Published in final edited form as:

Curr Opin Gastroenterol. 2013 November ; 29(6): 628–632. doi:10.1097/MOG.0b013e328365d326.

Fecal microbial transplantation for the treatment of *Clostridium difficile* infection: current promise and future needs

Mark J. Koenigsnecht¹ and Vincent B. Young^{#,1,2}

¹Department of Internal Medicine/Division of Infectious Diseases, The University of Michigan, Ann Arbor, MI, 48109, USA

²Department of Microbiology & Immunology, The University of Michigan, Ann Arbor, MI, 48109, USA

Abstract

Purpose of review (describe why this review is timely and relevant)—The use of Fecal Microbial Transplantation (FMT) as treatment for *C. difficile* infection (CDI) has increased rapidly over the past few years. *C. difficile* is the most common nosocomial infection in the United States and a major risk factor for CDI is prior antibiotic use. The use of antibiotics creates a dysbiotic state of the gut microbiota which can then be susceptible to CDI. FMT from a healthy individual restores the gut microbiota and subsequently colonization resistance against CDI.

Recent findings (describe the main themes in the literature covered by the article)—Recent studies have shown the success rate for FMT as treatment for CDI being greater than 90 %. Standardized, frozen preparations of stool can be used which increases the availability of stool for FMT and decreases the cost of screening individual donors. Additionally there have been recent advances in identifying a defined microbial community isolated from stool that can restore colonization resistance against *C. difficile*.

Summary (describe the implications of the findings for clinical practice or research)—Since the fecal microbiota for transplantation is being used to treat disease it meets the legal definition of a drug and biological product. Recent FDA regulations for FMT require an investigational new drug application for further clinical testing. The use of FMT is a successful treatment for CDI however more work needs to be done to standardize the treatment and understand how specific members of the gut microbiota can antagonize *C. difficile*.

Keywords

Fecal microbial transplantation (FMT); *Clostridium difficile*; fecal bacteriotherapy; recurrent *C. difficile* infection

[#]Corresponding author: Vincent B. Young, MD/PhD, The University of Michigan, 5510A MSRB I, SPC 5680, 1150 W. Medical Center Dr., Ann Arbor, MI 48109-5623, Office: 734-764-2237, Fax: 734-763-4168, youngvi@umich.edu.

Introduction: (This should be a paragraph outlining the scope of the review and mentioning any earlier work which will place the review in context)

The gastrointestinal (GI) tract harbors a highly diverse microbial ecosystem composed of 10 to 100 trillion microbes that provide essential functions for the host. Alterations in the community structure of this microbiota due to antibiotic use can result in the loss of colonization resistance, the mechanism by which the gut microbiota provides a protective role for the host against GI pathogens (1–3). *Clostridium difficile* is one pathogen that can thrive in a dysbiotic gut community, with prior antibiotic use being the most common risk factor for infection. Primary treatment for *C. difficile* infection (CDI) is traditionally either a two week course of oral metronidazole or vancomycin, which in itself puts the patient at risk for a recurrent infection once the antibiotic therapy is stopped. One old but recently popular therapy is a Fecal Microbial Transplantation (FMT) where the fecal microbiota from a healthy host is transferred to a patient with CDI in order to restore the microbiota to a resistant state against CDI. The purpose of this review is to highlight recent advances in the use of FMT for CDI, describe potential concerns from this treatment, and to identify future areas of research.

Re-emergence of CDI

In recent years a new focus has been put on *C. difficile* due to the emergence of hyper-endemic strains that have led to outbreaks around the world and an increasing incidence of disease (4). *C. difficile* is an anaerobic, spore-forming, gram-positive bacilli and is now the leading cause of hospital acquired infections, surpassing methicillin-resistant *Staphylococcus aureus* (MRSA) (5). In hospitals *C. difficile* is the number one cause of pseudomembranous colitis and nosocomial diarrhea cases (6). CDI is responsible for significant morbidity, mortality and increased economic burden in hospitalized patients, approaching 5 billion dollars annually (7, 8). Risk for the development of CDI is associated with the use of broad-spectrum antibiotic therapy as well as increasing patient age and hospitalization. As many as 50% of people become colonized with *C. difficile* after a 4 week hospital stay (9, 10). Furthermore, with a relapse rate approaching 25%, CDI can significantly increase hospital costs on the basis of extended stays alone (11). The risk of developing recurrent CDI increases with each recurrence event (12). There is a 40 % risk for an additional recurrence with 1 prior infection and a greater than 60 % risk with 2 prior infection (13, 14).

