REFERENSI

1.Shreiner, A. B., Kao, J. Y., & Young, V. B. (2015). The gut microbiome in health and in disease. Current Opinion in Gastroenterology, 31(1),69-75.

2.Pearson-Leary, J., Zhao, C., Bittinger, K., Eacret, D., Luz, S., Vigderman, A. S., Bhatnagar, S. (2019). The gut microbiome regulates the increases in depressive-type behaviors and in inflammatory processes in the ventral hippocampus of stress vulnerable rats. Molecular Psychiatry.

3.John F Cryan, Kenneth J O'Riordan, Kiran Sandhu, Veronica Peterson, Timothy G Dinan (2019). The gut microbiome in neurological disorders. Molecular Psychiatry.

4. Fontana, Panebianco, Picchianti-Diamanti, Laganà, Cavalieri, Potenza, Pazienza. (2019). Gut Microbiota Profiles Differ among Individuals Depending on Their Region of Origin: An Italian Pilot Study. International Journal of Environmental Research and Public Health, 16(21), 4065.

5. Aira, A., Fehér, C., Rubio, E., & Soriano, A. (2019). The Intestinal Microbiota as a Reservoir and a Therapeutic Target to Fight Multi-Drug-Resistant Bacteria: A Narrative Review of the Literature. Infectious Diseases and Therapy.

6. Aira, A., Fehér, C., Rubio, E., & Soriano, A. (2019). The Intestinal Microbiota as a Reservoir and a Therapeutic Target to Fight Multi-Drug-Resistant Bacteria: A Narrative Review of the Literature. Infectious Diseases and Therapy.

7. Collado MC, Rautava S, Isolauri E, Salminen S (2015). Gut microbiota: a source of novel tools to reduce the risk of human disease? Pediatr Res;77:182e8.

8. Gupta A, Khanna S. Fecal microbiota transplantation. (2017) JAMA;318:102.

9.Ianiro, G., Maida, M., Burisch, J., Simonelli, C., Hold, G., Ventimiglia, M., Cammarota, G. (2018). Efficacy of different faecal microbiota transplantation protocols for Clostridium difficile infection: A systematic review and meta-analysis. United European Gastroenterology Journal, 205064061878076.

10.Ge Hong (2016). Handbook of Emergency Conditions. 1st edition. Beijing: China Chinese Medicine Publisher.

11.Eiseman B, Silen W, Bascom GS, Kauvar AJ. Fecal enema as an adjunct in the treatment of pseudomembranous enterocolitis. Surgery. 1958;44:854–859.

12. Van Nood, E., Vrieze, A., Nieuwdorp, M., Fuentes, S., Zoetendal, E. G., de Vos, W. M., Keller, J. J. (2013). Duodenal Infusion of Donor Feces for Recurrent Clostridium difficile. New England Journal of Medicine, 368(5), 407–415.

13. Tetro JA. Applications of Fecal Microbiota Transplantation - The Human Microbiome Handbook. 2016

14. Colleen R. Kelly et all,. Fecal Microbiota Transplant is Highly Effective in Real-World Practice: Initial Results from the FMT National Registry. Gastroenterology, 2020.

15.Kashyap, P. C., Chia, N., Nelson, H., Segal, E., & Elinav, E. (2017). Microbiome at the Frontier of Personalized Medicine. Mayo Clinic Proceedings, 92(12), 1855–1864.

16.Kelly CR, Kahn S, Kashyap P, et al. Update on fecal microbiota transplantation 2015: indications, methodologies, mechanisms, and outlook. Gastroenterology. 2015;149:223-237.

17.Bakken JS, Borody T, Brandt LJ, et al. Treatment of Clostridium difficile infection with fecal microbiota transplantation. Clin Gastroenterol Hepatol. 2011;9(12):1044-1049.

18.Vindigni SM, Surawicz CM. Fecal microbiota transplantation. Gastroenterol Clin North Am. 2017;46:171–185

19.Kelly BJ, Tebas P. Clinical practice and infrastructure review of fecal microbiota transplantation for Clostridium difficile infection. Chest. 2018;153:266–277

20. Choi HH, Cho YS. Fecal microbiota transplantation: current applications, effectiveness, and future perspectives. Clin Endosc 2016;49:257e65

21.Kassam Z., Dubois N.E., Ling K., Ramakrisnha B., Quazi T., Allegretti J.R., Fischer M., Kelly C.R., Budree S., Panchal P., et al. 512—Donor Health Screening for Fecal Microbiota Transplantation: Prospective Evaluation of 15,317 Candidate Donors. Gastroenterology. 2019;156:S100–S101.

22. Bakken J.S., Polgreen P.M., Beekmann S.E., Riedo F.X., Streit J.A. Treatment approaches including fecal microbiota transplantation for recurrent Clostridium difficile infection (RCDI) among infectious disease physicians. Anaerobe. 2013;24:20–24.

23. Cammarota G, Ianiro G, Gasbarrini A. Fecal microbiota transplantation for the treatment of Clostridium difficile infection: a systematic review. J Clin Gastroenterol. 2014 Sep;48(8):693-702.

24.Cammarota G., Ianiro G., Kelly C.R., Mullish B.H., Allegretti J.R., Kassam Z., Putignani L., Fischer M., Keller J.J., Costello S.P., et al. International consensus conference on stool banking for faecal microbiota transplantation in clinical practice. Gut. 2019;68:2111–2121.

25.Cammarota G, Ianiro G, Tilg H, Rajilic-Stojanovic M, Kump P, Satokari R, et al. European consensus conference on faecal microbiota transplantation in clinical practice. Gut 2017;66: 569e80.

26.Fecal microbiota for transplantation: new safety information regarding additional protections for screening donors for COVID-19 and exposure to SARS-CoV-2 and testing for SARS-CoV-2. FDA. April 9, 2020. Accessed September 30, 2020. https://www.fda.gov/safety/medical-product-safety-information/fecal-microbiota-transplantation-new-safety-information-regarding-additional-protections-screening

27.Cammarota G, Ianiro G, Tilg H, Rajilic-Stojanovic M, Kump P, Satokari R, et al. European consensus conference on faecal microbiota transplantation in clinical practice. Gut 2017;66: 569e80.

28.Gough E, Shaikh H, Manges AR. Systematic review of microbiota transplantation (fecal bacteriotherapy) for recurrent Clostridium difficile infection. Clin Infect Dis. 2011;53(10):994–1002.

29.Abdali, Z. I., Roberts, T. E., Barton, P., & Hawkey, P. M. (2020). Economic evaluation of Faecal microbiota transplantation compared to antibiotics for the treatment of recurrent Clostridioides difficile infection. EClinicalMedicine, 24, 100420.

30.Youngster I, Sauk J, Pindar C, Wilson RG, Kaplan JL, Smith MB, et al. Fecal microbiota transplant for relapsing Clostridium difficile infection using a frozen inoculum from unrelated do- nors: a randomized, open-label, controlled pilot study. Clin Infect Dis 2014;58:1515e22.

31.Kao D, Roach B, Silva M, Beck P, Rioux K, Kaplan GG, et al. Effect of oral capsule- vs colonoscopy-delivered fecal micro- biota transplantation on recurrent Clostridium difficile infec- tion: a randomized clinical trial. JAMA 2017;318:1985e93.

32.Allegretti JR, Kassam Z, Osman M, Budree S, Fischer M, Kelly CR. The 5D framework: a clinical primer for fecal microbiota transplantation to treat Clostridium difficile infection. Gastrointest Endosc. 2018;87:18–29.

33.Fischer M, Kao D, Mehta SR, et al. Predictors of early failure after fecal microbiota transplantation for the therapy of Clostridium difficile infection: a multicenter study. Am J Gastroenterol. 2016;111:1024–1031

34. Blackburn LM, Bales A, Caldwell M, Cordell L, Hamilton S, Kreider H. Fecal microbiota transplantation in patients with cancer undergoing treatment. Clin J Oncol Nurs 2015;19: 111e4.

35.Goloshchapov, O.V., Olekhnovich, E.I., Sidorenko, S.V. et al. Long-term impact of fecal transplantation in healthy volunteers. BMC Microbiol 19, 312 (2019).

36. 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. Am J Gastroenterol 2012;107:1079e87.

37. Quera R, Espinoza R, Estay C, Rivera D. Bacteremia as an adverse event of fecal microbiota transplantation in a patient with Crohn's disease and recurrent Clostridium difficile infec- tion. J Crohns Colitis 2014;8:252e3.

38.Kelly CR, Ihunnah C, Fischer M, Khoruts A, Surawicz C, Afzali A, et al. Fecal microbiota transplant for treatment of Clostridium difficile infection in immunocompromised patients. Am J Gas- troenterol 2014;109:1065e71

39. Tang G, Yin W, Liu W. Is frozen fecal microbiota transplantation as effective as fresh fecal microbiota transplantation in patients with recurrent or refractory Clostridium difficile infection: a meta-analysis? Diagn Microbiol Infect Dis 2017;88: 322e9

40.David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature 2014;505:559e63

41. Roshan, N., Clancy, A.K. & Borody, T.J. Faecal Microbiota Transplantation is Effective for the Initial Treatment of *Clostridium difficile* Infection: A Retrospective Clinical Review. *Infect Dis Ther* (2020).

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4. National Symposium Hasanuddin Scientific Fair (HSF) MYRC 2019

Riwayat Prestasi

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REVIEW

The gut microbiome in health and in disease

Andrew B. Shreiner[a], John Y. Kao[a], and Vincent B. Young[b]

Purpose of review
Recent technological advancements and expanded efforts have led to a tremendous growth in the collective knowledge of the human microbiome. This review will highlight some of the important recent findings in this area of research.

Recent findings
Studies have described the structure and functional capacity of the bacterial microbiome in the healthy state and in a variety of disease states. Downstream analyses of the functional interactions between the host and its microbiome are starting to provide mechanistic insights into these interactions. These data are anticipated to lead to new opportunities for diagnosis, prognosis, and treatment of a variety of human diseases.

Summary
There is a fast growing collection of data describing the structure and functional capacity of the microbiome in a variety of conditions available to the research community for consideration and further exploration. Ongoing efforts to further characterize the functions of the microbiome and the mechanisms underlying host–microbe interactions will provide a better understanding of the role of the microbiome in health and disease.

Keywords
disease, dysbiosis, gut microbiome, health, microbiota

INTRODUCTION

The human microbiome is composed of bacteria, archaea, viruses, and eukaryotic microbes that reside in and on our bodies. These microbes have tremendous potential to impact our physiology, both in health and in disease. They contribute metabolic functions, protect against pathogens, educate the immune system, and, through these basic functions, affect directly or indirectly most of our physiologic functions.

The study of the human microbiome has been furthered by technological advancements for performing culture-independent analyses [1]. In most studies, the bacterial constituents of a microbial population are identified by sequencing of the 16S rRNA-encoding gene (hereafter, 16S) followed by comparison to known bacterial sequence databases. Metagenomic analysis by sequencing all microbial DNA in a complex community has the additional advantage of assessing the genetic potential of the microbial population. Other methodologies to analyze the microbial transcriptome, proteome, and metabolome provide additional information at successive levels of microbial physiology [2]. We will not go into further detail on specific technical considerations in this space, but interested readers are referred to recent review articles [3–5].

Great progress in characterizing the structure of the microbiome recently has paved the way for ongoing and future studies on the functional interactions between the microbiota and the host. Studies on the function of the microbiota will be critical to understanding the role of the microbiota in human homeostasis and disease pathogenesis. In this review, we will discuss recent advancements in our understanding of the structure and function of the microbiome associated with the healthy state and with specific diseased states.

