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Fecal microbiota transplantation for recurrent *Clostridioides difficile* infection in patients with concurrent ulcerative colitis

Serena Porcari [a,b], Andrea Severino [a,b], Debora Rondinella [a,b], Stefano Bibbò [a,b], Gianluca Quaranta [c], Luca Masucci [c], Marcello Maida [d], Franco Scaldaferri [a,b], Maurizio Sanguinetti [c], Antonio Gasbarrini [a,b], Giovanni Cammarota [a,b,1], Gianluca Ianiro [a,b,*,1]

[a] *Digestive Disease Center, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy*
[b] *Dipartimento Universitario di Medicina e Chirurgia Traslazionale, Università Cattolica del Sacro Cuore, Rome, Italy*
[c] *Microbiology Unit, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy*
[d] *Gastroenterology and Endoscopy Unit, S. Elia-Raimondi Hospital, Caltanissetta, Italy*

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ABSTRACT

Aims: Clostridioides difficile infection (CDI) is a major challenge for healthcare systems. Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease, is a risk factor for primary and recurrent CDI (rCDI). Moreover, CDI itself often worsens the clinical picture of IBD, increasing the risk of complications. Fecal microbiota transplantation (FMT) is a highly effective treatment for rCDI, but data from patients with IBD and CDI are limited and often referred to mixed cohorts. We aimed to report outcomes from a cohort of patients with UC treated with FMT for rCDI superinfection.

Methods and results: In a retrospective, single-centre cohort study we evaluated characteristics and outcomes of patients with UC who received FMT for rCDI. The primary outcome was negative *C. difficile* toxin 8 weeks after FMT. Thirty-five patients were included in the analysis. Sixteen patients were cured after single FMT, while 19 patients received repeat FMT. Overall, FMT cured rCDI in 32 patients (91%), and repeat FMT was significantly associated with sustained cure of CDI compared with single FMT (84% vs 50%, $p = 0.018$). Twenty-four patients (69%) experienced remission or an amelioration of UC activity. Serious adverse events were not observed.

Conclusions: In our cohort of patients with UC, FMT was highly effective in curing rCDI without severe adverse events and repeat FMT was significantly associated with CDI cure. Most patients also experienced remission or amelioration of UC activity after FMT. Our findings suggest that a sequential FMT protocol may be used routinely in patients with UC and rCDI.

1. Introduction

Clostridioides difficile infection (CDI) is the major cause of diarrhea associated with the use of antibiotics, and the most common one in hospitalized patients [1,2]. In the last decade the incidence of CDI has dramatically increased worldwide, especially in its recurrent form [3]. Increasing rates of recurrences are a major challenge for the management of CDI, accounting for nearly 35% of patients after their first episode of infection [4].These patients undergo repeated antibiotic cycles, that sustain the disruption of gut microbiota, increasing the risk of further recurrences (up to 65% after two or more recurrences) and of more severe clinical pictures [5–8]. Specific populations of patients appear to be more susceptible to acquire CDI and experience disease recurrence. Specifically, patients with inflammatory bowel disease (IBD), a group of chronic intestinal disorders that includes Crohn's disease (CD) and ulcerative colitis (UC), experience a 2.5 to 8-fold higher prevalence of CDI than standard population [9,10], as well as higher likelihood of recurrence after a first CDI episode [9,11,12]. CDI superinfection is also associated with an increase in hospitalization rates and length of hospital stay, severity of underlying IBD, escalation of IBD therapy, and complications as colectomy and death [13].Notably, IBD is associated with alteration of healthy gut microbiome (mainly loss of alpha diversity and decrease in the abundance of commensal bacteria) and impairment in host immunity [14–16], which are key factors in the

* Corresponding author. Fondazione Policlinico Universitario Gemelli, Università Cattolica del Sacro Cuore, Largo A. Gemelli 8, 00168, Rome, Italy.
E-mail address: gianluca.ianiro@unicatt.it (G. Ianiro).
[1] Joint Senior Authors

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pathogenesis of CDI [17].This evidence supports the identification of gut microbiome as a therapeutic target in these overlapping disorders.

Fecal microbiota transplantation (FMT), that is the transfer of healthy donor feces into the gut of a recipient with a disease associated with microbiome imbalance, is the most powerful modulator of gut microbiota. As recommended by several international guidelines [18–20], FMT is an established treatment for patients with multiply recurrent CDI (rCDI), being not only more effective than antibiotics [21],but also able to prevent CDI-related complications [22,23].