FMT as treatment for CDI

Establishment of a healthy gut microbiota is critical in order to resolve the symptoms of recurrent CDI. The gut microbiota provides multiple benefits to the host, one of which is to mediate colonization resistance against gut pathogens (15, 16). A dysbiotic gut microbiota after antibiotic treatment can be restored to a community that is resistant to CDI with a FMT. The first modern use of a FMT was described in 1958 as a treatment for pseudomembranous enterocolitis (17). However accounts of FMT date all the way back to the 4th century China where it was used to treat severe diarrhea (18). FMT is the transfer of a “healthy” (or non-dysbiotic) gut community present in the stool either by colonic or

nasogastric passage. A recent meta-analysis showed that FMT has an 89 % success rate in the treatment of CDI (19). Additionally, a long-term follow up of patients who received and FMT to treat recurrent CDI showed the primary cure rate was 91 % (20). The previous year resulted in multiple comprehensive reviews on FMT describing use for treatment of a variety of diseases (21), the preparation and screening of stool (22), and outcomes in clinical use (23). Despite the success of FMT in the treatment for CDI there have been several reasons that have prevented this therapy from becoming the first line of treatment. Notably the lack of randomized, controlled studies for success in treating CDI, the lack of a standardized procedure for the screening and production of the fecal slurry, and finally the “ick” factor of this treatment as perceived by the patient. There has been rapid progress to address these concerns and are summarized below.

Randomized, controlled studies recently performed

There have been several systematic reviews of the literature examining the success rate of FMT in the treatment of CDI (19, 20, 24). However in order to confirm the efficacy of this treatment randomized, controlled studies needed to be performed. A recent paper by van Noot *et. al* assessed the success rate of FMT via nasogastric tube(25). The study showed that resolution of recurrent CDI was more effective with FMT compared to vancomycin treatment alone. They found that 81 % of patients receiving an FMT had resolution of CDI symptoms without relapse for 10 weeks, compared to 31 % receiving vancomycin treatment. The success rate is similar to the systematic review of uncontrolled cases showing disease resolution 92% of the time(24). Interestingly this study found a higher successes rate with FMT via fecal enema or colonoscopy (92%) compared to nasogastric tube (76%). This is the first randomized, controlled study showing the efficacy of FMT for treatment of recurrent CDI. While the study was unblinded and imperfect, it is an important first step in establishing a protocol to make FMT a safe and widespread treatment.

Progress has been made in the standardization FMT preparation

Another hurdle for FMT was to increase the practicality of the procedure by developing a standardized, cost effective protocol to obtain and process donor stool. Stool is usually donated from a family member of the patient and rapidly screened for enteric pathogens (such as *C. difficile*, *H. pylori*, *Giardia* and *Cryptosporidium*) and viruses (such as hepatitis and HIV). The stool is then diluted (in either saline, milk, or water) and homogenize with a blender. Particulates are then filtered out and the stool is ready for transplantation. The procedure of obtaining, screening, processing the stool sample for FMT, dosage, and number of treatments have varied (19, 24), however it should be noted that even with this variation the FMT still resulted in greater than 80% resolution of CDI (24).

A recent report by Hamilton *et al.* described a protocol for the processing and freezing of donor stool that now allows for universal donors and stool for use when needed (26). Importantly this standardization protocol did not lose any apparent efficacy in resolving recurrent CDI even though the donor stool was frozen prior to FMT. The standardization process is important in several ways. First it showed that a standard, volunteer stool donation program was accepted for use by the patients. A recent survey assessing patient

perceptions for FMT to treat ulcerative colitis found that almost 50 % of patients preferred donor stool from a family member as opposed to whomever their doctor recommended (27). Secondly, it shows a protocol to cryopreserve the stool that is effective in treating recurrent CDI. This allows the stool to be processed in advance, stored, and can be shipped to other hospitals when needed. Finally, using universal donors and creating multiple preps is a cost-effective means of FMT due to a decreased cost in screening on the universal donor stool as opposed to each individual donor (28).