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ARTICLE

The gut microbiome regulates the increases in depressive-type behaviors and in inflammatory processes in the ventral hippocampus of stress vulnerable rats

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Abstract

Chronic exposure to stress is associated with increased incidence of depression, generalized anxiety, and PTSD. However, stress induces vulnerability to such disorders only in a sub-population of individuals, as others remain resilient. Inflammation has emerged as a putative mechanism for promoting stress vulnerability. Using a rodent model of social defeat, we have previously shown that rats with short-defeat latencies (SL/vulnerable rats) show increased anxiety- and depression-like behaviors, and these behaviors are mediated by inflammation in the ventral hippocampus. The other half of socially defeated rats show long-latencies to defeat (LL/resilient) and are similar to controls. Because gut microbiota are important activators of inflammatory substances, we assessed the role of the gut microbiome in mediating vulnerability to repeated social defeat stress. We analyzed the fecal microbiome of control, SL/vulnerable, and LL/resilient rats using shotgun metagenome sequencing and observed increased expression of immune-modulating microbiota, such as *Clostridia*, in SL/vulnerable rats. We then tested the importance of gut microbiota to the SL/vulnerable phenotype. In otherwise naive rats treated with microbiota from SL/vulnerable rats, there was higher microglial density and IL-1β expression in the vHPC, and higher depression-like behaviors relative to rats that received microbiota from LL/resilient rats, non-stressed control rats, or vehicle-treated rats. However, anxiety-like behavior during social interaction was not altered by transplant of the microbiome of SL/vulnerable rats into non-stressed rats. Taken together, the results suggest the gut microbiome contributes to the depression-like behavior and inflammatory processes in the vHPC of stress vulnerable individuals.

Introduction

Chronic stress increases the risk of developing many psychiatric disorders such as anxiety, depression, and post-traumatic stress disorder [1–3]. While these disorders can be triggered or increased by chronic stress, not all individuals develop psychiatric disorders in response to chronic stress [4–8]. The mechanisms underlying vulnerability to stress are unclear, however, mounting evidence suggests that increased central inflammatory processes may be involved. Indeed, inflammatory cytokines are elevated in depressed patients [9–11], and numerous animal studies have shown inflammatory mechanisms underlie depressive-type behaviors [9, 10, 12]. In a recent study in rats, we showed that vulnerability to social defeat is due, in part, to increases in pro-inflammatory processes and vascular remodeling in the ventral hippocampus (vHPC) [13]. Increased vascular density following vascular remodeling can facilitate neural transmission and communication across the so-called neurovascular unit [14], thereby promoting increased activity in stress-sensitive regions. These data are consistent with studies suggesting that inflammation is a contributing factor in stress-related mood disorders [15–18].

Supplementary information The online version of this article (https://doi.org/10.1038/s41380-019-0380-x) contains supplementary material, which is available to authorized users.

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Article

Gut Microbiota Profiles Differ among Individuals Depending on Their Region of Origin: An Italian Pilot Study

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Abstract: Background and aims: Microbiota heterogeneity among humans is mainly due to genetic background, age, dietary habits, lifestyle and local environments. In this study we investigated whether the gut microbiota profile of Italian healthy volunteers could differ based on their geographical origin. Materials and Methods: 16S rRNA gene sequencing was employed to analyze the gut microbiota of 31 healthy volunteers from three different Italian regions: Apulia (South), Lazio (Center) and Lombardy (North). Results: Differences in microbiota composition were detected when the study participants were grouped by their region of origin and when they were classified based on age classes (p-values < 0.05). Also species richness was significantly different both according to Italian Regions (median richness: 177.8 vs. 140.7 vs. 168.0 in Apulia, Lazio and Lombardy; $p < 0.001$) and according to age classes (median richness: 140.1 vs. 177.8 vs. 160.0 in subjects < 32, 32–41 and > 41 years; $p < 0.001$), whereas the Shannon index and beta diversity did not change. Conclusions: This study identified differences in the gut microbiota composition and richness among individuals with the same ethnicity coming from three different Italian regions. Our results underline the importance of studies on population-specific variations in human microbiota composition leading to geographically tailored approaches to microbiota engineering.

Keywords: microbiota; eubiosis; dysbiosis; geographical location

1. Introduction

The human microbiota with its 10^{14} symbiotic and pathogen microorganisms living within host's body, mostly (99%) in the gut [1], of almost 1.8 kg in weight, was considered the "forgotten" or "hidden" organ [2] due to its involvement in several physiological and pathological processes [3]. Although one third of our gut microbiota is in common with most of the people, the remaining two thirds is

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REVIEW

The Intestinal Microbiota as a Reservoir and a Therapeutic Target to Fight Multi-Drug-Resistant Bacteria: A Narrative Review of the Literature

Andrea Aira · Csaba Fehér · Elisa Rubio · Alex Soriano

Received: September 13, 2019

ABSTRACT

The appearance and dissemination of antibiotic-resistant bacteria, particularly in specific closed environments such as intensive care units of acute care hospitals, have become a major health concern. The intestinal microbiota has various functions including host protection from overgrowth or colonization by unwanted bacteria. The exposure to antibiotics significantly reduces the bacterial density of intestinal microbiota leaving an ecologic void that can be occupied by potentially pathogenic and/or resistant bacteria frequently present in hospital settings. Consequently, the intestinal microbiota of inpatients acts as a major reservoir and plays a critical role in perpetuating the spread of resistant bacteria. There are novel innovative methods to protect the host microbiota during antibiotic treatment, but they do not offer a solution for already established colonization by resistant microorganisms. Fecal microbiota transfer (FMT) is a promising intervention to achieve this goal; however, controlled trials report lower success rates than initial retrospective studies, especially in case of gram negatives. The aim of the present article is to highlight the importance of the intestinal microbiota in the global spread of multi-drug-resistant (MDR) microorganisms and to review the recent advances to protect the human microbiota from the action of antibiotics as well as a critical discussion about the evidence of decolonization of MDR microorganisms by FMT.

Keywords: Decolonization; Fecal microbiota transfer (FMT); Fecal microbiota transplant; Intestinal microbiota; Multi-drug-resistant (MDRO) bacteria; Reservoir

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Gut microbiota: source of novel tools to reduce the risk of human disease?

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Fecal Microbiota Transplantation

Fecal microbiota transplantation, also known as stool transplantation, is a procedure in which stool from a healthy donor is placed into another patient's intestine.

Candidate Patients for Stool Transplantation

Stool transplantation is used for difficult-to-treat or recurrent (3 or more episodes) *Clostridium difficile* infection. The intestines contain hundreds of types of bacteria. When the numbers of healthy bacteria decrease, often because of antibiotic use, harmful *C difficile* bacteria may proliferate and cause diarrhea. Although certain antibiotics treat *C difficile*, some individuals may not respond to these drugs; these patients may be helped by a stool transplant. Transplanting stool from healthy donors restores the balance of healthy bacteria and helps clear infection.

How Is Stool Transplantation Performed?

There are different ways to transplant stool, but in most cases, patients have a colonoscopy during which a health care clinician puts small amounts of liquefied and filtered stool into the colon. Other methods may be used, such as through a feeding tube, enema, or capsules.

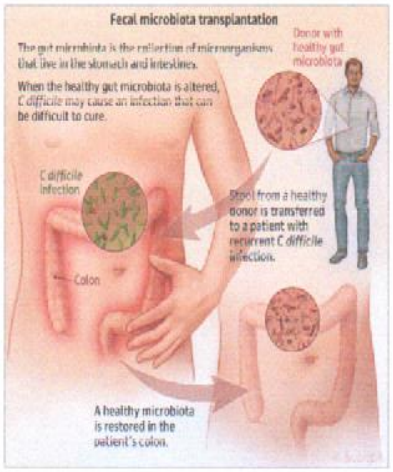
Stool may be available from healthy volunteers, a family member, or a friend. Stool donors should be free of illnesses and undergo a thorough medical evaluation to ensure optimal health; blood tests for human immunodeficiency virus and hepatitis A, B, and C viruses; and stool tests for bacterial, viral, and parasitic infections.

Symptomatic patients may need to undergo therapy with antibiotics to manage *C difficile*, which are then stopped at least 24 hours before the procedure for most patients. Other antibiotics should ideally be discontinued.

It is not recommended to perform stool transplantation at home without guidance from a physician.

Side Effects

The side effects of stool transplantation include mild and self-limiting abdominal discomfort, cramping, bloating, diarrhea or constipation, and, rarely, transmission of diseases that cannot be tested for by screening. You should seek medical attention if you experience fever, severe abdominal pain or swelling, or vomiting or stool that contains fresh (bright red) or old (black) blood.



Other Uses and Insurance Coverage

Stool transplantation is being studied for treatment of other disorders such as inflammatory bowel disease, but its use in these conditions is limited to research settings.

The US Food and Drug Administration permits stool transplantation after adequate donor screening and a discussion about risks and benefits. There may be a need for insurance prior authorization before stool transplantation. Contact your insurance company.

FOR MORE INFORMATION

American Gastroenterology Association
www.gastro.org/info_for_patients/clostridium-difficile-106-fmt-details

To find this and other JAMA Patient Pages, go to the For Patients collection at *jamanetworkpatientpages.com*.

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Source: Lee CH, Steiner T, Petrof EO, et al. Frozen vs fresh fecal microbiota transplantation and clinical resolution of diarrhea in patients with recurrent *Clostridium difficile* infection: a randomized clinical trial. *JAMA*. 2016;315(2):142-149.

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Efficacy of different faecal microbiota transplantation protocols for *Clostridium difficile* infection: A systematic review and meta-analysis

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Abstract

Background: Protocols for treating recurrent *Clostridium difficile* infection (rCDI) through faecal microbiota transplantation (FMT) are still not standardised. Our aim was to evaluate the efficacy of different FMT protocols for rCDI according to routes, number of infusions and infused material.

Methods: MEDLINE, Embase, SCOPUS, Web of Science and the Cochrane Library were searched through 31 May 2017. Studies offering multiple infusions if a single infusion failed to cure rCDI were included. Data were combined through a random effects meta-analysis.

Results: Fifteen studies (1150 subjects) were analysed. Multiple infusions increased efficacy rates overall (76% versus 93%) and in each route of delivery (duodenal delivery: 73% with single infusion versus 81% with multiple infusions; capsule: 80% versus 92%; colonoscopy: 78% versus 98% and enema: 56% versus 92%). Duodenal delivery and colonoscopy were associated, respectively, with lower efficacy rates ($p = 0.039$) and higher efficacy rates ($p = 0.006$) overall. Faecal amount ≤ 50 g ($p = 0.006$) and enema ($p = 0.019$) were associated with lower efficacy rates after a single infusion. The use of fresh or frozen faeces did not influence outcomes.

Conclusions: Routes, number of infusions and faecal dosage may influence efficacy rates of FMT for rCDI. These findings could help to optimise FMT protocols in clinical practice.

Keywords

Clostridium difficile, systematic review, meta-analysis, faecal microbiota transplantation, faecal transplant

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Key summary

- Faecal microbiota transplantation (FMT) is highly effective against recurrent *Clostridium difficile* infection (rCDI).
- However, there is still no clear evidence supporting the superiority of one working protocol over another.
- Routes of delivery, number of infusions and faecal dosage may influence efficacy of FMT for rCDI.
- These findings may be useful to optimise FMT protocols in clinical practice.

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Ge Hong and *Zhou Hou Jiu Zu Fang (A Handbook of Formulas for Emergencies)*

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Ge Hong (283–363), also known as Ge Yachuan and Bao Po Zi from Danyang (present Jurong, Jiangsu Province) was a famous Taoism theorist, herbalist and alchemist. He was of good stock, clever and keen to learn. But later he suffered a fall in his family fortune. Then he had to cut firewood as a career and bought pen, ink and paper after the firewood was sold. In the evening, he threw himself into readings and copying out books. He was well-read because he could even travel thousands of miles to look for ancient books and records.[1] Since his youth, he began to be interested in eternal life, so he started to learn alchemy from Zheng Yin, a diviner. In 303, he was appointed a general with the title of marquis by the imperial court because he had successfully put down a peasant uprising. The emperor wanted to favor him with high position and salary for several times which was turned down by him. For the sake of easy study of alchemy, he finally volunteered to be a county magistrate in Guangdong Province abounded in raw materials for alchemy. When he was proceeding to his post, he formerly took Bao Liang, Prefecture Chief of Nanhai as his master and learned skills of health preservation and medicine. Bao highly appreciated his talent and character. He decided to betroth his daughter Bao Gu to him.

