A Novel Treatment Approach to Treatment-Resistant, Recurrent C. diff: A Case Report

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Background

- *Clostridioides difficile* (C. diff) is a spore-forming gram-positive bacteria that proliferates following disruption of normal gut microbiota causing profuse watery diarrhea +/- bloody diarrhea, bloating, and weight loss
- Cornerstone of treatment is p.o. vancomycin/fidaxomicin now favored over metronidazole/vancomycin[1]
- After first time infection with C. diff, roughly 25% experience recurrence after treatment with vancomycin/metronidazole, and around 15-20% with fidaxomicin [1]
- After first reoccurrence, rate of recurrent infection increases to 45% and up to 65% after two or more recurrences[1,2]
- In antibiotic-resistant patients, fecal microbial transplant (FMT) has become the standard of care[3]
- In FMT, donor fecal material is transplanted with the goal of long-term engraftment and colonization of recipients' flora
- Other widely recognized treatment options of varying efficacies include probiotics, anion resins, secondary bile acids and anti-toxin antibodies[3]

Purpose

While FMT is widely used in refractory cases, there is limited data on real-world practices as well as guidance on optimal timing of the procedure. Regimens outlining the duration of antibiotic course and timing of fecal microbial transplant may guide therapy in similar patients suffering from persistent C. diff infection.

Case Description

- 36-year-old male with a previous medical history of recurrent C. diff, diabetes mellitus, anxiety, and depression
- First presented to the clinic in the fall of 2021 for evaluation of a two-year history of recurrent C. diff
- Reported onset of symptoms and a confirmatory C. diff serology in 2019 following use of prophylactic antibiotic therapy for a tooth extraction
- Unsuccessfully treated 12 times with various courses of vancomycin, metronidazole, and fidaxomicin at an outside clinic

Case Description

- Previous health records indicated most recent episode occurring two weeks prior to presentation with a confirmatory positive GI stool panel for C. diff and unsuccessful treatment with two-week course vancomycin 250 mg p.o.
- At time of presentation, he reported 10-20 loose bowel movements/day with occasional bright red blood, abdominal cramping, bloating, poor sleep from nocturnal diarrhea episodes, rectal pain and anal fissures from incessant stool passage and a 25 lb. weight loss over the past five months despite regular diet
- Physical exam revealed a fully alert and oriented male in no acute distress with no acute findings noted
- Colonoscopy was deferred due to current recommendations to wait at least 4-6 weeks after C. diff treatment to proceed with scope; Previous colonoscopy in 2019 was unremarkable and revealed no acute or chronic processes with the exclusion of a hyperplastic polyp
- Serology was again positive for C. diff upon presentation

FMT = Fecal Microbial Transplant

Discussion

Proposed Rationale

Decreased germination of spores with bile-acid sequestrant cholestyramine

Decreased bacterial load with bactericidal agent fidaxomicin

Sufficiently low bacterial and spore loads allow for successful FMT as the transplanted, healthy colonic gut flora will prevail over the relatively lowered C. diff bacterial titers

- **Cholestyramine** has been shown to be beneficial as an adjunctive therapy, observed mostly with vancomycin[4]
  - Primary bile acids such as taurocholate initiate germination of c. diff spores resulting in vegetative cells capable of replication and pathogenesis [5]
  - Therefore, the bile-acid sequestering drug cholestyramine blocks this process to reduce spore germination & delay colonization[5]
  - One study comparing cecal and intestinal extracts in clindamycin-treated and untreated mouse models demonstrated the administration of cholestyramine decreased the ability of taurocholate to germinate C. diff spores by 200-fold [4]
  - Sporicidal treatments such as nystatin have also demonstrated reduced disease recurrence in mouse models [2]
- **Fidaxomicin** is a a non-absorbed macrolide that is bactericidal towards C. diff and has lower rates of relapse when compared to vancomycin[1]
- Probiotic supplementation aims to reduce gut microbial dysbiosis contributing to C. diff proliferation, although varying evidence exists on its efficacy[2]

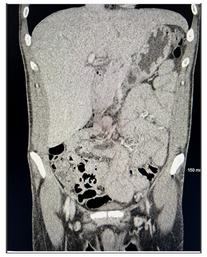

Figure 1. CT Abdomen/Pelvis revealed several loops of thickened small bowel wall with subtle surrounding fat stranding consistent with infection.

Treatment and Timeline

Patient started on 14-day course of fidaxomicin 200 mg p.o. BID

+

probiotic supplementation

One-week later CT Abdomen/Pelvis suggestive of enteritis (Figure 1)

+CBC differential of mild leukocytosis with left shift

+elevated lactoferrin levels suggestive of intestinal inflammation/ fecal calprotectin levels WNL

After completing 2-week course fidaxomicin, C. diff serology remained positive

Recommended to start unique treatment approach:

1) 14-day course fidaxomicin 200mg BID

2) Another 14-day course of fidaxomicin 200 mg each AM + cholestyramine 4 mg each PM

3) Followed by FMT

Following compliance with antibiotic regimen & completion of FMT, patient continued to struggle with persistent watery diarrhea for two weeks

However, serology for C. diff was negative & diarrhea was determined to be due to post-infectious inflammatory syndrome

He was treated supportively and symptoms resolved shortly thereafter

Subsequent follow-up revealed no evidence of C. diff recurrence

He gained back 40 lb. total weight deficit, returned to work and overall well-being improved

Conclusions

- ✓ The aim of this case report is to equip physicians with meaningful evidence of an exemplary protocol achieving fecal microbial transplant success in the context of suspected lowered bacterial and spore levels prior to transplant
- ✓ 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. and cholestyramine 4 mg p.o. followed by FMT

References

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