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Single Case

A Novel Treatment Approach to Treatment-Resistant, Recurrent *Clostridium difficile*

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Keywords
Recurrent *Clostridium difficile* infection · Fecal microbial transplant

Abstract
A 36-year-old male with a previous medical history of persistent *Clostridium difficile* presented to clinic for evaluation of diarrheal symptoms intermittently for the last 2 years. He reported recurrent episodes of *C. difficile* that initially began after prophylactic antibiotic use prior to a tooth extraction. He underwent 12 unsuccessful treatment trials at a nearby clinic with courses of vancomycin, metronidazole, and fidaxomicin. His chronic diarrhea had caused him to endure significant lifestyle alterations over the years. After multiple episodes of incomplete bacterial clearance, he was referred to a university-based tertiary care facility but instead opted for care at a nearby clinic. Upon work-up, his serology was again positive for *C. difficile*, and he was initiated on a 14-day course of fidaxomicin 200 mg p.o. BID, along with yogurt and probiotic supplementation. Despite fidaxomicin treatment, subsequent serological PCR testing for *C. difficile* remained positive, consistent with CT abdomen and pelvis findings suspicious for enteritis. His recurrent resistance to standard therapy protocols inspired an unconventional treatment approach: another 14-day course of fidaxomicin 200 mg p.o. BID, followed by fidaxomicin 200 mg p.o. each morning and cholestyramine 4 g p.o. each evening for another 2 weeks, concluded by fecal microbial transplant. Two weeks following this antibiotic regimen and fecal transplant, serology was negative for *C. difficile*. Subsequent follow-up revealed no evidence of recurrence.

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Introduction

The following case illustrates a 36-year-old male's experience with treatment-resistant, recurrent *Clostridium difficile* infection. *C. difficile* is a gram-positive, spore-forming, bacterium that proliferates following disruption of normal gut microbiota caused by recent hospitalizations, advanced age, or most commonly, antibiotic treatments, such as in this patient [1]. Following infection, patients typically experience profuse watery diarrhea, occasional bloody diarrhea, bloating, and weight loss. *C. difficile* colitis is an extremely common infection worldwide, with an estimated incidence of approximately 500,000 people in the USA in 2011 [2]. Standard treatment of *C. difficile* includes antibiotic courses of p.o. vancomycin, fidaxomicin, or metronidazole [3]. In antibiotic-resistant patients in whom symptoms persist despite standard therapy, fecal microbial transplant has become the standard of care [4]. In fecal microbial transplant, donor fecal material is transplanted with the goal of long-term engraftment and colonization of recipients' flora. The value of this treatment hinges upon the well-known importance of the "gut microbiome," estimated to contain thousands of bacterial species that overall comprise a profound effect on host immune function, metabolism, and overall health and disease [4] (Fig. 1a–d).

In patients suffering from *C. difficile* colitis, 15–30% experience recurrence after antibiotics courses, with rates in the USA increasing in recent years [3, 5]. While fecal microbial transplants are widely used in refractory cases, there is limited data on real-world practices as well as guidance on optimal timing of the procedure. Therefore, regimens outlining the duration of antibiotic course and timing of fecal microbial transplant may guide therapy in similar patients suffering from persistent *C. difficile* infection.

Case Report

The case patient is a 36-year-old male with a previous medical history of recurrent *C. difficile*, diabetes mellitus, anxiety, and depression. He first presented to the clinic in the fall of 2021 for evaluation of a 2-year history of recurrent *C. difficile*. He reported onset of symptoms and a confirmatory *C. difficile* serology in 2019 following use of prophylactic antibiotic therapy for a tooth extraction. Since, he had been unsuccessfully treated 12 times with various courses of vancomycin, metronidazole, and fidaxomicin at an outside clinic. Previous health records indicated that his most recent episode occurred 2 weeks prior to presentation with a confirmatory positive GI stool panel for *C. difficile* and unsuccessful treatment with Vancomycin 250 mg p.o.

The patient was complaining of 10–20 loose bowel movements a day with occasional bright red blood, both mixed in his stool and visible on tissue paper. He endorsed associated symptoms of abdominal cramping, bloating, poor sleep from nocturnal diarrhea episodes, rectal pain, and anal fissures from incessant stool passage, and a 25-pound weight loss over the past 5 months despite continuing his regular diet. Consequently, he was experiencing immense fatigue, social isolation, worsening panic attacks, anxiety, and depression with the severity of his symptoms causing significant disruption to his job and social activities. Physical exam revealed a fully alert and oriented male in no acute distress. Bowel sounds were hypoactive with no acute findings noted. Colonoscopy was deferred due to current recommendations to wait at least 4–6 weeks after *C. difficile* treatment to proceed with scope. His previous colonoscopy in 2019 was unremarkable, however, and revealed no acute or chronic processes with the exclusion of a hyperplastic polyp. Serologic PCR testing was again positive for *C. difficile*, and the patient was initiated on a 14-day course of fidaxomicin 200 mg p.o. BID, along with yogurt and Culturelle probiotic supplementation.

