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Fecal transplant is superior to oral vancomycin for treatment of recurrent *Clostridium difficile*

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ABSTRACT A critical appraisal and clinical application of Van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, et al. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N Engl J Med*. 2013;368(5):407-415. doi: [10.1056/NEJMoa1205037](https://doi.org/10.1056/NEJMoa1205037).

Keywords: *Clostridium difficile*, fecal transplant, recurrent infection

Clinical Context

An 80-year-old Caucasian female with a past medical history of hypertension, type II diabetes mellitus, and recurrent *Clostridium difficile* (*C. diff*) presented to a large urban hospital with left lower quadrant abdominal pain and multiple episodes of watery, non-bloody diarrhea for the past four days. Four months prior to admission, the patient was treated with a 7-day course of clindamycin for a foot infection. One week after finishing antibiotics she developed multiple episodes of watery diarrhea and had a stool test positive for *C. diff* toxin. A 14-day course of oral vancomycin was prescribed but her insurance did not cover this medication and she was given 14 days of 500 mg metronidazole three times a day, which she completed. The patient returned to the emergency room three days after completing treatment with watery diarrhea and incontinence and had stool studies positive for *C. diff* toxin. She was hospitalized for three days and discharged on 14 days of oral vancomycin 125 mg four times a day. The patient had a resolution of her symptoms for six weeks before returning to the emergency room with watery stools and a stool test positive for *C. diff* toxin. She was discharged on 10 days of oral vancomycin 125 mg every six hours and had formed stool for four weeks before returning to the hospital with her fourth episode of stool positive for *C. diff* toxin. One dose of oral vancomycin was given in the emergency department before she was transferred to the general floor. Discussions started on whether to complete treatment with oral vancomycin alone or initiate the protocol for fecal transplant. Our patient was uncomfortable and exhausted upon admission and wanted a treatment that would provide long term relief and decrease her frustration. She lives with her daughter and receives home healthcare but her frequent bathroom trips and incontinence were causing tension and impacting her quality of life. When we told her that a fecal transplant may be a good option for her, she was relieved. However, she remained hesitant, as she was concerned about the smell and color of the fecal transplant and ultimately embarrassed to discuss this treatment modality with her family. After extensive conversation, our patient decided she was open to trying fecal transplant because of the potential to sustainably improve her quality of life.

Clinical Question

Is fecal transplant superior to oral (PO) vancomycin for treatment of recurrent *C. diff*?

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Research Article

Van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, et al. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N Engl J Med.* 2013;368(5):407-415. doi: [10.1056/NEJMoa1205037](https://doi.org/10.1056/NEJMoa1205037)

Related Literature

Treatment of *C. diff* was reviewed on UpToDate as a starting point for current guidelines. A literature search using PubMed with the keywords “*Clostridium difficile*” and “recurrence” and “fecal transplant” or “fecal bacteriotherapy” or “fecal biotherapy” or “donor feces” was then used. The search was further confined to clinical trials and generated 316 relevant articles with abstracts and titles being reviewed. My intention was to find a randomized controlled trial (RCT) looking at the cure rate of recurrent *C. diff* with fecal transplant compared to standard therapy. The majority of recent articles had a small patient population, or were based on chart review rather than a clinical trial, and were therefore not considered.

The aforementioned search yielded various studies exploring the efficacy of various fecal delivery methodologies such as nasogastric tube, enema, colonoscopy and pills.¹ These articles discuss the benefits of fecal transplant but do not compare treatment to PO vancomycin and were therefore not selected. Literature review also showed the efficacy of fecal transplant for multiple diarrhea related illnesses such as ulcerative colitis and Crohn’s disease.²⁻⁴ These articles were not reviewed because they are not specific to the illness my patient has.