Soon afterwards, Ge spent latter half of his life in seclusion in Luofu Mountain, Guangdong Province, where he engaged in alchemy, gathering herbs and writing books. Later, Bao Gu, his wife, became the first female acupuncturist in China.

Ge was a prolific writer, but most of his books are lost. After widely collection of predecessors' medical formulas, folk and secret recipes, he eventually wrote *Jin Gui Yao Fang (Prescriptions of Golden Chamber)*, a large-scale medical book with 100 volumes. In consideration of easy reading and carrying, on the basis of the book he compiled a new book known as *Zhou Hou Jiu Zu Fang (A Handbook of Formulas for Emergencies)*. This is a medical book dealing with emergencies[2] and most of the medicinal herbs listed in it are those easily to get in countryside. Indications are narrated in verses for easy memorization and the acupuncture techniques are simply described for easy practice and study.

Stroke, coma, acute abdomen, etc. are firstly discussed in this book. In the treatment of coma, it is recommended to heavily press GV 26 (Renzhong) with fingernail or do moxibustion on CV 24 (Chengjiang) under the lips. Other first-aid for coma includes blowing pinellia tuber powder into the nose, or putting a calamus pill as large as a jujube pit under the tongue. These simple emergency treatments are still used today. The book records a lot of diseases, covering acute infectious disease, parasitic disease, and therapies for internal medicine, gynecology, pediatrics and ENT. It's worth noting that it made a profound statement about cause, symptoms and treatment of some diseases which had not been clearly expounded previously. For example, in the part of treatment of malaria, the book records an anti-malarial herb. It says: "Have a handful of herb of sweet wormwood and soak it in two *sheng* (200 mL) of water. Squeeze it to get the juice and drink."[3] Such short remarks not only tell us about its efficacy but also lay the reliable foundation for the development of new anti-malarial agents. Prof. Tu Youyou was inspired by what Ge said and extracted artemisinin from it. Artemisinin is a new

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ORIGINAL ARTICLE

Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

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ABSTRACT

BACKGROUND

Recurrent *Clostridium difficile* infection is difficult to treat, and failure rates for antibiotic therapy are high. We studied the effect of duodenal infusion of donor feces in patients with recurrent *C. difficile* infection.

METHODS

We randomly assigned patients to receive one of three therapies: an initial vancomycin regimen (500 mg orally four times per day for 4 days), followed by bowel lavage and subsequent infusion of a solution of donor feces through a nasoduodenal tube; a standard vancomycin regimen (500 mg orally four times per day for 14 days); or a standard vancomycin regimen with bowel lavage. The primary end point was the resolution of diarrhea associated with *C. difficile* infection without relapse after 10 weeks.

RESULTS

The study was stopped after an interim analysis. Of 16 patients in the infusion group, 13 (81%) had resolution of *C. difficile*–associated diarrhea after the first infusion. The 3 remaining patients received a second infusion with feces from a different donor, with resolution in 2 patients. Resolution of *C. difficile* infection occurred in 4 of 13 patients (31%) receiving vancomycin alone and in 3 of 13 patients (23%) receiving vancomycin with bowel lavage ($P<0.001$ for both comparisons with the infusion group). No significant differences in adverse events among the three study groups were observed except for mild diarrhea and abdominal cramping in the infusion group on the infusion day. After donor-feces infusion, patients showed increased fecal bacterial diversity, similar to that in healthy donors, with an increase in Bacteroidetes species and clostridium clusters IV and XIVa and a decrease in Proteobacteria species.

CONCLUSIONS

The infusion of donor feces was significantly more effective for the treatment of recurrent *C. difficile* infection than the use of vancomycin. (Funded by the Netherlands Organization for Health Research and Development and the Netherlands Organization for Scientific Research; Netherlands Trial Register number, NTR1177.)

From the Departments of Internal Medicine (E.N., A.V., M.N., P.S.), Microbiology (C.E.V.), Gastroenterology (J.F.W.M.B., J.J.K.), and Cardiology (J.G.P.T.) and the Clinical Research Unit (M.G.W.D.), Academic Medical Center, University of Amsterdam, Amsterdam; the Laboratory of Microbiology, Wageningen University, Wageningen (S.F., E.G.Z., W.M.V.); the Department of Experimental and Medical Microbiology, Leiden University Medical Center, Leiden (E.J.K.); and the Department of Gastroenterology, Hagaziekenhuis, The Hague (J.J.K.) — all in the Netherlands; and the Department of Bacteriology and Immunology, Medical Faculty, University of Helsinki, Helsinki (W.M.V.). Address reprint requests to Dr. Keller at the Academic Medical Center, Department of Gastroenterology, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands, or at keller@hagaziekenhuis.nl.

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The Human Microbiome Handbook

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Journal Pre-proof

Fecal Microbiota Transplant is Highly Effective in Real-World Practice: Initial Results from the FMT National Registry

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Microbiome at the Frontier of Personalized Medicine

Purna C. Kashyap, MBBS; Nicholas Chia, PhD; Heidi Nelson, MD; Eran Segal, PhD; and Eran Elinav, MD, PhD

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Abstract

The genomic revolution promises to transform our approach to treat patients by individualizing treatments, reducing adverse events, and decreasing health care costs. The early advances using this have been realized primarily by optimizing preventive and therapeutic approaches in cancer using human genome sequencing. The ability to characterize the microbiome, which includes all the microbes that reside within and upon us and all their genetic elements, using next-generation sequencing allows us to now incorporate this important contributor to human disease into developing new preventive and therapeutic strategies. In this review we highlight the importance of the microbiome in all aspects of human disease, including pathogenesis, phenotype, prognosis, and response to treatment, as well as their role as diagnostic and therapeutic biomarkers. We provide a role for next-generation sequencing in both precise microbial identification of infectious diseases and characterization of microbial communities and their function. Taken together, the microbiome is emerging as an integral part of precision medicine approach as it not only contributes to interindividual variability in all aspects of a disease but also represents a potentially modifiable factor that is amenable to targeting by therapeutics.

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Update on FMT 2015: Indications, Methodologies, Mechanisms and Outlook

Members of the Steering Committee for the AGA FMT Registry, Colleen R. Kelly, MD, Stacy Kahn, MD, Purna Kashyap, MBBS, Loren Laine, MD, David Rubin, MD, Ashish Atreja, MD, MPH, Thomas Moore, MD, Gary Wu, MD

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PERSPECTIVE

Treating *Clostridium difficile* Infection With Fecal Microbiota Transplantation

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***Clostridium difficile* infection is increasing in incidence, severity, and mortality. Treatment options are limited and appear to be losing efficacy. Recurrent disease is especially challenging; extended treatment with oral vancomycin is becoming increasingly common but is expensive. Fecal microbiota transplantation is safe, inexpensive, and effective; according to case and small series reports, about 90% of patients are cured. We discuss the rationale, methods, and use of fecal microbiota transplantation.**

Keywords: Clostridium difficile; Transplantation; Microbiota; Fecal Enema; Recurrent Infection; Diarrhea.

During the last 15 years, *Clostridium difficile* infection (CDI) has become epidemic and continues to gain momentum, with greater incidence, morbidity, and mortality than in past decades. In the United States, the National Hospital Discharge Survey revealed doubling of CDI diagnoses from 31/100,000 in 1996 to 61/100,000 in 2003.[1] This rise has been accompanied by increasing rates of colectomy and mortality during the same time period.[2] In 2010, the yearly incidence of CDI was estimated at 500,000, with mortality at 15,000–20,000,[3–5] and the cost of managing CDI was estimated to be at least $1 billion per year in the U.S. alone.[6] One major reason for this growing problem is the emergence of newer, more virulent, and more antibiotic-resistant strains including North American pulsed-field gel electrophoresis type 1, restriction endonuclease analysis group BI, and polymerase chain reaction (PCR) ribotype 027 (NAP1/BI/027) among others.[7,8] Although acquisition of CDI still occurs most commonly in health care facilities, it is increasingly recognized that CDI can also be acquired in the community by young, healthy individuals without prior exposure to antibiotics or hospitals. Furthermore, patients at greater risk are no longer just elderly people but also patients with inflammatory bowel disease, compromised immune systems, and peripartum women.[5,8]

As the *C difficile* epidemic continues to grow, the numbers of failed treatments and patients who experience relapses or recurrences also are increasing. Metronidazole and vancomycin are the first-line agents for *C difficile* treatment; however, recent data suggest that metronidazole is losing its efficacy, and expert opinion is shifting toward the use of vancomycin as first-line therapy.[9] Furthermore, the rates of recurrent and severe CDI continue to increase despite the efficacy of these agents. Recurrent CDI has been documented to occur in as many as 15%–30% of patients after an initial bout of CDI, and up to 65% of patients who experience 1 recurrence will have subsequent recurrences after antibiotic therapy is stopped.[10,11] Recurrent CDI can turn into a chronic, recalcitrant disease in which repeated bouts of infection can continue for years, leading to persistent use of antibiotics, repeated hospitalizations, and even death.

The basic pathophysiology of recurrent CDI is not completely understood. Antibiotics suppress and disrupt the distal bowel microbial communities that normally keep expansion of *C difficile* populations in check. Because *C difficile* spores are largely resistant to antibiotics, they can germinate back into vegetative forms after antibiotic treatment has been discontinued. If residual normal intestinal microbiota cannot restrain the infection, *C difficile* bacteria proliferate and once again produce toxins that cause destruction of colonic epithelial cells and return of inflammation with resultant disease symptoms. Although spores are thought to play a role in the pathophysiology of recurrent CDI, some patients might become reinfected

Abbreviations used in this paper: **CDI, *Clostridium difficile* infection; EIA, enzyme immunoassay; FDA, Food and Drug Administration; FMT, fecal microbiota transplantation; GI, gastrointestinal; HAV, hepatitis A virus; HCT/Ps, human cell tissues and cellular tissue-based products; HIV, human immunodeficiency virus; IBS, irritable bowel syndrome; Ig, immunoglobulin; IVIG, intravenous immunoglobulin; mTOR, mammalian target of rapamycin; PCR, polymerase chain reaction.**

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Fecal Microbiota Transplantation

Stephen M. Vindigni, MD, MPH[a,*], Christina M. Surawicz, MD[b]

KEYWORDS

- *Clostridium difficile* • Fecal microbiota transplant • Stool transplant • FMT • Microbiome

KEY POINTS

- Fecal microbiota transplantation (FMT) is effective for treatment of recurrent *Clostridium difficile* infection (CDI) when standard therapy has failed.
- FMT may have a role in some patients with severe and complicated CDI.
- The following factors are important in selecting patients for FMT:
  - Appropriate indications.
  - Appropriate donor selection.
  - Appropriate method of administering FMT.
  - Appropriate follow-up.

