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Treatment of Recurrent *Clostridium difficile* Infection With Fecal Transplantation

ABSTRACT

Clostridium difficile infection is an increasingly common clinical challenge in hospitals and healthcare facilities. The infection often results in severe complications for the infected individual including relentless diarrhea, abdominal pain, dehydration, and mortality. Currently, there is a significant gap between research and practice in the management of recurrent *Clostridium difficile* infection, and treatment guidelines are limited. Numerous attempts at treating this infection have been made including the practice of fecal transplantation. A comprehensive literature search was conducted and 6 studies were reviewed to evaluate the safety and effectiveness of fecal transplantation as a modality in treating recurrent *Clostridium difficile* infection refractory to other treatment methodologies.

The implementation of fecal transplantation is suggested to restore normal bowel flora in individuals with *Clostridium difficile* and rid patients of the infection. Additional studies have since revealed perceived barriers toward the implementation of this treatment modality, although it has shown promising results with success rates of 83%–100%. Further efficacy testing validation is needed in larger, prospective controlled trials to guide healthcare providers in the direction of a reliable, standardized treatment protocol for recurrent *Clostridium difficile* infection.

Clostridium difficile is an anaerobic, gram-positive bacterium whose spores are found extensively in nature and naturally in the bowel of a small percentage of people (Gerding & Johnson, 2012). The bacterium is especially well known for its abundance in both hospitals and long-term care facilities. When *C. difficile* is contracted by an individual, it is carried in the stool and can present either symptomatically or asymptomatically. If the normal flora of the bowel has been disrupted, for example, by antibiotic use, chronic disease, or critical illness, *C. difficile* can overwhelm the intestinal tract resulting in *C. difficile* infection (CDI).

Received August 5, 2012; accepted September 15, 2012.

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The author thanks Patti Griffith, MSN, RN, CRNP-BC, for the thoughtful and helpful review of this article.

The author declares no conflict of interest.

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DOI: 10.1097/SGA.0000000000000035

Background

Clostridium difficile infection is a colonic disease that often results in bloating, abdominal pain, and severe diarrhea as well as pseudomembranous colitis, all of which can lead to serious complications in the infected individual. Approximately 30% of patients with first-time antibiotic CDI treatment experience further recurrent symptoms, and up to 65% of these patients continue to have repeated episodes over months to years (Yoon & Brandt, 2010). Regrettably, these individuals often have poor responses to current treatment modalities. Fortunately, fecal transplantation, the administration of a suspension of feces from a healthy individual into the gastrointestinal (GI) tract of an individual with colonic disease, has been demonstrated a viable treatment option for such patients.

As the level of antimicrobial use is high and the environment continually contaminated, more than 20% of hospitalized patients are infected with *C. difficile* virus. Over the past 20 years, *C. difficile* has emerged as the most common microbial cause of nosocomial diarrhea (Gerding & Johnson, 2012). In addition, there has been an increased incidence,

diagnosis rate, and severity level of CDI in hospitalized patients with an estimated annual 3.5 billion dollars in excess healthcare costs (Townsend, Beauchamp, Evers, & Mattox, 2012). Those at risk of infection include the elderly, individuals with renal disease, chronic obstructive pulmonary disease, impaired immune defense, underlying malignancy, GI disease, exposure to broad spectrum antimicrobial use, postoperative patients, or individuals who have encountered prolonged hospitalization; in essence, the majority of hospitalized or institutionalized patients are at risk for CDI and the implications from such an infection are grave (Townsend et al., 2012). As previously mentioned, the disease often results in extensive, watery diarrhea with subsequent dehydration, tachycardia, raised leukocyte count, abdominal pain, and bloating. In severe cases, the progression to pseudomembranous colitis, fulminate colitis, and toxic megacolon can further lead to shock, multisystem organ failure, and death.

Traditionally, cephalosporins, clindamycin, and ampicillin-amoxicillin were most frequently linked with CDI. Fluoroquinolone antibiotics, however, have now emerged as the most prominent class of antibiotics increasing the risk of CDI. In fact, the increased use of newer generation fluoroquinolones is implicated in outbreaks of a fluoroquinolone-resistant strain of *Clostridium difficile* (Townsend et al., 2012). More recently, the association between proton pump inhibitors and the risk of recurrent CDI has also been debated (Lowes, 2012).

