

# Fecal Transplantation for the Treatment of Recurrent *Clostridium Difficile* Infection

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## Abstract

*Clostridium difficile* infection (CDI) is currently a leading cause of antibiotic and health care-related diarrhea. The incidence and the severity of CDI-related diarrhea have increased dramatically in the USA and Europe in the past few decades. The emergence of multidrug-resistant hypervirulent strains of *C. difficile* has led to an increase in mortality. Fecal microbiota transplantation (FMT) (also known as fecal bacteriotherapy) has been utilized sporadically since the 1950s; and currently, the interest in using FMT has grown again in the past few years for the treatment of CDI and other chronic gastrointestinal diseases. FMT has shown to be effective, cheap, and has very few side effects. It is believed to manipulate and restore the gut microbiota, and therefore enhances the growth of “healthy” bacteria that break the cycle of recurrent CDI. This article focus on the recent case reports on FMT, and general approach to patients undergoing this therapy. Data were obtained through a literature search via PubMed and Google.

**Keywords:** *Clostridium difficile* infection, Fecal transplantation, Stool transplantation

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## Introduction

*Clostridium difficile* infection (CDI) is the leading cause of antibiotic and nosocomial-related diarrhea.<sup>[1]</sup> CDI cost more than \$3.2 billion in the US between 2000-2002,<sup>[2]</sup> and this number continues to rise. This rise is accompanied by increase rates of colectomy (1.2 per 1000 in 1993 to 3.4 per 1000 in 2003) and mortality (case fatality 7.84% in 1993 to 9.26% in 2003).<sup>[3]</sup> CDI has also become more severe, more refractory to standard therapy, and more likely to relapse.<sup>[4,5]</sup> One main reason for this growing problem is the emergence of newer, more virulent, and antibiotic-resistant strains including (NAP/BI/027) among others.<sup>[4,6]</sup>

*C. difficile* is a gram-positive, spore-forming bacillus that accounts for approximately 15-20% of antibiotic-related

diarrhea.<sup>[7]</sup> It is shed in the feces and spread through the fecal-oral route. Ingesting the organism or its spores transmit the infection between patients. CDI is usually transmitted between patients indirectly either through contaminated hands of health care workers or via contaminated environmental surfaces.<sup>[7]</sup>

## Risk Factors

The main cause of CDI is the use of antibiotics; fluoroquinolones are more associated with CDI than other antibiotics including clindamycin and *b*-lactams.<sup>[8-10]</sup> The risk increases with duration and dose of antibiotics.<sup>[11]</sup> Additional risk factors include advanced age (older than 65 years), longer hospital stay, increased numbers of morbidities, taking immunosuppressive medications or chemotherapy, recent gastrointestinal (GI) surgery, inflammatory bowel disease, and history of CDI in the past. Recently, proton pump inhibitors are also believed to increase the risk of CDI, possibly by gastric acid suppression.<sup>[12-17]</sup>

## Clinical Presentation

Most patients present with foul-smelling watery diarrhea; however, patients may present with abdominal

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pain, fever, nausea and vomiting, decreased appetite and elevated white count.<sup>[18]</sup> In some cases, toxic megacolon can occur, and up to 20% of cases, patients may present with ileus and abdominal distention.<sup>[19]</sup> In severe or fulminant CDI, patients may exhibit signs of systemic inflammatory response including leukocytosis, hypotension, increase serum lactic acid level, acute renal failure, and respiratory failure.<sup>[20-22]</sup>

## Standard Treatment

Removal of the offending antibiotic should be the first step in treating CDI, current guidelines from the Infectious Disease Society of America focus on vancomycin- and metronidazole-based regimens.<sup>[1]</sup> Recommendations include metronidazole 500 mg orally three times a day for 10-14 days for initial episode of mild to moderate CDI. vancomycin 125 mg orally four times a day for 10-14 days for initial severe episode of CDI, and vancomycin 500 mg oral (and per rectum, if ileus is present) with or without intravenous metronidazole for severe, complicated infection.

