Published in final edited form as:
J Clin Gastroenterol. 2013 September ; 47(8): 735–737. doi:10.1097/MCG.0b013e31829004ae.

Resolution of Severe *Clostridium difficile* Infection Following Sequential Fecal Microbiota Transplantation

Alexa R. Weingarden, BA[1], **Matthew J. Hamilton, PhD**[1], **Michael J. Sadowsky, PhD**[1,†], and **Alexander Khoruts, MD**[2,*,†]

Alexa R. Weingarden: wein0343@umn.edu; Matthew J. Hamilton: hami0192@umn.edu; Michael J. Sadowsky: sadowsky@umn.edu; Alexander Khoruts: khoru001@umn.edu

[1]Department of Soil, Water, and Climate, BioTechnology Institute, and Microbial and Plant Genomics Institute, University of Minnesota, St. Paul, Minnesota, USA

[2]Division of Gastroenterology, Department of Medicine, Center for Immunology, University of Minnesota, Minneapolis, Minnesota, USA

Keywords

Fecal microbiota transplantation; severe *Clostridium difficile* infection

Over the past two decades *Clostridium difficile* infection (CDI) has steadily risen in both incidence and severity, correlating with emergence of new, hypervirulent strains of the bacterium.[1] Most of the immediate mortality associated with CDI is associated with severe infection that can lead to fulminant colitis and multisystem organ failure.[2] Early surgical intervention, typically a subtotal colectomy, can be lifesaving, but is nevertheless associated with postoperative mortality of approximately 50%.[3, 4] In 1958, Eiseman and colleagues originally reported fecal microbiota transplantation (FMT) as an alternative to surgical therapy for treatment of refractory pseudomembranous colitis.[5] However, in recent years the focus of FMT practice has been primarily on multiply recurrent forms of CDI, while only a handful of case reports exist on the use of FMT in acute, severe, or fulminant CDI.[6–8]

Between March 2011 and February 2012 we treated four patients with FMT for severe CDI that was refractory to antibiotic therapy. Patients satisfied clinical parameters consistent with severe disease including fever, abdominal pain and distension, WBC count $\geq 20 \times 10^{-9}$/L, albumin ≤ 2.5 g/dL, thickened colon on abdominal CT and presence of ascites.[9] Subtotal colectomy was considered in all patients, but was felt to be prohibitively risky or was refused by the patient (Patient 4). Systemic antibiotics, including metronidazole, were discontinued for at least 48 hours prior to the procedure. Vancomycin, which is poorly absorbed, was discontinued 12–24 hours prior to the procedure, and the patients were administered 2–3 liters of polyethylene glycol electrolyte solution via NG tube or orally. FMT was performed via colonoscopy by an experienced endoscopist using a standardized preparation of concentrated fecal microbiota as we previously described.[10] Patient 1 received the preparation the day it was processed. For Patients 2–4, the microbiota

*Corresponding Author: Alexander Khoruts, 2101 6th St. S.E., Medical Biosciences Building, Room 3-184; University of Minnesota, Minneapolis, MN, 55455. khoru001@umn.edu; Phone: 612-624-2101; Fax: 612-625-2101.
†These authors contributed equally to this work.

Disclosure of Potential Conflicts of Interest

AK and MJS received funding from CIPAC LLC to carry out research on FMT using frozen microbiota. AK and MJS have provided consulting services for CIPAC and conflicts of interest are being managed by the University of Minnesota Conflicts of Interest Program.

preparation was frozen in 10% (v/v) glycerol and stored frozen at −80°C until used. The colonoscope was advanced gently to the farthest point possible maintaining minimal loop formation and using carbon dioxide for insufflation. Pseudomembranous colitis was present on colonoscopy for the initial FMT in all cases.

Each patient in this series had a unique clinical narrative and individual histories are provided in Appendix I (Supplementary Materials). All patients had a prompt positive clinical response to the procedure. This was especially dramatic in Patient 1 who was monitored in the medical intensive care unit, where hemodynamic improvement was evident within a few hours after FMT, with lessening vasopressor and ventilatory support and defervescence. A precipitous fall in white blood cell (WBC) count from 25×10^9/L to near normal levels was seen over 24 h, and the CRP began decreasing within hours of the procedure. The improvement, however, was not sustained. Symptoms and signs of CDI returned in Patients 1 and 2 within 3 to 5 days. Patient 1 underwent subtotal colectomy on day 5 post-FMT. Patient 2 was restarted on vancomycin on day 5 after FMT and continued on vancomycin for 2 weeks as an outpatient, which was followed by a second FMT. During this second procedure his colon was noted to be normal without any residual pseudomembranes. After the experience with these two patients, we recommended re-initiation of antibiotics after a holding period of several days following the first FMT in Patients 3 and 4, with the plan to repeat the FMT on an outpatient basis after completing the antibiotic course. This plan was implemented in Patient 3, who was started on fidaxomicin on day 2 following her first FMT and had the second FMT done on day 14. Patient 4 was also started on fidaxomicin on day 3 after her first FMT, but refused to undergo the second FMT. She ultimately succumbed to fulminant CDI, and elected comfort care in a hospice program. Patients 2 and 3 have not had recurrence of CDI in over a year of follow-up despite receiving subsequent antibiotics for different indications, including pneumonia and urinary tract infection.