INTRODUCTION

Fecal microbiota transplantation (FMT) is the transfer of stool from a "healthy" donor to a recipient believed to harbor an altered colonic microbiome resulting in disease. The goal is to restore eubiosis, or a "healthy" microbiome. Often referred to as stool transplantation, fecal transplantation, fecal flora reconstitution, or fecal bacteriotherapy, FMT has increasingly become a focus in both the public media and peer-reviewed literature. FMT is an effective treatment strategy for recurrent *Clostridium difficile* infection (rCDI) that has not responded to standard therapy. There is interest in using

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[Topics in Practice Management]

CHEST

Clinical Practice and Infrastructure Review of Fecal Microbiota Transplantation for *Clostridium difficile* Infection

Brendan J. Kelly, MD, MSCE; and Pablo Tebas, MD

A significant proportion of *Clostridium difficile* infection (CDI) cases recur after completion of antibiotic therapy, and antibiotic cure rates diminish with each recurrence of CDI. Fecal microbiota transplantation (FMT) is an effective therapy for recurrent FMT, which otherwise requires prolonged or indefinite antibiotic treatment. FMT is performed by introducing the fecal microbial community obtained from a healthy donor or pool of donors into the stomach, small intestine, or colon of a patient with CDI. Multiple clinical trials support the usefulness of FMT in treating recurrent CDI, and CDI treatment guidelines now include consideration of FMT at the third CDI recurrence. However, there remain significant challenges to incorporating FMT into clinical practice. First, methods of fecal bacterial community processing vary, as do methods of FMT administration. Second, the optimal dosing strategy and expected benefit of FMT for refractory CDI, particularly for severe and severe complicated cases, are uncertain. Third, the US Food and Drug Administration (FDA) considers FMT an investigational treatment. Fourth, insurance reimbursement for FMT usually falls short of FMT administration costs. In the setting of rising *C difficile* incidence and growing evidence for FMT efficacy, the demand for FMT has increased. However, uncertainty surrounding optimal FMT preparation and administration methods, FDA oversight, and insurance reimbursement presently limits the clinical practice of FMT.

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KEY WORDS: *Clostridium difficile* infection; fecal microbiota transplantation; microbiome

Clostridium difficile infection (CDI) is a clinical syndrome typically characterized by loose, frequent bowel movements and abdominal pain, which occur as a result of toxin production by colonic *C difficile*.[1-4] CDI occurs in patients colonized with toxigenic *C difficile* and in patients who have newly acquired *C difficile*. Estimates of the relative contributions of persistent colonization and new acquisition to incident CDI vary.[5,6] In both cases, the pathogenesis of CDI involves depletion of non-*C difficile* colonic microbiota, altered bile acid metabolism, germination of (resident or recently ingested) *C difficile* spores, expansion of a population of vegetative *C difficile*, toxin production, and colonic inflammation.[7-12]

ABBREVIATIONS: CDI = *Clostridium difficile* infection; EIA = enzyme immunoassay; FDA = Food and Drug Administration; FMT = fecal microbiota transplantation; GDH = glutamate dehydrogenase; IBD = inflammatory bowel disease; IBS = irritable bowel syndrome; IND = Investigational New Drug; MDRO = multidrug-resistant organism; NAAT = nucleic acid amplification test; R-CDI = recurrent *C difficile* infection; SC-CDI = severe complicated *C difficile* infection

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Fecal Microbiota Transplantation: Current Applications, Effectiveness, and Future Perspectives

Hyun Ho Choi and Young-Seok Cho

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Fecal microbiota transplantation (FMT) is the infusion of liquid filtrate feces from a healthy donor into the gut of a recipient to cure a specific disease. A fecal suspension can be administered by nasogastric or nasoduodenal tube, colonoscope, enema, or capsule. The high success rate and safety in the short term reported for recurrent *Clostridium difficile* infection has elevated FMT as an emerging treatment for a wide range of disorders, including Parkinson's disease, fibromyalgia, chronic fatigue syndrome, myoclonus dystopia, multiple sclerosis, obesity, insulin resistance, metabolic syndrome, and autism. There are many unanswered questions regarding FMT, including donor selection and screening, standardized protocols, long-term safety, and regulatory issues. This article reviews the efficacy and safety of FMT used in treating a variety of diseases, methodology, criteria for donor selection and screening, and various concerns regarding FMT. **Clin Endosc 2016;49:257-265**

Key Words: Fecal microbiota transplantation; *Clostridium difficile* infection; Colitis, ulcerative; Crohn disease; Irritable bowel syndrome

INTRODUCTION

The gut microbiota provides an intestinal biological barrier against pathogens and has a pivotal role in the maintenance of intestinal homeostasis and modulation of the host immune system.[1] The specific changes in the composition of gut microbiota, termed dysbiosis, have been associated not only with many gastrointestinal (GI) diseases but also with metabolic diseases, autoimmune diseases, allergic disorders, and neuropsychiatric disorders.[2] Restoring a healthy microbial community is therefore a promising therapeutic strategy for diseases related with gut dysbiosis.[3] Fecal microbiota transplantation (FMT), also called stool/fecal transplantation or fecal bacteriotherapy, is the infusion or engraftment of liquid filtrate feces from a healthy donor into the gut of a recipient to cure a specific disease.[4] The concept of FMT for treatment of human GI disease was described approximately 1,700 years ago by a Chinese medical scientist named Ge Hong.[5] At that time, he orally administered human fecal suspension to treat patients who had food poisoning or severe diarrhea. Borody et al.[4] and Brandt et al.[6] noted that FMT may have been first used in veterinary medicine by the Italian anatomist Fabricius Aquapendente in the 17th century. It was first reported in the English language by Eiseman et al.,[7] who used fecal enemas to treat pseudomembranous colitis in 1958. Recently, FMT is becoming interesting with its effectiveness in treating refractory and recurrent *Clostridium difficile* infection (CDI) and the possibilities for treating other diverse conditions.[8] We review the efficacy of FMT used in treating a variety of diseases and preclinical conditions. In addition, we describe the methodology, criteria for donor selection and screening, and safety data.

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CORRESPONDENCE

Donor Screening for Fecal Microbiota Transplantation

TO THE EDITOR: Fecal microbiota transplantation (FMT) has emerged as a treatment for recurrent *Clostridioides difficile* infection.[1] Procurement of safe donors for FMT and for biologically sourced microbiome therapies is complex, particularly given recent concerns over antibiotic-resistant bacteria (including emerging resistant strains), and there is a paucity of data on the identification of appropriate donors.[2] Current studies highlight considerable variability in donor eligibility rates, ranging from 2 to 32%, despite the use of similar screening programs, but the studies are small.[3,4] Accordingly, we characterized the reasons for exclusion and report the eligibility rate for donors from a stool bank (OpenBiome, Cambridge, MA).

Enrollment was conducted prospectively in a four-stage process that included oversight by an institutional review board, and all participants provided informed consent (see the Supplementary Appendix and the protocol, available with the full text of this letter at NEJM.org). In stage 1, donor candidates completed an online prescreening survey for assessment of their general health and risk of infectious disease and to determine whether they met any criteria for exclusion (see the Supplementary Appendix). Obesity (body-mass index [the weight in kilograms divided by the square of the height in meters] greater than 30) and active cigarette smoking were criteria for exclusion because they are associated with perturbations in the gut microbiome.[3-5] For logistical reasons, candidates who did not live in the same region as the donation facility or were unable to donate on a regular basis were excluded. In stage 2, eligible participants were invited to complete a 200-item clinical assessment and an in-person evaluation (see the Supplementary Appendix). This evaluation was conducted to exclude risk factors for transmissible diseases and potential microbiome-mediated conditions and was performed by a trained nurse or physician and overseen by an internal medicine specialist at a single center. The risk factors included gastrointestinal, autoimmune, atopic, allergic, metabolic, neurologic, and psychiatric conditions that have been associated with an abnormal intestinal microbiome profile.[3] Prospective donors subsequently completed stage 3, which involved stool and nasal screening. In 2016, enhanced testing was added for the following antibiotic-resistant bacteria: carbapenem-resistant Enterobacteriaceae (CRE), extended-spectrum beta-lactamase–producing (ESBL) organisms, and methicillin-resistant *Staphylococcus aureus* (MRSA). Stage 4, which involved serologic laboratory screening (see the Supplementary Appendix), was then completed.

From February 2014 through April 2018, the donor program prospectively evaluated 15,317 consecutive donor candidates (Fig. 1, and Tables S3 through S6 in the Supplementary Appendix). At the prescreening survey (stage 1), 10,046 candidates (66%) were excluded, and an additional 4700 (89%) were excluded at clinical assessment (stage 2). The remaining candidates underwent stool and nasal screening (stage 3), and 166 (29%) were excluded, including 3 candidate donors for antibiotic-resistant bacteria (each had a positive test result for vancomycin-resistant enterococcus; none were positive for CRE, MRSA, or ESBL). At stage 4, a total of 19 participants (5%) were excluded on serologic screening, including 6 who had infectious disease (3 with a positive test for strongyloides, 2 with human T-lymphotropic virus type 1 or type 2, and 1 with hepatitis B virus). Overall, 386 participants qualified as donors, resulting in a 3% qualification rate. This experience highlights the point that healthy, screened donors are not easy to find.

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Clinical microbiology

Treatment approaches including fecal microbiota transplantation for recurrent *Clostridium difficile* infection (RCDI) among infectious disease physicians

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ABSTRACT

Background: *Clostridium difficile* infection (CDI) was the most common nosocomial infection in the U.S. in 2010. Most cases of CDI respond to a standard course of antibiotics, but recurrent *C. difficile* infections (RCDI) are increasingly common. Given the lack of randomized clinical trials, it is important to understand how infectious disease physicians are managing RCDI to inform future clinical research.

Methods: An electronic survey was conducted among members of the Emerging Infections Network (EIN) in October 2012. Respondents were asked to answer specific questions about their treatment approaches toward patients with CDI, including fecal microbiota transplantation (FMT).

Results: The overall response rate was 621/1212 (51%). The vast majority of respondents had cared for small to moderate numbers of patients with CDI over the prior 6 months, and reported recurrence rates were consistent with published data. Preferred treatment regimens for RCDI showed significant variance from recommendations published in national guidelines. Eighty percent (424/527) of the respondents would consider FMT for patients with RCDI, and of 149 who had FMT available at their institution, 107 (72%) had actually treated >1 patient with FMT in the preceding year. However, significant barriers to institutional adoption of FMT remain for many respondents, despite very good success rates with its use.

Conclusions: Physicians who regularly care for patients with CDI use a variety of treatment approaches for treating severe or recurrent CDI cases. The results of our survey demonstrate that FMT is used by a growing number of infectious disease providers as an effective and safe treatment alternative for patients with multiple recurrences of *C. difficile* infection.

1. Background

Clostridium difficile infection (CDI) is a nosocomial infection that has steadily increased in incidence and severity during the last decade [1]. CDI was reported as the leading nosocomial infection in the United States in 2011 [2]. The spectrum of CDI ranges from mild watery diarrhea to fulminant pseudomembranous colitis associated with significant morbidity and mortality [3]. Most cases are a consequence of a preceding treatment with antimicrobial agent(s), and fluoroquinolones, cephalosporins, and clindamycin are associated with the highest risk for CDI [3,5]. Factors that predispose to CDI recurrence include age older than 65 years, low serum albumin concentration, recent abdominal surgery, prolonged hospitalization and stay in the intensive care unit [1,3–5]. Patients who have suffered one recurrence of CDI after antibiotic treatment are at increased risk for subsequent episodes of diarrhea [6,7].

CDI usually responds to treatment with oral metronidazole or vancomycin, but between 5 and 35% of treated patients experience recurrent diarrhea in spite of appropriate therapy [3,4]. Unfortunately, alternative treatment strategies with new antimicrobials (e.g., rifaximin, nitazoxanide, tolevamer, and fidaxomicin) have failed to consistently demonstrate a significant benefit in the treatment of recurrent *C. difficile* infections (RCDI) [3,4]. Due to the limited treatment effectiveness of many therapeutic approaches to RCDI, fecal microbiota transplantation (FMT, previously known as fecal transplantation therapy) has been used to successfully treat

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Fecal Microbiota Transplantation for the Treatment of *Clostridium difficile* Infection

A Systematic Review

Giovanni Cammarota, MD, Gianluca Ianiro, MD, and Antonio Gasbarrini, MD

Goal: By systematic review, we assessed the impact of fecal microbiota transplantation (FMT) for the treatment of *Clostridium difficile* (CD)-associated diarrhea.

