GUT MICROBES
2016, VOL. 7, NO. 4, 323–328
http://dx.doi.org/10.1080/19490976.2016.1151608

Taylor & Francis
Taylor & Francis Group

ADDENDUM

OPEN ACCESS

Step-up fecal microbiota transplantation (FMT) strategy

Bota Cui[a,b,#], Pan Li[a,b,#], Lijuan Xu[a,b], Zhaoyuan Peng[a,b], Jie Xiang[a,b], Zhi He[a,b], Ting Zhang[a,b], Guozhong Ji[a,b], Yongzhan Nie[c], Kaichun Wu[c], Daiming Fan[c], and Faming Zhang[a,b]

[a]Medical Center for Digestive Diseases, the Second Affiliated Hospital of Nanjing Medical University, Nanjing, China; [b]Key Lab of Holistic Integrative Enterology, Nanjing Medical University, Nanjing, China; [c]State Key Laboratory of Cancer Biology & Xijing Hospital of Digestive Diseases, the Fourth Military Medical University, Xi'an, China

ABSTRACT

Gut dysbiosis is a characteristic of inflammatory bowel disease (IBD) and is believed to play a role in the pathogenesis of IBD. Fecal microbiota transplantation (FMT) is an effective strategy to restore intestinal microbial diversity and has been reported to have a potential therapeutic value in IBD. Our recent study reported a holistic integrative therapy called "step-up FMT strategy," which was beneficial in treating steroid-dependent IBD patients. This strategy consists of scheduled FMTs combined with steroids, anti-TNF-α antibody treatment or enteral nutrition. Herein, we will elaborate the strategy thoroughly, introducing the concept, potential indication, methodology, and safety of "step-up FMT strategy" in detail.

ARTICLE HISTORY
Received 21 December 2015
Revised 1 February 2016
Accepted 2 February 2016

KEYWORDS
dysbiosis; Inflammatory bowel disease; Steroids; Step-up fecal microbiota transplantation; Ulcerative colitis

Introduction

Inflammatory bowel disease (IBD) includes Crohn's disease (CD) and ulcerative colitis (UC) and is a chronic immunologically-mediated disease characterized by remission and relapse.[1] Genetics, immunology, gut microbial dysbiosis and environmental factors play a key role in IBD pathogenesis.[1,2] Corticosteroids is one of the most effective therapies to control active IBD,[3] but it is not recommended for IBD maintenance therapy, and its efficacy in refractory IBD is limited.

Fecal microbiota transplantation (FMT), a concept originally recorded in China a millennia ago,[4] is a strategy to treat dysbiosis by restoring intestinal microbial diversity.[5,6] There is growing evidence that has indicated a potential therapeutic role for FMT in IBD.[5,7-10] According to data (accessed December 31, 2015) from www.clinicaltrials.gov, a total of 35 FMT studies have been registered, with 74.3% (26/35) of these studies beginning in 2014 or afterwards. This trend further reflects the growing public interest in FMT for IBD treatment.

From October 2012 to December 2015, more than 500 cases of FMT have been performed in the Medical Center for Digestive Disease of the Second Affiliated Hospital of Nanjing Medical University, Nanjing, China. We previously reported the safety, feasibility, and efficacy of a single FMT through the mid-gut as rescue therapy for patients with medically-refractory CD.[8] However, for the patients with steroid-dependent IBD, a single FMT showed limited therapeutic effect. Anecdotally, some patients failed to benefit from the first FMT, but would achieve clinical improvement or remission after a second FMT or a single FMT followed by a short course of corticosteroid treatment. We were inspired to further study this phenomenon and evaluate the efficacy of combination FMT and steroid therapy for steroid-dependent UC, a technique we termed "step-up FMT strategy." Our recent study demonstrated that 57.1% (8/14) of patients with steroid dependent UC had clinical improvement or remission and were able to discontinue steroids after using this step-up FMT strategy.[7] This is an addendum to the published paper.[7]

CONTACT Faming Zhang fzhang@njmu.edu.cn Medical Center for Digestive Diseases, the Second Affiliated Hospital of Nanjing Medical University, 121 Jiangjiayuan, Nanjing 210011, China
[#]These authors contributed equally to this work.

