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Evaluating a Patient for Fecal Microbiota Transplantation (FMT) for the Treatment of *C. difficile*

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Abstract

Fecal Microbiota Transplantation (FMT) has been shown to treat 80-90% of *C. difficile* infections not responsive to antibiotic therapy in clinical trials and real-world settings. However, the utility of FMT depends on accurate CDI diagnosis and patient selection. As many as 25% of patients may be incorrectly referred for FMT.¹ This paper covers the considerations when evaluating patients for FMT for the treatment of *C. difficile*.

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Introduction

Over the past decade, Fecal Microbiota Transplantation (FMT) has developed from a fringe medical procedure to the standard of care for recurrent *C. difficile* infections (CDI), as defined in guidelines from medical professional societies.²⁻⁴

According to the United States' Food and Drug Administration's (FDA) policy of enforcement discretion patients should have CDI not responsive to standard therapy. In guidelines set forth by the American College of Gastroenterology, patients must fulfill the following criteria to be eligible for FMT:

- Failed to respond to at least two courses of standard-of-care antibiotic therapy for mild or moderate CDI OR
- Have severe/fulminant CDI that has failed standard-of-care antibiotic therapy.

Data from clinical trials and real-world settings has demonstrated that FMT can resolve between 80-90% of recurrent and severe/fulminant *C. difficile* infections.⁵⁻⁷ However, the success of FMT depends on accurate CDI diagnosis, as misdiagnosis could unnecessarily expose patients to the risks of FMT and associated procedures with no added benefit.

A retrospective review of patients referred to a health center for FMT demonstrated that 25% of patients were determined to have a non-CDI diagnoses, highlighting the need for rigorous patient evaluation.¹

Diagnosing *C. difficile*

Although there are several diagnostic approaches for *C. difficile*—outlined in [Appendix 1](#)—the diagnosis of CDI remains a challenge.⁸ Consensus-based guidelines from multiple groups^{2,9,10} recommend a 2-step algorithm (Figure 1) for more accurate diagnosis combining molecular screening for the *C. difficile* toxin gene and immunoassay for the detection of the toxin produced by *C. difficile*. This approach aims to distinguish between colonization and active infection to minimize the risk that a patient is colonized by *C. difficile*, but a different etiology is responsible for their diarrhea.

The diagnostic algorithm uses a 2-step approach (Figure 1)

1. First, patients should take a test with high sensitivity and negative prediction value such as **enzyme immunoassay for glutamate dehydrogenase** (GDH EIA) or a **nucleic acid amplification test** (NAAT) ([Appendix 1](#)). These tests, which detect enzymes produced by *C. difficile* or *C. difficile* genetic material respectively, test for the presence of *C. difficile*. If the test is negative, no additional testing

regarding *C. difficile* needs to be performed and the physician should consider alternative explanations for the patient's symptoms (Appendix 1).

If the test is positive, patients should undergo a second test with high specificity and positive prediction value such as **enzyme immunoassay for toxin A/B** (Toxin A/B EIA) (Appendix 1). A negative test indicates that the patient may be colonized with *C. difficile* bacteria that are not producing toxins or have not yet produced enough toxin to be detected. In this case, the patient's symptoms are likely due to an alternative etiology if the clinical index of suspicion for *C. difficile* infection is low. A positive test indicates that the patient should be treated for *C. difficile* infection.

Key Takeaway

Accurate *C. difficile* diagnosis relies on a 2-step testing algorithm—where a patient first undergoes a highly sensitive test before a highly specific test— to distinguish true infection from colonization.

Special Populations

Although data from clinical trials and real-world settings suggest that FMT has a good short-term safety profile for the general patient population, special consideration of the risks and benefits should be taken when offering FMT to special patient populations and when evaluating which modality is most suitable.

Patient-related considerations

1. **Severely immunocompromised patients (e.g. neutropenic).** Given their vulnerability to infection, FMT is not recommended for this patient population.
2. **Pregnancy.** Given limited data, FMT is not recommended for pregnant patients.
3. **Patients who will require long term antibiotics (e.g. long-term broad spectrum prophylaxis).** This is not an absolute contraindication, but antibiotic-mediated disruption of the microbiome will increase the chance of FMT failure.
4. **Inflammatory bowel disease (IBD).** Limited data suggest that FMT may be an efficacious treatment for patients with both IBD and *C. difficile*, and that FMT does not cause IBD flares at a significant rate.¹¹ However, these patients may have a complicated clinical course and may experience worsening of their IBD secondary to prolonged CDI, changes in IBD therapy, or FMT.

More information on the safety of FMT and special patient populations can be found in the White Paper titled "[Current Evidence on the Safety of Fecal Microbiota Transplantation](#)".

Procedure-related considerations

Fecal transplant material can be delivered through several modalities, each with potential benefits and drawbacks that are summarized below.⁹

Retention Enema: This modality—which does not require sedation and has little procedural risk—is often used in pediatric patients and patients with colostomies. Enema appears to have the lowest efficacy rates of all FMT modalities, but multiple treatments can lead to cure rates of about 80 percent.

Sigmoidoscopy: A less invasive lower delivery option than colonoscopy that may be especially suitable for patients who are at high risk from colonoscopy.

Colonoscopy: Colonoscopic delivery is the most common FMT modality and is supported by randomized controlled clinical trials and data gathered from real-world settings. Colonoscopy requires additional costs and technical expertise but can also be used to assess patients for IBD.

Nasoenteric tube: Nasoenteric delivery does not require sedation but carries risk of vomiting and aspiration. Patients are also more likely to perceive this route of administration as least appealing. Physicians should reduce the amount of FMT material delivered via nasoenteric tube to reduce the risk of vomiting and aspiration. (OpenBiome's upper delivery FMT formulation contains 30 mL of FMT material.)