A meta-analysis by Drekonja D, et al. assessed the efficacy of fecal transplant for *C. diff* infection.⁵ The study used data from two RCT and 28 case-series studies. The two RCT that were identified were analyzed.^{6,7} The study by Youngster I, et al. compared two fecal transplant approaches using either nasogastric tube or colonoscopy.¹ This study contained 20 patients and had an overall cure rate of 90%. It was not chosen due to a lack of standard therapy (vancomycin or metronidazole) to compare treatment outcomes to. The second RCT was Van Nood E, et al. and compared fecal transplant with nasoduodenal tube to two control groups (vancomycin and vancomycin plus bowel lavage).⁶

A subsequent RCT by Cammarota G, et al. examined the effect of fecal transplant via colonoscopy in patients with recurrent *C. diff* compared to the standard vancomycin regimen.⁸ The results from this study showed a 90% resolution of *C. diff* with fecal transplant and a 26% resolution with vancomycin treatment. The study was terminated after one year because of the superior results seen with fecal transplant. This study references the clinical trial by Van Nood E, et al. and discusses the similar results seen in both clinical trials. Both the Van Nood and Cammarota clinical trials were non-blinded, RCT that had outcomes showing efficacy of fecal transplant over vancomycin. The recurrence of *C. diff* in the vancomycin treatment group was handled differently by each trial. The Cammarota trial did not treat the vancomycin patients that had recurrent *C. diff* with fecal transplant. The Van Nood trial offered fecal transplant to the vancomycin group with recurrent *C. diff* off-protocol and showed an 83% cure rate. Regardless of being performed off-protocol, it adds an additional analysis when deciding which treatment is superior. The trial by Van Nood has been cited approximately 1,500 times compared to less than 200 for Cammarota. Both trials contained a similar number of subjects and inclusion criteria. Since the Van Nood trial has been referenced significantly more and included data about fecal transfer in the vancomycin treated group, this article was ultimately chosen for the critical appraisal.

Critical Appraisal

The study by Van Nood, et al. was a single center, open-label, parallel group RCT. According to the Oxford Center for Evidence-based Medicine, this article would be considered a level 1b study since it is an RCT with a narrow confidence interval.⁹ Patients were randomized to three different treatment groups: 1) donor feces infusion through nasoduodenal tube preceded by 4 days of PO vancomycin and bowel lavage 2) PO vancomycin 500 mg 4 times per day for 14 days 3) PO vancomycin 500 mg 4 times per day for 14 days with bowel lavage on day 4 or 5.1 The use of three different treatment groups allowed two different controls (vancomycin and vancomycin + bowel lavage) to be used to ensure more accurate analysis and rule out the possibility that bowel lavage rather than fecal transplant leads to *C. diff* cure.

The study included 43 patients and took place at the Academic Medical Center in Amsterdam with patient enrollment between 2008-2010. The small patient population and recruitment from one medical center could possibly limit the generalizability. Inclusion

criteria included age over 18 with a life expectancy of at least three months and relapse of *C. diff* after at least one course of adequate antibiotic treatment (≥ 10 days of vancomycin ≥ 125 mg QID or metronidazole 500 TID). The definition of *C. diff* was at least three episodes of watery stool per day for two consecutive days or eight loose stools in 48 hours and a positive stool test for *C. diff* toxin. Patients excluded from the study include immunocompromised (chemo, HIV+ with CD4 <240, prolonged steroid use), pregnancy, recent antibiotic use for other indications, and ICU admission or therapy with vasopressor medication. Of the 43 patients included in the study, 41 had a history of antibiotic use prior to initial *C. diff* episode.⁶ Some of the patients at highest risk for *C. diff* were excluded from this study, which limits the ability to apply the study to this at-risk population. The patient population was mostly elderly (mean age 66-73), had an equal distribution of men and women, and a median *C. diff* recurrence of 2-3 episodes. Recurrent *C. diff* is more common in the elderly population and fecal transplant is not usually considered until at least two *C. diff* recurrences, which allows this study to be applied to the most commonly affected group. Prior antibiotic use is the most common cause of *C. diff* infection and a history of antibiotics use is present in over 95% of study participants, which reflects the population usually seen in daily practice.