First recurrence episode is treated similarly; second recurrence is usually treated with tapered or pulsed vancomycin regimen.<sup>[1]</sup> Antimotility agents including narcotics and loperamide should be avoided as they increase the risk of toxic megacolon.<sup>[8]</sup> Recently, the FDA has approved the use of fidaxomicin for CDI, which has had a lower recurrence rate compared to vancomycin in two studies.<sup>[23]</sup>

The success of other alternatives to standard treatment including probiotics; toxin-binding agents, and vaccine remains unclear. The use of probiotics is conflicting,<sup>[24-26]</sup> *Saccharomyces boulardii* has been found to decrease the recurrence rate of CDI by 30-33% when is used with antibiotics.<sup>[26]</sup> Toxin-binding agents such as tolevamer was also found to reduce the recurrence of CDI by 20-24% compared to standard antibiotics, however, it was not as effective as metronidazole or vancomycin in treating the primary episode of CDI (46% vs. 76-81%, respectively).<sup>[27,28]</sup>

## Fecal Microbiota Transplantation

The major problem in treating CDI is the high recurrence rate; the emergence of new resistant strains has also complicated matters more.<sup>[18,29,30]</sup> Recurrent CDI has been estimated to be 15-30% after the initial episode and reaches 65% after subsequent ones.<sup>[31]</sup> Recurrent CDI is typically treated with tapered vancomycin dose with 31% recurrence rate or pulsed regimen of metronidazole and vancomycin with a recurrence rate of 14%.<sup>[32,33]</sup> Given this poor success rate, investigations for alternative therapies continued over several decades.<sup>[32,34-37]</sup>

The human gut contains  $10^{12}$  microorganisms per gram of stool, which are referred to as gut microbiota. These microbiota play a role in digestion, immune function, energy production, and metabolism.<sup>[38]</sup> The microbiome varies between individuals.<sup>[38]</sup> Diet, environment, and genetics influence the gut microbiome. Diets high in protein and animal fats favor *Bacteroides* and *Ruminococcus* predominant bacteria, while those high in carbohydrates favor *Prevotella* predominant ones.<sup>[39,40]</sup> The microbiotas of twin siblings are more similar than those of a mother-child pairs, and those are more similar than a stranger pairs. The microbiota starts to grow after birth from the mother's skin, fecal and vaginal flora, and it's hugely affected by mode of delivery and method of feeding.<sup>[41,42]</sup> The microbiota changes with age showing higher ratio of *Bacteroidetes* phyla in infancy and old age, and a smaller ratio in adulthood.<sup>[43]</sup> Antibiotics, dietary change, and suppression of immunity can compromise the microbiota and predispose host to CDI.<sup>[38]</sup>

Chang *et al.*,<sup>[44]</sup> analyzed the fecal microbiota of seven patients with CDI using 16S rDNA sequencing, they found marked reduction of *Bacteroidetes* phyla and an increased numbers of *Proteobacteria* and *Verrucomicrobia* phyla, both are usually minor in noninfected individuals. A 1989 report by Tvede and Rask-Madsen<sup>[45]</sup> noted an absence of *Bacteroides* species in patients with recurrent CDI, those deficiencies were reversed after fecal microbiota transplantation (FMT).

The concept of FMT was first reported in 1958 by Eiseman *et al.*,<sup>[46]</sup> for the treatment of pseudomembranous colitis. Over the following decades, there have been scattered case reports and case series of FMT for CDI as well as other chronic GI diseases. In the past few years, the interest in FMT evolved because of its potential to restore the gut microbiota. A review article in 2011 found 22 reports of FMT, they included 239 patients. Resolution of symptoms was successful in 87% (145/166) of the patients described to have fulminant or refractory CDI.<sup>[47]</sup> In 2010 and 2011, 11 studies and case reports were done in different centers; the success rate of FMT was very high approaching 92% [Table 1].<sup>[48-58]</sup>

Recently, an open-label, randomized-controlled study was published by van Nood *et al.*,<sup>[59]</sup> in January 2013, it randomized patients with recurrent CDI to receive either vancomycin 500 mg orally four times a day for 4 days followed by bowel lavage and FMT through nasoduodenal tube, a standard vancomycin treatment for 14 days, or a standard vancomycin treatment with bowel lavage at days 4-5. A total of 81% (13/16) of the FMT group had resolution of CDI and 94% (15/16) after a different donor was used for the remaining three patients. A total of 31% of patients receiving vancomycin

