World Journal of Gastrointestinal Pathophysiology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.4291/wjgp.v4.i4.91

World J Gastrointest Pathophysiol 2013 November 15; 4(4): 91-93
ISSN 2150-5330 (online)

MINIREVIEWS

Prospects and challenges for intestinal microbiome therapy in pediatric gastrointestinal disorders

Richard Kellermayer

Richard Kellermayer, Department of Pediatrics, Section of Pediatric Gastroenterology, Hepatology and Nutrition, Baylor College of Medicine, Texas Children's Hospital, Houston, TX 77030-2399, United States
Author contributions: Richard Kellermayer wrote the manuscript.
Correspondence to: Dr. Richard Kellermayer, MD, PhD, Department of Pediatrics, Section of Pediatric Gastroenterology, Hepatology and Nutrition, Baylor College of Medicine, Texas Children's Hospital, 6621 Fannin St., CC1010.00, Houston, TX 77030-2399, United States. kellerma@bcm.edu
Telephone: +1-713-7980319 Fax: +1-832-8253633
Received: April 30, 2013 Revised: July 23, 2013
Accepted: August 8, 2013
Published online: November 15, 2013

Abstract

Fecal microbiome (microbiota) transplantation is an emerging treatment not only for refractory/recurrent *Clostridium difficile* infections and chronic gastrointestinal diseases, but also for metabolic syndrome, and even possibly for neurological disorders. This non-conventional therapy has been perhaps more appropriately designated as fecal bacteriotherapy (FB) as well. The employment of FB is spreading into pediatric gastroenterology. This focused review highlights the pediatric applications of FB and discusses hypotheses for its mechanism of action. We propose that intestinal microbiome therapy may be a more appropriate term for FB, which integrates its potential future applications.

Key words: Microbiome; Fecal transplant; Children; Inflammatory bowel disease; Ulcerative colitis; *Clostridium difficile*

Core tip: This review provides a focused overview of fecal bacteriotherapy and discusses possible mechanisms of action for this unconventional treatment. It also highlights the challenges, which this therapy faces.

Kellermayer R. Prospects and challenges for intestinal microbiome therapy in pediatric gastrointestinal disorders. *World J Gastrointest Pathophysiol* 2013; 4(4): 91-93 Available from: URL: http://www.wjgnet.com/2150-5330/full/v4/i4/91.htm DOI: http://dx.doi.org/10.4291/wjgp.v4.i4.91

INTRODUCTION

The alarming increase in recurrent *Clostridium difficile* (*C. difficile*) infections (CDI) and associated deaths[1] geared the attention of gastroenterologists around the world towards fecal microbiome (or microbiota) transplantation (FMT)[2]. This non-conventional therapeutic approach has also been designated as fecal bacteriotherapy (FB)[3].

Human fecal preparations have been used for centuries in traditional Chinese medicine to treat various disorders[4]. However, it was not until 1958 when fecal preparations from healthy donors were employed by bold surgeons as enemas to treat critically ill patients with pseudomembranous colitis (PC)[5]. In spite of the surgeons' dramatic success, fecal bacteriotherapy has received less attention up to the 1980's perhaps secondary to the recognition that *C. difficile* is the pathogen for PC and that it can be effectively treated with antibiotics. Indeed, the short term efficacy of current antimicrobials is around 90% against CDI[6]. However, the infection may recur in 13%-24% of cases within 4 wk[6]. In such instances FB has been utilized with a cure approaching 90% irrespective of the mode of delivery (*i.e.*, upper gastrointestinal, colonoscopic, or large volume retention enema)[7]. The first randomized control trial comparing FB with vancomycin therapy for recurrent CDI showed the overwhelming superiority of the fecal preparation[8]. In-spite of this finding we do not understand clearly