A growing body of evidence shows that FMT is an effective treatment in patients with IBD and rCDI superinfection, being able not only to cure the infection but also to improve disease activity and decrease the need for escalation of IBD therapy [24–27].

Recently, we reported outcomes from a case series of 18 patients with IBD treated with FMT for rCDI. Our results were in line with previous reports, but we also found that this population required multiple fecal infusion (sequential FMT) more often than patients without IBD to cure CDI [28].To strengthen our findings, and as patients with UC achieved different cure rates after FMT than those with CD, we aimed expanding our cohort and focusing only on patients with UC and rCDI, reporting outcomes of FMT in this specific population.

2. Methods

2.1. Study design and patients

This is a single-centre retrospective cohort study, reported according to the STROBE guidelines [29]. It included consecutive patients with confirmed diagnosis of UC who received FMT for rCDI at our centre between May 2014 and May 2022.

We retrieved from the electronic medical records of our centre the following data: patient demographics, characteristics of UC including extension, activity and concomitant medical therapy at the time of FMT, characteristics of CDI including disease severity, characteristics of FMT, outcomes after FMT, adverse events (AEs). Concomitant diseases were assessed for each patient and the impact of comorbidities was evaluated by the Charlson Comorbidity Index (CCI) [30]. Patients with at least one of the following exclusion criteria were not considered the analysis: pediatric age (younger than 16 year old); history of partial or total colectomy; post-FMT follow-up shorter than 8 weeks; latest evaluation of UC characteristics earlier than one month prior to FMT; clinical activity of UC not assessed or assessed without objective scoring; unavailability of data on CDI severity.

All enrolled subjects provided their written informed consent. The study protocol was approved by the local ethics committee (ID 18063).

2.2. Outcomes and definitions

The primary outcome was negative *C. difficile* toxin at 8 weeks after FMT regardless clinical symptoms. Secondary outcomes were clinical and endoscopic activity of UC and safety of FMT at 8-week follow-up.

We considered the following objective scores for the evaluation of UC activity: partial Mayo score [31] for clinical activity and endoscopic Mayo score for endoscopic activity of disease [32]. UC was considered to be active if partial Mayo score was equal or higher than 2, while clinical remission was identified by partial Mayo score lower than 2. Severity of CDI was defined according to the latest guidelines from the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) [20].

AEs arising after procedures were defined as related, likely related or unrelated. Serious AEs (SAEs) included death, life-threatening disorders or other relevant clinical conditions appeared after FMT during follow-up. Notably, 16 patients of this cohort have already been included in a previous prospective study from our group [28].

2.3. Fecal microbiota transplantation

Screening and selection of donors were performed according to international guidelines. Our protocol first followed guidelines from Cammarota et al. between 2014 and September 2019 [33],then those from Cammarota et al. between September 2019 and March 2020 [18] and, after March 2020, those from Ianiro et al. that included dedicated measures to prevent COVID-19 diffusion [34,35].

Specifically, anonymous healthy volunteers younger than 50 years of age were selected by a multi-level approach that included three main steps. At the beginning, a specific questionnaire aimed at addressing: known history or lifestyle-related risk factors for potentially communicable diseases (e.g. drug addiction or promiscuous sexual behaviour), recent (<6 months) use of specific drugs (e.g. antibiotics), a family history of gastrointestinal cancer or inflammatory bowel disease; systemic diseases; the use of drugs that could be excreted in feces with potential risk for the recipients. As second step, selected subjects underwent blood and stool exams to exclude potentially transmittable diseases. Specifically, the blood samples were tested for blood cell counts, transaminase, C-reactive protein, albumin, creatinine, viral hepatitis (A, B, C), HIV-1 and -2 antibodies, Epstein–Barr virus, *Treponema pallidum*, Strongyloides stercoralis and Entamoeba histolytica. The following pathogens were searched in the feces: *C. difficile* (culture and toxin), enteric bacteria, protozoa and helminths of the large and small bowel, vancomycin-resistant Enterococci (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA), Gram-negative multi-drug-resistant (MDR) bacteria, SARS-CoV-2 (this last item after March 2020 [34,35]).

As final step, at the time of each donation the chosen subjects underwent a further questionnaire to screen for any recent acute digestive disease, newly contracted infectious diseases or other potentially harmful situations (e.g. risky sexual contacts), and a nasopharyngeal swab for SARS-CoV-2 (after March 2020 [34,35]); moreover, the donated fecal batch was tested by multiplex PCR for intestinal pathogens (since September 2019 [18]), and after March 2020 [34,35], also for SARS-CoV2.