FMT is now an investigational new drug

The recent progress in the standardization of FMT is an important advancement for the field. However some have argued that use of this treatment is expanding too rapidly without proper review and testing of the procedure. Recently the Food and Drug Administration (FDA) has designated FMT an investigational new drug, meaning physicians must apply to a federal board and obtain permission to perform the procedure. This requires the doctor to wait 30 days for approval of the procedure, however emergency approval is available when needed. The debate continues between physicians that feel their access to this treatment is being overly complicated by new rules and others who feel we need to allow FDA to ensure the safety of drugs, including FMT. However with this new decision from the FDA comes an urgent need for clinical trials using a standardized protocol for obtaining and processing of the stool. Additionally work needs to be done to define exactly what is the drug (is a gut microbial community or a protocol to process stool), what it is approved for (how many recurrent CDI infections does a patient need before treatment), the duration and route of administration. Recent work has shown FMT to be a safe and effective treatment for CDI, however more research is needed in order to develop a safe and reliable drug that decreases any potential long-term consequences from this treatment.

Could a FMT have unintended consequences

As our knowledge of the gut microbiota increases so does our understanding that the gut microbiota plays a role in several disease states. We know the gut microbiota plays a role in many gastrointestinal diseases including in obesity (ref), inflammatory bowel disease (IBD), and colon cancer (ref). Additionally links have been made with correlating a dysbiotic gut microbiota to neurologic (ref) and autoimmune disorders (ref). With many diseases correlating with a dysbiotic gut microbiota, the use of FMT has spread beyond treatment for CDI to treat other disease states (reviewed in (21)). However with great promise for this treatment comes the need for caution. We still do not understand the mechanism behind these disease states and the role that the microbiota specifically plays. For example if ulcerative colitis is due in part to one or several specific bacteria, we still do not understand who the bacteria are and what role they play in the disease. Since so much is still unknown we cannot screen out potentially harmful bacteria the same way we can screen out *C. difficile* from stool used to treat CDI. Before FMT is used in the treatment of these diseases much more work needs to be done to establish the efficacy and safety of the treatment.

The use of FMT for treatment of CDI has been shown to be very safe. Systematic reviews and meta-analysis done on the use of FMT for CDI showed no adverse effects from the

treatment (19, 24). The recent study by van Noot *et. al* found only minor side effects to the treatment, including cramping and belching. However all symptoms resolved within 3 hours after treatment (25). However a recent report described a patient developed ulcerative colitis after FMT used in the treatment of CDI (29). This patient had a history of quiescent ulcerative colitis for the previous 20 years, however symptoms reemerged after FMT. It is possible the patient's genetic susceptibility ulcerative colitis could have played a role in disease reemergence. Care needs to be taken when using this treatment on patients with previous gastrointestinal disorders. While disease development from FMT is very small compared to the successful resolution of CDI, it is important to understand potential unintended consequences from this treatment and identify areas of research to minimize these consequences.

Specific bacteriotherapy to treat CDI

For many people the thought of ingesting stool is not an attractive treatment option. This “ick” factor turns people away from this treatment option (30). While treatment with FMT is becoming more widespread, there is much interest in identifying the species of bacteria in stool that mediate colonization resistance against *C. difficile*. Single species have been isolated that decrease the clinical signs of CDI in a germ-free mouse model of infection (31) (and a few more). Additionally, groups of single species have been identified that can result in the resolution of CDI. Recent work by Lawley showed that a few as 6 species of bacteria can restore colonization resistance during a CDI using a murine model of infection(32). In humans a recent study identified 33 bacterial isolates that resolved CDI(33).

