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**Fecal Transplant vs Vancomycin for Recurrent Clostridium difficile**  
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# Fecal Transplant vs Vancomycin for Recurrent Clostridium Difficile

Capstone Project

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## Abstract

**Objective:** To compare fecal transplant and vancomycin in the treatment of recurrent clostridium difficile to determine which has the higher cure rate. **Design:** Systematic literature review. **Methods:** Pubmed, Google Scholar, and TRIP database using the search terms “recurrent clostridium difficile.” Filters were implemented in the Pubmed database including: randomized control trials, English, and published in the past 5 years. Records were screened for RCT with fecal transplant and full-text. **Results:** van Nood et al. revealed an initial cure rate of 81% for the infusion group, and a re-treated cure rate of 94%, compared to the vancomycin alone group of 31% cure rate and the vancomycin plus bowel lavage group of 23% cure rate. Cammarota et al. determined an initial cure rate of 65% for the infusion group, and a re-treated cure rate of 90%, compared to the vancomycin only group of 26% cure rate. **Conclusion:** An initial abbreviated dose of vancomycin at the start of fecal transplant has a significantly higher cure rate in treating recurrent clostridium difficile infections when compared to standard vancomycin therapy.

## Introduction

Clostridium difficile (*C. difficile*), a gram-positive, anaerobic bacillus bacterium, is spread via the fecal-oral route, and is known for its colonization of the gastrointestinal tract, commonly after a regimen of antibiotic therapy has been used, altering the normal gut flora of the patient.<sup>1,2,3</sup> In the United States, *C. difficile* infection is the most common healthcare associated infection, and is increasing in both frequency and severity of infection.<sup>3,2</sup> High-risk populations include 65 years or older, less than 1 year old with underlying condition, male gender, increased hospitalization time, and recent antimicrobial therapy.<sup>3</sup> Known antibiotics associated with the development of *C. difficile* include fluoroquinolones, clindamycin, penicillins, and cephalosporins.<sup>4</sup> According to Barbut et al, *C. difficile* infections may cost up to \$3.2 billion per year, along with causing an estimated 15,000 – 20,000 deaths annually in the United States alone.<sup>5</sup>

There are seven stages of *C. diff* infection, including: Carrier stage, *C. difficile*-associated diarrhea, *C. difficile*-associated Colitis, Pseudomembranous Colitis, Fulminant Colitis, Recurrent Clostridium difficile infection (CDI), and Extracolonic Infections.<sup>3</sup> The studies included in this systematic literature review are looking at recurrent Clostridium difficile primarily, which involves the complete resolution of symptoms associated with the initial occurrence of *C. difficile* after therapy, followed by a relapse of symptoms and *C. difficile* infection.<sup>4</sup> In approximately 10 – 25% of patients who have completed *C. difficile* therapy, recurrence will occur.<sup>4</sup> Symptoms associated with recurrent *C. difficile* include the cardinal symptom of watery diarrhea with at least 3 stools within 24 hours, abdominal pain, low-grade fever, nausea, and anorexia.<sup>4</sup> Diagnosis of CDI infection is primarily clinical, with a history including recent antimicrobial use and diarrhea.<sup>3</sup> Laboratory tests are performed on unformed stool samples.<sup>3</sup>The best sample for diagnosis consists of watery or loose stool, as fresh as

possible. Culture may be performed, but is not routinely done due to the cost and clinician experience needed. If culture is performed, it is recommended to do so with the assistance of infectious disease specialist and/or gastroenterology specialists. There is a variety of toxin assays that may be used for the detection of *Clostridium difficile*, including cell culture neutralization assay, which is highly sensitive and specific, but time-consuming and labor-intensive. Immunoassay detects both toxins A and B, utilizing methods such as enzyme immunoassay and immunochromatography. Nucleic Acid Amplification, with sensitivity of 90-100% and specificity of 94-100%, are the most recent methods, able to identify genes of *Clostridium difficile*. Latex agglutination assay detects glutamate dehydrogenase, but is not used routinely. If there are normal stool laboratory test results with high suspicion, then sigmoidoscopy and colonoscopy may be used for diagnosis.<sup>3</sup>