Donor stool batches that passed this screening were manufactured in the microbiology laboratory of our hospital by expert microbiologists (G.Q. and L.M.) following working protocols recommended by international guidelines for fresh and frozen feces [18,33].At least 50 g of frozen feces per sample were used. Feces were collected by the donor on the day of preparation, and rapidly transported to our hospital in a refrigerated bag. Then feces were filtrated and diluted with at least 200 mL of sterile saline (0.9%). The deriving solution was blended and, after the supernatant was strained, transferred into a sterile flask. Then glycerol was added up to a final concentration of 10% before freezing. Finally, samples were stored at 80 °C and thawed in a warm (37 °C) water bath on the day of fecal infusion.

Before fecal infusion, all patients underwent a 3-day pre-treatment with oral vancomycin (250 mg by mouth 4 times a day) and bowel cleansing with 2 L of macrogol/day for 2 days. All fecal infusions were done by colonoscopy, as previously described [36].All procedures were performed by expert endoscopists (S.P., S.B., G.C., and G.I.) using pediatric colonoscopes and carbon dioxide insufflation, within 6 h after thawing. The infusate was delivered in the caecum through the operative channel of the colonoscope, using 50-mL syringes. After the procedure, patients were monitored in the recovery room of the endoscopy unit for 2–3 h. Each patient received at least one fecal infusion, and FMT was repeated in specific cases. First, if patients experienced diarrhea after the first FMT, they underwent dosage of *C. difficile* toxin (Premier Toxins A&B - Liaison *C. difficile* GDH-Toxin A/B – DiaSorin Inc., Stillwater, MN, USA) and, if positive, were offered further fecal infusions.

Moreover, patients with severe CDI received a priori multiple FMT, as this sequential protocol was shown to increase success rates in this subpopulation [25]. At least two fecal infusions, were scheduled for these patients, and, in those with pseudomembranous colitis (PMC), infusions were repeated until the disappearance of pseudomembranes,

as already described [22]. FMTs were repeated every 2–3 days, and patients also kept a light diet and underwent a restricted bowel preparation (2 L of macrogol) before each procedure.

2.4. Statistical analysis

Continuous variables were reported as mean ± standard deviation, and categoric variables were expressed as frequency and percentage. Comparisons of variables, including age, sex, characteristics of IBD (disease localization and activity, disease duration, current biologic therapy), CDI (severity of infection, presence of pseudomembranes) and FMT (number of infusions, quantity of infusate) were made by *t*-test, and Fisher's exact test as appropriate. A p-value of less than 0.05 was considered to indicate statistical significance.

All statistical analyses were performed using SPSS v. 28.0 for Macintosh (SPSS Inc., Chicago, USA).

3. Results

3.1. Demographics and baseline characteristics of patients

Baseline characteristics of patients are detailed in Table 1. In the study period, 40 patients with UC received FMT for rCDI at our centre.

Table 1
Characteristics of patients at baseline, of treatments, and of outcomes after FMT.

Baseline characteristics of patients	N
Total number of patients	35
Males/females	24/11
Median age (SD)	51 ± 22
Median time (years) from UC diagnosis (SD)	4 ± 7
Clinical activity of disease at baseline (pMayo score)	
Mild	9
Moderate	20
Severe	6
Median Charlson Comorbidity Index (SD)	2 ± 2.5
Location	
E1 (proctitis)	5
E2 (left sided)	13
E3 (pancolitis)	17
Endoscopic activity of disease at baseline (endoscopic Mayo Score)	
Mild	9
Moderate	20
Severe	6
UC Therapies (%)	
Systemic 5-ASA	12 (34)
Topic 5-ASA	6 (17)
Systemic corticosteroids	5 (14)
Topic corticosteroids	5 (14)
Immunosuppressants	1 (3)
Biologics	7 (20)
Median number of CDI recurrences (range)	2 (1–5)
Clinical picture of CDI (%)	
Mild	27 (77)
Severe	8 (23)
Pseudomembranous colitis	3 (9)
Antibiotic treatments before FMT	
Vancomycin	28
Metronidazole	5
Fidaxomicin	2
Fecal microbiota transplantation	
Unrelated donors	35
Related donors	0
Number of fecal infusions (%)	
N = 1	16/32 (50)
N = 2	13/35 (37)
N = 3	6/35 (17)
Post-FMT outcomes	
Eradication of CDI (negative toxin) (%)	32/35 (91)
After single infusion (%)	16/32 (50)
After repeat infusions (%)	13/19 (84)
Serious adverse events after FMT	0

Five of them were excluded from the analysis because of loss at follow-up earlier than 8 weeks (n = 3) and UC not assessed with objective scores (n = 2). A total of thirty-five patients with UC (mean age 51 ± 22 years old, 11 females) were included in the final analysis. The median time from the diagnosis of UC was 4 ± 7 years). Six patients presented with severe disease (pMayo ≥8), 20 patients with a moderately active disease (p Mayo 6–7), and nine of them had mild disease activity (pMayo 1). The mean value of Charlson Comorbidity Index was 2 ± 2.5.