DISCUSSION

Severe CDI is a potentially lethal disease, and even the best surgical treatment is associated with high mortality.[2–4] FMT has the potential to correct the underlying problem associated with CDI and should be investigated as a much less invasive alternative to surgery.[8] In practice some of the barriers to FMT include limited time window of opportunity needed to recruit and screen a suitable donor and prepare the material. We previously described a solution to this problem with a standardized frozen preparation of fecal microbiota that can be thawed and used emergently, as we did here in Patients 2 through 4.[10] FMT resulted in short-term clinical improvement in all four of our patients, and this was sufficient to stabilize them for several days. In fact, the speed of improvement in Patient 1 raises the possibility of an active signal from microbiota that counters the systemic inflammatory state. However, a single FMT was not sufficient to achieve sustained clearance of the infection as we typically observe in outpatients with the recurrent form of the disease. Nevertheless, the short-term improvement was sufficient to de-escalate the clinical status of our severe CDI patients from surgical emergency to an antibiotic-responsive state. These gains allowed us to complete a full course of antibiotic therapy and ensure long-term recovery with the second FMT. Our experience does not suggest superiority of fidaxomicin for this interim antibiotic treatment over vancomycin. In fact, Patient 4, who was treated with fidaxomicin and elected not to undergo the second FMT, ultimately succumbed to CDI. A possible explanation for lack of sustained response to a single FMT in treating acutely ill patients is residual active infection with *C. difficile* organisms. It is also possible that the patients were promptly re-infected because they returned to their hospital beds, which were likely contaminated with this bacterium.

In summary, our experience adds to the limited literature on successful use of FMT in treating severe CDI. We suggest a protocol consisting of one FMT followed by a holding period of several days, followed by a two week course of antibiotics, and a second FMT that may be done on an outpatient basis. Randomized clinical trials using standardized fecal material should be performed for this condition and compared against surgical outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported, in part, by NIH Grant R21AI091907 (to AK and MJS), research funding by CIPAC LLC (to AK and MJS). ARW was supported by the Interdisciplinary Doctoral Fellowship from the University of Minnesota Graduate School. MJH was supported by a fellowship from the NIH, NIDCR T32 Institutional Training Grant: Minnesota Craniofacial Research Training (MinnCResT) Program.

Abbreviations

CDI	*Clostridium difficile* infection
CRP	C-reactive protein
FMT	fecal microbiota transplantation
MICU	medical intensive care unit
WBC	white blood cell

References

1. Kelly CP, LaMont JT. Clostridium difficile--more difficult than ever. N Engl J Med. 2008; 359:1932–40. [PubMed: 18971494]
2. Dallal RM, Harbrecht BG, Boujoukas AJ, et al. Fulminant Clostridium difficile: an underappreciated and increasing cause of death and complications. Ann Surg. 2002; 235:363–72. [PubMed: 11882758]
3. Markelov A, Livert D, Kohli H. Predictors of fatal outcome after colectomy for fulminant Clostridium difficile Colitis: a 10-year experience dr.markelov@gmail.com. Am Surg. 2011; 77:977–80. [PubMed: 21944509]
4. Lamontagne F, Labbe AC, Haeck O, et al. Impact of emergency colectomy on survival of patients with fulminant Clostridium difficile colitis during an epidemic caused by a hypervirulent strain. Ann Surg. 2007; 245:267–72. [PubMed: 17245181]
5. Eiseman B, Silen W, Bascom GS, et al. Fecal enema as an adjunct in the treatment of pseudomembranous enterocolitis. Surgery. 1958; 44:854–9. [PubMed: 13592638]
6. van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal Infusion of Donor Feces for Recurrent Clostridium difficile. N Engl J Med. 2013
7. Borody TJ, Khoruts A. Fecal microbiota transplantation and emerging applications. Nat Rev Gastroenterol Hepatol. 2011
8. Brandt LJ, Borody TJ, Campbell J. Endoscopic Fecal Microbiota Transplantation: “First-Line” Treatment for Severe Clostridium difficile Infection? J Clin Gastroenterol. 2011
9. Abou Chakra CN, Pepin J, Valiquette L. Prediction tools for unfavourable outcomes in Clostridium difficile infection: a systematic review. PLoS One. 2012; 7:e30258. [PubMed: 22291926]
10. Hamilton MJ, Weingarden AR, Sadowsky MJ, et al. Standardized Frozen Preparation for Transplantation of Fecal Microbiota for Recurrent Clostridium difficile Infection. Am J Gastroenterol. 2012