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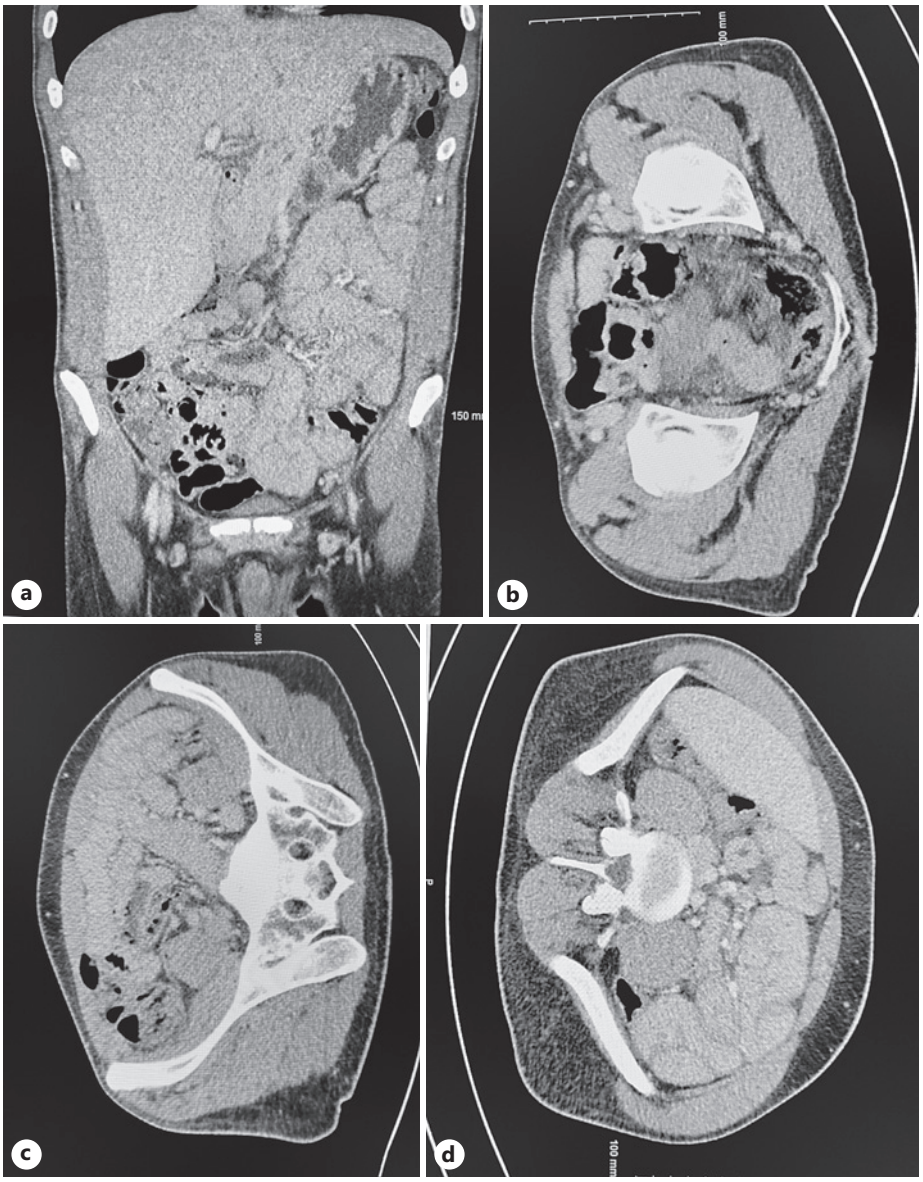

Fig. 1. a–d Images from the CT abdomen and pelvis that was done for further work-up following positive PCR testing for *C. difficile* upon presentation, 1 week after initiating the recommended – 14-day course of fidaxomicin 200 mg p.o. BID, along with yogurt and probiotic supplementation. The images reveal several loops of thickened small bowel wall with subtle surrounding fat stranding, suggestive of enteritis.