Initial treatment for a patient with *C. difficile* begins with the cessation of any current antibiotics that the patient may be taking, if possible.<sup>1</sup> After stopping the offending medication, current treatment options for recurrent *Clostridium difficile* include primarily a course of vancomycin or fidaxomicin; however, fecal transplant is now becoming a viable option. Standard vancomycin for the treatment of *Clostridium difficile* is 500 mg PO QID.<sup>3</sup> According to Goudarzi et al., approximately 25% of patients with *C. difficile* who have been treated with either metronidazole or vancomycin experience recurrent symptoms, within 4 weeks of completing therapy.<sup>3</sup>

The basis of fecal microbiota transplant involves the restoration and re-colonization of healthy, normal gut flora in the affected gastrointestinal tract due to *C. difficile* invasion or irritable bowel disease, along with other various causes of altered gut flora. Fecal transplant implements a donor that undergoes extensive screening and testing. The donors are screened via a questionnaire on such things as medical history, lifestyle habits, antibiotic use in the past 6 months, intestinal diseases and/or symptoms. The donor stool is screened for *C. difficile* enteric bacteria, protozoa, helminthes, as well as drug resistant bacteria. The donor's blood is also tested for hepatitis A, B and C, HIV-1 and HIV-2 antibodies, Epstein-Barr virus, *Treponema pallidum*, *Strongyloides stercoralis* and *Entamoeba histolytica*. First the feces is collected from the donors on the day of infusion and then diluted with 500 mL of sterile saline (0.9%) and blended. Finally the supernatant was strained and stored in a sterile container until infusion. The feces can be given to the patient via nasogastric tube, colonoscopy, enema, and via capsulated pill. Of these routes, for patients with recurrent *C. difficile*, colonoscopic fecal microbial transplant is superior to nasogastric fecal transplant in regards to the cure rate of this infection.<sup>6</sup> Diarrhea, constipation, abdominal cramping, gurgling, and gas are the adverse effects that have been present after a fecal microbial transplant, although considered brief and minor occurrences.<sup>6</sup>

Infection control is an important aspect throughout the treatment of a CDI infection. One of the most important aspects of CDI prevention is hand washing with both soap and water, which is more effective compared to an alcohol based solution.<sup>3,1</sup> Appropriate contact precaution including wearing gloves and gowns when working with these patients is important to reduce the spread as well.

## Clinical Question:

In patients over 18 years old who have developed recurrent *Clostridium difficile*, is fecal transplantation compared to vancomycin more efficacious in the treatment of recurrent *Clostridium difficile* infection?

## Methods

In October of 2015 the PubMed database was searched using the terms recurrent *clostridium difficile*, which yielded 669 results initially. Searches of Google Scholar and TRIP databases produced no additional articles. These results were then limited to English only and randomized control trials within the past 5 years. This reduced the number of results to 10. Next these trials were reviewed and only those that involved fecal microbiota transplant were chosen. There were a total of three trials that met these criteria. Of the three trials only two looked at fecal microbiota transplant v.s. vancomycin. The third trial was a pilot RCT assessing administration routes for fecal microbiota transplant and was eliminated. The two articles meeting these criteria were *Duodenal Infusion of Donor Feces for Recurrent Clostridium difficile*. Van Nood et al and *Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent Clostridium difficile infection*. Cammarota et al. Figure 1 provides a visual PRISMA flow diagram of this process.