Background: Fecal microbiota microbiota transplantation from a healthy donor into an individual with CD infection (CDI) can resolve symptoms.

Study: We conducted systematic searches in PubMed, SCOPUS, Web of Science, and Cochrane Library. The last search was run on February 8, 2013. The following Medical Subject Headings terms and keywords were used alone or in combination: *Clostridium difficile*; Clostridium infection; pseudomembranous colitis; feces; stools; fecal suspension; fecal transplantation; fecal transfer; fecal infusion; microbiota; bacteriotherapy; enema; nasogastric tube; colonoscopy; gastroscopy; fecal donation; donor. A critical appraisal of the clinical research evidence on the effectiveness and safety of FMT for the treatment of patients with CD-associated diarrhea was made.

Results: Twenty full-text case series, 15 case reports, and 1 randomized controlled study were included for the final analysis. Almost all patients treated with donors' fecal infusion experienced recurrent episodes of CD-associated diarrhea despite standard antibiotic treatment. Of a total of 536 patients treated, 467 (87%) experienced resolution of diarrhea. Diarrhea resolution rates varied according to the site of infusion: 81% in the stomach; 86% in the duodenum/jejunum; 93% in the cecum/ascending colon; and 84% in the distal colon. No severe adverse events were reported with the procedure.

Conclusions: FMT seems efficacious and safe for the treatment of recurrent CDI. Hospitals should encourage the development of fecal transplantation programs to improve therapy of local patients.

Key Words: *Clostridium difficile*, fecal microbiota transplantation, recurrent, treatment

(*J Clin Gastroenterol* 2014;48:693–702)

Fecal microbiota transplantation (FMT) was performed since 1958 against pseudomembranous colitis and has now reached the stage where it is considered a reliable and effective form of treatment against *Clostridium difficile* (CD) infection.[1]

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CDI causes severe diarrhea, intestinal inflammation, and cell death as a result of toxin-mediated infection with the pathogenic bacteria.[2] During the past several years, *Clostridium difficile*–associated diarrhea (CDAD) has become more frequent, more severe, more refractory to standard therapy, and more likely to relapse.[2–4] This pattern is widely observed in Canada, the United States, and Europe and is attributed to a new more virulent strain of CD called NAP1/B1/027.[5–7] Patients are typically treated with antibiotics, which not only kill the pathogenic CD but also exhibit activity against the dominant colonic microbiota phyla. The standard first-line treatment envisages the possibility of using vancomycin or metronidazole, with a 97% or 87% eradication rate, respectively. However, after an initial therapeutic success, 20% to 35% of patients treated experience a first recurrence of the infection, which occurs as a consequence of the persistence of spores or reinfection.[2,8] Some patients experience multiple recurrences, leading to repeated bouts of diarrhea and long courses of antibiotic therapy.[9,10] Continued disruption of the normal colonic microflora by repeated cycles of antibiotic therapy used to treat recurrent CDI perpetuates the risk of repeated recurrences. A total of 40% to 45% of them has a second recurrence, and after 2 or 3 recurrences 60% to 65% of the patients have multiple recurrences.[2,4,8–15] Relapse is more frequent in long-term inpatients who are over 65 years of age.[10,16,17] Recurrent CDI greatly exposes to the risk of severe complications (septic shock, perforation).[2,3]

DESCRIPTION OF FMT

Transplantation of fecal microbiota from a healthy donor into an individual with CDI can restore the healthy gut microbiota in the patient's diseased colon, leading to the resolution of symptoms. The exact mechanism that achieved this normalization remains to be elucidated. It is plausible that the reconstruction and function of intestinal microbiota is of paramount importance, as it is a crucial resistance factor against CD and other pathogens, with mechanisms including resistance to bacterial colonization and immune stimulation.[18]

FMT refers to the process of instilling a liquid suspension of stool from a healthy donor into the patient's gastrointestinal (GI) tract. FMT can be considered a form of "organ transplantation." The idea of a human microbial organ is a novel notion, which is well supported by modern science.[19] FMT is certainly simpler to perform than other organ transplants, without the need for immunologic matching of donor and recipient, or the need for immunesuppression after the procedure. FMT can be performed by various routes, depending on which is deemed safest for the

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International consensus conference on stool banking for faecal microbiota transplantation in clinical practice

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ABSTRACT

Although faecal microbiota transplantation (FMT) has a well-established role in the treatment of recurrent *Clostridioides difficile* infection (CDI), its widespread dissemination is limited by several obstacles, including lack of dedicated centres, difficulties with donor recruitment and complexities related to regulation and safety monitoring. Given the considerable burden of CDI on global healthcare systems, FMT should be widely available to most centres.

Stool banks may guarantee reliable, timely and equitable access to FMT for patients and a traceable workflow that ensures safety and quality of procedures. In this consensus project, FMT experts from Europe, North America and Australia gathered and released statements on the following issues related to the stool banking: general principles, objectives and organisation of the stool bank; selection and screening of donors; collection, preparation and storage of faeces; services and clients; registries, monitoring of outcomes and ethical issues; and the evolving role of FMT in clinical practice.

Consensus on each statement was achieved through a Delphi process and then in a plenary face-to-face meeting. For each key issue, the best available evidence was assessed, with the aim of providing guidance for the development of stool banks in order to promote accessibility to FMT in clinical practice.

INTRODUCTION

Faecal microbiota transplantation (FMT) has a well-established role in the treatment of recurrent *Clostridioides difficile* infection (CDI).[1–13] FMT working protocols have undergone considerable advancements in recent years, including the use of frozen faeces,[2] capsules[6] and the release of guidelines to provide methodological guidance.[14–17]

Despite these improvements, the dissemination of FMT has been limited owing to lack of dedicated centres, difficulties with donor recruitment, regulatory and safety concerns. Given the increasing burden of CDI,[18 19] the provision of FMT should be widely and rapidly accessible. Moreover, as recently highlighted in a warning from the Food and Drug Administration (FDA), FMT requires strict quality control to prevent harmful consequences.[20]

Stool banks can provide reliable, timely and equitable access to FMT for CDI, and also facilitate a standardised, cost-effective and traceable workflow that ensures safety and quality of procedures[21] compared with single FMT centres. Stool banks are currently unevenly distributed and differ considerably in legislation, organisation and structure.[22–24]

The aim of this consensus report is to provide guidance on the general organisation and the criteria required to establish a stool bank.

METHODS

Consensus development process

The consensus process was developed according to the following steps: selection of expert panel members, identification of key issues and related working group (WG), development of statements based on best available evidence, achievement of consensus through the Delphi technique and a face-to-face final meeting.

Twenty-nine consensus members, with documented expertise in the field of FMT and stool banking, took part in the expert panel. Based on personal expertise, each member was assigned to one of six WGs: general principles, objectives and organisation of the stool bank; selection and screening of donors; collection, preparation and storage of faeces; services and clients; registries, monitoring of outcomes, and ethical issues; and update on FMT in clinical practice. Each WG proposed a list of key issues and developed statements related to the assigned topic(s).

For each key issue, the best available evidence was obtained through a systematic review of the pertinent literature. If the related statements were suitable for Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment, based on PICO (population, intervention, comparator, outcome) questions, they have been graded accordingly.[25 26] Otherwise, statements were released only as expert opinions.

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European consensus conference on faecal microbiota transplantation in clinical practice

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ABSTRACT

Faecal microbiota transplantation (FMT) is an important therapeutic option for *Clostridium difficile* infection. Promising findings suggest that FMT may play a role also in the management of other disorders associated with the alteration of gut microbiota. Although the health community is assessing FMT with renewed interest and patients are becoming more aware, there are technical and logistical issues in establishing such a non-standardised treatment into the clinical practice with safety and proper governance. In view of this, an evidence-based recommendation is needed to drive the practical implementation of FMT. In this European Consensus Conference, 28 experts from 10 countries collaborated, in separate working groups and through an evidence-based process, to provide statements on the following key issues: FMT indications; donor selection; preparation of faecal material; clinical management and faecal delivery and basic requirements for implementing an FMT centre. Statements developed by each working group were evaluated and voted by all members, first through an electronic Delphi process, and then in a plenary consensus conference. The recommendations were released according to best available evidence, in order to act as guidance for physicians who plan to implement FMT, aiming at supporting the broad availability of the procedure, discussing other issues relevant to FMT and promoting future clinical research in the area of gut microbiota manipulation. This consensus report strongly recommends the implementation of FMT centres for the treatment of *C. difficile* infection as well as traces the guidelines of technicality, regulatory, administrative and laboratory requirements.

INTRODUCTION

Faecal microbiota transplantation (FMT) consists of the infusion of faeces from a healthy donor to the GI tract of a recipient patient, in order to treat a specific disease associated with alteration of gut microbiota. A large body of evidence, including randomised controlled trials (RCTs), systematic reviews and meta-analyses, proved clear evidence that FMT is a highly effective treatment against recurrent *Clostridium difficile* infection (rCDI).[1–7] Due to the rising prevalence, severity and mortality of this infection, the therapeutic role played by FMT is therefore important to save human lives and to decrease the economic burden on healthcare systems.[8–11] Based on these data, both the European Society for Microbiology and Infectious Disease and the American College of Gastroenterology recommend FMT as a treatment for rCDI.[12 13]

Beyond the treatment of CDI, FMT has also been investigated in other disorders associated with the alteration of gut microbiota. In particular, studies in humans include RCTs in patients with UC and metabolic syndrome (MS).[14–16]

The global interest in FMT is increasing, and both doctors and patients are increasingly aware and informed. Although the dissemination of FMT in the clinical practice is restricted by regulatory and bureaucratic issues (principally related to costs, donor programme, safety control),[17–19] the FMT practice is booming, ranging from highly organised stool banking programmes to individual treatments with patient-identified directed donors, and even to individual and harmful do-it-yourself practices. Working groups (WGs) from the USA, Austria and France released recommendations on indications and methods of FMT.[20–22] Authoritative published guidelines and recommendations have been released as expert opinions rather than evidence-based consensus reports. A rigorous and formal evidence-based process to drive the wide range of FMT practice has not been performed yet.

The aim of this evidence-based consensus report is to define indications and methodology for the use of FMT in the treatment of CDI, to discuss the suitability of FMT for indications other than CDI and to address the minimum requirements needed to implement a FMT centre. The final aim is to encourage and drive the dissemination of the procedure and to promote further clinical research in the area.

METHODS

Consensus development process

The process of development of the consensus conference, aimed at drawing up evidence-based recommendations for the use of FMT in clinical practice, included the following steps: selection of

REVIEW ARTICLE

Systematic Review of Intestinal Microbiota Transplantation (Fecal Bacteriotherapy) for Recurrent *Clostridium difficile* Infection

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***Clostridium difficile* infection (CDI) is a gastrointestinal disease believed to be causally related to perturbations to the intestinal microbiota. When standard treatment has failed, intestinal microbiota transplantation (IMT) is an alternative therapy for patients with CDI. IMT involves infusing intestinal microorganisms (in a suspension of healthy donor stool) into the intestine of a sick patient to restore the microbiota. However, protocols and reported efficacy for IMT vary. We conducted a systematic literature review of IMT treatment for recurrent CDI and pseudomembranous colitis. In 317 patients treated across 27 case series and reports, IMT was highly effective, showing disease resolution in 92% of cases. Effectiveness varied by route of instillation, relationship to stool donor, volume of IMT given, and treatment before infusion. Death and adverse events were uncommon. These findings can guide physicians interested in implementing the procedure until better designed studies are conducted to confirm best practices.**

Clostridium difficile infection (CDI) is a gastrointestinal disease believed to be causally related to perturbations to the intestinal microbiota [1]. The term *microbiota* refers to the community of microorganisms that inhabit a particular region of the body [2]. In the human gut, there are ~300–500 species of microorganisms (intestinal microbiota), with roughly 10^{12} bacterial cells per gram of stool [3]. These organisms aid in several functions, including digestion of complex carbohydrates, energy storage, immune functions, and protection against invasion by pathogens [3]. Existing evidence shows that certain classes of antimicrobials have profound effects on the intestinal microbiota [4]. The widely accepted model for *C. difficile* pathogenesis is that the use of broad spectrum antimicrobials alters the balance of the intestinal microbiota, allowing pathogenic strains of *C. difficile* to infect the intestine [1–3].