Conclude

For the treatment of CDI many people have shown to prefer FMT over antibiotics (ref). However for patients at a high risk of CDI coming off a course of antibiotics, restoration of the gut microbiota by FMT might not be their first option [ref???]. The use of FMT in the treatment of ulcerative colitis showed that patient perceptions (27). A recent meta-analysis showed that probiotics reduced *C. difficile*-associated diarrhea (34). A recent survey found that more patients would be will to undergo FMT if it was offered as a pill (30). Expand and make cohesive

Also, there is a historical reference from Tvede M in Lancet 1989.

Will specific bacteriotherapy work for everyone

The idea of sing stool for a gut microbiota is as close to a “one-size fits all” approach we have right now. However we know that there is variability from person to person in the gut microbiota. So using a defined bacteriotherapy might not reach the success rates stool has for clearing CDI. Additionally, we know that probiotics/bacteriotherapy require a specific gut community to stick.

Understanding mechanism of colonization resistance mechanisms can allow us to develop targeted bacteriotherapy. “The naive simplicity of this concept has become evident when the results of a body of work performed by a large number of investigators showing that there

really is no such thing as a “normal” flora (microbiota) for the human intestinal tract have been examined (Qin J, Li R, et al. A human gut microbial gene catalogue established by metagenomic sequencing. *Nature*. 2010;464:59–65. And Costello EK, Stagaman K, et al. The application of ecological theory toward an understanding of the human microbiome. *Science*. 2012;336:1255–62.)” identical from Fecal Bacteriotherapy for Recurrent *Clostridium difficile* Infection: What's Old Is New Again?

Conclusions

The use of FMT for the treatment of recurrent CDI is an important treatment option for this infection. Recent work has shown this to be a safe and effective treatment for CDI that has the potential to be scaled up for widespread distribution and use (25, 26). Currently this is a treatment of last resort after multiple rounds of antibiotics are unable to resolve the infection. However we don't understand mechanistically how FMT resolves CDI, we simply know that it works. Before FMT can become the primary treatment option for CDI more research is needed to understand mechanism of FMT restoring colonization resistance against CDI.

Acknowledgments

Funding from National Institutes of Health (NIH) grant 1U19AI090871-01 (VBY) and by NIH training grant 5T32 AI007528 (MJK)

References

1. Spencer RC. The role of antimicrobial agents in the aetiology of *Clostridium difficile*-associated disease. *J Antimicrob Chemother*. 1998 May; 41(Suppl C):21–27. PubMed PMID: 9630371. Epub 1998/06/18. eng. [PubMed: 9630371]
2. Rousseau C, Levenez F, Fouqueray C, Dore J, Collignon A, Lepage P. *Clostridium difficile* colonization in early infancy is accompanied by changes in intestinal microbiota composition. *J Clin Microbiol*. 2011 Mar; 49(3):858–865. PubMed PMID: 21177896. Pubmed Central PMCID: 3067754. Epub 2010/12/24. eng. [PubMed: 21177896]
3. van der Waaij D, Berghuis-de Vries JM, Lekkerkerk L-v. Colonization resistance of the digestive tract in conventional and antibiotic-treated mice. *J Hyg (Lond)*. 1971 Sep; 69(3):405–411. PubMed PMID: 4999450. Pubmed Central PMCID: 2130899. Epub 1971/09/01. eng. [PubMed: 4999450]
4. Chen X, Katchar K, Goldsmith JD, Nanthakumar N, Cheknis A, Gerding DN, et al. A mouse model of *Clostridium difficile*-associated disease. *Gastroenterology*. 2008 Dec; 135(6):1984–1992. PubMed PMID: 18848941. Epub 2008/10/14. eng. [PubMed: 18848941]
5. Voelker R. Increased *Clostridium difficile* virulence demands new treatment approach. *Jama*. 2010 May 26; 303(20):2017–2019. PubMed PMID: 20501917. Epub 2010/05/27. eng. [PubMed: 20501917]
6. McFee RB, Abdelsayed GG. *Clostridium difficile*. *Dis Mon*. 2009 Jul; 55(7):439–470. PubMed PMID: 19540996. Epub 2009/06/23. eng. [PubMed: 19540996]
7. Khanna S, Pardi DS. The growing incidence and severity of *Clostridium difficile* infection in inpatient and outpatient settings. *Expert Rev Gastroenterol Hepatol*. 2010 Aug; 4(4):409–416. PubMed PMID: 20678014. Epub 2010/08/04. eng. [PubMed: 20678014]
8. Dubberke ER, Olsen MA. Burden of *Clostridium difficile* on the healthcare system. *Clin Infect Dis*. 2012 Aug; 55(Suppl 2):S88–S92. PubMed PMID: 22752870. Pubmed Central PMCID: 3388018. Epub 2012/07/07. eng. [PubMed: 22752870]
9. Johnson S, Gerding DN. *Clostridium difficile*-associated diarrhea. *Clin Infect Dis*. 1998 May; 26(5):1027–1034. quiz 35-6. PubMed PMID: 9597221. Epub 1998/05/23. eng. [PubMed: 9597221]

