Fecal Microbiota Transplantation plus selected use of antibiotics for severe-complicated *Clostridium difficile* infection: description of a protocol with high success rate

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SUMMARY (250 words)

Background

Severe and severe/complicated *Clostridium difficile infection* (CDI) can result in ICU admission, sepsis, toxic megacolon, and death. In this setting, colectomy is the standard of care but it is associated with a 50% mortality.

Aim

Evaluate safety and efficacy of a sequential FMT and antibiotic protocol in severe and severe/complicated CDI patients who are at high risk for colectomy.

Methods

All patients with severe and severe/complicated CDI refractory to oral vancomycin ± rectal vancomycin and intravenous metronidazole therapy were offered FMT. Treatment consisted of sequential FMTs via colonoscopy with the need for repeat FMT and continued vancomycin guided by clinical response and pseudomembranes at colonoscopy.

Results

A total of 29 patients underwent FMT between July 2013 and August 2014. The overall treatment response of endoscopic sequential FMT was 93% (27/29), with 100% (10/10) for severe CDI and 89% (17/19) for severe/complicated CDI. A single FMT was performed in 62%, two FMTs were performed in 31%, and three FMTs in 7% of patients. The use of non-CDI antibiotics predicted repeat FMT (Odds ratio=17.5). The 30-day all-cause mortality after FMT was 7%, and the cumulative 3-month survival was 76%. Of the two patients who died within 30

days, one underwent colectomy and succumbed to sepsis; the other died from septic shock related to CDI.

Conclusions

We describe the largest reported series of FMT for severe and severe/complicated CDI. The success of a treatment protocol involving FMT and continued vancomycin in selected patients was high and warrants further evaluation.

INTRODUCTION

Two randomized controlled trials and numerous case series support the efficacy of fecal microbiota transplantation (FMT) in patients with recurrent *Clostridium difficile* infection (CDI).[1,2] Many patients in studies of recurrent disease were relatively healthy outpatients. However, 3-10% of patients with CDI progress to a severe life-threatening illness that requires colectomy in up to 30% of patients.[3] Few studies describe the efficacy of FMT in patients with severe or fulminant CDI.[4-9]

In our early clinical experience, we encountered several patients with severe CDI who died despite FMT. In particular, we noted that patients with severe or fulminant CDI and extensive pseudomembranes at endoscopy tended to respond poorly to single FMTs. Khoruts et al. described a dramatic, but unsustained, improvement in CDI after a single FMT in a patient with fulminant CDI and suggested that reinitiation of antibiotics against CDI and repeat FMT might be needed for cure in some cases of severe FMT.[7] Based on this suggestion and our anecdotal experience, we developed a protocol for treatment of severe CDI based on FMT, continued vancomycin therapy in patients with extensive pseudomembranes at the time of FMT, and repeat FMT for patients without clinical response. In this report, we describe a retrospectively evaluated cohort of 29 consecutive patients treated with this protocol.

PATIENTS AND METHODS

Definitions

Severe and severe/complicated CDI were defined as per the 2013 American College of Gastroenterology guidelines.[10] Diagnosis of CDI was made based upon the presence of diarrhea (≥ 3 loose stools/day) and positive stool C. *difficile* toxin. Severe CDI was defined as a serum

albumin < 3g/dl plus either white blood count (WBC) ≥15,000 cells/mm^3 or abdominal tenderness. Severe/complicated CDI was defined as any of the following attributable to CDI: admission to ICU for CDI, hypotension with or without required use of vasopressors, fever ≥ 38.5°C, ileus, significant abdominal distention, mental status changes, WBC ≥35,000 cells/mm^3 or <2,000 cells/mm^3, serum lactate levels >2.2mmol/l, and end organ failure (e.g. mechanical ventilation, renal failure). [10] The Charlson co-morbidity index (age adjusted) was calculated to assess disease burden from co-morbid conditions and the likelihood of dying within 1 year (http://farmacologiaclinica.info/scales/Charlson_Comorbidity/calc/). [11] Treatment success was defined as complete resolution of diarrhea, no further need of anti-CDI therapy, avoidance of colectomy, and discharge from the hospital.

