Successful Therapy of Severe Pseudomembranous 
Clostridium difficile Colitis Using a Combination of 
Fecal Microbiota Therapy and Fidaxomicin

Peter C. Konturek, Drilon Haziri, Harry Helfritzsch, Thomas Hess, Igor A. Harsch

Departments of Internal Medicine and Visceral and Thorax Surgery, Thuringia Clinic Saalfeld, Teaching Hospital of the University of Jena, Saalfeld, Germany

Keywords
Fecal microbiota transplantation · Fidaxomicin · Clostridium difficile colitis

Abstract
Objective: The aim of this work was to describe the use of a combination of fidaxomicin and fecal microbiota therapy (FMT) in Clostridium difficile infection (CDI). Clinical Presentation and Intervention: A 78-year-old female, who was admitted for surgery due to acute diverticulitis caused by postoperative complications and broad antibiotic therapy, developed CDI-induced colitis. Despite the introduction of metronidazole and vancomycin therapy, her clinical condition continued to deteriorate. She was transferred to the intensive care unit where FMT followed by fidaxomicin were performed because her C-reactive protein and leucocyte levels remained elevated. Further clinical improvement and the resolution of colitis was observed. Conclusion: In this case, severe CDI colitis was successfully treated with the combination of FMT and fidaxomicin.

Introduction

Clostridium difficile infection (CDI) is the most common cause of infectious diarrhea and represents a significant healthcare burden worldwide [1, 2]. Important risk factors for this infection are age >65 years, antibiotic exposure, and the presence of immunodeficiency [3]. Unfortunately, the antibiotic treatment alone frequently fails to cure the disease and perpetuates its recurrence, which is a major risk factor for complications [4].

Recent studies indicate that the main cause of CDI is the disruption of the normal gut microbiota termed dysbiosis [1, 4]. After colonization of the intestinal mucosa, C. difficile is able to produce major toxins A and B that lead to the increased permeability of the intestinal barrier due to the disruption of tight junctions and increased local production of proinflammatory mediators in the colonic mucosa [5].

Since gut dysbiosis plays a crucial role in the pathogenesis of CDI, the restoration of the gut microbiota composition via fecal microbiota therapy (FMT) has recently gained increasing attention, in which FMT is administered as a fecal solution from a healthy donor into the intestinal tract of the recipient. This procedure was demonstrated to be a very effective therapy, leading to the resolution of recurrent C. difficile colitis in more than 90% of patients [6].
Fig. 1. Colonoscopic view of the severe pseudomembranous colitis before (a) and 6 months after (b) FMT in combination with fidaxomicin.

Fig. 2. Level changes of CRP (a), leucocytes (b), and stool frequency (c) before and after FMT in combination with fidaxomicin.
Fidaxomicin is a novel bactericidal macrocyclic antibiotic that was recently approved for the treatment of CDI [7]. It has a high degree of specificity against \textit{C. difficile} and has little effect on the composition of the gut microbiota regarding its major phylogenetic clusters.

Studies on the combination of fecal microbiota transplantation and fidaxomicin therapy in the treatment of severe \textit{C. difficile} colitis are lacking. Hence, we describe the use of a combination of fidaxomicin with FMT in severe CDI.

**Case Report**

A 76-year-old female patient with a history of chronic recurrent diverticulitis was admitted for surgical treatment of acute diverticulitis. Perioperatively, the patient was treated with cefuroxime 1.5 g/day. The postoperative course was complicated by small bowel-ileus due to mesenteric ischemia. The patient was treated with 2 relaparotomies followed by the introduction of broad spectrum antibiotics (piperacillin-tazobactam 3 × 4.5 g/day). The patient’s clinical condition deteriorated and she developed fever and acute diarrhea (>15/day). Her C-reactive protein (CRP; 310 mg/L) and leucocyte counts (24 × 10^9/L) were markedly increased. A fecal sample was positive for cytotoxin-B producing \textit{C. difficile} by culture and cytotoxin assay. Colonoscopy demonstrated a severe colitis with multiple pseudomembranes (Fig. 1). Antibiotic therapy with metronidazole and vancomycin was subsequently initiated. Despite these measures, the clinical condition of the patient further deteriorated. She was transferred to the intensive care unit and required mechanical ventilation and catecholamines.