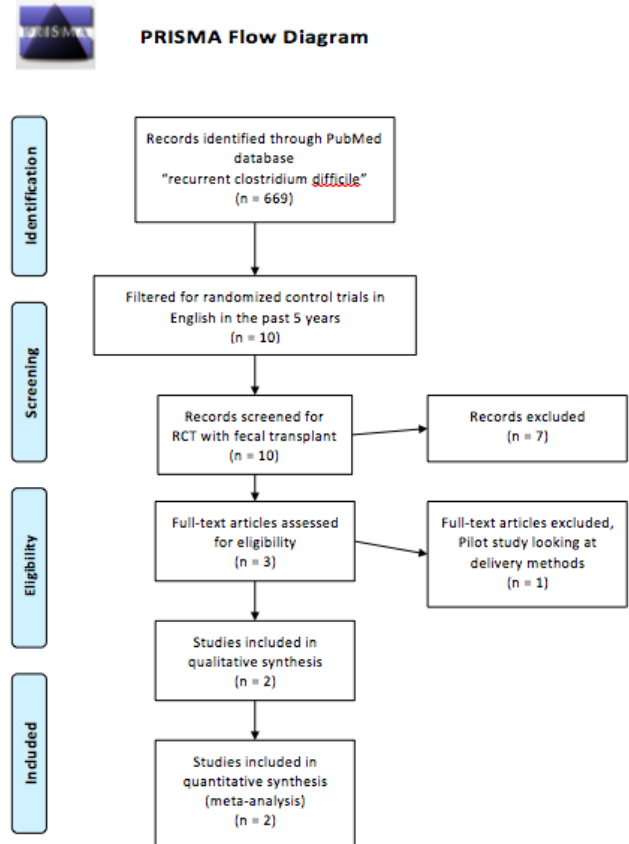


Figure 1. PRISMA Flow Diagram.

## Results

### Study #1

*Duodenal Infusion of Donor Feces for Recurrent Clostridium difficile*. Els van Nood et al.<sup>7</sup>

### Study Objective

To determine if fecal transplant with vancomycin for the treatment options for recurrent *Clostridium difficile* is more effective compared to vancomycin alone or vancomycin with bowel lavage.

### Study Design

In this open label, randomized controlled trial, 43 patients were divided into three treatment groups: initial abbreviated vancomycin regimen with bowel lavage and donor feces, standard vancomycin regimen with bowel lavage, and standard vancomycin regimen. The Table 1 demonstrates the study population via inclusion and exclusion criteria. The feces donor criteria are outlined in Table 2 that was given to the fecal transplant group via nasoduodenal tube. If the fecal transplant group required a second treatment, the second infusion was performed using a different donor.

<b>Table 1. Patient Inclusion and Exclusion Criteria</b>	
<b>Inclusion Criteria</b>	<b>Exclusion Criteria</b>
≥ 18 years old Life expectancy ≥ 3 months Relapse of <i>C. difficile</i> infection after at least one course of adequate antibiotic therapy	Prolonged immunodeficiency due to recent chemotherapy HIV infection with a CD4 count < 240 Prolonged use of prednisolone at a dose of ≥ 60 mg/day Pregnancy Use of antibiotics other than for treatment of <i>C. difficile</i> infection at baseline Admission to an intensive care unit Need for vasopressor medication

<b>Table 2. Feces Donor Inclusion and Exclusion Criteria</b>	
<b>Inclusion Criteria</b>	<b>Exclusion Criteria</b>
<60 years of age	History of parasites, <i>C. difficile</i> , and enteropathogenic bacteria, HIV, Human T-cell lymphotropic virus types 1 and 2, Hepatitis A, B, and C, Cytomegalovirus, Epstein-Barr virus Recent illness

### Study Results

The infusion group initially had an 81% (13/16 patients) cure rate, that increased to 94% (15/16 patients) after 3 more participants were re-treated with an additional infusion from a different donor. The vancomycin alone group had a 31% (4/13 patients) cure rate. The vancomycin plus bowel prep group had a 23% (3/13 patients) cure rate. Adverse events reported immediately after infusion were 94% of patients reported diarrhea, 31% cramping, and 19% belching. All of the effects were self-limiting and resolved within 3 hours of presentation. During the follow up visit 19% of patients reported constipation. No adverse events were reported in the other two groups. This

study was terminated early by the monitoring board due to a high number of relapse in both of the vancomycin groups.