One week later, further work-up including CT abdomen and pelvis revealed several loops of thickened small bowel wall with subtle surrounding fat stranding, suggestive of enteritis. Laboratory evaluation revealed CBC with a differential of mild leukocytosis with left shift, elevated lactoferrin levels suggestive of intestinal inflammation, and fecal calprotectin levels within normal limits. Despite completing the 2-week course of fidaxomicin, *C. difficile* serology continued to remain positive. It was at this time that the patient was recommended to start an unconventional treatment approach: fidaxomicin 200 mg p.o. each morning and cholestyramine 4 mg p.o. each evening for 2 weeks, followed by a fecal microbial transplant. Following

patient compliance with this antibiotic regimen and completion of fecal microbial transplant, the patient continued to struggle for 2 weeks with persistent, watery diarrhea. Serologic PCR testing for *C. difficile* was negative, however, and his diarrhea was determined to be due to post-infectious inflammatory syndrome. He was treated supportively, and his symptoms resolved shortly thereafter. Subsequent follow-up revealed no evidence of *C. difficile* recurrence.

Conclusion

This patient presentation illustrates the use of a systematic antibiotic regimen prior to fecal microbial transplant to ensure successful outcomes in patients with recurrent *C. difficile* colitis. While there is currently limited literature on the ideal timing and duration of antibiotic administration prior to fecal microbial transplant, there is vastly sufficient evidence supporting the efficacy of fecal microbial transplants when administered properly. One study demonstrates that fecal microbial transplants have a 65–80% cure rate in patients with recurrent *C. difficile* infections after one treatment and a 90–95% cure rate after multiple treatments [4]. This contrasts with the 25–27% cure rate demonstrated by one course of antibiotics in *C. difficile* clearance [4]. Therefore, it may prove highly beneficial to equip providers with literature that exemplifies proper medication administration prior to fecal microbial transplants with the goal of improving cure rates in patients after one fecal microbial transplant and thus, reducing the number of patients requiring multiple treatments. Treatment of *C. difficile* infection costs the USA healthcare system 4.8 billion dollars annually [2]. Not only are these treatments a major healthcare burden, but persistent *C. difficile* colitis can also take a tremendous toll on patients' functional status and overall well-being.

The rationale behind the proposed treatment approach was to reduce the bacterial load with bactericidal agent fidaxomicin with the morning dose and reduce the spore load with spore-binding agent cholestyramine with the evening dose. The success of this approach can be attributed to bacterial and spore growth being the two major components contributing to *C. difficile* proliferation within the gut [6]. Once sufficient reductions in bacteria and spore loads were achieved, the treatment regimen would then proceed to fecal microbial transplant. Sufficiently low bacterial and spore loads allow for successful fecal microbial transplants, as the transplanted, healthy colonic gut flora will exist in high enough titers to prevail over the relatively lowered *C. difficile* bacterial titers. Fecal microbial transplants then restore the normal gut microbiome composition, thus rendering *C. difficile* growth incapable of producing clinically significant disease [5].

Recent research on mouse models shows that entry of spores into intestinal cells can lead to persistent and recurrent infection. Therefore, sporicidal treatments, such as nystatin, have demonstrated reduced disease recurrence in mouse models [7]. For similar reasons, concurrent treatment with cholestyramine ensures reduced spore entry into intestinal epithelial cells and reduced episodes of recurrence. This case demonstrates how adequate reductions in bacterial and spore loads prior to fecal microbial transplantation ensure *C. difficile* remission. Therefore, in replication of this proposed systematic therapy, patients may be treated in precisely the same way as the illustrated case patient: a 14-day course of fidaxomicin 200 mg p.o. BID, followed by another 14-day course of fidaxomicin 200 mg p.o. each morning and cholestyramine 4 mg p.o. each evening. Yogurt and probiotic supplementation should be given throughout, as probiotic use has been demonstrated to reduce gut microbial dysbiosis, a colonic bacterial imbalance also contributing to *C. difficile* proliferation [8].

In conclusion, timing of fecal microbial transplant is pivotal to ensure successful *C. difficile* clearance. This is well demonstrated by our case patient who had struggled with recurrent

C. difficile for 2 years prior to trialing this systematic approach. By adhering to this protocol, he achieved remission in a short, 4-month period without any further reported relapse. He was able to gain back his 40-pound total weight deficit, return to work and improve his overall well-being. The aim of this case report is to equip physicians with meaningful evidence to improve cure rates in treatment-resistant, recurrent *C. difficile* patients with an exemplary protocol ensuring fecal microbial transplant success due to low bacterial and spore levels prior to transplant.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Megha Gangadhar and Anita Kottapalli wrote the manuscript, conducted literature review, and edited each other's work. Ven Kottapalli provided feedback and guidance throughout the entire process while making edits on all versions of the manuscript. Megha Gangadhar, Anita Kottapalli, and Ven Kottapalli read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study and that support the findings of this study are included in this article. Further inquiries can be directed to the corresponding author.

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