10. Bartlett JG. *Clostridium difficile* : progress and challenges. Ann N Y Acad Sci. 2010 Dec.1213:62–69. PubMed PMID: 21175676. Epub 2010/12/24. eng. [PubMed: 21175676]
11. Limbago BM, Long CM, Thompson AD, Killgore GE, Hannett GE, Havill NL, et al. *Clostridium difficile* strains from community-associated infections. J Clin Microbiol. 2009 Sep; 47(9):3004–3007. PubMed PMID: 19571021. Pubmed Central PMCID: 2738099. Epub 2009/07/03. eng. [PubMed: 19571021]
12. Kelly CP. Current strategies for management of initial *Clostridium difficile* infection. Journal of hospital medicine : an official publication of the Society of Hospital Medicine. 2012 Mar; 7(Suppl 3):S5–S10. PubMed PMID: 22407996. [PubMed: 22407996]
13. McFarland LV, Surawicz CM, Greenberg RN, Fekety R, Elmer GW, Moyer KA, et al. A randomized placebo-controlled trial of *Saccharomyces boulardii* in combination with standard antibiotics for *Clostridium difficile* disease. Jama. 1994 Jun 22–29; 271(24):1913–1918. PubMed PMID: 8201735. [PubMed: 8201735]
14. McFarland LV, Elmer GW, Surawicz CM. Breaking the cycle: treatment strategies for 163 cases of recurrent *Clostridium difficile* disease. The American journal of gastroenterology. 2002 Jul; 97(7):1769–1775. PubMed PMID: 12135033. [PubMed: 12135033]
15. Britton RA, Young VB. Interaction between the intestinal microbiota and host in *Clostridium difficile* colonization resistance. Trends Microbiol. 2012 Jul; 20(7):313–319. PubMed PMID: 22595318. Epub 2012/05/19. eng. [PubMed: 22595318]
16. Lawley TD, Walker AW. Intestinal colonization resistance. Immunology. 2013 Jan; 138(1):1–11. PubMed PMID: 23240815. Pubmed Central PMCID: 3533696. [PubMed: 23240815]
17. Eiseman B, Silen W, Bascom GS, Kauvar AJ. Fecal enema as an adjunct in the treatment of pseudomembranous enterocolitis. Surgery. 1958 Nov; 44(5):854–859. PubMed PMID: 13592638. [PubMed: 13592638]
18. Zhang F, Luo W, Shi Y, Fan Z, Ji G. Should we standardize the 1,700-year-old fecal microbiota transplantation? The American journal of gastroenterology. 2012 Nov.107(11):1755. author reply p-6. PubMed PMID: 23160295. [PubMed: 23160295]
19. Kassam Z, Lee CH, Yuan Y, Hunt RH. Fecal Microbiota Transplantation for *Clostridium difficile* Infection: Systematic Review and Meta-Analysis. The American journal of gastroenterology. 2013 Apr; 108(4):500–508. PubMed PMID: 23511459. [PubMed: 23511459]
20. Brandt LJ, Aroniadis OC, Mellow M, Kanatzar A, Kelly C, Park T, et al. Long-term follow-up of colonoscopic fecal microbiota transplant for recurrent *Clostridium difficile* infection. The American journal of gastroenterology. 2012 Jul; 107(7):1079–1087. PubMed PMID: 22450732. [PubMed: 22450732]
21. Aroniadis OC, Brandt LJ. Fecal microbiota transplantation: past, present and future. Current opinion in gastroenterology. 2013 Jan; 29(1):79–84. PubMed PMID: 23041678. [PubMed: 23041678]
22. Brandt LJ, Aroniadis OC. An overview of fecal microbiota transplantation: techniques, indications, and outcomes. Gastrointest Endosc. 2013 May 2. PubMed PMID: 23642791.
23. Borody TJ, Campbell J. Fecal microbiota transplantation: techniques, applications, and issues. Gastroenterology clinics of North America. 2012 Dec; 41(4):781–803. PubMed PMID: 23101687. [PubMed: 23101687]
24. Gough E, Shaikh H, Manges AR. Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent *Clostridium difficile* infection. Clin Infect Dis. 2011 Nov; 53(10):994–1002. PubMed PMID: 22002980. [PubMed: 22002980]
25. van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, et al. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. The New England journal of medicine. 2013 Jan 31; 368(5):407–415. PubMed PMID: 23323867. [PubMed: 23323867]
26. Hamilton MJ, Weingarten AR, Sadowsky MJ, Khoruts A. Standardized frozen preparation for transplantation of fecal microbiota for recurrent *Clostridium difficile* infection. The American journal of gastroenterology. 2012 May; 107(5):761–767. PubMed PMID: 22290405. [PubMed: 22290405]