At colonoscopic evaluation during the first FMT, five patients presented with proctitis, 13 with left-sides colitis, and 17 with pancolitis, and the endoscopic disease activity was mild in nine patients, moderate in twenty patients, and severe in the remaining six patients. At baseline twelve (34%) patients were on systemic salicylates, six (17%) on topic salicylates, five (14%) on systemic corticosteroids, five (14%) on topic corticosteroids, one (3%) on azathioprine, and seven (20%) on biologics (infliximab, adalimumab, golimumab, or vedolizumab).

At the time of our evaluation, patients had experienced a median number of two CDI recurrences (range 1–5). Twenty-seven patients presented with mild CDI, while eight patients experienced a severe clinical picture. PMC was reported in three (9%) patients at the time of colonoscopy. All patients had history of antibiotic therapy for CDI before FMT. Specifically, patients had been treated with vancomycin (n = 28), metronidazole (n = 5) and fidaxomicin (n = 2).

3.2. Characteristics and outcomes of fecal microbiota transplantation

Characteristics and outcomes of FMT are detailed in Table 1. All patients received frozen fecal infusions from unrelated donors. All patients underwent at least one fecal infusion. Three (8%) patients with PMC received an a priori sequential FMT protocol (two infusions in one patient and three infusions in the two remaining ones), and none of them recurred at 8-week follow-up. Sixteen (50%) of the remaining 32 patients experienced recurrence of CDI within 7 days after the first FMT and received further fecal infusions. Thirteen of these 16 patients were successfully cured after repeat FMT, while the remaining three patients were treated with fidaxomicin and vancomycin taper regimen, with clinical success. Thirteen patients received two fecal infusions and six patients underwent three fecal infusions. Overall, FMT cured rCDI in 32 of 35 patients (91%) and repeat FMT was significantly associated with sustained cure of CDI compared with single FMT (84% vs 50%, p = 0.0183). No other variables were significantly associated with clinical success.

Interestingly, we also observed an improvement of clinical picture in most (69%) of patients, as 16 patients were on clinical remission (45%) and 8 patients (22%) experienced an amelioration of disease activity

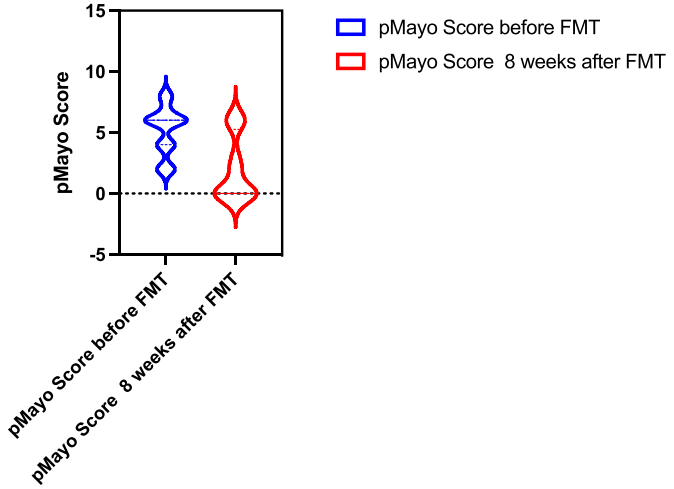

Fig. 1. Partial Mayo score before and 8 weeks after FMT in our cohort.

(from moderate to mild activity, [n = 4] and from severe to moderate activity [n = 4]) at 8-week follow-up. Fig. 1 summarizes differences in the partial Mayo score before FMT and at 8-week follow-up. Finally, we did not observe any serious adverse event after FMT.

4. Discussion

FMT is a well-established therapy against rCDI, with cure rates that reach nearly 90% [37], and increasing evidence suggests that it can be an effective treatment also in patients with IBD and CDI superinfection.

In this retrospective cohort study, we found that FMT cured rCDI in 91% of patients with UC, similarly to what previously observed in the general population [38].

