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FIELD OF VISION

Stool therapy may become a preferred treatment of recurrent *Clostridium difficile*?

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Abstract

Fecal enemas were first reported to successfully treat life threatening enterocolitis in 1958, but fecal therapy to treat *Clostridium difficile* (*C. difficile*) infection has remained esoteric and not well investigated until recently. In the past few years, systematic reviews of case series and case reports of fecal microbiota transplant for recurrent *C. difficile* infection have become available and validate use of fecal transplant for *C. difficile* enterocolitis. Methods of fecal transplant reported in the literature include: nasogastric tube, gastroscope, duodenal tube, colonoscopy, rectal tube, and fecal enemas administered at home; no method has been shown to be superior. A recent randomized study published in *New England Journal of Medicine* found fecal transplant to be superior to oral vancomycin alone in treatment of recurrent *C. difficile* enterocolitis. The significance of this trial cannot be underestimated as it lends credibility to the idea of intentionally using microbes to combat disease, providing an alternative to the older paradigm of disease eradication through use of antimicrobials.

Key words: *Clostridium difficile*; Enterocolitis; Pseudomembranous; Fecal transplantation; Vancomycin

Core tip: Recurrent *Clostridium difficile* has been a challenge for patients, clinicians and hospital alike. Drug therapy for this epidemic is still not very effective. A more traditional method of fecal transplant has been discussed in this article, but it has been an uphill task to execute. We are discussing this first randomized control study, showing overarching benefits of stool transplant over traditional drug treatment. More studies needed with similar results, before making a strong recommendation in favor of it.

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COMMENTARY ON HOT TOPICS

Recurrent *Clostridium difficile* (*C. difficile*) is a growing epidemic with high rate of recurrence despite use of antibiotics. Fecal therapy to treat enterocolitis has been discussed in the literature since the late 1950's; despite anecdotal evidence suggesting its safety and efficacy, fecal therapy has remained an esoteric treatment. We read the recent article by van Nood *et al*[1] describing the results of the European randomized study investigating fecal therapy *vs* oral vancomycin for treatment of recurrent *C. difficile* infection with great interest. This is first randomized study investigating and validating use of fecal transplant for treatment of recurrent *C. difficile* infection.

C. difficile infection is identified as the cause of 25%-55.4% cases of antibiotic-associated diarrhea[2,3],

costs over $1 billion dollars annually in the United States to treat[4], and is a growing epidemic with twice as many cases reported in 2003 as in 1996 in part due to emergence of the more virulent, flouroquinolone-resistant NAP1/BI/027 strain[4,5]. *C. difficile* infection has a risk of initial recurrence rate following treatment with antibiotics of 20%-35%[6,7]; risk of recurrence is increased by use of antibiotics for other infections, being female, having initial infection in the spring, and having number of previous *C. difficile* infection recurrences[8]. Up to 65% of patients with recurrent disease ultimately develop pattern of recurrent *C. difficile* infection[6,8]. Patients with recurrent *C. difficile* infection are at risk of developing antibiotic resistance, and complications from *C. difficile* infection including: colitis, pseudomembranous colitis, toxic megacolon, and death[7,9]. Current therapies to treat recurrent *C. difficile* infection include tapered or pulsed dose oral vancomycin or metronidazole; these therapies are associated with high recurrence rates making it important that an effective treatment option for recurrent *C. difficile* infection become available[6].

Regardless of the method, fecal transplant for recurrent *C. difficile* infection appears to resolve symptoms in 83%-96% patients with most patients having durable response following single treatment[2,5,6,9]. Of patients requiring retreatment, 87.5% of patients experience symptom resolution[6]. Fecal transplant for pseudomembranous colitis appears promising with 72%-88% patients reporting improvement in symptoms[9]. Additionally, a case series found fecal transplant to be effective at treating the more pathogenic NAP1/BI/027 *C. difficile* strain in 89% patients[10]. Fecal transplant was associated with few and infrequent adverse events related to the procedure in all available case series and reports[2,6].