Treatment of CDI

As increasing incidences of CDI and resistant strains of *C. difficile* continue, treatment strategies to eradicate the disease are more important than ever. Although some CDI patients respond to discontinuation of antibiotics to eradicate symptoms, others require antibiotic treatment to eliminate the infection. Current practices with antibiotic management include the use of oral vancomycin or either oral or intravenous metronidazole (Johnson, 2009; Townsend et al., 2012). However, nearly 30% of patients who complete antibiotic treatment further experience symptoms and repeated episodes. Unfortunately, data are lacking to support any particular treatment strategy for these individuals with recurrent CDI (Johnson, 2009).

The treatment of recurrent CDI remains challenging. This challenge has been discussed throughout the literature since the 1950s, yet there are few data from randomized controlled studies to support any particular method for the treatment of recurrent CDI. Some guidelines suggest the continued use of metronidazole or vancomycin for first CDI recurrence, whereas for second CDI recurrences, a vancomycin taper followed by vancomycin pulse treatment is often preferred. Still, this treatment option is very expensive, and patients who experience recurrent CDI frequently encounter more than two recurrences with a risk of relapse up to 60% after the third recurrence (Myers, 2011).

Other treatment approaches include nitazoxanide and intravenous immunoglobulin administration; however, there are limited data to recommend either strategy's use. Lack of recommended treatment options repeatedly prompts surgical intervention and often results in tremendous patient morbidity and mortality (Johnson, 2009). Treatment of recurrent CDI remains unclear; therefore, more effective therapy options need to be explored (Johnson, 2009).

Fecal Transplantation

It is hypothesized that the fundamental factor responsible for the development of CDI is the disruption of normal bowel flora. Thus, restoring the normal flora of the bowel may prove a viable treatment option (Garborg, Waagsbo, Stallemo, Matre, & Sundoy, 2010; Grehan et al., 2010; Ho & Prasad, 2011; Rohlke, Surawicz, & Stollman, 2010; Silverman, Davis, & Pillai, 2010; Yoon & Brandt, 2010). Fecal transplantation, the administration of a suspension of feces from a healthy individual into the GI tract of an individual with colonic disease, has been discussed throughout the literature because a case series of four patients undergoing human fecal enemas in 1958 proved a 100% success rate in eradicating severe, pseudomembranous enterocolitis (Eiseman, Silen, & Bascom, 1958; Grehan et al., 2010). Since this time, multiple case series and clinical trials have replicated the idea brought forth by the Eiseman et al. (1958) case series.

Individuals with recurrent CDI experience multiple symptomatic episodes often refractory to traditional treatments. Three possible pathophysiologic explanations for recurrent CDI have been explored. These include treatment failure to eliminate vegetative *C. difficile* spores within the patient's GI tract, *C. difficile* reinfection, and *C. difficile* spore recrudescence (Myers, 2011). The therapeutic goal of fecal transplantation in recurrent CDI is to restore normal bowel flora, an innate defense mechanism against pathogenic *C. difficile* (Eiseman et al., 1958; Garborg et al., 2010; Grehan et al., 2010; Ho & Prasad, 2011; Johnson, 2009; Pant, Sferra, Deshpande, & Minocha, 2011; Rohlke et al., 2010; Silverman et al., 2010). Administration of normal bacterial flora from healthy donated stool aids in restoring normal flora in the GI individual with CDI. In addition, healthy transplanted stools promote colonic homeostasis through the restoration of bacterial production of short chain fatty acids, further fostering *C. difficile* spore elimination (Pant et al., 2011).

Review of Literature

A comprehensive search of the literature was conducted for research studies evaluating the treatment of recurrent CDI with fecal transplantation published between 2002 and 2012. The key words *fecal transplant*, *stool transplantation, Clostridium difficile*, and *fecal bacteriotherapy* were entered into the databases MEDLINE, Ovid, National Guideline Clearinghouse, and PubMed Plus. Only human studies published in English were included. Six of the most recent studies evaluating CDI in adult populations were selected for review.

Results

Of the six studies reviewed, four retrospective reviews and two prospective case studies were used to evaluate success rates for treatment of CDI in individuals with refractory or recurrent CDI. As summarized in Table 1, fecal transplantation has been associated with durable clinical response with diminished incidences of CDI symptoms in participants and no reported adverse effects or sequelae (Garborg et al., 2010; Kassam, Hundal, Marshall, & Lee, 2012; Kelly, Leon, & Jasutkar, 2012; Rohlke et al., 2010; Silverman et al., 2010; Yoon & Brandt, 2010).