27. Kahn SA, Vachon A, Rodriguez D, Goeppinger SR, Surma B, Marks J, et al. Patient Perceptions of Fecal Microbiota Transplantation for Ulcerative Colitis. *Inflammatory bowel diseases*. 2013 Apr 24. PubMed PMID: 23624888.
28. Borody TJ, Khoruts A. Fecal microbiota transplantation and emerging applications. *Nature reviews Gastroenterology & hepatology*. 2012 Feb; 9(2):88–96. PubMed PMID: 22183182.
29. de Leon LM, Watson JB, Kelly CR. Transient Flare of Ulcerative Colitis after Fecal Microbiota Transplantation for Recurrent *Clostridium difficile* Infection. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*. 2013 May 10. PubMed PMID: 23669309.
30. Zipursky JS, Sidorsky TI, Freedman CA, Sidorsky MN, Kirkland KB. Patient attitudes toward the use of fecal microbiota transplantation in the treatment of recurrent *Clostridium difficile* infection. *Clin Infect Dis*. 2012 Dec; 55(12):1652–1658. PubMed PMID: 22990849. [PubMed: 22990849]
31. Reeves AE, Koenigskecht MJ, Bergin IL, Young VB. Suppression of *Clostridium difficile* in the Gastrointestinal Tracts of Germfree Mice Inoculated with a Murine Isolate from the Family *Lachnospiraceae*. *Infect Immun*. 2012 Nov; 80(11):3786–3794. PubMed PMID: 22890996. Pubmed Central PMCID: 3486043. Epub 2012/08/15. eng. [PubMed: 22890996]
32. Lawley TD, Clare S, Walker AW, Stares MD, Connor TR, Raisen C, et al. Targeted restoration of the intestinal microbiota with a simple, defined bacteriotherapy resolves relapsing *Clostridium difficile* disease in mice. *PLoS pathogens*. 2012; 8(10):e1002995. PubMed PMID: 23133377. Pubmed Central PMCID: 3486913. [PubMed: 23133377]
33. Petrof E, Gloor G, Vanner S, Weese S, Carter D, Daigneault M, et al. Stool substitute transplant therapy for the eradication of *Clostridium difficile* infection: 'RePOOPulating' the gut. *Microbiome*. 2013; 1(1):3. PubMed PMID: doi: 10.1186/2049-2618-1-3. [PubMed: 24467987]
34. Johnston BC, Ma SS, Goldenberg JZ, Thorlund K, Vandvik PO, Loeb M, et al. Probiotics for the prevention of *Clostridium difficile*-associated diarrhea: a systematic review and meta-analysis. *Ann Intern Med*. 2012 Dec 18; 157(12):878–888. PubMed PMID: 23362517. [PubMed: 23362517]