how FB works. It appears that live bacteria are required for FB to be efficacious based on mouse model studies[9]. Many researchers argue that it is true engraftment of the donor microbiota that occurs in the recipients through FB, hence is designation as "transplantation"[10]. Only limited high-throughput metagenomic studies have addressed this question, especially over a prolonged time course after the treatments. Work with an artificial fecal bacterial preparation of 33 species found that there was a steady decline in the transplanted strains within the stool of the 2 recipients studied[11]. More specifically, only about 25%-30% of the species received remained in the recipient community by 6 mo after the "transplant". This result shows that some donor bacteria truly populate the recipient microbiome at least for several months. However, I propose that FB works by shock therapy or "enslapment" of the recipient microbiota, rather than just engrafting absent bacterial species into the recipient population. More specifically, a brief shock from a healthy donor bacterial community may restructure the recipient microbiota, which acts as a dynamic organ. The short-term to long-term engraftment of a few bacterial species from the donor stool into the restructuring recipient microbiota may aid/participate in this process. I use the example of crystallization induced by a bit of crystal placed into an over-saturated solution, such as in the case of sodium acetate (http://www.youtube.com/watch?v=HnSg2cl09PI) to demonstrate my hypothesis. In the case of FB, the stool donor is the bit of crystal and the dysbiotic recipient microbiota is the over-saturated solution. Upon the induction from the healthy donor stool, the recipient microbiota reverts back ("crystallizes") to a healthier state of the microbial community supporting its ability to overcome CDI. The arguments for the shock therapy are: (1) a single FB enema works as effectively as any other mode of delivery. Enema volumes are about 5%-10% of the colonic volume. Those reach only the hepatic flexure at best, and are evacuated within a few hours after delivery. It is physiologically rather difficult to imagine that such a preparation could truly transplant the whole intestine of the recipient with microbes; and (2) a simple cultured mixture of 10 bacterial species worked as effectively in treating CDI as a retention enema preparation[12]. It is unlikely that the treated recipients harbored only the 10 "transplanted" species following the resolution of CDI.

Based on the above, FB appears to be a more appropriate designation of this treatment modality than fecal transplantation. Even more, "intestinal microbiome therapy" (IMT) may be the most proper term for FB, since the future will likely bring the development of restricted microbial communities for the treatment of human diseases. In fact, FB has been used with benefit in inflammatory bowel diseases (IBD)[13], chronic constipation and irritable bowel syndrome[14], metabolic syndrome[15], and even in isolated cases of neurological diseases[2]. As for IBD, it was an academic physician, Justin Bennet, who innovatively treated his own ulcerative colitis (UC) with serial large volume retention enemas of stool preparation from a healthy donor[16]. Thereafter, Thomas Borody and colleagues treated 6 UC patients with 5 consecutive daily enemas resulting in over 1 year remission off all medications in all[17]. One of these patients has been in remission for over 11 years implicating the potential curative nature of FB for UC. However, in a recent review Borody *et al*[18] states that more than 5 enemas are needed for most patients, but does not define how many. This statement leads to valid concerns raised about FB in the medical community[19]. The absence of consensus in regards to volume, route, donor screening, safety measures, and the potential lack of medical supervision has been discussed. Consequently, a fecal microbiota FMT workgroup has formed, and established guidelines for donor screening and recipient selection primarily for CDI[20]. To further standardization, "universal" frozen stool preparations to treat CDI were employed with success[21]. The establishment and adherence to stringent guidelines and methods should aid the safety and future utilization of this unconventional treatment option for various human diseases.

FB has been less investigated in children, most likely secondary to safety concerns. In the meantime, parents of children suffering from UC, for example, are eager for this treatment option to become available[22]. There are only two case reports in children supporting the safety and efficacy of FB for pediatric recurrent CDI[23,24]. Additionally, a very recent publication demonstrated that serial retention enemas from healthy donors can be of benefit for pediatric and young-adult patients with mild to moderately active UC[25]. The study participants experienced only mild to moderate, self-resolving side effects from FB. These publications clearly indicate the potential utility of FB in pediatric gastrointestinal disorders as well.

At present, FB appears to hold great prospects, but also significant challenges for the treatment of human diseases. For chronic disorders, such as IBD, the end point of therapy may be difficult to define. Long-term potential side effects such as modified metabolism, changes in mood and affect, altered susceptibility to malignancies, *etc*. have not been examined. The most optimal route of delivery may vary between diseases, and between differing phenotypes of a single disease. The need for donor-recipient matching is also of question. The importance of age, gender, race, and microbiome composition (among others) are also unknown in this respect. The potential significance of fungi and viruses during IMT has not even been addressed to date. Perhaps the greatest challenge for the future will be to define restricted microbial communities for specific diseases. Only dedicated academic scientists will be able to meet these challenges and optimize metagenomic medicine for current and future generations to come.