In 2010, Garborg and colleagues conducted the largest reported case series of patients treated with fecal transplantation for suspected or verified recurrent CDI. In that series, 40 medical records of patients who underwent fecal transplantation via gastroscope or colonoscope were retrospectively reviewed. Clinical resolution of CDI was reported in 83% of patients with no adverse events from the transplantation identified. The main limitation of the study relates to its retrospective design.

In 2010, Rohlke and colleagues conducted a subsequent retrospective case series of 19 patients with confirmed recurrent CDI who underwent fecal transplantation through colonoscopic infusion. Eighteen patients (95%) responded to initial treatment. The participant who did not immediately respond to fecal transplant later responded to a second transplantation. All patients maintained prolonged cured status until submission of the study, ranging from 6 months to 5 years. Like the review conducted by Garborg and colleagues (2010), this study was limited to an uncontrolled, retrospective case series. Furthermore, this included a small sample population with an unequal gender spread of 89% female, limiting the generalizability of these results. However, the study further discusses female gender as a possible risk factor for CDI. Female predisposition has been discussed throughout earlier literature, although pathologic understanding of this tendency in CDI is limited (Garborg et al., 2010; McFarland, Surawicz, & Rubin, 1999). These factors may explain the sample population utilized in the Garborg et al. (2010) study.

In 2010, a study conducted at Montefiore Medical Center in New York City by Yoon and Brandt (2010) evaluated 12 patients with recurrent, refractory CDI treated with fecal transplantation via colonoscope. In this case series, 100% of patients experienced a durable clinical response to fecal transplantation. As with the previous studies, this case series was limited by a retrospective design. There was also a 9:3 predominance female-to-male participant ratio.

With retrospective review case series demonstrating promising results for recurrent CDI treatment, a Canadian prospective study published in 2010 by Silverman and colleagues was conducted to evaluate the benefit of self- or family member-administered home fecal transplantation by low-volume enema as a definitive treatment in refractory CDI. Seven patients were included in the case series. Patients and family members were given instructions on home enema administration. The findings revealed a 100% success rate. No patient had recurrent CDI postprocedure. Major limitations of the study included the uncontrolled, unblinded design. Moreover, the patient population involved was highly motivated and self-selected, limiting extrapolation potential to individuals expressing less motivation.

Similar to the case series conducted by Silverman and colleagues (2010), Kassam and colleagues (2012) further investigated treatment of refractory or recurrent CDI with fecal transplantation via retention enema. In that series, 27 patients who underwent fecal transplantation via retention enema were retrospectively reviewed. Clinical resolution of CDI was reported in 93% of patients with no relapses or adverse events from the transplantation. Several limitations of this study were identified. Because fecal transplantation was carried out by way of retention enema, the route of administration may be limited in those unable to retain the infusate. Furthermore, the study did not contain a control and the outcome assessments of patients were not blinded.

Fecal transplantation by means of colonoscopy in the treatment of recurrent, refractory CDI was also studied by Kelly and colleagues (2012). This case series included 26 participants with a reported 92% success rate. Twenty-four of the participants remained symptom free without CDI relapse after the procedure. The use of a small population size consisting solely of Caucasian participants limits the study. In addition, 24 of the 26 participants were female.

Although this evidence suggests numerous benefits associated with fecal transplantation, the most effective route of administration has been debated (Kelly et al., 2012). Methods used to administer fecal