**Table 1: List of reported studies in 2010-2011 and their success rate**

Study/year	Number of patients	*Success rate %
Arkkila <i>et al.</i> , 2010 <sup>[48]</sup>	37	34/37 92
Khoruts <i>et al.</i> , 2010 <sup>[49]</sup>	1	1/1 100
Yoon <i>et al.</i> , 2010 <sup>[50]</sup>	12	12/12 100
Rohlke <i>et al.</i> , 2010 <sup>[51]</sup>	19	18/19 95
Silverman <i>et al.</i> , 2010 <sup>[52]</sup>	7	7/7 100
Garborg <i>et al.</i> , 2010 <sup>[53]</sup>	40	33/40 83
Russell <i>et al.</i> , 2010 <sup>[54]</sup>	1	1/1 100
Kelly <i>et al.</i> , 2010 <sup>[55]</sup>	12	12/12 100
Mellow <i>et al.</i> , 2010 <sup>[56]</sup>	13	12/13 92
Kassam <i>et al.</i> , 2010 <sup>[57]</sup>	14	14/14 100
Kelly <i>et al.</i> , 2011 <sup>[58]</sup>	26	24/26 92

\*Eradication by negative culture or toxin assay and/or clinical response

alone and 23% receiving vancomycin and bowel lavage had resolution of their infection.

The exact mechanisms of FMT in the treatment of CDI are unclear but may involve restoring the gut microbiota with the missing components, to generate an environment resistant to CDI.<sup>[60]</sup> Unlike antibiotics that offer transient antibacterial activity and add to the insult on the stool microbiota, FMT seems to offer prolonged presence of antagonistic activity against CDI.

### Patient Indication

FMT is indicated for patients with recurrent or relapsing patients CDI; who had three or more episodes of mild to moderate CDI or who failed 6-8 weeks of tapered vancomycin treatment. It is also indicated in patients who had two or more severe episodes of CDI that required hospitalization. Last FMT is indicated in patients with a moderate or a severe episode of CDI, which did not respond to standard antibiotic treatment at 1 week and 48 h, respectively.<sup>[61]</sup>

### Donor Selection

Typical donors are household members or a relative as there is some theoretical belief that they share close microbiota due to common environmental exposures or genetics. No screening guidelines are present at this time, but most donors undergo testing for hepatitis A, B, and C, HIV, syphilis, stool for ova and parasite, CD, *Helicobacter pylori*, stool culture for enteric pathogens, and stool acid-fast stain for *Cyclospora*, *Isospora*, and *Cryptosporidium*. Donors should not have taken antibiotics in the preceding 3 months, and should not have any chronic GI disease or malignancy.<sup>[61]</sup> Donors are also excluded if they have any autoimmune diseases, allergic diseases, or metabolic syndrome.<sup>[61]</sup>

## Recipient Preparation and Administration

Various routes of instillation have been described for transplantation of donor's stool. Nasogastric, nasoduodenal, colonoscopic, and retention enema are the most common ones. Samples should be used immediately within 6 h. The volume of the sample varies depending on the route of administration, lower volume with nasogastric route (25-50 mL), where larger volume is used with colonoscopy or enema (250-500 mL). Antidiarrheal agents should be considered after the colonoscopic route, proton pump inhibitors should be used the night before for the nasogastric route.<sup>[61]</sup>

Many questions are left to answer, whether one route of administration is better than the other, the possible need of antibiotics before the procedure and duration of antibiotic use remain uncertain. The possibility of applying FMT in other chronic GI and non-GI illnesses is an area of investigation. Although the majority of studies focused on recurrent CDI, Brandt *et al.*,<sup>[62]</sup> advocated the use of FMT as a primary treatment for CDI, as it is safe, superior, and less costly than antibiotic use.

## Conclusion

CDI and its complications are on the rise; it is the leading cause of antibiotic and health care-related diarrhea. Traditional antibiotic treatments are becoming less effective with the emergence of new and more virulent strains. CDI recurrence is high even after successful initial response to antibiotics. Probiotics and other new medications such as toxin-binding agents have been tried with unsatisfactory results. FMT has been gaining acceptance recently, as several case reports have shown encouraging results with eradication of CDI, reduction in the recurrence rate, low cost, and very few side effects. A recent open-label randomized-controlled study supported the use of FMT in treatment of refractory and recurrent CDI.<sup>[59]</sup>

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