Addendum to: Cui B, Li P, Xu L, Zhao Y, Wang H, Peng Z, Xu H, Xiang J, He Z, Zhang T, et al. Step-up fecal microbiota transplantation strategy: a pilot study for steroid-dependent ulcerative colitis. J Trans Med 2015 12;13: 298. doi: 10.1186/s12967-015-0646-2.

The step-up FMT concept: Holistic integrative strategy

We recently reported on the concept and efficacy of a step-up FMT strategy using a protocol of 2 FMTs followed by a course of steroid therapy.[7] We propose that the therapeutic effects of FMT along with standard IBD therapies may work synergistically to control IBD activity.[7] In brief, the step-up FMT strategy in the study was composed of 3 steps.[8] After a patient was treated with the first FMT, the efficacy would be evaluated based on clinical symptoms and laboratory examinations. Patients who failed to benefit from the first step would undergo the second FMT within approximately one week. If the patient still did not have clinical response to the second FMT within one week, a course of steroids by oral or intravenous injection would be given, which would be tapered off by oral after 2–4 weeks of full dose therapy (recommend prednisone 0.75-1.0mg/kg.d). Patients who had no response at any of these steps could choose to switch to a different therapy. In our center, beside this combination of scheduled FMT followed by steroids, the step-up FMT strategy has also been employed using FMT followed by anti-TNF-α antibody or FMT followed by exclusive enteral nutrition (Fig. 1). Our coming reports will further describe the performance of these strategies.

Step-up FMT strategy combines FMT and standard IBD medications in a way that allows these therapies to work synergistically in patients who have failed individual components of this therapy. The exact mechanism of how this strategy could work better than 2 or 3 individual therapies is still unclear. We hypothesize that remodeling the intestinal microbiota by one or 2 FMTs might improve patients' ability to respond to other therapies since the intestinal microbiota play multiple physiologic functions, such as modulating immunity, maintaining epithelial homeostasis, participating in digestion and fat metabolism, as well as formulating and developing of nervous system.[11-16] In prior studies of FMT for IBD, patients with successful responses following FMT had gut microbiome compositions that were highly similar to their related donors,[5,7,17] and the results of lymphocyte detection in the patients after FMT implied a restoration of patients' immune homeostasis.[8] Though it is difficult to demonstrate the mechanism of a step-up FMT strategy, it is presumed that FMT, as the most effective way of remodeling the intestinal microbiota, is the core and the first step of this holistic integrative strategy.

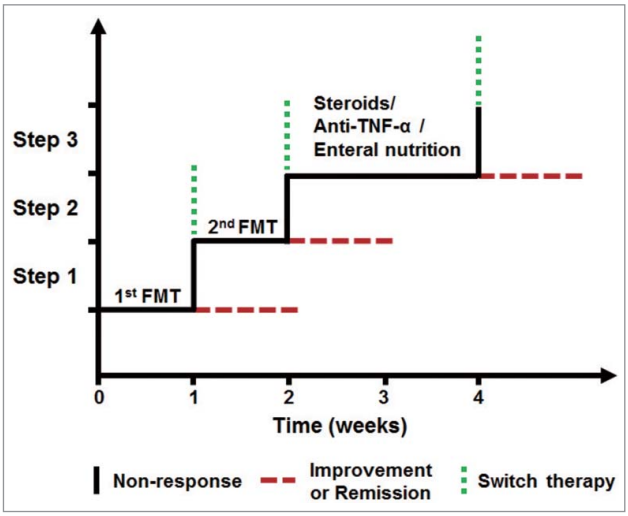

Figure 1. Flow chart of the Step-up FMT strategy.

The step-up FMT strategy: Potential indications

Our recently published study[7] and unpublished data suggest that the step-up FMT strategy of using FMT followed steroids can be used for both UC and CD. In our preliminary observations, several patients who failed to have sustained clinical response to anti-TNFα antibody therapy also failed to have positive responses to FMT. However, we noted that they benefited from anti-TNFα antibody therapy again following initial non-response to FMT. Furthermore, 2 CD patients who developed infusion reactions to anti-TNFα antibody in the past could safely undergo this biologic therapy again after FMT. This indicates that FMT can be used as desensitization therapy in certain conditions. Interestingly, we also demonstrated this concept in 2012 in a case of a 35 y old gentleman with refractory eosinophilic gastroenteritis.[18] This man presented with frequent bowel obstructions and diarrhea He was misdiagnosed as Crohn's disease in 2 other hospitals and underwent surgery for intestinal obstruction. Before this gentleman was transferred to our center, he had failed a 2-week course of prednisone. Ultimately, he benefited from a combination of FMT followed by treatment with prednisone. Additionally, FMT may improve clinical response to enteral nutrition in patients who did not respond to nutritional therapy prior to FMT.[8,19] All of these potential indications require

further evidence from large, controlled clinical trials. However, further research on which patient is most appropriate for treatment with "step-up FMT" is also a critical scientific question.