TABLE 1. Review of Primary Sources

Reference	Aims	Sample	Study Design	Route of FT	Mean Follow-up	Study Findings
Garborg et al. (2010)	To identify the success rate of FT in patients with recurrent CDI	Medium-sized Norwegian hospital Total = 40 male = 19, female = 21	Uncontrolled, retrospective chart review	Gastroscope or colonoscope	No follow-up performed	33 (83%) patients were successfully treated 7 patients failed to respond; 2 were suggested to have immunologic colitis; 5 had serious comorbid conditions No adverse events
Rohlke et al. (2010)	To evaluate results using FT and promulgate the methodology to the GI community to foster more widespread use in appropriate candidates	2 Medical centers Total = 19 outpatients male: 2, female: 17	Uncontrolled, retrospective case series	Colonoscope	27.2 months	100% success rate 18/19 patients initially responded to FT; 1 patient required a second FT No adverse events
Silverman et al. (2010)	To investigate whether self- or family- administered fecal transplantation by low volume enema could be used to definitively treat refractory CDI	Self-selected sample Total = 7 male = 4, female = 3	Uncontrolled, prospective case series	Low-volume enema	8.6 months	100% clinical success Effective, safe option for patients refractory to other therapies
Yoon & Brandt (2010)	To examine 12 patients with refractory/recurrent CDI treated by human stool transplanted via colonoscopy	Montefiore Medical Center chart review Total = 12 male = 3, female = 9	Uncontrolled, retrospective case series	Colonoscope	3 weeks–8 years (at the time of publication)	100% durable clinical response No adverse events
Kelly et al. (2012)	To present data detailing the success with FT and to provide a simple treatment protocol	Women and Infants Hospital Total = 26 outpatients male = 2, female = 24	Uncontrolled, prospective case series	Colonoscope	10.7 months	92% effective in preventing further diarrhea or CDI relapse No adverse events
Kassam et al. (2012)	To describe FT via retention enema in patients with refractory or recurrent CDI	Case records post-FT via retention enema Total = 27 male = 14, female = 13	Uncontrolled, retrospective review	Retention enema	14.24 months	93% clinical CDI resolution 22/27 patients responded within 24 hours of transplant; 5 patients underwent a second FT; 3 out of the 5 had symptom resolution; 2 patients continued to have CDI symptoms No adverse events

Note. CDI = *Clostridium difficile* infection; FT = fecal transplantation; GI = gastrointestinal.

transplants have included fecal suspensions given through nasogastric and nasoduodenal tubes, as retention enemas, with the use of a colonoscope at the time of colonoscopy, or via gastroscope (Kelly et al., 2012). Currently, no randomized control trial comparing efficacy of two varying methods has been published; however, reported outcomes appear similar (Myers, 2011).

With no current practice guidelines in place to aid practitioners in fecal transplant administration route, preference is provider specific. With that, there are recognized benefits and limitations with each specific route of administration. Current criticisms claim that colonoscopy infusion is more difficult than other routes of fecal transplantation, whereas nasogastric routes have been critiqued for limited effectiveness in patients with decreased bowel motility. However, nasogastric infusion ensures full bowel follow-through of donor material, an advantage unique to this administration route. Repopulation of the GI tract through fecal enema is thought to recolonize the rectum and colon with healthy flora. This segmental repopulation also proves positive results in CDI elimination and provides a safe, cost-effective alternative to other methods of administration. Nonetheless, route of donation administration is currently left to provider partiality.

Donor Criteria

When considering fecal transplantation, it is essential to have a treatment plan and stool donor available. Currently, there are no specific guidelines regarding stool donor criterion. However, stool donor preference in all but one study was given to intimate domestic partners or close family members chosen by the patient; although healthy volunteers are also viable candidates as was demonstrated in the Kassam and colleagues (2012) study. Still, each study had varying degrees of interpretation for appropriate donors. For example, Garborg et al. (2010) and Kelly and colleagues (2012) identified close relatives or other household members without symptoms of GI disease or history of chronic infectious disease as suitable for stool donation, whereas Silverman et al. (2010) allotted only family members as potential donors. Contraindications for stool donation were also identified in the Silverman et al. (2010) case series and included history of GI illness, peptic ulcer disease, gastroesophageal reflux, irritable bowel syndrome, inflammatory bowel disease, or GI polyps. History of malignancy, as well as antibiotic use or hospitalization within the preceding 3 months of donor interview, was also contraindicated.

In comparison, Rohlke et al. (2010) defined exclusionary donor factors as individuals who had recent antibiotic use and those with current or recent diarrheal illness. This study also limited potential donors conveying at-risk sexual behaviors and excluded hospital and healthcare workers. Yoon and Brandt (2010) did not refine donor inclusion or exclusion requirements in their study but also gave preference to domestic partners and close family members.