Primary episodes of CDI are treated with metronidazole or vancomycin after cessation of the antibiotic believed to be related to the infection [4], and up to 35% of patients treated experience a recurrence of symptoms after initial improvement [5, 6]. Up to 65% of these patients develop a chronic recurrent pattern of disease (recurrent CDI) [1, 5]. Recurrent CDI is typically treated using a tapered (31% recurrence rate) or pulsed (14% recurrence rate) regimen of metronidazole or vancomycin [4, 5]. Given the poor treatment outcomes for CDI, especially recurrent CDI, it is not surprising that investigation of treatment alternatives has continued over several decades [2, 4, 7–9].

One potential alternative to standard therapy is the use of indigenous intestinal microorganisms from a healthy donor (via infusion of a liquid suspension of stool) to restore the intestinal microbiota of a diseased individual. First documented in humans in 1958 [10], fecal bacteriotherapy, also called intestinal microbiota transplantation (IMT), may be a useful treatment for CDI through restoration of the intestinal microbiota [5].

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Research Paper

Economic evaluation of Faecal microbiota transplantation compared to antibiotics for the treatment of recurrent *Clostridioides difficile* infection

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Vancomycin

ABSTRACT

Background: *Clostridioides difficile* infection (CDI) is a hospital acquired disease associated with significant morbidity, hospitalisation and mortality. Almost 30% of treated patients experience at least one recurrence after treatment of their first episode. Treatment of recurrent CDI (rCDI) utilises vancomycin or fidaxomicin, however, a newer treatment option is faecal microbial transplantation (FMT) administered by nasogastric tube (NGT) or colonoscopy. It is associated with higher cure and lower recurrence rates than fidaxomicin or vancomycin. The aim of this analysis is to evaluate the cost effectiveness of FMT for rCDI using the latest and best evidence.

Method: A cost utility analysis was conducted using a decision model representing the cost per additional Quality Adjusted Life Year (QALY) from a National Health Service (NHS) perspective. A Markov model was constructed to compare FMT NGT and colonoscopy to antibiotic treatment (fidaxomicin or vancomycin). The model was informed by a literature review of clinical evidence, specifically focussing on hospitalised patients with rCDI over 65 years. Both deterministic and probabilistic sensitivity analyses were performed to assess uncertainties around the model inputs and assumptions.

Findings: The base case analysis showed that FMT is a less costly and more effective treatment than either fidaxomicin or vancomycin. FMT colonoscopy was slightly more effective than FMT NGT leading to an additional 0.012 QALYs but more expensive and the incremental cost effectiveness ratio (ICER) was £242,514/QALY. The Probabilistic sensitivity analysis based on 10,000 simulations suggested the probability of FMT NGT being cost effective was almost 78% at £20,000/QALY Willingness–To-Pay (WTP) threshold.

Interpretation: FMT is both more effective and less costly option than antimicrobial therapy. FMT NGT was the preferred route of administration and is likely to be considered the most cost-effective strategy by decision makers given current acceptable thresholds.

1. Introduction

Clostridioides difficile infection (CDI) is the leading cause of antibiotic associated gastrointestinal disease causing significant morbidity and mortality [1,2]. The risk factors associated with developing CDI include the excessive use of antibiotics, advanced age, other comorbidities and prolonged hospitalisation [2,3].

Approximately 30% of individuals with CDI will experience either a recurrence or will fail to respond to initial treatment.[1] It is *recurrent* CDI (rCDI) that is both the most dangerous and costly [4-6] with the majority of the costs associated with the required hospital admission. [7,8] The available evidence suggests that rCDI is associated with a substantial risk of death within 6 months of the initial treatment [9].

Standard treatment for rCDI relies on using antibiotics such as fidaxomicin or vancomycin whilst Faecal Microbial Transplantation (FMT) is advocated as an effective alternative to antibiotic treatment for rCDI [2]. To perform FMT, healthy individuals who have been screened for a wide range of potentially transmittable conditions, according to national guidelines, provide faeces for processing [1] [10]. Faeces are then emulsified with a cryoprotectant, filtered and dispensed into aliquots and frozen at −80 °C. [1,10] A number of routes of administration are available: nasogastric tube (NGT), colonoscopy, enema or oral capsules, the first two being the most commonly used [1,11].

The National Institute for Health and Care Excellence (NICE) guidance supports the use of FMT for rCDI where patients fail to respond

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MAJOR ARTICLE

Fecal Microbiota Transplant for Relapsing *Clostridium difficile* Infection Using a Frozen Inoculum From Unrelated Donors: A Randomized, Open-Label, Controlled Pilot Study

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Background. Recurrent *Clostridium difficile* infection (CDI) with poor response to standard antimicrobial therapy is a growing medical concern. We aimed to investigate the outcomes of fecal microbiota transplant (FMT) for relapsing CDI using a frozen suspension from unrelated donors, comparing colonoscopic and nasogastric tube (NGT) administration.

Methods. Healthy volunteer donors were screened and a frozen fecal suspension was generated. Patients with relapsing/refractory CDI were randomized to receive an infusion of donor stools by colonoscopy or NGT. The primary endpoint was clinical resolution of diarrhea without relapse after 8 weeks. The secondary endpoint was self-reported health score using standardized questionnaires.

Results. A total of 20 patients were enrolled, 10 in each treatment arm. Patients had a median of 4 (range, 2–16) relapses prior to study enrollment, with 5 (range, 3–15) antibiotic treatment failures. Resolution of diarrhea was achieved in 14 patients (70%) after a single FMT (8 of 10 in the colonoscopy group and 6 of 10 in the NGT group). Five patients were retreated, with 4 obtaining cure, resulting in an overall cure rate of 90%. Daily number of bowel movements changed from a median of 7 (interquartile range [IQR], 5–10) the day prior to FMT to 2 (IQR, 1–2) after the infusion. Self-ranked health score improved significantly, from a median of 4 (IQR, 2–6) before transplant to 8 (IQR, 5–9) after transplant. No serious or unexpected adverse events occurred.

Conclusions. In our initial feasibility study, FMT using a frozen inoculum from unrelated donors is effective in treating relapsing CDI. NGT administration appears to be as effective as colonoscopic administration.

Clinical Trials Registration. NCT01704937.

Keywords. fecal microbiota transplant; *Clostridium difficile*; microbiome; frozen inoculum.

Recurrent and refractory *Clostridium difficile* infection (CDI) is a growing medical concern, with a recent dramatic increase in the number of patients globally [1–4]. In the United States, the incidence of CDI has tripled over the last 15 years [3]. Response to standard antimicrobial therapy with oral vancomycin or metronidazole is suboptimal, with CDI recurring in up to 30% of individuals treated for a first episode. After 2 or more episodes of CDI, the estimated risk for subsequent recurrence exceeds 60% with antimicrobial therapy [3, 5–8]. Often, patients with recurrent CDI are treated with prolonged administration of oral vancomycin with tapering of the medication over many months, but this approach is poorly studied. The emergence of a virulent strain of the organism (NAP1/BI/027) has been associated with even higher rates of treatment failure [9, 10]. The consequences of recurrence can be

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JAMA | Original Investigation

Effect of Oral Capsule– vs Colonoscopy-Delivered Fecal Microbiota Transplantation on Recurrent *Clostridium difficile* Infection
A Randomized Clinical Trial

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IMPORTANCE Fecal microbiota transplantation (FMT) is effective in preventing recurrent *Clostridium difficile* infection (RCDI). However, it is not known whether clinical efficacy differs by route of delivery.

OBJECTIVE To determine whether FMT by oral capsule is noninferior to colonoscopy delivery in efficacy.

DESIGN, SETTING, AND PARTICIPANTS Noninferiority, unblinded, randomized trial conducted in 3 academic centers in Alberta, Canada. A total of 116 adult patients with RCDI were enrolled between October 2014 and September 2016, with follow-up to December 2016. The noninferiority margin was 15%.

INTERVENTIONS Participants were randomly assigned to FMT by capsule or by colonoscopy at a 1:1 ratio.

MAIN OUTCOMES AND MEASURES The primary outcome was the proportion of patients without RCDI 12 weeks after FMT. Secondary outcomes included (1) serious and minor adverse events, (2) changes in quality of life by the 36-Item Short Form Survey on a scale of 0 (worst possible quality of life) to 100 (best quality of life), and (3) patient perception on a scale of 1 (not at all unpleasant) to 10 (extremely unpleasant) and satisfaction on a scale of 1 (best) to 10 (worst).

RESULTS Among 116 patients randomized (mean [SD] age, 58 [19] years; 79 women [68%]), 105 (91%) completed the trial, with 57 patients randomized to the capsule group and 59 to the colonoscopy group. In per-protocol analysis, prevention of RCDI after a single treatment was achieved in 96.2% in both the capsule group (51/53) and the colonoscopy group (50/52) (difference, 0%; 1-sided 95% CI, −6.1% to infinity; $P < .001$), meeting the criterion for noninferiority. One patient in each group died of underlying cardiopulmonary illness unrelated to FMT. Rates of minor adverse events were 5.4% for the capsule group vs 12.5% for the colonoscopy group. There was no significant between-group difference in improvement in quality of life. A significantly greater proportion of participants receiving capsules rated their experience as "not at all unpleasant" (66% vs 44%; difference, 22% [95% CI, 3%-40%]; $P = .01$).

CONCLUSIONS AND RELEVANCE Among adults with RCDI, FMT via oral capsules was not inferior to delivery by colonoscopy for preventing recurrent infection over 12 weeks. Treatment with oral capsules may be an effective approach to treating RCDI.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT02254811

Editorial page 1979

Supplemental content

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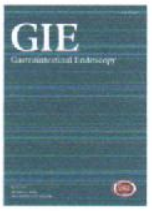

The 5D Framework: A Clinical Primer for Fecal Microbiota Transplantation to Treat *Clostridium difficile infection*

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Predictors of Early Failure After Fecal Microbiota Transplantation for the Therapy of *Clostridium Difficile* Infection: A Multicenter Study

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OBJECTIVES: **Fecal microbiota transplant (FMT) is a highly efficacious treatment for recurrent or refractory *Clostridium difficile* infection (CDI); however, 10–20% of patients fail to achieve cure after a single FMT. The aim of this study was to identify risk factors associated with FMT failure and to develop and validate a prediction model for FMT failure.**

METHODS: **Patient characteristics, CDI history, FMT characteristics, and outcomes data for patients treated between 2011 and 2015 at three academic tertiary referral centers were prospectively collected. Early FMT failure was defined as non-response or recurrence of diarrhea associated with positive stool *C. difficile* toxin or PCR within 1 month of FMT. Late FMT failure was defined as recurrence of diarrhea associated with positive stool *C. difficile* toxin or PCR between 1 and 3 months of the FMT. Patient data from two centers were used to determine independent predictors of FMT failure and to build a prediction model. A risk index was constructed based on coefficients of final predictors. The patient cohort from the third center was used to validate the prediction model.**

RESULTS: **Of 328 patients in the developmental cohort, 73.5% (*N*=241) were females with a mean age of 61.4±19.3 years; 19.2% (*N*=63) had inflammatory bowel disease (IBD), and 23.5% (*N*=77) were immunocompromised. The indication for FMT was recurrent CDI in 87.2% (*N*=286) and severe or severe-complicated in 12.8% (*N*=42). FMT was performed as an inpatient in 16.7% (*N*=54). The stool source was patient-directed donors in 40% (*N*=130) of cases. The early FMT failure rate was 18.6%, and the late failure rate was 2.7%. In the multivariable analysis, predictors of early FMT failure included severe or severe-complicated CDI (odds ratio (OR) 5.95, 95% confidence interval (CI): 2.26–15.62), inpatient status during FMT (OR 3.78, 95% CI: 1.55–9.24), and previous CDI-related hospitalization (OR 1.43, 95% CI: 1.18–1.75); with each additional hospitalization, the odds of failure increased by 43%. Risk scores ranged from 0 to 13, with 0 indicating low risk, 1–2 indicating moderate risk, and ≥3 indicating high risk. In the developmental cohort, early FMT failure rates were 5.6% for low risk, 12.7% for moderate risk, and 41% for high-risk patients. Of 134 patients in the validation cohort, 57% (*N*=77) were females with a mean age of 66±18.1 years; 9.7% (*N*=13) had IBD, and 17.9% (*N*=24) were immunocompromised. The early FMT failure rate at 1 month was 19.4%, with an additional 3% failing by 3 months. In the validation cohort, FMT failure rates were 2.1% for low risk, 16.1% for moderate risk, and 35.7% for high risk patients. The area under the receiver operating characteristic curve (AUROC) for FMT failure was 0.81 in the developmental cohort and 0.84 in the validation cohort.**

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Fecal Microbiota Transplantation in Patients With Cancer Undergoing Treatment

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Fecal microbiota transplantation (FMT) is a technique used to restore the normal body flora to the gut in cases of *Clostridium difficile* infection (CDI). It involves instillation of the stool of a healthy donor through a nasogastric tube or colonoscopy into the gastrointestinal tract of the patient. More research is needed to determine the parameters of FMT use in patients with cancer.