Due to the failure of antibiotic therapy, the decision was taken to perform FMT via colonoscopy. A total of 500 mL of diluted fecal solution from a healthy donor was applied at the cecum and colon ascends. Within 72 h after FMT, a significant improvement of the inflammatory parameters was observed (Fig. 2). Because the colitis was not fully resolved, increased CRP (113 mg/L) and the presence of prognostically unfavorable clinical parameters (advanced age, pseudomembranes, fever, increased creatinine to 160 μmol/L) raised concerns about the efficacy of the FMT. Hence, fidaxomicin was introduced at a dose of 2×200 mg per os (p.o.) 7 days after FMT. Within the next 3 weeks we observed a complete clinical recovery and the stool specimens were negative for CDI. A colonoscopy performed 6 months later showed no pathologic findings in the colon. During the 14-month follow-up, no recurrence of \textit{C. difficile} infection was observed.

**Discussion**

In this case, the combination of FMT and fidaxomicin was an efficacious therapy in a patient with severe and complicated CDI. The cause of the disease was antibiotic therapy due to postoperative complications and the patient’s advanced age. Conventional therapy consisting of vancomycin and metronidazole failed to heal the CDI. The combination therapy of FMT and fidaxomicin led to the complete healing of CDI colitis and prevented the recurrence of the disease in 14 months of follow-up.

According to previous studies, the presence of severe CDI is associated with the increased risk of failure of FMT therapy [8]. Therefore, the strategy to restore the intestinal microbiota by FMT in combination with fidaxomicin could represent an effective treatment modality in patients with severe CDI. However, the data on the use of this method in fulminant \textit{C. difficile} colitis are limited. Recently, a successful treatment with fecal microbiota transplantation in patients with \textit{C. difficile}-induced toxic megacolon was reported [9]. In addition, a small report indicates that the combination of FMT with antibiotic therapy with fidaxomicin could represent an important therapeutic option in patients with severe \textit{C. difficile} colitis [10].

**Conclusion**

In the present case, severe CDI colitis was successfully treated with the combination of FMT and fidaxomicin.

**References**

1. Martin JS, Monaghan TM, Wilcox MH: \textit{Clostridium difficile}: epidemiology, diagnosis and understanding transmission. Nat Rev Gastroenterol Hepatol 2016;13:206–216.
2. Aly NY, Omar AA, Badawy DA, et al: Audit of physicians’ adherence to the antibiotic policy guidelines in Kuwait. Med Princ Pract 2012;21:310–317.
3. Surawicz CM: \textit{C. difficile} infection: risk factors, diagnosis and management. Curr Treat Options Gastroenterol 2015;13:121–129.
4. Ofous A: \textit{Clostridium difficile} infection: a review of current and emerging therapies. Ann Gastroenterol 2016;29:147–154.
5. Knight CL, Surawicz CM: \textit{Clostridium difficile} infection. Med Clin North Am 2013;97:523–536.
6. van Nood E, Bartelsman JF, Tijssen JG, et al: Duodenal infusion of donor feces for recurrent \textit{Clostridium difficile}: N Engl J Med 2013;368:407–415.
7. Zhanel GG, Walkty AJ, Karlowsky JA: Fidaxomycin: a novel agent for the treatment of \textit{Clostridium difficile} infection. Can J Infect Dis Med Microbiol 2015;26:305–312.
8. Fischer M, Kao D, Mehta SR, et al: Predictors of early failure after fecal microbiota transplantation for the therapy of \textit{Clostridium difficile} infection: a multicenter study. Am J Gastroenterol 2016;111:1024–1031.
9. Gweon T-G, Lee KJ, Kang D, et al: A case of toxic megacolon caused by \textit{Clostridium difficile} infection and treated with fecal microbiota transplantation. Gut Liver 2015;9:247–250.
10. Pecere S, Sabatelli M, Fantoni M, et al: Letter: faecal microbiota transplantation in combination with fidaxomycin to treat severe complicated recurrent \textit{Clostridium difficile} infection. Aliment Pharmacol Ther 2015;42:1030.