The step-up FMT strategy: Related methodology

Different FMT protocols have been reported from different medical centers,[20-26] including our own,[9,27] with corresponding variability in FMT efficacy.[5,9,10,17,27-29] It is possible that these different FMT methodologies may play an important role in the resulting FMT outcomes.[9,27,30]

Donor selection: Who is the best donor?

Two recent randomized controlled trials of FMT for ulcerative colitis indicated that FMT efficacy was dependent on donor selection.[9,27] However, Paramsothy et al.[31] reported that only 10% (12/116) of healthy persons screened met the strict criteria required of FMT donors. Yet all the currently published donor criteria are exclusion criteria, and there are no known unique characteristics that can identify the ideal donor for FMT for IBD indications. Screening suitable donors by their intestinal microbiota composition may be a promising concept. For example, Vermeire et al.[32] reported that donor species richness determines the efficacy of FMT for IBD. In one of our recent studies, donor ages ranged from 8 to 18 year-old. The reason for this included safety considerations and guidance from traditional Chinese medicine literature. First, children between these ages have less risk of sexually transmitted diseases in China because they generally have no sexual life. Secondly, the donor selection recommended for FMT in traditional Chinese medicine was at this age period.[25] Whether donors screened from this age cohort lead to better clinical outcomes is yet to be confirmed by a well-designed clinical trial.

The status of isolated microbiota: The difference for IBD and CDI?

Clostridium difficile infection (CDI) is an infection disease which often occurs as a result of marked disruption of the intestinal microbiota by antibiotics.[33] Treatment with FMT results in high cure rates for recurrent CDI,[34,35] regardless of donor characteristics (barring screening for infectious organisms), amount of stool material infused or delivery method. Furthermore, there are no significant differences in the efficacy of fresh versus frozen microbiota. [36] Compared to CDI, IBD etiology is a more complex interaction of chronic intestinal inflammation and factors including genetic, immunological, environmental, and gut microbial composition determinants.[1,37] It is unclear if the dysbiosis seen in IBD is a cause or a consequence of the diseaese.[14,38] The different pathogenic mechanisms of CDI vs. IBD may therefore require different donor microbiota. Our previous study showed the rate of clinical response at 3 months after FMT in CD patients treated with frozen fecal microbiota was lower than that in patients treated with fresh microbiota;[8] however, this was not statistically different likely due to the small study size. Therefore, we hypothesize that the decreased IBD clinical response in patients treated with frozen stool may be because of the inactivation or killing of bacteria during the freezing process.

Since we do not know the changing of fecal viable organism after the feces is defecated from the colon, it may be the best way to deliver them into the place (intestine) where they should be as soon as possible.[30] To that end, our FMT workflow is designed to be completed within one hour, from stool collection to transplantation or storage, using the support of the automatic system GenFMTer (FMT medical, Nanjing, China).[25] To better standardize and shorten the process of donor stool preparation, we recently established a clinical laboratory abiding by the standards of the Good Manufacturing Process (GMP) applicable to pharmaceuticals and medical devices (Fig. 2). The entire stool preparation process is completed in this GMP laboratory, including stool collection, purification of fecal microbiota using the GenFMTer system, and storage in the fecal microbiota bank.

Delivering way: Mid-gut or lower-gut?

The reported delivery pathways for FMT can be summarized and divided into upper-gut, mid-gut and lower-gut. The upper-gut delivery methods include oral capsules of fecal microbiota.[39] Mid-gut delivery methods include delivery through nasointestinal tubes,[40,41] endoscopic channels[8] and percutaneous endoscopic gastrostomy with jejunal (PEGJ) tubes. Lower-gut methods include colonoscopy,[26,42] enema,[23] infusions through colonic stomas[23] and a

Figure 2. The lab at GMP level with the GenFMTer.

novel delivering method using colonic transendoscopic enteral tubing (TET) designed by us and using in multicenter as trial.[43] At least for IBD, FMT delivery through colonoscopy or enema may not be the best choice as certain patients often have difficulty retaining the infused contents.