At a Glance

- CDI is common in patients with cancer because of the frequent use of broad-spectrum antibiotics that can alter the normal microbiota in the gastrointestinal tract.
- CDI reoccurs frequently and can be difficult to treat.
- CDI can delay continued treatment, prolong hospitalizations, and greatly affect a patient's quality of life.

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Key words: fecal microbiota transplantation; stool transplantation; *Clostridium difficile*
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Patients with cancer who are undergoing treatment may experience diarrhea for many reasons related to disease (e.g., graft-versus-host disease, intestinal bacteria or virus, obstruction of the bowel) or to therapy (e.g., chemotherapy, medications, nutritional therapy, radiation therapy to the abdomen, surgical resection of the bowel). *Clostridium difficile*, or *C. diff*, is a gram-positive, spore-forming anaerobic bacillus linked to a pathogenic toxin in the stool of patients with pseudomembranous colitis. Complications from diarrhea caused by *C. diff* infection (CDI) can range from dehydration to death. In severe cases of CDI, colectomy may be the only treatment option (Zipursky, Sidorsky, Freedman, Sidorsky, & Kirkland, 2012).

CDI is the leading cause of nosocomial antibiotic-associated diarrhea, and the rates are continuously increasing (Cohen et al., 2010). Recurrence is a common problem that affects more than 20% of patients after their initial course of therapy. In addition, mortality related to CDI has been reported in as many as 6.9% of cases (King & Lager, 2011; Loo et al., 2005).

Because of the increasing frequency of initial CDI, its recurrence, and associated mortality, alternative treatment approaches have been explored. Fecal microbiota transplantation (FMT), also known as stool transplantation, is a therapy designed to restore normal gut microflora, which may in turn protect against toxic CDI. Previously, the use of FMT in immunocompromised patients had been limited because of safety concerns. However, retrospective studies have concluded that FMT is an effective treatment for CDI in this population (Kelly et al., 2014).

Case Study

B.J., a 39-year-old man with T-cell acute lymphocytic leukemia who was treated with adolescent and young adult protocol, was diagnosed with CDI soon after starting induction therapy. He was initially treated with oral vancomycin and IV metronidazole, which resolved his infection.

Several months later, B.J. was admitted to the hospital with neutropenic fever, nausea, vomiting, and diarrhea. B.J. was given IV cefepime and IV vancomycin. A stool culture tested positive for *C. diff* toxin, and B.J. was then administered high-dose oral vancomycin and IV metronidazole. Diarrhea and other symptoms persisted, so B.J. was given oral fidaxomicin. Symptoms continued despite aggressive treatment. Because of recurrence of the CDI, the failed standardized multidrug treatment for CDI, and continued diarrhea symptoms, the physicians and patient agreed to treat the infection with an FMT.

After receiving standard bowel preparation the evening prior, FMT was completed by colonoscopy. Immediately following the procedure, B.J. began to experience relief of symptoms. He reported decreased distension and decreased pain. That evening, he began drinking liquids and advanced his diet quickly with no nausea. B.J. had no bowel movements on the day following FMT, but had one soft bowel movement two days after the procedure. His condition improved so significantly that he was able to be discharged from the

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RESEARCH ARTICLE Open Access

Long-term impact of fecal transplantation in healthy volunteers

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Abstract

Background: Fecal microbiota transplantation (FMT) has been recently approved by FDA for the treatment of refractory recurrent clostridial colitis (rCDI). Success of FTM in treatment of rCDI led to a number of studies investigating the effectiveness of its application in the other gastrointestinal diseases. However, in the majority of studies the effects of FMT were evaluated on the patients with initially altered microbiota. The aim of our study was to estimate effects of FMT on the gut microbiota composition in healthy volunteers and to monitor its long-term outcomes.

Results: We have performed a combined analysis of three healthy volunteers before and after capsule FMT by evaluating their general condition, adverse clinical effects, changes of basic laboratory parameters, and several immune markers. Intestinal microbiota samples were evaluated by 16S rRNA gene and shotgun sequencing. The data analysis demonstrated profound shift towards the donor microbiota taxonomic composition in all volunteers. Following FMT, all the volunteers exhibited gut colonization with donor gut bacteria and persistence of this effect for almost ~1 year of observation. Transient changes of immune parameters were consistent with suppression of T-cell cytotoxicity. FMT was well tolerated with mild gastrointestinal adverse events, however, one volunteer developed a systemic inflammatory response syndrome.

Conclusions: The FMT leads to significant long-term changes of the gut microbiota in healthy volunteers with the shift towards donor microbiota composition and represents a relatively safe procedure to the recipients without long-term adverse events.

Keywords: Fecal microbiota transplantation, Healthy volunteers, Metagenomics, 16S rRNA gene sequencing, Shotgun sequencing, Metagenome-assembled genome, Compositional data analysis

Background

Human gut microbiota is a key player in human body metabolism. Gut microbiota begins to develop from birth and its composition depends on multiple factors: delivery type, nosocomial microflora at the obstetrics unit, maternal diet, breastfeeding etc. [1, 2]. The microbiota is extremely important for the maintenance of physiological homeostasis including synthesis of vitamins and essential amino acids, short-chain fatty acids (SCFA), e.g., butyrate, propionate, acetate which serve as energy substrates for epithelial cells as well as inactivation of toxic substances [3]. Antibacterial and/or cytostatic treatments trigger profound changes in gut microbiota composition reducing bacterial diversity and increasing predominance of pathogenic microorganisms that facilitate damage to a gut epithelium barrier and/or alter immune system response [4].

Fecal microbiota transplantation (FMT) from allogeneic donors has become a popular approach to the

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CME

Long-Term Follow-Up of Colonoscopic Fecal Microbiota Transplant for Recurrent *Clostridium difficile* Infection

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OBJECTIVES: ***Clostridium difficile*** **infection (CDI) has increased to epidemic proportions over the past 15 years, and recurrence rates of 30–65% with failure to respond to multiple courses of antimicrobials are common. The aim of this study was to report the efficacy of fecal microbiota transplantation (FMT) in patients with recurrent CDI in five geographically disparate medical centers across the United States.**

METHODS: **A multicenter long-term follow-up study was performed on the use of FMT for recurrent CDI. We were able to contact 77 of 94 eligible patients who had colonoscopic FMT for recurrent CDI ≥3 months before. Respondents completed a 36-item questionnaire via mail and/or phone that solicited pre-FMT, post-FMT, and donor data. Study outcomes included *primary cure rate* (resolution of symptoms without recurrence within 90 days of FMT) and *secondary cure rate* (resolution of symptoms after one further course of vancomycin with or without repeat FMT).**

RESULTS: **Seventy-three percent of patients were women and the average age was 65 years. The long-term follow-up period ranged from 3 to 68 months between FMT and data collection (mean: 17 months). The majority of patients were living independently at the time of FMT; however, 40% were ill enough to be hospitalized, homebound, or living in a skilled nursing facility. Spouses and partners accounted for 60% of donors and 27% were either first-degree relatives or otherwise related to the patient. The average symptom duration before FMT was 11 months and patients had failed an average of five conventional antimicrobial regimens; nonetheless, 74% of patients had resolution of their diarrhea in ≤3 days. Diarrhea resolved in 82% and improved in 17% of patients within an average of 5 days after FMT. The primary cure rate was 91%. Seven patients either failed to respond or experienced early CDI recurrence (≤90 days) after FMT. Four of these patients were successfully treated with vancomycin with or without probiotics; two patients were treated unsuccessfully with vancomycin, but subsequent FMT was successful; one patient was not treated and died in hospice care of unclear cause. The secondary cure rate was 98%. All late recurrences of CDI occurred in the setting of antimicrobial therapy for treatment of infections unrelated to *C. difficile*. In all, 53% of patients stated they would have FMT as their preferred first treatment option if CDI were to recur. While no definite adverse effects of FMT were noted, two patients had improvement in a pre-existing medical condition and four patients developed diseases of potential interest after FMT.**

CONCLUSIONS: **FMT is a rational, durable, safe, and acceptable treatment option for patients with recurrent CDI.**

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INTRODUCTION

The incidence of *Clostridium difficile* infection (CDI) has increased to epidemic proportion over the past 15 years. In the United States, from 1996 to 2003, CDI doubled from 98,000 to 178,000 cases and from 31 to 61/100,000 hospital discharges (1). Such doubling was accompanied by an increased unadjusted case-fatality rate from 1.2% in 2000 to 2.3% in 2004 (2). It is currently estimated that three million cases of CDI occur per year in US

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LETTER TO THE EDITOR

Bacteremia as an adverse event of fecal microbiota transplantation in a patient with Crohn's disease and recurrent *Clostridium difficile* infection

Dear Sir,

A 61-year-old male with Crohn's disease (CD) compromising jejunum and terminal ileum managed with mesalamine, azathioprine and infliximab. Ever since 2009 our patient has presented a tortuous evolution based on multiple episodes of active CD, acute diverticulitis, *Clostridium difficile* infection (CDI) and bacteremia for multidrug-sensitive *Escherichia coli* (MDSEC) (Fig. 1).

On September 2009 the patient presented fever, after a thorough work-up was done to exclude primary infection sources, bacteremia was confirmed for MDSEC. Treatment consisted in antibiotics (quinolones–cephalosporins) with symptom resolution, similar in the 5 episodes.

In August 2010, CDI was confirmed by A toxin and image of pseudomembranous colitis. We started a 14-day treatment with oral vancomycin with positive clinical response. The third episode, presented a positive clinical course with the same regimen however he relapsed on the third day after treatment. Tapered oral vancomycin was used with satisfactory response. In January 2013, our patient presented CDI that was managed with vancomycin with initial good response but relapsing on the fourth day after treatment. The patient had severe symptoms and required admission (i.v. metronidazole and oral vancomycin). On the third day with no response, we decided to perform Fecal Microbiota Transplantation (FMT) through a colonoscopy. An exhaustive screening was done in donor's blood and stool samples to rule out concomitant pathologies. Infliximab was discontinued 6 weeks before FMT, azathioprine five days before and antibiotics 24 h before. Twenty-four hours after FMT, the patient presented high fever (T° 39 °C) and positive blood cultures for MDSEC strain. Bacteremia was treated with aztreonam (5 days) with excellent clinical and laboratory response. At 5-month follow-up the patient is completely asymptomatic and PCR for *C. difficile* is negative.

