Diarrhea after fecal microbiota transplantation for recurrent *Clostridioides difficile* infection

Cole Krensky BSc, Susan M. Poutanen MD MPH, Susy S. Hota MD MSc

■ Cite as: *CMAJ* 2019 May 21;191:E559-61. doi: 10.1503/cmaj.181193

A 33-year-old woman, 3 months postpartum, was referred to our infectious disease clinic after multiple episodes of *Clostridioides difficile* (previously known as *Clostridium difficile*) infection.[1] Her first episode occurred 2 years earlier after a course of ciprofloxacin was prescribed to treat mild diarrhea. Although the initial episode of *C. difficile* infection resolved after a course of metronidazole (formerly the first-line therapy as per the Infectious Diseases Society of America [IDSA] guideline[2]), the patient experienced 3 further recurrences within 2 years, each confirmed by testing stool for *C. difficile* toxins, and each responding to therapy. The first recurrence was treated with metronidazole, and the subsequent 2 recurrences were treated with fidaxomicin because of a remote history of allergy to vancomycin. Only the last of the 3 recurrences had an identifiable precipitating event, when ciprofloxacin was prescribed to treat postpartum mastitis. The patient was referred to our clinic while on a course of fidaxomicin for consideration of fecal microbiota transplantation (FMT).

Before receiving FMT, the patient experienced another episode of recurrent *C. difficile* infection. She was treated with fidaxomicin, then switched to oral vancomycin after immunologic testing and an oral challenge with vancomycin showed no allergic reaction. Oral vancomycin was continued as a prolonged taper for a total of 7 weeks until it was discontinued 48 hours before FMT.

The patient underwent 3 separate FMT administrations by enema at the University of Toronto Microbiota Therapeutics Outcomes Program (MTOP). Each procedure was 3 days apart as per the MTOP protocol. A total of 300 mL of FMT product, containing 50 g of donor stool, was used during each administration. The patient retained the entire transplant on each occasion. There were no adverse events during or immediately after FMT. The donor stool had been collected from a thoroughly screened FMT donor at MTOP. The donor screening procedure consisted of a complete donor medical assessment and laboratory testing of donor stool for infectious pathogens, conducted at recruitment and every 1–3 months thereafter before release of archived FMT, in keeping with guidance from Health Canada.[3] The administered samples were previously collected, manufactured into FMT and stored at –80°C.

KEY POINTS

- In patients experiencing diarrhea after fecal microbiota transplantation (FMT) to treat recurrent *Clostridioides difficile* infection, non–*C. difficile* etiologies should be considered and thoroughly investigated.
- Current *C. difficile* testing cannot differentiate between *C. difficile* colonization and infection after FMT, potentially leading to inappropriate treatment decisions.
- If a pathogen other than *C. difficile* is identified in patients with diarrhea after FMT, retesting of donor stool filtrate should be completed to identify a possible transmission event.

Nine days after FMT, the patient began experiencing nausea, vomiting, abdominal cramps and 4 episodes of diarrhea. Because of her concerns of a recurrence of *C. difficile* infection, the patient self-medicated with vancomycin. She developed an urticarial reaction and promptly visited the emergency department. The patient was afebrile, hemodynamically stable and in no apparent respiratory distress. The physical examination was unremarkable except for a diffuse urticarial rash. Complete blood count, electrolyte panel, creatinine and liver enzymes were within normal ranges. Abdominal radiography showed mild haustral thickening seen within the transverse and descending colon, consistent with mild ongoing colitis. Despite her previous allergy testing, the patient was advised to discontinue the vancomycin because of suspicions it had precipitated the urticarial rash. A stool sample was submitted for detection of *C. difficile* toxins A and B by polymerase chain reaction (PCR) (ARIES *C. difficile* Assay, Luminex), routine bacterial culture, and ova and parasite microscopic examination. All these investigations were negative.

The samples were subsequently tested by our MTOP team with an extended enteric gastrointestinal pathogen panel (FILMARRAY GI Panel, bioMérieux), which can identify 22 viral, bacterial and parasitic targets. The pathogen panel was positive for sapovirus, which was consistent with her symptoms. The patient's presentation was diagnosed as a sapovirus gastroenteritis. It was later determined that the patient's children had concurrent infectious gastroenteritis symptoms. Subsequent

testing of pooled safety aliquots from the FMT donor stool samples used in the FMT was negative for sapovirus, ruling out transmission via FMT. The patient's symptoms self-resolved in a few days.

