Fecal Microbiota Transplant for Severe or Fulminant CDI Protocol at UNC

Sarah McGill, MD MSc, Adapted by Fischer et al.[1]

Patients

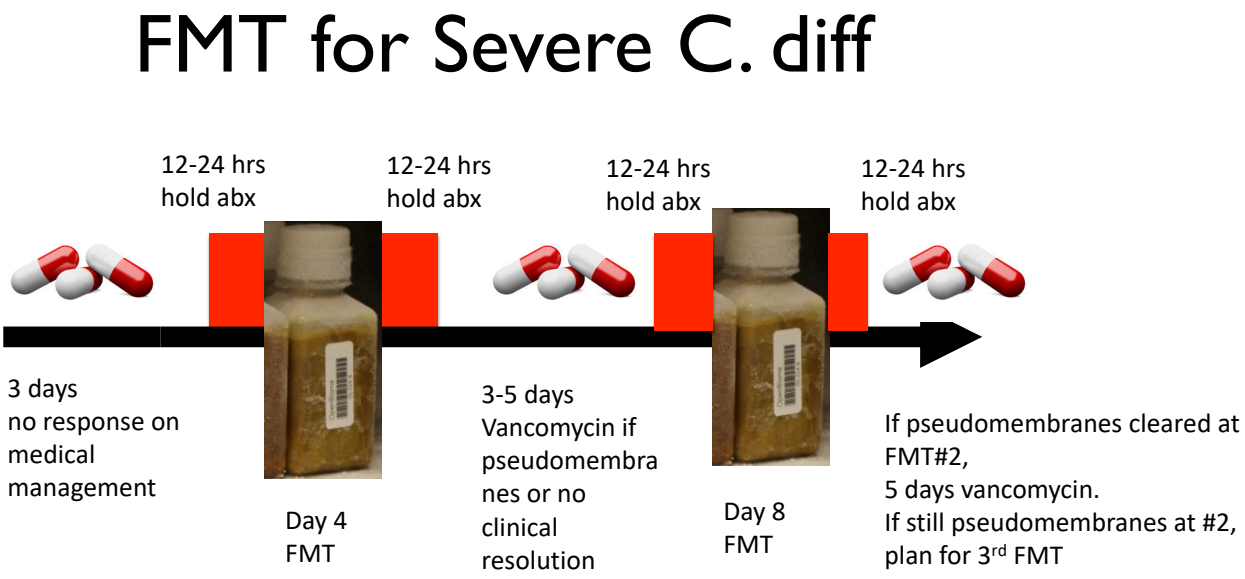
Patients with severe (WBC>20 or acute kidney injury with creatinine>1.5) or fulminant C. Difficile infection (shock, ICU status, ileus or megacolon) should be considered for FMT if they have not responded to medical management after **3 days**.

Standard management of severe CDI is standardly dosed vancomycin or fidaxomicin.
Standard management of fulminant CDI is high-dose vancomycin (vancomycin 500mg qid), with or without iv flagyl (in case of ileus) or vancomycin enema (ileus), consider for subtotal colectomy.

Consider a multidisciplinary team. Immunocompromised ID and GI Surgery would like to be involved early in these cases; General ID does not need to routinely be involved.

Participants with precipitous deterioration or consideration for colectomy prior to the day 3 time period can also be offered FMT.

Treatment protocol



Overall, the protocol administers serial fecal microbiota transplant following bowel purge q3-5 days while continuing standard of care antibiotics and halting those temporarily.