Patients

Consecutive patients admitted to Indiana University Hospital between July 2013 and August 2014 with severe and severe/complicated CDI unresponsive to antimicrobial CDI therapy (oral vancomycin 500-2000 mg/day or fidaxomicin 400 mg/day and rectal vancomycin 2000 mg/day in patients with ileus, in combination with or without intravenous metronidazole 1500 mg/day administered for at least for 5 days). All patients were being evaluated for colectomy, were under evaluation of a multidisciplinary team consisting of a gastroenterologist, internist, infectious disease specialist and a surgeon, and were offered the opportunity to receive FMT. Patients with precipitous clinical deterioration, who were considered for colectomy before the 5-day minimum of CDI antimicrobial therapy, were also offered FMT.

Treatment protocol

In the protocol, the following steps were performed: 1) Antibiotics were discontinued 12 to 24 hours before FMT, 2) Colonic bowel prep (split dose 4 L Golytely) was administered if no ileus or obstruction was present, 3) Fresh stool was obtained from either a screened patient-selected donor or universal donor within 6 hours of the procedure (donor selection, screening for relevant communicable diseases, and stool processing were performed as outlined by the Fecal Microbiota Transplantation Working Group).[12] 4) Fifty to 200 grams of stool homogenized in 300 ml of non-bacteriostatic saline was administered carefully via flexible sigmoidoscopy or colonoscopy with assessment for pseudomembranes and injection of FMT either proximal or distal to the splenic flexure at the discretion of the endoscopist. 5) Oral vancomycin (125 mg every 6 hours) was resumed 24 to 48 hours after FMT for a minimum of 5 days if there were pseudomembranes present at colonoscopy. 6) For patients who did not improve by days 6-7, the vancomycin was stopped, and bowel prep was administered if no ileus was present. 7) The next day (day 7-8), a repeat FMT, from the same donor as the first FMT if patient directed, was performed by sigmoidoscopy or colonoscopy. If pseudomembranes were present, oral vancomycin was resumed for an additional 5 days. If no pseudomembranes were detected, antibiotics were not resumed following the repeat FMT.

Patients with clinical improvement were assessed daily for possible discharge. If a patient could not be discharged due to ongoing CDI-related symptoms, vancomycin was stopped on day 12-13 and a 3rd FMT was performed on day 13-14. Cessation of FMT was based on resolution of symptoms. Vancomycin was stopped when patients were improved or when

pseudomembranes were no longer present. Patients were prospectively followed after treatment completion for evidence of recurrence and adverse events.

The FMT procedure protocol was approved by Indiana University Health. Baseline data and outcomes were prospectively captured using a research database that had been approved by the Institutional Review Board at Indiana University - Purdue University.

Statistical analysis

Baseline patient characteristics were analyzed using descriptive statistical methods. Continuous variables were summarized using mean ± standard deviation and range values and categorical variables were summarized using proportions. Difference in length of hospital stay for patients with severe and severe/complicated CDI was summarized using median and interquartile range (IQR) due to the skewness of the data and evaluated using the Wilcoxon rank sum test. A logistic regression model was used to examine the potential risk factors for repeat FMT. The evaluated risk factors included patients' demographic, clinical, and laboratory variables such as age, sex, severity of CDI, number of CDI episodes, use of non-CDI antibiotic during the same hospitalization, WBC, serum albumin concentration, presence of abdominal pain, admission to ICU, presence of toxic megacolon, acute renal failure, immunosuppression, Charlson comorbidity index, and source of stool. Due to the large number of potential risk factors relative to the sample size, we used a forward stepwise procedure to select important risk factors. The effect of the selected risk factors on repeat FMT were obtained using the Firth logistic regression model with a penalized likelihood approach due to the small sample size. Time to death was analyzed using the Kaplan-Meier approach. All statistical analysis was performed using SPSS software (version 22.0; IBM Corp, Armonk, NU, USA).