Cure was the primary endpoint of the study and defined as “without relapse within ten weeks after the initiation of therapy.”⁶ If patients in the fecal transplant group required a second transfusion then follow-up was extended to 10 weeks after the second infusion. The absence of diarrhea and three consecutive negative stool tests was considered cure and relapse was defined as diarrhea with a positive stool test for *C. diff* toxin.⁶ Of importance, a committee whose members did not know which group each patient belonged was responsible for determining cure vs. relapse. This reduced bias because even though patients knew which treatment they received, the committee members were blinded. The patients’ stool was checked when diarrhea occurred and on days 14, 21, 35, and 70. Though the study was partly unblinded, *C. diff* testing and diarrhea are objective outcomes and data points were collected at regular intervals in all three groups.

The study planned to have 40 patients per treatment group, but the study was terminated early after an interim analysis. The data and safety monitoring board recommended early termination due to *C. diff* relapse in control groups. Of the 43 patients originally enrolled in the study, 41 were included in the analysis. One patient in the vancomycin only group discontinued all medication and one patient in the fecal transplant group required prednisone for an unrelated medical problem. In the fecal transplant group, 13 of 16 patients (81%) were cured after one fecal transplant and 2 of 3 were cured after a second fecal transplant for a success rate of 15 out of 16 (94%). In the vancomycin alone group, 4 of 13 patients (31%) were cured and in the vancomycin plus bowel lavage 3 of 13 patients (23%) were cured. The results show fecal transplant is superior to vancomycin ($P < 0.01$ for the primary endpoint with 99.9% CI). The absolute risk reduction between one fecal transplant and PO vancomycin alone was 50% with a number needed to treat of two. The results look convincing, but the small patient population raises concerns for generalizability and the study was terminated early. The treatment failure of vancomycin in this study is significantly higher than in any other study. This could be due to the fact the ten-week follow-up is longer than in most studies and could capture more relapses or it could point to a problem with methodology.

Adverse events to fecal transfer with nasoduodenal tube include diarrhea immediately after infusion (94%), cramping (31%), belching (19%), and constipation during the follow-up period (19%). The adverse events were manageable and show that fecal transplant is relatively safe and effective. Additional studies are warranted that address whether nasoduodenal tube is the best delivery system for fecal transplant.

Off protocol, 18 patients with relapse after vancomycin treatment were given fecal transplants with 15 patients being cured (83%). These patients were not offered a prolonged tapering schedule of vancomycin. Since this was the vancomycin treated group, the study should have offered patients fecal transplant or prolonged vancomycin treatment.

Although this clinical trial had a small number of patients and the study excluded critically ill ICU patients and immunocompromised patients, it is still one of the strongest pieces of evidence in support of fecal transplant for recurrent *C. diff*. The trial includes elderly patients previous treated with antibiotics which is the patient population commonly encountered in daily practice. The number needed to treat is low and fecal transplant had a mild side effect profile.

Clinical Application

The study by Van Nood provided evidence that fecal transplant is superior to vancomycin treatment with recurrent *C. diff*.⁶ Our patient was frustrated by her lack of long term treatment with PO vancomycin and was willing to try the treatment we thought would be the most beneficial to help improve her quality of life. Although she struggled with the concept of fecal transplant, she was open to the idea because her recurrent *C. diff* was impacting her life significantly and placing strain on her relationship with her daughter. Our patient was slightly older than the average age in the study (80 vs. 73) but her age group was still included in the study, making it clinically applicable. She initially developed *C. diff* after treatment of a foot infection with clindamycin. Over 95% of study participants were exposed to antibiotics prior to *C. diff* infection which also increases the applicability of this study to our patient. Our patient met inclusion criteria and did not fall into any of the groups excluded from the study. Since she previously failed treatment with vancomycin multiple times and the adverse events with fecal transplant based on the study were manageable, we referred our patient for fecal transplant after getting insurance approval. It was important to have insurance authorization before discharge to prevent another situation similar to vancomycin not being approved after discharge. With proper documentation, we did not encounter any problems with her insurance company. We felt fecal transplant offered our patient the best option to improve her quality of life, relieve family tension, and reduce transportation burden.

Learning points:

1. It is important for physicians to consider alternative treatments for *C. diff* when vancomycin fails rather than continue with the same regimen.
2. Fecal transplant is more effective than vancomycin with recurrent *C. diff* when vancomycin has been previously tried.
3. It is important to pay close attention to exclusion criteria when reviewing scientific literature to make sure your patient has not been excluded.

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