- Discontinue antibiotics 12-24 hours before FMT

- Patient consent must include that FMT is investigational and there are rare risks of pathogen transmission. Also should include FMT seems a very effective method of treating severe CDI.
    - Contraindications to FMT include severe allergic/ anaphylaxis to food, allergic to glycerol, severely immunocompromised. If immunocompromised, must discuss that stool has not been screened for CMV
- Administer split dose bowel prep (4 L golytely), just until clear (patient should drink enough Golytely to be clear night prior to FMT and then morning of, clear liquid diet and 2 hours strict NPO prior to FMT)
- Perform colonoscopy to the safest extent thought possible and administer Openbiome lower FMT there, careful to avoid looping
    - Upper FMT: If lower FMT is not feasible for some reason, and the patient has no ileus on Xray, upper administration via nasoduodenal tube may be performed with Xray confirmation of tube prior. Patient prep is one proton pump inhibitor night before and morning of FMT, then clear liquid diet day of FMT, then NPO two hours prior
        - Gastroparesis, intestinal obstruction are contraindications to upper
- If pseudomembranes were present, resume vancomycin in 24-48 hours after FMT for minimum of 5 days and plan for likely second FMT
- If CDI with diarrhea still present after 3-5 days of vancomycin, prepare for second FMT with bowel prep and temporary suspension of vancomycin on day 7-10
- If pseudomembranes on second FMT, resume vancomycin and continue for at least 5 days and consider repeat FMT if no clinical resolution of CDI (in studies, this was performed on day 12-13)

Rationale

Fecal microbiota transplant is recommended as first-line therapy for multiply-recurrent CDI in society guidelines.[2] FMT delivers secondary bile acids that inhibit germination of C. Diff spores[3] and restores fecal biodiversity.[4]

It is also seems quite safe. The vigorous immune responses seen in organ transplants and even blood transfusions simply do not happen with FMT. The Food and Drug Administration directs providers to counsel that the procedure is experimental, and there have been rare reports of pathogen transmission. In 2019, two clinical trial patients without CDI developed bacteremia from extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* after FMT; one of the patients was neutropenic and passed away.[5]

Despite its safety and efficacy in recurrent infection, we do not understand well the efficacy of FMT in severe or fulminant CDI as there is no randomized trial of FMT vs standard of care (and for ethical reasons probably will never be**). The data to date suggests that FMT improves outcomes if performed serially and in conjunction with continued antibiotics.** Severe CDI is characterized by white blood cell count>15,000 or creatinine >1.5 and treatment is standardly-dosed vancomycin or fidaxomicin. Fulminant CDI—defined by hypotension, shock, ileus or megacolon, and previously described as severe-complicated—is treated with high-dose vancomycin at 500mg every six hours, with or intravenous metronidazole, and consideration of subtotal colectomy.[2] Roughly half of patients with severe or fulminant CDI die from the disease.[6] The addition of FMT to these treatment algorithms holds promise to improve the lives of these patients.

The most pertinent studies are described below. In a prior retrospective study by Fischer et al., 52 of 57 patients with severe or fulminant CDI had treatment success at 1 month with a hospital protocol of serial fecal microbiota transplant administered via colonoscopy every 5 days along with standard antibiotics.[1, 7] The fact that >90% of these patients survived at 1 month is remarkable.

The serial colo-FMT protocol was validated by a prospective trial in Rome that randomized patients with severe CDI who had not responded to 10 days of antibiotics to either single colonoscopy- FMT or serial colonoscopy- FMTs until resolution of pseudomembranes.[8] All 28 patients who received serial FMTs experienced cure with resolution of diarrhea at two months; 75% of those who received a single infusion were cured. Lastly, in a cohort study of 60 patients with severe CDI, the number of patients needed to treat with early, nasogastric tube-delivered FMT to save one life at 3 months was 2.[9] Only 17% of patients who received FMT following bowel lavage died, compared to 69% mortality in those who received standard of care.

In a separate French cohort study of 60 patients with severe CDI, the number of patients needed to treat with early, nasogastric tube-delivered FMT to save one life at 3 months was 2. Only 17% of patients who received FMT following bowel lavage died, compared to 69% mortality in those who received standard of care.

A recent small study evaluating enema-based serial FMT had poorer results. Only 5 patients sustained clinical cure at 30 days. Five patients died, and four had recurrence of CDI following discharge. No study has trialed enemas head-to-head against other modalities, but patient cohorts with recurrent CDI have historically done worse when given FMT enemas compared to capsule, nasoduodenal or colonoscopic administration.

Potential conflicts of Interest: research funding from Finch pharmaceuticals.

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