Discussion

Clostridioides difficile infection, an infectious diarrheal disease, comprises 15%–25% of all antibiotic-associated diarrhea.[4] The current treatment guideline from the Association of Medical Microbiology and Infectious Disease Canada recommends a 10–14-day course of antibiotic treatment with vancomycin or fidaxomicin for the initial presentation.[5] After multiple recurrences, which occur in about 20%–25% of cases, FMT may be considered as a treatment option.[2,6] Recent systematic reviews of both case series and randomized controlled trials evaluating the effectiveness of FMT for resolving recurrent *C. difficile* infection show it to be comparable, if not superior, to antibiotic treatment.[7,8]

Although several consensus statements have been developed for administration of FMT, little focus has been placed on how to provide optimal follow-up to recipients after the procedure and how to determine whether recurrence of diarrhea represents a failure of FMT. Recurrence of *C. difficile* infection is defined by the IDSA as an acute flare of diarrhea followed by a positive laboratory result for *C. difficile* within a 2–8-week period of the last symptomatic episode.[2] However, both diarrhea and a positive *C. difficile* toxin test are not specific to *C. difficile* infection. The decision to treat diarrheal symptoms as recurrent *C. difficile* infection after FMT should be made only after using a judicious approach that involves a thorough clinical history and appropriate investigations. Although it is common in this setting for clinicians to assume recurrence of *C. difficile* infection and treat accordingly, antimicrobial therapy will undermine the FMT procedure and reverse any expected clinical benefit.

The clinical symptoms of *C. difficile* infection are challenging to interpret because they overlap with multiple gastrointestinal disorders. A retrospective analysis of 117 patients referred to an infectious disease clinic for a presumed recurrence of *C. difficile* infection found that 25% of patients had been misdiagnosed because of erroneous clinical assumptions based on the patient's symptoms and previous laboratory results.[9] The most common alternative diagnosis was postinfectious irritable bowel syndrome.[9] Extrapolating this data to the post-FMT setting, in which diarrhea is often initially assumed to be a recurrence of *C. difficile* infection, it is unclear what fraction of patients with a positive *C. difficile* test after FMT have diarrheal symptoms with causes other than recurrent *C. difficile* infection. A careful history with consideration of likely alternative etiologies is necessary before deciding whether treatment for recurrent *C. difficile* infection is warranted.

Testing for *C. difficile* is challenging because patients may be colonized with *C. difficile* and have a positive *C. difficile* test without having *C. difficile* infection. This is compounded by the use of nucleic acid amplification tests (NAATs), including PCR assays, which are highly sensitive and capable of detecting lower amounts of *C. difficile* than enzyme immunoassays.[2] As such, a negative NAAT for *C. difficile* toxins is an effective tool in ruling out *C. difficile* infection in the post-FMT setting. On the other hand, a positive NAAT must be clinically correlated with the patient's presentation to diagnose a true recurrence of *C. difficile* infection.

The diagnostic dilemma occurs when a health care provider is presented with nonspecific symptoms and a positive *C. difficile* test. In this context, clinical judgment is vital to determine if alternative etiologies are justifiably probable. In the setting where alternative etiologies are unlikely, treatment for recurrent *C. difficile* infection is appropriate. If alternative etiologies are reasonably suspected, further testing of stool for non–*C. difficile* pathogens is warranted before treatment for recurrent *C. difficile* infection is started. If these investigations are unremarkable, the decision to treat as a *C. difficile* infection is justified, though watchful waiting may still be appropriate if the clinical suspicion for a *C. difficile* infection is low. The current IDSA guideline does not recommend repeat NAAT testing because of the likelihood of persistent colonization.[2] It is important for clinicians assessing patients presenting with diarrhea after FMT to not start treatment for recurrent *C. difficile* infection without a thoughtful diagnostic approach that considers alternative etiologies and uses appropriate laboratory investigations.

In addition, an underappreciated aspect of the follow-up care of FMT recipients involves monitoring for the full extent of safety of the FMT. This should include not only the procedure-related risks but also the risks of infectious transmission from donor stool. Based on Health Canada's guidance document, donors should be periodically retested.[3] It does not explicitly state that individual donations be screened. Therefore, although the risk of a transmission event is greatly reduced by periodic rescreening of donors, it is not eliminated. If non–*C. difficile* pathogens are found to be causing post-FMT diarrhea, we suggest testing of donor stool samples to rule out a procedure-related transmission event. Aliquots of donor stool used in the FMT procedure should be stored for this purpose. Future guidelines should emphasize the need for a high-quality trace-back system for FMT.