Number Needed to Treat (NNT): 1.58. We chose the use the vancomycin alone group as the control to determine the number needed to treat compared to the infusion group. The NNT may be interpreted as 1.58 patients must be treated over a period of 1 year to prevent one recurrence of CDI.

### *Study Critique*

There was no comparison between the standard vancomycin regimen with bowel lavage to the standard vancomycin regimen groups. Both groups were compared to the initial vancomycin regimen with bowel lavage and donor feces, but not to each other. The small population size is also a disadvantage of this study resulting in a possible type II error or failing to show statistical significance when there is actually a difference between the two study groups. This study also terminated early due to high recurrence rates of the vancomycin group. For patients that were in the vancomycin groups, if their therapy failed, they were able to choose to have the donor feces given off protocol, which adds confounding variables to this study.

### **Study #2**

*Randomized clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent Clostridium difficile infection. Cammarota et al<sup>8</sup>*

#### *Study Objective*

To investigate if fecal transplantation is more effective at treating recurrent Clostridium difficile compared to vancomycin standard therapy.

#### *Study Design*

Open label, blocked randomized clinical trial comparing faecal microbiota transplantation with vancomycin treatment to vancomycin only treatment. Blocked randomized clinical trial refers to the addition of an external person, which is not involved in the study, and a random number generator software that uses random subgroup "block" sizes of 6 in addition to a ratio, which reduces variability within groups and reduces likelihood of confounding<sup>8</sup>. All patients who met the inclusion and exclusion criteria as outlined in Table 3, began the study with a three-day abbreviated treatment of vancomycin (125 mg by mouth four times a day). At day 2 and 3, the fecal transplant group also had a bowel lavage. At day four, they then either continued with the vancomycin regimen, or stopped the vancomycin and began the first faecal infusion from a fecal donor that met the inclusion and exclusion criteria as outlined in Table 4. The vancomycin only treatment group continued with the 125 mg until day 11, when they switched to vancomycin pulse regimen (125-500 mg/day every 2-3 days). Patients that were diagnosed with pseudomembranous colitis were given a fecal infusion every 3 days, and patients in the fecal transplant group who relapsed after the first fecal transplant, were given a second fecal transplant by a different donor within 1 week.

<b>Table 3. Patient Inclusion and Exclusion Criteria</b>	
<b>Inclusion Criteria</b>	<b>Exclusion Criteria</b>
≥18 years of age Life expectancy ≥ 3 months Recurrence of <i>C. difficile</i> after one or more courses of specific antibiotic therapy Believed able to undergo colonoscopy	Prolonged immunodeficiency due to recent chemotherapy HIV infection Prolonged use of steroids Pregnancy Use of antibiotics other than metronidazole, vancomycin or fidaxomicin at baseline Admission to an intensive care unit Requirement for vasoactive drugs Other infectious causes of diarrhea

<b>Table 4. Feces Donor Inclusion and Exclusion Criteria</b>	
<b>Inclusion Criteria</b>	<b>Exclusion Criteria</b>
Healthy volunteers < 50 years of age, preferable the patient's relatives or intimates	Antibiotics taken within the last 6 months Exhibited significant intestinal symptoms of other intestinal diseases Lifestyle associated with increased risk for contracting infections Recent (≤3 month) travels in tropical areas New sexual relationship in the last 6 months Recent needlestick accident Previous reception of blood products Body tattoos Gastrointestinal diseases or complaints Family history of gastrointestinal cancer or inflammatory bowel disease Systemic diseases such as diabetes or neurological disorder Use of drugs that could be excreted in feces with potential risk for the recipients