The step-up FMT strategy: Safety consideration

Though there have been no severe complications from FMT at our hospital, institutions from Austria,[44] North America,[45,46] Europe[27] and China[8] have reported minor adverse events after FMT, such as fever, diarrhea, abdominal pain, bloating and IBD flares. From a review of all the FMT cases from our center and from the national fecal microbiota bank platform (www.fmtBank.org) in China, adverse events occurred in patients with definite or potential immunocompromised status, extensive and deep mucosal ulcers (eg. IBD), but not in those with functional intestinal diseases. Therefore, the safety consideration must be given to step-up FMT strategy.

Conclusion

Step-up FMT strategy should be a therapeutic option for steroid dependent IBD. Further researches on its possible conditions, methodology and mechanism are important for improving our recognition on the significance of remodeling gut microbiota in human diseases.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Acknowledgments

We appreciate Dr. Lea Ann Chen (Division of Gastroenterology, NYU Langone Medical Center, New York, USA) for kindly editing the manuscript and giving professional suggestions.

Funding

This study was supported by public donated Intestine Initiative Foundation, Clinical Science and Technology Foundation of Jiangsu Province (BL2014097) and National Gastroenterology Research Project (2015BAI13B07).

References

[1] Ananthakrishnan AN. Epidemiology and risk factors for IBD. Nat Rev Gastroenterol Hepatol 2015; 12:205-17; PMID:25732745; http://dx.doi.org/10.1038/nrgastro.2015.34

[2] Kaser A, Zeissig S, Blumberg RS. Inflammatory bowel disease. Annu Rev Immunol 2010; 28:573-621; PMID:20192811; http://dx.doi.org/10.1146/annurev-immunol-030409-101225

[3] Mowat C, Cole A, Windsor A, Ahmad T, Arnott I, Driscoll R, Mitton S, Orchard T, Rutter M, Younge L, et al. Guidelines for the management of inflammatory bowel disease in adults. Gut 2011; 60:571-607; PMID:21464096; http://dx.doi.org/10.1136/gut.2010.224154

[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; PMID:23160295; http://dx.doi.org/10.1038/ajg.2012.251

[5] Kao D, Hotte N, Gillevet P, Madsen K. Fecal microbiota transplantation inducing remission in Crohn's colitis and the associated changes in fecal microbial profile. J Clin Gastroenterol 2014; 48:625-8; PMID:24667590; http://dx.doi.org/10.1097/MCG.0000000000000131

[6] Kassam Z, Lee CH, Yuan Y, Hunt RH. Fecal microbiota transplantation for Clostridium difficile infection: systematic review and meta-analysis. Am J Gastroenterol 2013; 108:500-8; PMID:23511459; http://dx.doi.org/10.1038/ajg.2013.59

[7] Cui B, Li P, Xu L, Zhao Y, Wang H, Peng Z, Xu H, Xiang J, He Z, Zhang T, et al. Step-up fecal microbiota transplantation strategy: a pilot study for steroid-dependent ulcerative colitis. J Transl Med 2015; 13:298; PMID:26363929; http://dx.doi.org/10.1186/s12967-015-0646-2

[8] Cui B, Feng Q, Wang H, Wang M, Peng Z, Li P, Huang G, Liu Z, Wu P, Fan Z, et al. Fecal microbiota transplantation through mid-gut for refractory Crohn's disease: safety, feasibility, and efficacy trial results. J Gastroenterol Hepatol 2015; 30:51-8; PMID:25168749; http://dx.doi.org/10.1111/jgh.12727

[9] Moayyedi P, Surette MG, Kim PT, Libertucci J, Wolfe M, Onischi C, Armstrong D, Marshall JK, Kassam Z, Reinisch W, et al. Fecal Microbiota Transplantation Induces

Remission in Patients With Active Ulcerative Colitis in a Randomized Controlled Trial. Gastroenterology 2015; 149:102-9 e6; PMID:25857665; http://dx.doi.org/10.1053/j.gastro.2015.04.001

[10] Gordon H, Harbord M. A patient with severe Crohn's colitis responds to Faecal Microbiota Transplantation. J Crohns Colitis 2014; 8:256-7; PMID:24239403; http://dx.doi.org/10.1016/j.crohns.2013.10.007