Our case highlights the need for post-FMT follow-up guidelines, including further guidance on how to evaluate diarrhea in the post-FMT setting. In most cases, diarrheal symptoms and a positive *C. difficile* laboratory finding would indicate an unsuccessful FMT procedure and a recurrence of *C. difficile* infection. However, there is a reasonable justification to investigate further with consideration for alternative causes of a patient's symptoms, recognizing the risk for *C. difficile* colonization after FMT, especially if there is clinical or epidemiologic suspicion for an alternative enteric pathogen. In cases where a symptomatic patient tests negative for *C. difficile* toxins using a NAAT, extensive gastrointestinal pathogen testing is warranted. If a non–*C. difficile* pathogen is found, retesting of donor stool filtrate should be completed to identify a possible transmission event.

Future research should investigate the extent of post-FMT *C. difficile* colonization and the potential implications of alternative diarrheal etiologies in the context of both positive and negative *C. difficile* laboratory results.

References

1. Lawson PA, Citron DM, Tyrrell KL, et al. Reclassification of *Clostridium difficile* as *Clostridioides difficile* (Hall and O'Toole 1935) Prévot 1938. *Anaerobe* 2016;40:95-9.
2. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis* 2018;66:987-94.
3. Guidance document: fecal microbiota therapy used in the treatment of *Clostridium difficile* infection not responsive to conventional therapies. Ottawa: Health Canada; 2015; Available: www.hc-sc.gc.ca/dhp-mps/consultation/biolog/fecal_microbiota-bacterio_fecale-eng.php (accessed 2018 July 25).
4. Bartlett JG, Gerding DN. Clinical recognition and diagnosis of *Clostridium difficile* Infection. *Clin Infect Dis* 2008;46(Suppl 1):S12-8.
5. Loo VG, Davis I, Embil J, et al. Association of Medical Microbiology and Infectious Disease Canada treatment practice guidelines for *Clostridium difficile* infection. *JAMMI* 2018;3:71-92. Available: http://jammi.utpjournals.press/doi/10.3138/jammi.2018.02.13 (accessed 2018 July 28).
6. Vardakas KZ, Polyzos KA, Patouni K, et al. Treatment failure and recurrence of *Clostridium difficile* infection following treatment with vancomycin or metronidazole: a systematic review of the evidence. *Int J Antimicrob Agents* 2012;40:1-8.
7. Kassam Z, Lee CH, Yuan Y, et al. Fecal microbiota transplantation for *Clostridium difficile* infection: systematic review and meta-analysis. *Am J Gastroenterol* 2013;108:500-8.
8. Moayyedi P, Yuan Y, Baharith H, et al. Faecal microbiota transplantation for *Clostridium difficile*-associated diarrhoea: a systematic review of randomised controlled trials. *Med J Aust* 2017;207:166-72.
9. Jackson M, Olefson S, Machan J, et al. High rate of alternative diagnoses in patients referred for presumed *Clostridium difficile* infection. *J Clin Gastroenterol* 2016;50:742-6.

Competing interests: Susan Poutanen reports receiving honoraria for involvement in advisory board and speaking events, and travel reimbursement for speaking events from Merck Pharmaceuticals; advisory board honoraria from Paladin Labs, Verity Pharmaceuticals and Cipher Pharmaceuticals; research support from Accelerate Diagnostics, Bio-Rad and bioMérieux; and travel reimbursement from Copan outside the submitted work. Cole Krensky and Susy Hota have no competing interests to declare.

This article has been peer reviewed.

The authors have obtained patient consent.

Affiliations: Faculty of Medicine (Krensky), University of Toronto; Department of Microbiology (Poutanen), University Health Network and Sinai Health System; Departments of Laboratory Medicine and Pathobiology (Poutanen) and of Medicine (Hota), University of Toronto; Department of Infection Prevention and Control (Hota), University Health Network, Toronto, Ont.

Contributors: All authors contributed to the development and design of the case report. Cole Krensky drafted the manuscript. All authors edited and revised the manuscript, ensured accuracy and quality, and approved the final version for publication. All authors agree to be held accountable for all aspects of the case report.

Correspondence to: Susy Hota, susy.hota@uhn.ca