## Study Results

<b>Table 5. Overview of Studies</b>					
	<b>van Nood et al.</b>			<b>Cammarota et al.</b>	
<b>Population</b>	Referring hospitals in collaboration with the Academic Medical Center in Amsterdam			The A. Gemelli University Hospital in Rome.	
<b>Primary Interest</b>	To compare fecal transplant with an abbreviated vancomycin treatment to vancomycin standard therapy and vancomycin with bowel lavage in the treatment of recurrent <i>Clostridium difficile</i>			To compare fecal transplant with an abbreviated vancomycin treatment to vancomycin standard treatment in the treatment of recurrent <i>Clostridium difficile</i>	
	Fecal Transplant	Vancomycin Only	Vancomycin + Bowel Lavage	Fecal Transplant	Vancomycin Only
<b>Patients, N</b>	16	13	13	20	19
<b>Gender</b>	50% F, 50% M	54% F, 46% M	23% F, 77% M	60% F, 40% M	58% F, 42% M
<b>Average Age</b>	73 +/- 13	66 +/- 14	69 +/- 16	71	75
<b>Randomized</b>	Yes			Yes	
<b>Analysis</b>	Intention to treat			Intention to treat	
<b>Definition of Cure</b>	10 weeks of no diarrhea			10 weeks of no diarrhea	

<b>Blinding</b>	Preceptors and participants were not blinded, but the assessors of “cured” were blinded.	No
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The infusion group initially had a 65% (13/20 patients) cure rate that increased to 90% (18/20 patients) after multiple infusions. Two of the patients in this group died before the end of the study due to C. diff complications. The vancomycin only treatment was 26% effective with 5 of the 19 cured after treatment. Two of the patients in this group died before the end of the study due to C. diff complications as well. Overall intention to treat analysis of the transplant group compared to the vancomycin group demonstrated that the infusion group was superior and statistically significant with  $p < 0.0001$  (90% vs. 26%). After one year an interim analysis was done revealing a significantly higher efficacy than vancomycin and the study was stopped with a total of only 39 enrolled patients. Immediately after infusion 94% experienced diarrhea and 60% bloating/cramping, all symptoms resolved within 12 hrs. There were no adverse events reported in the vancomycin group.

Number Needed to Treat (NNT): 1.57. We used the vancomycin only treatment group and the faecal microbiota transplantation with vancomycin treatment group to determine the NNT. The NNT may be interpreted as 1.57 patients must be treated over a period of 1 year to prevent recurrence of CDI.

### *Study Critique*

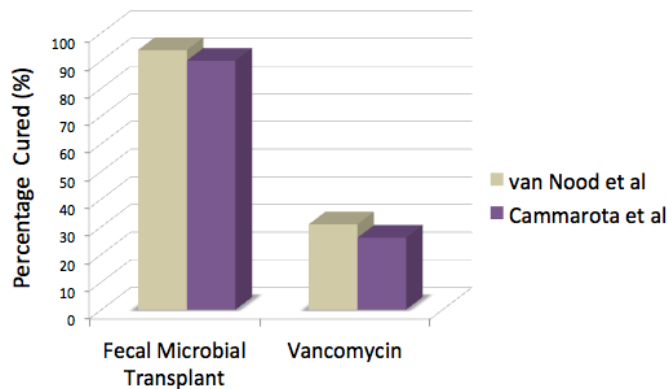
Patients involved in infusion group were able to repeat the fecal transplant as many times as needed to improve the cure rate. For the patients with pseudomembranous colitis, the fecal transplant frequency increased to an infusion every 3 days until cured, although the study does not address the maximum time or number of infusions that were done before the patients were cured. The cost and risk of complications for the treatment groups was not discussed either. The vancomycin group may or may not have had patients with pseudomembranous colitis, since this was not determined via colonoscopy as it was for the fecal transplant group. The small population size is a disadvantage of this study. The early termination of the study caused the study to fall short of the projected power goal of 90% with 41 patients per group.

### **Discussion**

The mainstay of treatment for C.difficile infection since the 1970's has been metronidazole and oral vancomycin with the addition of fidaxomicin in 2011.<sup>9</sup> Phase three clinical trials showed a risk of recurrent infection around 25% with vancomycin.<sup>10</sup> Given the relatively high mortality, morbidity, and recurrence rates of this infection the investigation of other viable treatment options is warranted.