Infectious disease transmission is a cause for concern with fecal transplantation; therefore, routine testing for blood-borne pathogens including HIV-1 and HIV-2, syphilis, and hepatitis A, B, and C is common practice. Additional stool cultures assessing for strains of *C. difficile*, enteric bacterial pathogens, and ova and parasites are routine screening modalities for fecal donor eligibility (Garborg et al., 2010; Kassam et al., 2012; Kelly et al., 2012; Myers, 2011; Rohlke et al., 2010; Silverman et al., 2010; Yoon & Brandt, 2010).

Clinical Relevance

Since 2000, there has been a dramatic increase in the rate and severity of CDI (Kelly et al., 2012). The consequent mortality rate has increased from 1.3% to 2.4% (Kelly et al., 2012). As the CDI epidemic continues to grow, the number of patients who experience recurrent CDI and failed treatments are also rising (Townsend et al., 2012). Metronidazole and vancomycin are currently the first-line agents for CDI treatment; however, recent data suggest that metronidazole is losing its effectiveness, and expert opinion is changing toward the use of vancomycin as first-line therapy (Townsend et al., 2012). Furthermore, studies evaluating the use of alternate antibiotics, probiotics, and intravenous immunoglobulin have been performed, but results of these trials are ambiguous.

Fecal transplantation has many benefits including low cost, absence of side effects, no drug resistance issues, and high success rates in numerous case series (Garborg et al., 2010; Kassam et al., 2012; Kelly et al., 2012; Rohlke et al., 2010; Silverman et al., 2010; Yoon & Brandt, 2010). *Clostridium difficile* infection poses a particular risk for older adults, who are subject to more serious symptoms than younger patients and are especially vulnerable to dehydration, organ failure, and mortality (Johnson, 2009).

The evaluation of the current research demonstrates that the use of fecal transplantation is a safe technique that appears to eliminate recurrent CDI symptoms refractory to other treatment methodologies. As a result, the incorporation and acceptance of fecal transplantation into practice may aid in achieving optimal treatment outcomes, improved patient quality of life, and reduction of excess healthcare costs.

Barriers to Implementation

Several reports have revealed barriers to implementing fecal transplantation including lack of provider

acceptance, patient safety concerns (e.g., infectious transmission from donor to recipient), sanitation issues, and aesthetic objection (Ho & Prasad, 2011; Martin, 2011). Despite promising results dating back to the 1950s, employing the treatment modality for CDI has remained an underused clinical practice (Ho & Prasad, 2011). Perceived barriers may be contributory to the low implementation rate into practice.

The lack of financial benefit (e.g., profit) generated from fecal transplantation has also been documented as a perceived barrier to implementation (Martin, 2011). However, this has been argued a negligible barrier with an unfortunate connotation if true. Concerns of patient safety and infectious disease transmission have been acknowledged as an objection to fecal transplantation; nevertheless, this concern may be remedied with diligent screening practices of stool donors that are currently in place with the use of fecal transplantation (Martin, 2011).

An aesthetic objection to the procedure by patients and providers is a concept that must be overcome. Garborg and colleagues (2010) presented a novel idea throughout their 2010 case study in which the notion of fecal transplantation as a potentially curative treatment option was introduced to patients at an early stage of recurrent CDI. The approach was intended to allow for patient acquaintance to the idea so aesthetic barriers could be more easily overcome. In this series, there were no reported objections to the aesthetic components of fecal transplantation due to the patient's debilitation from CDI. These results coincide with other published literature that has reported limited objection from patients and family members to fecal transplantation therapy (Martin, 2011; Silverman et al., 2010).

With a high burden of distress and disease severity, individuals with recurrent CDI frequently experience incapacitating symptomatic episodes for months to years (Townsend et al., 2012; Yoon & Brandt, 2010). In addition to a decline in physical function and health, quality of life is often severely limited by extensive, watery diarrhea; abdominal pain; bloating; and sequelae. Social exclusion, inability to work, frequent hospitalization, and associated CDI costs are devastating (McFarland et al., 1999). Utilization of the Garborg et al. (2010) approach in introduction of fecal transplantation may further benefit appreciation of this viable treatment option.

Aesthetic objections by healthcare personnel may also prove a difficult barrier to overcome. Several reports by bedside nurses and ordering providers have documented negative emotions about providing such a unique therapy. From these reports, provider acceptance through administration ease and success rates for patients have been powerful influences in advocating for fecal transplantation use in recurrent CDI (Myers, 2011).