RESULTS

Twenty-nine patients were admitted with severe and severe/complicated CDI refractory to maximum medical therapy and were considered for colectomy. All 29 patients opted to undergo FMT rather than continued antibiotics or colectomy. Mean age was 65.2 years ± 17.9 (range, 25-92); 59% were women and 100% were Caucasian. Mean white blood cell count ± SD (range) was 21 k/mm^3 ± 11.2 (5.5-56) and albumin 2.3 g/dL ± 0.36 (1.5-2.9). A history of recurrent CDI was present in 69% (20/29) with an average number of prior CDI episodes of 3 ± 2.4 (1-12). Ten (34%) patients had severe CDI and 19 (66%) had severe/complicated CDI. A summary of demographics, baseline clinical, and laboratory data of these two groups is shown in Table 1.

Detailed individual patient's characteristics including demographic, clinical, laboratory data, number of previous CDI episodes, ICU stay, concomitant non-CDI antibiotic use, comorbid conditions, and immunosuppression, source and type of stool, number of FMTs received and outcomes are described in Table S1 (Online Supporting Material). Twelve of the 19 severe/complicated patients were in the ICU at the time of FMT and had the following sequelae: five patients with toxic megacolon (cecal diameter > 12 cm or rectosigmoid diameter > 6.5 cm); seven patients with acute renal failure and hypovolemic/septic shock, four of whom required vasopressors, three with mental status changes, and two patients on mechanical ventilation. Four patients were on immunosuppressive medications, and five patients had inflammatory bowel disease (three with Crohn's disease and two with ulcerative colitis).

A total of 44 FMTs were administered during the study period. The source was a patient-selected donor (n=16) or a universal donor (n=28). Stool was delivered proximal to the splenic flexure in 18 transplants and distal to the splenic flexure in 26 transplants as deemed safe by the endoscopist depending on the severity of colitis. The mean number of FMT administered was 1.5 (range 1-3).

The overall success rate at 30 days was 93% (27 of 29). A summary flowchart of FMT results is depicted in Figure1. Outcomes and number of FMTs needed based upon categories of severe versus severe/complicated CDI are shown in Table 2. All ten severe CDI infections had a successful outcome, whereas, the severe/complicated patients success rate was 89% (17/19). The two treatment failures were: 1) death from sepsis (arterial pH 7.1 at the time of FMT) within 24 hours of the first FMT, 2) death following colectomy after failing three FMTs in a patient who was 6 weeks post-orthotopic liver transplantation.

Treatment success was achieved with a single FMT in 51% of patients and two FMTs in 38%. A single FMT was sufficient in 7 of 10 (70%) severe CDI cases and 8 of 19 (42%) of severe/complicated CDI cases. Table 2 highlights the results of FMT stratified by CDI severity. Pseudomembranes were present in 7 of 10 (70%) of severe and in 14 of 19 (74%) severe/complicated cases at the time of initial FMT. The median length of hospital stay was 10 days (IQR 6-18 days) for the entire study cohort. The median length of hospital stay was 9 days (IQR 5.2-15.5) in severe CDI patients compared to 11.5 days (IQR 7-23) in severe/complicated patients (p-value = 0.16). Following the first FMT, the median length of hospital stay was 6 days (IQR 3.25-13) in severe patients and 9 days (IQR 7-23) in severe/complicated patients (p=0.26). Median follow-up was 4.5 months (IQR 2.75-8.25). Evaluation of the risk factors for the repeat FMT showed that the use of non-CDI antibiotics during the same

hospitalization was significantly associated with repeat FMT.Specifically, 70.6% (12/17) of the patients who used non-CDI antibiotics had a repeat FMT while only 8.3% (1/12) of the patients without use of non-CDI antibiotics had a repeat FMT. Based on the Firth logistic regression model, patients who used non-CDI antibiotics were found to be 17.4 times more likely than those who did not use non-CDI antibiotics to have a repeat FMT(Odds ratio=17.5; 95% CI=2.2-135.3; p=0.006).