An overview of these two studies may provide some insight into the efficacy of this unusual treatment. Both the Els van Nood et al and the Cammarota et al studies were

open-label randomized trials, although the Cammarota et al study did not assign a control group. The recipient group inclusion/exclusion criteria for the two studies were



nearly identical, although the donor criteria differed heavily (Tables 1 and 3). The inclusion/exclusion criteria for the donors were very different and are outlined in tables 2 and 4. The treatment protocols were very similar but varied slightly between studies. For obvious reasons, neither study could blind the patients or the treating clinicians although van Nood et al did use a masked committee to determine which patients were

cured. Cammarota et al study used a lower 125mg dose of vancomycin compared to the 500mg dose used by Els van Nood et al study. Both studies started the infusion groups off with an abbreviated 3-5 day course of vancomycin. The delivery methods differed between the studies, Els van Nood et al used nasoduodenal infusion where Cammarota used colonoscopy. Both studies used 10 weeks as the primary end point for cure of infection without relapse. The two studies did their statistical analyses on an intention to treat basis, Cammarota et al did elect to also analyze their data on a per protocol model as well. According to both of these studies, the difference between the fecal transplant with the vancomycin and the vancomycin only is statistically significant with  $P < 0.001$  and  $P < 0.0001$  for Els van Nood et al and Cammarota et al respectively. We independently calculated the number needed to treat values for both studies to be 1.58 for Els van Nood et al and 1.57 for Cammaroda et al. The two studies we reviewed were very similar with regard to statistical power, design, cure rates, and number needed to treat. They did differ in delivery methods, dosing, and in regard to donor selection. Figure 2 provides a visual comparison between the percentage of patients in these two studies who were “cured” for both the fecal transplant with abbreviated vancomycin treatment and the standard vancomycin only treatment.

Figure 2. Percentage cured at the end of treatment, comparing the vancomycin group to the fecal transplant group between the two research papers.

## Conclusion

The differences between these studies may have impacted the data - such as the delivery route of nasoduodenal tube versus colonoscopy. Currently there are some

randomized controlled trials investigating the most efficient route for administration and as soon as the best route is identified future studies may be able to utilize similar routes and reduce the error that this may produce in determining efficacy of fecal transplant. The screening of the donors also differed in the criteria that were used to determine the eligibility of the donor. A standard protocol for donor selection would help reduce bias as well as help to protect against the transmission of pathogens. These two studies combined included a total of 68 participants for both the infusion and vancomycin groups. Overall these two studies suggest strongly that fecal microbiota transplant is superior to vancomycin at treating recurrent *C. difficile* infection. Given the limited sample size of these two studies and the potential for the transmission of pathogens from donor to recipients we feel that more larger scale RCT are warranted before this very promising treatment option is accepted as a safe effective alternative to the current standard of antibiotic therapy.

Potential harms of fecal transplant include the inherent risks from the different delivery methods such as trauma from the insertion of the nasogastric tube or the endoscope for the colonoscopy. There is the possibility of transmission of infectious diseases but there has yet to be any documented cases of this so far.

The risk associated with oral vancomycin include nephrotoxicity, hypokalemia, fever, rash (Stevens-Johnson syndrome), ototoxicity, anaphylaxis, and superinfection.

Both of these studies compare standard vancomycin treatment to an abbreviated vancomycin in addition to fecal transplant. It will be interesting to see a study that compares an abbreviated course of vancomycin in addition to fecal transplant to a stand-alone fecal transplant therapy to further differentiate between the efficacy of the two treatments. Another area of interest for future studies includes using intensive care unit patients that were excluded from these two studies, to help determine the effectiveness of vancomycin versus fecal transplant, since these patients may be more at risk to develop *C. difficile* compared to the general population.

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Great job!

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