[11] Hill DA, Artis D. Intestinal bacteria and the regulation of immune cell homeostasis. Annu Rev Immunol 2010; 28:623-67; PMID:20192812; http://dx.doi.org/10.1146/annurev-immunol-030409-101330

[12] Yurist-Doutsch S, Arrieta MC, Vogt SL, Finlay BB. Gastrointestinal microbiota-mediated control of enteric pathogens. Annu Rev Genet 2014; 48:361-82; PMID:25251855; http://dx.doi.org/10.1146/annurev-genet-120213-092421

[13] Kamada N, Seo SU, Chen GY, Nunez G. Role of the gut microbiota in immunity and inflammatory disease. Nat Rev Immunol 2013; 13:321-35; PMID:23618829; http://dx.doi.org/10.1038/nri3430

[14] Manichanh C, Borruel N, Casellas F, Guarner F. The gut microbiota in IBD. Nat Rev Gastroenterol Hepatol 2012; 9:599-608; PMID:22907164; http://dx.doi.org/10.1038/nrgastro.2012.152

[15] Lozupone CA, Stombaugh JI, Gordon JI, Jansson JK, Knight R. Diversity, stability and resilience of the human gut microbiota. Nature 2012; 489:220-30; PMID:22972295; http://dx.doi.org/10.1038/nature11550

[16] Dogra S, Sakwinska O, Soh SE, Ngom-Bru C, Bruck WM, Berger B, Brussow H, Karnani N, Lee YS, Yap F, et al. Rate of establishing the gut microbiota in infancy has consequences for future health. Gut Microbes 2015; 6:321-5; PMID:26516657; http://dx.doi.org/10.1080/19490976.2015.1078051

[17] Angelberger S, Reinisch W, Makristathis A, Lichtenberger C, Dejaco C, Papay P, Novacek G, Trauner M, Loy A, Berry D. Temporal bacterial community dynamics vary among ulcerative colitis patients after fecal microbiota transplantation. Am J Gastroenterol 2013; 108:1620-30; PMID:24060759; http://dx.doi.org/10.1038/ajg.2013.257

[18] Dai YX, Shi CB, Cui BT, Wang M, Ji GZ, Zhang FM. Fecal microbiota transplantation and prednisone for severe eosinophilic gastroenteritis. World J Gastroenterol 2014; 20:16368-71; PMID:25473198

[19] Zhang FM, Wang HG, Wang M, Cui BT, Fan ZN, Ji GZ. Fecal microbiota transplantation for severe enterocolonic fistulizing Crohn's disease. World J Gastroenterol 2013; 19:7213-6; PMID:24222969; http://dx.doi.org/10.3748/wjg.v19.i41.7213

[20] Aroniadis OC, Brandt LJ. Fecal microbiota transplantation: past, present and future. Curr Opin Gastroenterol 2013; 29:79-84; PMID:23041678; http://dx.doi.org/10.1097/MOG.0b013e32835a4b3e

[21] Borody TJ, Brandt LJ, Paramsothy S. Therapeutic faecal microbiota transplantation: current status and future developments. Curr Opin Gastroenterol 2014; 30:97-105; PMID:24257037; http://dx.doi.org/10.1097/MOG.0000000000000027

[22] Borody TJ, Paramsothy S, Agrawal G. Fecal microbiota transplantation: indications, methods, evidence, and future directions. Curr Gastroenterol Rep 2013; 15:337; PMID:23852569; http://dx.doi.org/10.1007/s11894-013-0337-1

[23] Brandt LJ, Aroniadis OC. An overview of fecal microbiota transplantation: techniques, indications, and outcomes. Gastrointestinal Endoscopy 2013; 78:240-9; PMID:23642791; http://dx.doi.org/10.1016/j.gie.2013.03.1329

[24] Kelly CR, Kahn S, Kashyap P, Laine L, Rubin D, Atreja A, Moore T, Wu G. Update on Fecal Microbiota Transplantation 2015: Indications, Methodologies, Mechanisms, and Outlook. Gastroenterology 2015; 149:223-37; PMID:25982290; http://dx.doi.org/10.1053/j.gastro.2015.05.008

[25] Cui B, Li P, Xu L, Peng Z, Zhao Y, Wang H, He Z, Zhang T, Ji G, Wu K, et al. Fecal microbiota transplantation is an effective rescue therapy for refractory inflammatory bowel disease. Inflamm Cell Signal 2015; 2:e757.