This finding is highly relevant, as patients with IBD are more susceptible to acquire CDI and less likely to be cured with antibiotics than patients without IBD.· [12] Therefore, FMT may represent a useful therapeutic approach to cure CDI in this specific setting.

Another relevant issue related to CDI superinfection in patients with UC includes the known worsening of underlying UC by the infection. This known finding was also confirmed in our study, where most patients presented with moderate and severe UC activity.

Previous reports [24] suggest that FMT may be effective also in improving the clinical and endoscopic activity of underlying IBD. Our study confirmed these findings, as 69% of our patients experienced improvement or remission of clinical disease activity after FMT. These data suggest that FMT may be considered a reliable treatment option for IBD, also without CDI [25].

This hypothesis is supported both by biological and clinical lines of evidence. First, UC is characterized by decreased alpha diversity and unbalanced microbiome composition, with loss of several beneficial bacteria (e.g. short-chain fatty acid producers), and these alterations are known to play a key role in the pathogenesis of the disease [14], therefore the introduction of a new healthy microbiome may in theory be a reliable therapeutic strategy to improve the disease.

This hypothesis has been investigated in several randomized trials, where FMT was more effective than placebo in inducing remission of UC [37,39,40]. However, conclusive data on the efficacy of FMT in UC are still not available, and future studies aimed at exploring the importance of specific items, e.g. the role of donors [41] and/or microbial engraftment [42] are advocated to improve clinical outcomes in this patient setting.

Another interesting finding of our study is the significant difference in cure rates of our patients based on the number of fecal infusions. The cure rate of rCDI after single FMT was nearly 50%, while the use of further infusions increased it up to 91%, being statistically significant and similar to results achieved in the general population with rCDI. This finding, already observed in our previous study [28] as well as in patients with severe CDI and PMC [22], supports the use of repeat FMT to cure CDI in patients with UC, but more evidence and dedicated randomized controlled trials are needed to assess clearly if sequential FMT is more effective than single FMT in this population. Interestingly, a sustained capsulized FMT protocol was highly effective in patients with UC alone, supporting this hypothesis [37].

Finally, we did not observe any severe adverse event, confirming that FMT is a safe and well tolerated procedure not only in the general population [43], but also in patients with UC, that are often immunosuppressed (37% of our cohort).

Our study had several limitations. First, the retrospective design and the small sample size prevent the generalizability of our findings as well as the possibility to perform multivariate analyses to identify independent predictors of success, therefore large prospective controlled trial are advocated to clearly assess the efficacy of FMT in patients with CDI and underlying UC. Moreover, we did not perform any microbiome analysis on these patients, so we cannot identify any microbial shift that occurred after FMT in this population. The profiling of gut microbiota may give insights on the different mechanisms of action of FMT and is advocated for future studies.

5. Conclusions

In our cohort of patients with UC, FMT achieved a highly satisfactory cure rate (91%) of rCDI, without any severe adverse event, and repeat FMT was significantly associated with clinical success. Moreover, most patients (69%) experienced remission or amelioration of disease activity after FMT. Should our results be confirmed by further studies, a sequential FMT protocol could be used routinely in clinical practice in patients with UC and rCDI superinfection.

Authors contribution

SP, GC and GI conceived and designed the study; SP, SB, AS, FS, AG, GC and GI recruited and followed up patients; SP, AS, DR, SB and GI screened FMT donors; LM, GQ and MS prepared fecal infusates. SP, AS, DR and GI built the clinical dataset; SP, SB, GC and GI performed FMT procedures; MM performed statistical analysis of clinical data; SP, MM, GC and GI analyzed and interpreted data; SP, MM, GC and GI wrote the paper. All authors critically revised the paper for important intellectual content.

Declaration of competing interest

A.G. reports personal fees for consultancy from Eisai Srl, 3PSolutions, Real Time Meeting, Fondazione Istituto Danone, SinergieSrl, Board MRGE and Sanofi SpA personal fees for acting as a speaker for Takeda SpA, AbbVie and Sandoz SpA and personal fees for acting on advisory boards for VSL3 and Eisai. G.C. has received personal fees for acting as advisor for Ferring Therapeutics. G.I. has received personal fees for acting as speaker for Biocodex, Danone, Sofar, Malesci, Metagenics and Tillotts Pharma, and for acting as consultant and/or advisor for Ferring Therapeutics, Giuliani, Malesci and Tillotts Pharma. All other authors have no conflicts of interest to disclose.

Data availability

Data will be made available on request.

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