Microbial dysbiosis plays a fundamental role in the pathogenesis of inflammatory bowel disease (IBD) and CDI. Recent studies have shown that FMT indices a remarkable change of the microbiota and is an effective alternative in RCDI with >90% success rate[1]. Patients with IBD present a higher risk for CDI, even in the absence of antibiotics use[2]. CDI is a proven factor of relapse and refractoriness of IBD, increasing their morbidity and mortality. There is insufficient information about

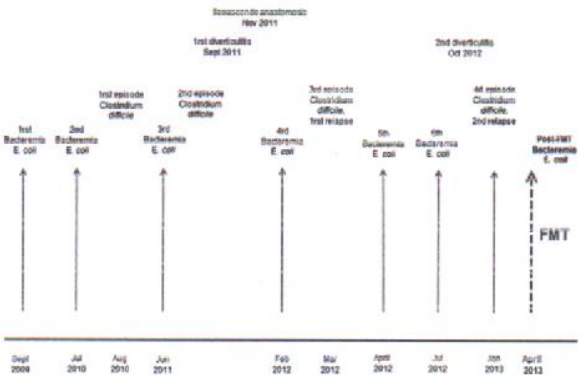

Fig. 1 Temporal evolution of episodes of bacteremia, infection for *Clostridium difficile*, diverticulitis and surgery for Crohn's disease. FMT: fecal microbiota transplantation. *E. coli*: *Escherichia coli*.

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Fecal Microbiota Transplant for Treatment of *Clostridium difficile* Infection in Immunocompromised Patients

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OBJECTIVES: **Patients who are immunocompromised (IC) are at increased risk of *Clostridium difficile* infection (CDI), which has increased to epidemic proportions over the past decade. Fecal microbiota transplantation (FMT) appears effective for the treatment of CDI, although there is concern that IC patients may be at increased risk of having adverse events (AEs) related to FMT. This study describes the multicenter experience of FMT in IC patients.**

METHODS: **A multicenter retrospective series was performed on the use of FMT in IC patients with CDI that was recurrent, refractory, or severe. We aimed to describe rates of CDI cure after FMT as well as AEs experienced by IC patients after FMT. A 32-item questionnaire soliciting demographic and pre- and post-FMT data was completed for 99 patients at 16 centers, of whom 80 were eligible for inclusion. Outcomes included (i) rates of CDI cure after FMT, (ii) serious adverse events (SAEs) such as death or hospitalization within 12 weeks of FMT, (iii) infection within 12 weeks of FMT, and (iv) AEs (related and unrelated) to FMT.**

RESULTS: **Cases included adult (75) and pediatric (5) patients treated with FMT for recurrent (55%), refractory (11%), and severe and/or overlap of recurrent/refractory and severe CDI (34%). In all, 79% were outpatients at the time of FMT. The mean follow-up period between FMT and data collection was 11 months (range 3–46 months). Reasons for IC included: HIV/AIDS (3), solid organ transplant (19), oncologic condition (7), immunosuppressive therapy for inflammatory bowel disease (IBD; 36), and other medical conditions/medications (15). The CDI cure rate after a single FMT was 78%, with 62 patients suffering no recurrence at least 12 weeks post FMT. Twelve patients underwent repeat FMT, of whom eight had no further CDI. Thus, the overall cure rate was 89%. Twelve (15%) had any SAE within 12 weeks post FMT, of which 10 were hospitalizations. Two deaths occurred within 12 weeks of FMT, one of which was the result of aspiration during sedation for FMT administered via colonoscopy; the other was unrelated to FMT. None suffered infections definitely related to FMT, but two patients developed unrelated infections and five had self-limited diarrheal illness in which no causal organism was identified. One patient had a superficial mucosal tear caused by the colonoscopy**

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Colleen R. Kelly affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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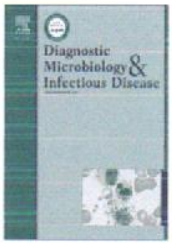

Is frozen fecal microbiota transplantation as effective as fresh fecal microbiota transplantation in patients with recurrent or refractory clostridium difficile infection: a meta-analysis?

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LETTER

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Diet rapidly and reproducibly alters the human gut microbiome

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Long-term dietary intake influences the structure and activity of the trillions of microorganisms residing in the human gut[1–5], but it remains unclear how rapidly and reproducibly the human gut microbiome responds to short-term macronutrient change. Here we show that the short-term consumption of diets composed entirely of animal or plant products alters microbial community structure and overwhelms inter-individual differences in microbial gene expression. The animal-based diet increased the abundance of bile-tolerant microorganisms (*Alistipes*, *Bilophila* and *Bacteroides*) and decreased the levels of Firmicutes that metabolize dietary plant polysaccharides (*Roseburia*, *Eubacterium rectale* and *Ruminococcus bromii*). Microbial activity mirrored differences between herbivorous and carnivorous mammals[2], reflecting trade-offs between carbohydrate and protein fermentation. Foodborne microbes from both diets transiently colonized the gut, including bacteria, fungi and even viruses. Finally, increases in the abundance and activity of *Bilophila wadsworthia* on the animal-based diet support a link between dietary fat, bile acids and the outgrowth of microorganisms capable of triggering inflammatory bowel disease[5]. In concert, these results demonstrate that the gut microbiome can rapidly respond to altered diet, potentially facilitating the diversity of human dietary lifestyles.

There is growing concern that recent lifestyle innovations, most notably the high-fat/high-sugar 'Western' diet, have altered the genetic composition and metabolic activity of our resident microorganisms (the human gut microbiome)[7]. Such diet-induced changes to gut-associated microbial communities are now suspected of contributing to growing epidemics of chronic illness in the developed world, including obesity[4,8] and inflammatory bowel disease[5]. Yet, it remains unclear how quickly and reproducibly gut bacteria respond to dietary change. Work in inbred mice shows that shifting dietary macronutrients can broadly and consistently alter the gut microbiome within a single day[7,9]. By contrast, dietary interventions in human cohorts have only measured community changes on timescales of weeks[10] to months[4], failed to find significant diet-specific effects[1], or else have demonstrated responses among a limited number of bacterial taxa[3,5].

We examined whether dietary interventions in humans can alter gut microbial communities in a rapid, diet-specific manner. We prepared two diets that varied according to their primary food source: a 'plant-based diet', which was rich in grains, legumes, fruits and vegetables; and an 'animal-based diet', which was composed of meats, eggs and cheeses (Supplementary Table 1). We picked these sources to span the global diversity of modern human diets, which includes exclusively plant-based and nearly exclusively animal-based regimes[11] (the latter being the case among some high-latitude and pastoralist cultures). Each diet was consumed *ad libitum* for five consecutive days by six male and four female American volunteers between the ages of 21 and 33, whose body mass indices ranged from 19 to 32 kg m^{-2} (Supplementary Table 2). Study volunteers were observed for 4 days before each diet arm to measure normal eating habits (the baseline period) and for 6 days after each diet arm to assess microbial recovery (the washout period; Extended Data Fig. 1). Subjects' baseline nutritional intake correlated well with their estimated long-term diet (Supplementary Table 3). Our study cohort included a lifetime vegetarian (see Extended Data Fig. 2, Supplementary Discussion and Supplementary Table 4 for a detailed analysis of his diet and gut microbiota).

Each diet arm significantly shifted subjects' macronutrient intake (Fig. 1a–c). On the animal-based diet, dietary fat increased from 32.5 ± 2.2% to 69.5 ± 0.4% kcal and dietary protein increased from 16.2 ± 1.3% to 30.1 ± 0.5% kcal ($P < 0.01$ for both comparisons, Wilcoxon signed-rank test; Supplementary Table 5). Fibre intake was nearly zero, in contrast to baseline levels of 9.3 ± 2.1 g per 1,000 kcal. On the plant-based diet, fibre intake rose to 25.6 ± 1.1 g per 1,000 kcal, whereas both fat and protein intake declined to 22.1 ± 1.7% and 10.0 ± 0.3% kcal, respectively ($P < 0.05$ for all comparisons). Subjects' weights on the plant-based diet remained stable, but decreased significantly by day 3 of the animal-based diet ($q < 0.05$, Bonferroni-corrected Mann–Whitney *U* test; Extended Data Fig. 3). Differential weight loss between the two diets cannot be explained simply by energy intake, as subjects consumed equal numbers of calories on the plant- and animal-based diets (1,695 ± 172 kcal and 1,777 ± 221 kcal, respectively; $P = 0.44$).

To characterize temporal patterns of microbial community structure, we performed 16S ribosomal RNA gene sequencing on samples collected each day of the study (Supplementary Table 6). We quantified the microbial diversity within each subject at a given time point (α diversity) and the difference between each subject's baseline and diet-associated gut microbiota (β diversity) (Fig. 1d, e). Although no significant differences in α diversity were detected on either diet, we observed a significant increase in β diversity that was unique to the animal-based diet ($q < 0.05$, Bonferroni-corrected Mann–Whitney *U* test). This change occurred only 1 day after the diet reached the distal gut microbiota (as indicated by the food tracking dye; Extended Data Fig. 3a). Subjects' gut microbiota reverted to their original structure 2 days after the animal-based diet ended (Fig. 1e).

Analysis of the relative abundance of bacterial taxonomic groups supported our finding that the animal-based diet had a greater impact on the gut microbiota than the plant-based diet (Fig. 2). We hierarchically clustered species-level bacterial phylotypes by the similarity of their dynamics across diets and subjects (see Methods and Supplementary Tables 7, 8). Statistical testing identified 22 clusters whose abundance significantly changed while on the animal-based diet, whereas only 3 clusters showed significant abundance changes while on the plant-based diet ($q < 0.05$, Wilcoxon signed-rank test; Supplementary Table 9). Notably, the genus *Prevotella*, one of the leading sources of inter-individual gut microbiota variation[12] and hypothesized to be sensitive to long-term fibre intake[1,13], was reduced in our vegetarian subject during consumption of the animal-based diet (see Supplementary

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ORIGINAL RESEARCH

Faecal Microbiota Transplantation is Effective for the Initial Treatment of *Clostridium difficile* Infection: A Retrospective Clinical Review

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ABSTRACT

Introduction: *Clostridium difficile* (*C. difficile*) infection (CDI) is commonly recognised as a nosocomial infection but is increasingly identified in patients in the community. Antimicrobial exposure which compromises gut microbiota is the main risk factor for CDI, although antibiotics remain the main treatment for this infection. Faecal microbiota transplantation (FMT) is also an effective treatment for CDI. FMT involves the transfer of microbiota from a healthy donor to an unwell patient. Currently FMT is mostly used after repeated antibiotic treatments fail to cure CDI. This study investigated the effect of FMT as first-line treatment for CDI to avoid repeated antibiotic damage of the microbiome.

Methods: This retrospective, single-centre study included 59 patients between 2012 and 2017 whose first episode of CDI was treated with FMT. The patients' symptoms and presence of *C. difficile* in stool samples both at the baseline and post treatment were documented.

Results: Fifty-four patients completed a final stool test 4–8 weeks post treatment in which 98% of patients were negative for *C. difficile*. There were no adverse effects. There was a significant reduction in abdominal pain, diarrhoea, bloating and blood in the stool at 4–8 weeks post treatment. Data from 24 patients who completed an extended 6 months follow-up showed significant reduction in abdominal pain, diarrhoea and blood in the stool.

Conclusion: This study demonstrates the safety and efficacy of FMT as first-line treatment for patients' initial episode of CDI. Future randomised studies are required to confirm FMT as the initial treatment for CDI.

Keywords: *Clostridium difficile*; Faecal microbiota transplantation; Gut microbiota

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