients could guide the optimal treatment and allow this treatment to be offered earlier.

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