REFERENCES

1 **Peery AF**, Dellon ES, Lund J, Crockett SD, McGowan CE, Bulsiewicz WJ, Gangarosa LM, Thiny MT, Stizenberg K,

Morgan DR, Ringel Y, Kim HP, Dibonaventura MD, Carroll CF, Allen JK, Cook SF, Sandler RS, Kappelman MD, Shaheen NJ. Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology* 2012; **143**: 1179-1187. e1-e3 [PMID: 22885331 DOI: 10.1053/j.gastro.2012.08.002]

2 **Brandt LJ**. American Journal of Gastroenterology Lecture: Intestinal microbiota and the role of fecal microbiota transplant (FMT) in treatment of C. difficile infection. *Am J Gastroenterol* 2013; **108**: 177-185 [PMID: 23318479 DOI: 10.1038/ajg.2012.450]

3 **Suwantarat N**, Bobak DA. Fecal Bacteriotherapy for Recurrent Clostridium difficile Infection: What's Old Is New Again? *Curr Infect Dis Rep* 2013; **15**: 101-103 [PMID: 23549617 DOI: 10.1007/s11908-013-0314-8]

4 **Zhang F**, Luo W, Shi Y, Fan Z, Ji G. Should we standardize the 1,700-year-old fecal microbiota transplantation? *Am J Gastroenterol* 2012; **107**: 1755; author reply 1755-1756 [PMID: 23160295 DOI: 10.1038/ajg.2012.251]

5 **EISEMAN B**, SILEN W, BASCOM GS, KAUVAR AJ. Fecal enema as an adjunct in the treatment of pseudomembranous enterocolitis. *Surgery* 1958; **44**: 854-859 [PMID: 13592638]

6 **Louie TJ**, Miller MA, Mullane KM, Weiss K, Lentnek A, Golan Y, Gorbach S, Sears P, Shue YK. Fidaxomicin versus vancomycin for Clostridium difficile infection. *N Engl J Med* 2011; **364**: 422-431 [PMID: 21288078 DOI: 10.1056/NEJMoa0910812]

7 **Sofi AA**, Silverman AL, Khuder S, Garborg K, Westerink JM, Nawras A. Relationship of symptom duration and fecal bacteriotherapy in Clostridium difficile infection-pooled data analysis and a systematic review. *Scand J Gastroenterol* 2013; **48**: 266-273 [PMID: 23163886 DOI: 10.3109/00365521.2012.743585]

8 **van Nood E**, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, Visser CE, Kuijper EJ, Bartelsman JF, Tijssen JG, Speelman P, Dijkgraaf MG, Keller JJ. Duodenal infusion of donor feces for recurrent Clostridium difficile. *N Engl J Med* 2013; **368**: 407-415 [PMID: 23323867 DOI: 10.1056/NEJMoa1205037]

9 **Lawley TD**, Clare S, Walker AW, Stares MD, Connor TR, Raisen C, Goulding D, Rad R, Schreiber F, Brandt C, Deakin LJ, Pickard DJ, Duncan SH, Flint HJ, Clark TG, Parkhill J, Dougan G. Targeted restoration of the intestinal microbiota with a simple, defined bacteriotherapy resolves relapsing Clostridium difficile disease in mice. *PLoS Pathog* 2012; **8**: e1002995 [PMID: 23133377 DOI: 10.1371/journal.ppat.1002995]

10 **Hamilton MJ**, Weingarden AR, Unno T, Khoruts A, Sadowsky MJ. High-throughput DNA sequence analysis reveals stable engraftment of gut microbiota following transplantation of previously frozen fecal bacteria. *Gut Microbes* 2013; **4**: 125-135 [PMID: 23333862 DOI: 10.4161/gmic.23571]

11 **Petrof EO**, Gloor GB, Vanner SJ, Weese SJ, Carter D, Daigneault MC, Brown EM, Schroeter K, Allen-Vercoe E. Stool substitute transplant therapy for the eradication of Clostridium difficile infection: 'RePOOPulating' the gut. *Microbiome* 2013; **1**: 3 [DOI: 10.1186/2049-2618-1-3]

12 **Tvede M**, Rask-Madsen J. Bacteriotherapy for chronic relapsing Clostridium difficile diarrhoea in six patients. *Lancet* 1989; **1**: 1156-1160 [PMID: 2566734]