The overall cumulative survival after FMT was 93% (95% CI: 84%-100%) at 1 month and 76% (95% CI: 62%-93%) at 3 months. A Kaplan-Meier survival curve following the first FMT is shown in Figure 2. Three patients died during the follow-up period due to CDI associated causes: the above-mentioned two patients and another patient who responded to the initial FMT/vancomycin sequential therapy and was discharged but succumbed to CDI sepsis after being treated with antibiotics for a urinary tract infection 92 days following first FMT. Five patients died due to causes unrelated to CDI.

DISCUSSION

This study is the largest reported experience with FMT for severe and severe/complicated CDI in the medical literature. To our knowledge, the size of this experience exceeds the combined size of previous reports.[4-9] We combined FMT and selected use of continued vancomycin and achieved an overall success rate of 93%. The size of the trial and the high success rate indicate that this protocol deserves additional evaluation for severe and severe/complicated CDI.

We found that severely ill patients with CDI were successfully treated in many cases by FMT combined with continued vancomycin for patients with pseudomembranes. With the application of the current protocol, we achieved a higher success rate in this critically ill population than our previous and others' experience after administration of a single FMT.[7,9,13] One interpretation is that a single FMT in patients with severe and, in particular, in severe/complicated CDI with pseudomembranes is insufficient in achieving complete resolution of CDI symptoms, but sufficient to decrease the C. *difficile* burden enabling a response to anti-CDI therapy. In the Cammarota trial, where patients with recurrent CDI were randomized to FMT versus oral vancomycin, seven had pseudomembranous colitis.[13] The first two patients with pseudomembranous colitis briefly responded to a single FMT, but ultimately succumbed to CDI-related death despite delayed reinitiation of vancomycin and/or repeat FMT. Their findings suggest as well that pseudomembranes are indicative of disease severity and a lower likelihood of response to a single FMT. Subsequently, Cammarota and colleagues changed the study protocol in which all patients with pseudomembranous colitis were treated with repeat FMTs at 3-day intervals until the colitis had resolved. Their short interval between FMT alone achieved a high rate of success but it required twice as many FMTs compared to our study with FMT alternating with vancomycin (2.8 FMTs vs. 1.5 FMTs).

In this study, we initially used patient selected donors because it was believed that using a house member mitigated the risk of communicable diseases and the donor had a robust microbiota protecting them from CDI.[14,15] However, recent studies demonstrated that universal donors (non-related, volunteers) are just as safe and effective as patient directed donors.[16,17] Over time, we found that using a frozen stool bank greatly simplified the logistics of FMT which was key for urgent FMTs for severe and severe/complicated CDI.

This study has multiple limitations. First, as noted above, the importance of the individual elements of the protocol and the decision making process is uncertain. Second, the study is observational and not controlled. However, there is too little information on an optimal protocol for patients with severe and severe/complicated disease to currently initiate a controlled trial of FMT in this group of patients. During the study, our goal was to identify a protocol that improved the outcome of our seriously ill patients with CDI. Third, the severity of illness in our patients might be different from that in other studies of severe and severe/complicated CDI. We explicitly defined the criteria by which our patients met the definitions of severe and severe/complicated CDI (Table S1, Online Supporting Material). This seems appropriate for all investigators developing FMT protocols for this population, as the severity of illness should be clearly understood when interpreting the clinical treatment outcomes. Future randomized studies might compare these protocols for severe and complicated CDI. Also, embedding microbiome profiling to navigate mechanistic insights, notably the impact of vancomycin on post-FMT microbiota, and longer follow-up seem appropriate.

In conclusion, given the high colectomy and mortality rates associated with fulminant CDI, the success described here indicates that this protocol warrants additional and controlled study.

AUTHORSHIP STATEMENT

Guarantor of article: MF

Specific author contributions: MF: protocol design, study concept, data acquisition, analysis and interpretation of data, drafting and critical revision of the manuscript for important intellectual content; BS: drafting of the manuscript, analysis of data, critical revision of the manuscript for important intellectual content; NR and BR: data acquisition, critical revision of the manuscript

for important intellectual content; GK: data acquisition, analysis of data; RV and DR: interpretation of data, drafting and critical revision of the manuscript for important intellectual content.

All authors approved the final version of the article, including the authorship list.

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Declaration of personal interests. MF has served on the data safety monitoring board for Rebiotix.

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