However promising the data from the systematic reviews of the case studies and case reports, it is not a substitute for data from prospective randomized controlled clinical trial data, as case reports and series are subject to bias from retrospective review of the data, subject selection and possible underreporting of adverse events. Results from a 3 arm randomized controlled clinical trial was recently reported by van Nood *et al*[1] in the *New England Journal of Medicine* comparing fecal transplant to vancomycin ± bowel lavage. More than 50% of patients enrolled in the trial had experienced multiple episodes of recurrent *C. difficile* infection and had been previously exposed to tapered vancomycin. The trial was stopped after an interim analysis showing superiority of fecal transplant arm to the other arms; 94% patients on the fecal transplant arm experienced symptom resolution - 81% (13/16) following initial infusion, and 66% (2/3) having symptom resolution following second infusion from another donor, *vs* 31% (4/13) patients with symptom resolution on the vancomycin alone arm and 23% (3/13) patients with symptom resolution on the vancomycin and bowel lavage. Adverse events from this trial confirm fecal transplant to be well tolerated with most common events experienced to be diarrhea (94% patients), abdominal cramping (31%), and belching (19%) immediately following fecal transplant and resolving within 3 h; and constipation (19%) as major adverse event reported during follow-up[1]. This study is far from perfect as it enrolled a small number of participants (16 on fecal transplant arm, 13 each on vancomycin and vancomycin and bowel lavage arms), was not blinded, patients on vancomycin ± bowel lavage arms frequently crossed-over following recurrence of *C. difficile* infection (non-protocol directed) and received fecal transplant, and although it enrolled primarily elderly patients it excluded many patients at higher risk of recurrent *C. difficile* infection including: patients with prolonged immunodeficiency, critically ill intensive care unit patients, and patients requiring antibiotics to treat another infection. Despite the studies limitations, it appears to favor fecal transplant for treatment of recurrent *C. difficile* infection with results similar to previous systematic reviews of case reports and case series available in the literature.

Data from the randomized trial by van Nood *et al*[1] provides further evidence that the efficacy of fecal transplant is not likely due to bowel preparation as it included a vancomycin and bowel lavage arm, but appears to be due to reconstitution of microbes in the gastrointestinal tract. As noted by observations the early 1980's, *C. difficile* growth can inhibit growth of certain strains of *Peptococcus, Peptostreptococcus,* and *Bacteroides* and its growth can also be inhibited by certain strains of *Staphylococcus, Pseudomonas, Bacteroides* and *Lactobacillus*, and recurrent *C. difficile* infection is likely due to germination of spores before balance of large bowel flora restored[11], or reinfection with a new strain of *C. difficile* due to the lack of protective bacteria in the colon[5]. Fecal transplant likely works by repopulating normal gut flora and preventing colonization with pathogenic *C. difficile* bacteria[5].

Fecal microbiota transplant has had empiric evidence demonstrating effectiveness and safety in treating recurrent *C. difficile* infection and pseudomembranous colitis enduring for over 50 years and is relatively less cost than other treatment options, so why has it remained an esoteric treatment for these disorders and not been investigated in randomized controlled trials until recently? Some possibilities include concerns of transmitting infections from donors to recipients *via* fecal material, no clear fecal transplant protocol as several methods have been described in the literature, and the idea of transplanting fecal material from one individual to another is aesthetically unappealing[9,11,12]. It should be noted that patients are reportedly receptive to the idea of fecal transplant following frustration at repeated antibiotic failure[13] and high out of pocket medical expenses to treat recurrent *C. difficile* infection[14].

Given the growing epidemic of *C. difficile* infection, cost and complications of treating recurrent disease, increasing antibiotic resistance, and growing body of evidence to support fecal microbiota transplant as a cost-effective and widely available therapy to treat recurrent *C. difficile* infection it is important that further research on fecal transplant be performed to identify methods and

indications for its use. The significance of the randomized study by van Nood *et al*[11] cannot be underestimated as it lends credibility to the idea of intentionally using microbes to combat disease, providing an alternative to the older paradigm of disease eradication through use of antimicrobials.

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