13 **Anderson JL**, Edney RJ, Whelan K. Systematic review: faecal microbiota transplantation in the management of inflammatory bowel disease. *Aliment Pharmacol Ther* 2012; **36**: 503-516 [PMID: 22827693 DOI: 10.1111/j.1365-2036.2012.05220]

14 **Andrews PJ**, Borody TJ. "Putting back the bugs": bacterial treatment relieves chronic constipation and symptoms of irritable bowel syndrome. *Med J Aust* 1993; **159**: 633-634 [PMID: 8155121]

15 **Vrieze A**, Van Nood E, Holleman F, Salojärvi J, Kootte RS, Bartelsman JF, Dallinga-Thie GM, Ackermans MT, Serlie MJ, Oozeer R, Derrien M, Druesne A, Van Hylckama Vlieg JE, Bloks VW, Groen AK, Heilig HG, Zoetendal EG, Stroes ES, de Vos WM, Hoekstra JB, Nieuwdorp M. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. *Gastroenterology* 2012; **143**: 913-916. e7 [PMID: 22728514 DOI: 10.1053/j.gastro.2012.06.031]

16 **Bennet JD**, Brinkman M. Treatment of ulcerative colitis by implantation of normal colonic flora. *Lancet* 1989; **1**: 164 [PMID: 2563083]

17 **Borody TJ**, Warren EF, Leis S, Surace R, Ashman O. Treatment of ulcerative colitis using fecal bacteriotherapy. *J Clin Gastroenterol* 2003; **37**: 42-47 [PMID: 12811208]

18 **Borody TJ**, Campbell J. Fecal microbiota transplantation: current status and future directions. *Expert Rev Gastroenterol Hepatol* 2011; **5**: 653-655 [PMID: 22017691 DOI: 10.1586/egh.11.71]

19 **El-Matary W**, Simpson R, Ricketts-Burns N. Fecal microbiota transplantation: are we opening a can of worms? *Gastroenterology* 2012; **143**: e19; author reply e19-e20 [PMID: 22732575 DOI: 10.1053/j.gastro.2012.04.055]

20 **Bakken JS**, Borody T, Brandt LJ, Brill JV, Demarco DC, Franzos MA, Kelly C, Khoruts A, Louie T, Martinelli LP, Moore TA, Russell G, Surawicz C. Treating Clostridium difficile infection with fecal microbiota transplantation. *Clin Gastroenterol Hepatol* 2011; **9**: 1044-1049 [PMID: 21871249 DOI: 10.1016/j.cgh.2011.08.014]

21 **Hamilton MJ**, Weingarden AR, Sadowsky MJ, Khoruts A. Standardized frozen preparation for transplantation of fecal microbiota for recurrent Clostridium difficile infection. *Am J Gastroenterol* 2012; **107**: 761-767 [PMID: 22290405 DOI: 10.1038/ajg.2011.482]

22 **Kahn SA**, Gorawara-Bhat R, Rubin DT. Fecal bacteriotherapy for ulcerative colitis: patients are ready, are we? *Inflamm Bowel Dis* 2012; **18**: 676-684 [PMID: 21618362 DOI: 10.1002/ibd.21775]

23 **Russell G**, Kaplan J, Ferraro M, Michelow IC. Fecal bacteriotherapy for relapsing Clostridium difficile infection in a child: a proposed treatment protocol. *Pediatrics* 2010; **126**: e239-e242 [PMID: 20547640 DOI: 10.1542/peds.2009-3363]

24 **Kahn SA**, Young S, Rubin DT. Colonoscopic fecal microbiota transplant for recurrent Clostridium difficile infection in a child. *Am J Gastroenterol* 2012; **107**: 1930-1931 [PMID: 23211865 DOI: 10.1038/ajg.2012.351]

25 **Kunde S**, Pham A, Bonczyk S, Crumb T, Duba M, Conrad H, Cloney D, Kugathasan S. Safety, tolerability, and clinical response after fecal transplantation in children and young adults with ulcerative colitis. *J Pediatr Gastroenterol Nutr* 2013; **56**: 597-601 [PMID: 23542823 DOI: 10.1097/MPG.0b013e318292fa0d]

P- Reviewer: Zhang FM **S- Editor**: Qi Y
L- Editor: A **E- Editor:** Liu XM

百世登

Baishideng®

Published by **Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai, Hong Kong, China
Telephone: +852-6555-7188
Fax: +852-3177-9906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com