Application to Practice

Clostridium difficile infection is increasing in frequency and attesting a great concern in all patient populations. Eradicating *C. difficile* in vulnerable individuals may reduce morbidity and mortality rates. In addition, the query of progressive disease with each recurrent episode is an area of clinical concern and supports early treatment of recurrent CDI. Approximately half of all patients experiencing a relapse of CDI are infected with a new strain of *C. difficile*. In these cases, disease control practices are key to preventing recurrence. Appropriate healthcare measures include ensuring a clean patient environment and adequate hand hygiene with soap and water before and after patient contact, as spores are resistant to alcohol (Myers, 2011).

Although most patients can be effectively treated using typical antibiotic regimens approved for CDI that should remain the first-line interventions for most patients, the subpopulation of patients with recurrent disease may benefit from fecal transplantation as a rational intervention (Rohlke et al., 2010). Although there are no clear guidelines regarding timing of fecal transplant, growing consensus is to attempt this therapy after the third or fourth CDI recurrence (Myers, 2011). However, those at risk for severe complication, such as the elderly and severely ill, should be recognized for earlier intervention.

As previously mentioned, early fecal transplantation in recurrent CDI may eradicate infection, prevent negative complications of disease, and improve patient outcomes. Providing patient and family education regarding fecal transplant is essential. With a myriad of administration routes available, patient preparation is provider specific. In cases of colonoscope administration, most providers require a standard bowel cleanse the night prior to treatment. Fortunately, as many of the studies demonstrate, positive patient results in the elimination of recurrent CDI may occur immediately after initial fecal transplant administration. It is important to note that additional treatments may be necessary and patient monitoring for recurrent CDI symptomology is required.

Although standardization of this practice is limited, reported donor stool preparation has been documented similarly throughout the literature. This process includes requiring donors to provide stool for transplantation the morning of procedure, no more than 6 hours before treatment. Common practice is to then suspend donor fecal matter in nonbacteriostatic saline and blend; general agreement is to create a total volume ranging from 100 to 400 ml. In reports utilizing colonoscopy for administration, stool suspensions are further filtered through gauze sheets or coffee filters to remove particulate matter (Garborg et al., 2010; Rohlke et al., 2010; Myers, 2011; Yoon & Brandt, 2010). Fecal suspension

by low-volume enema does not require further filtering of the stool transplant solution.

Recommendations for Future Research

The case series in this review consisted of small sample sizes, many of which were composed predominantly of women, limiting the ability to generalize these findings to the population at large. Additional studies enrolling larger samples with equalized gender spread would provide further evidence for clinicians managing and caring for patients with recurrent, refractory CDI. Furthermore, the studies presented were neither blinded nor randomized. The 2008 FECAL trial, fecal therapy to eliminate *C. difficile*-associated longstanding diarrhea, is the first randomized controlled study comparing donor feces instillation with antibiotic therapy. Results from the trial are pending (Netherlands Trial Register, 2012). Additional randomized controlled trials are in progress. Necessity of these trials is warranted. Larger, randomized studies may potentially address speculations regarding the practice of fecal transplantation.

Other areas worth investigating further include the most advantageous route of fecal transplantation and the impact of fecal transplant in cost reduction for patients with recurrent CDI. It is recommended that additional studies investigate fecal transplantation in treating recurrent CDI in patients with a multitude of comorbidities including those with other colonic diseases. Specific treatment recommendations and dosing regimens prior to transplantation should be explored, along with standardizing stool donor requirements and exclusion variables.

Conclusion

Currently there is a significant gap between research and practice in the management of recurrent CDI. Recurrent CDI can turn into a chronic, intractable disease in which repeated bouts of infection can continue for years, leading to persistent use of antibiotics, repeated hospitalizations, and even death (Borody et al., 2004).

One intervention aimed at treatment of CDI, fecal transplantation, has been examined through multiple case series with success rates ranging from 83% to 100% (Garborg et al., 2010; Kassam et al., 2012; Kelly et al., 2012, Rohlke et al., 2010; Silverman et al., 2010; Yoon & Brandt, 2010). This treatment methodology is inexpensive and safe, with no reported adverse events to date. Although not yet the standard of care, fecal transplant should be an option for patients who have failed treatment with traditional therapies. Still, additional research into the efficacy and technique of fecal transplantation is warranted. ✪

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