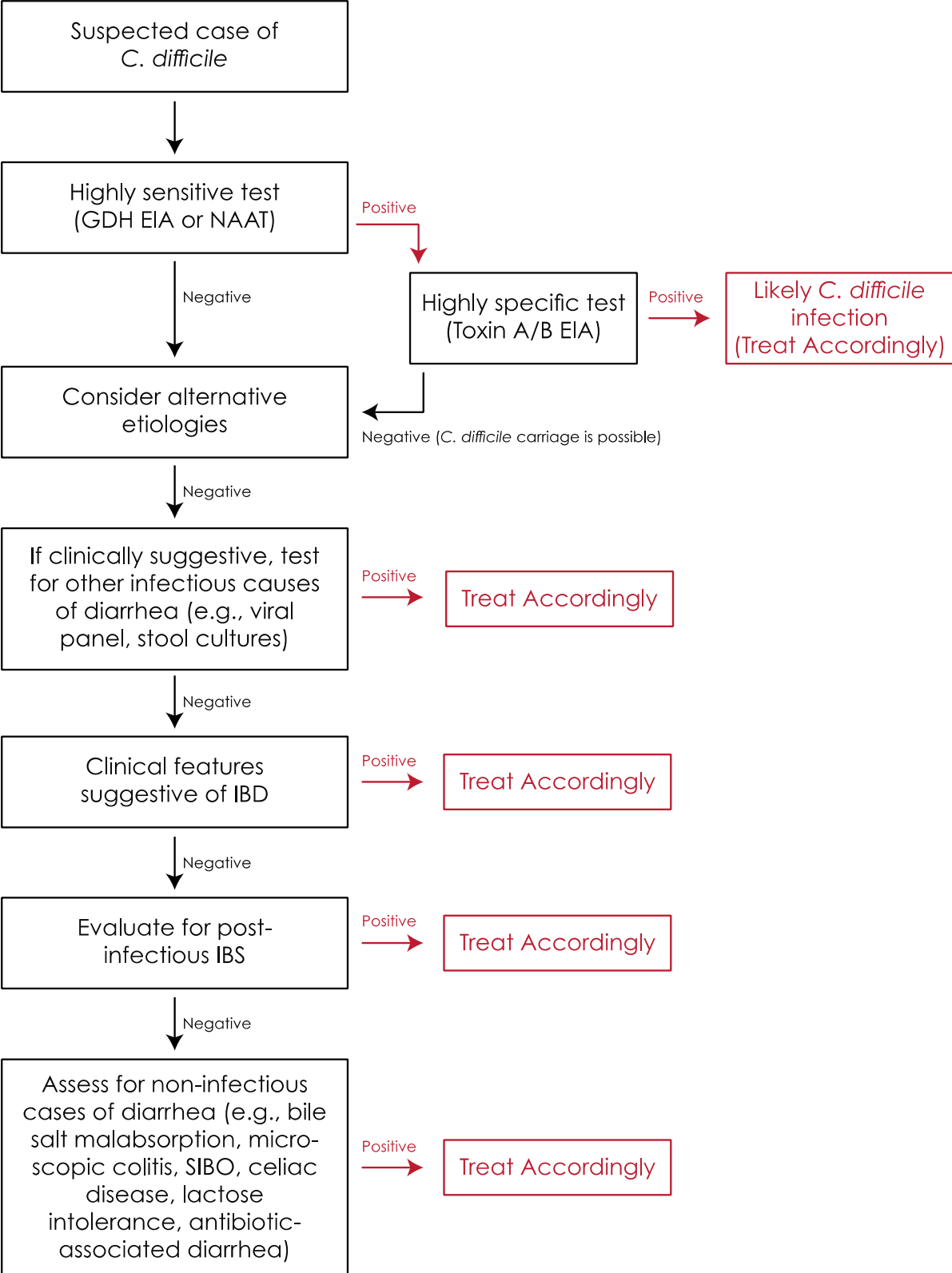
Upper Endoscopy: This route is similar to using a nasoenteric tube but requires sedation and thus carries additional procedural risks. In general, upper delivery may be appropriate in patients who have had GI surgery, have an inflamed colon, or do not have an intact colon. Upper endoscopy also allows for confirmed delivery into the small intestine (push enteroscopy) which can reduce the risk of vomiting or aspiration.

Capsules: Capsules are a newer treatment option that may be more appealing to patients than the modalities listed above. Capsules are simple to administer and increase access to FMT by lessening the need for healthcare resources and clinician procedure time. Capsules are contraindicated for patients with dysphagia or a history of aspiration, gastroparesis, and/or intestinal obstruction.

Key Takeaway

The risk-benefit assessment for FMT and its delivery modality will vary depending on the patient's unique medical history and comorbidities. Physicians should balance the risks and benefits of FMT against alternatives such as bezlotoxumab, continued antibiotic therapy, or surgery.

Figure 1: *C. difficile* testing algorithm



Appendix 1: Summary of *C. difficile* Diagnostic Tests

GDH EIA: An enzyme immunoassay (EIA) that detects glutamate dehydrogenase (GDH)—an enzyme produced by both toxigenic and nontoxigenic strains of *C. difficile*. GDH is considered a sensitive test with high negative prediction value.

Toxin A/B EIA: An enzyme immunoassay (EIA) that detects toxins A and B. Toxin A/B EIA is considered a specific test with high positive prediction value.

*Note: Several testing kits have the ability to perform both GDH EIA and Toxin A/B EIA

NAAT: Nucleic acid amplification tests that detect the presence of Toxin A/B genes. NAAT is considered a sensitive test with high negative prediction value.

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