[26] Allegretti JR, Korzenik JR, Hamilton MJ. Fecal microbiota transplantation via colonoscopy for recurrent C. difficile Infection. J Vis Exp 2014; PMID:25549239

[27] Rossen NG, Fuentes S, van der Spek MJ, Tijssen JG, Hartman JH, Duflou A, Lowenberg M, van den Brink GR, Mathus-Vliegen EM, de Vos WM, et al. Findings From a Randomized Controlled Trial of Fecal Transplantation for Patients With Ulcerative Colitis. Gastroenterology 2015; 149:110-8.e4; PMID:25836986; http://dx.doi.org/10.1053/j.gastro.2015.03.045

[28] Kump PK, Grochenig HP, Lackner S, Trajanoski S, Reicht G, Hoffmann KM, Deutschmann A, Wenzl HH, Petritsch W, Krejs GJ, et al. Alteration of intestinal dysbiosis by fecal microbiota transplantation does not induce remission in patients with chronic active ulcerative colitis. Inflamm Bowel Dis 2013; 19:2155-65; PMID:23899544; http://dx.doi.org/10.1097/MIB.0b013e31829ea325

[29] Colman RJ, Rubin DT. Fecal microbiota transplantation as therapy for inflammatory bowel disease: A systematic review and meta-analysis. J Crohns Colitis 2014; 8:1569-81; PMID:25223604; http://dx.doi.org/10.1016/j.crohns.2014.08.006

[30] Cui B, Xu F, Zhang F. Methodology, Not Concept of Fecal Microbiota Transplantation, Affects Clinical Findings. Gastroenterology 2016; 150:285-6; PMID:26616573; http://dx.doi.org/10.1053/j.gastro.2015.05.065

[31] Paramsothy S, Borody TJ, Lin E, Finlayson S, Walsh AJ, Samuel D, van den Bogaerde J, Leong RW, Connor S, Ng W, et al. Donor Recruitment for Fecal Microbiota Transplantation. Inflamm Bowel Dis 2015; 21:1600-6; PMID:26070003; http://dx.doi.org/10.1097/MIB.0000000000000405

[32] Vermeire S, Joossens M, Verbeke K, Wang J, Machiels K, Sabino J, Ferrante M, Van Assche G, Rutgeerts P, Raes J. Donor species richness determines fecal microbiota transplantation success in inflammatory bowel disease. J Crohns Colitis 2015; PMID:26519463

[33] Brandt LJ. Intestinal microbiota and the role of fecal microbiota transplant (FMT) in treatment of C. difficile infection. Am J Gastroenterol 2013; 108:177-85; PMID:23318479; http://dx.doi.org/10.1038/ajg.2012.450

[34] van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, Visser CE, Kuijper EJ, Bartelsman JF, Tijssen JG, et al. Duodenal infusion of donor feces for recurrent Clostridium difficile. N Engl J Med 2013; 368:407-15; PMID:23323867; http://dx.doi.org/10.1056/NEJMoa1205037

[35] Surawicz CM, Brandt LJ, Binion DG, Ananthakrishnan AN, Curry SR, Gilligan PH, McFarland LV, Mellow M, Zuckerbraun BS. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. Am J Gastroenterol 2013; 108:478-98; quiz 99; PMID:23439232; http://dx.doi.org/10.1038/ajg.2013.4

[36] Lee CH, Steiner T, Petrof EO, Smieja M, Roscoe D, Nematallah A, Weese JS, Collins S, Moayyedi P, Crowther M, 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; 315:142-9; PMID:26757463; http://dx.doi.org/10.1001/jama.2015.18098

[37] Cader MZ, Kaser A. Recent advances in inflammatory bowel disease: mucosal immune cells in intestinal inflammation. Gut 2013; 62:1653-64; PMID:24104886; http://dx.doi.org/10.1136/gutjnl-2012-303955

[38] Sartor R, Mazmanian S. Intestinal microbes in inflammatory bowel diseases. Am J Gastroenterol 2012; 1:15-21; http://dx.doi.org/10.1038/ajgsup.2012.4

[39] Youngster I, Russell GH, Pindar C, Ziv-Baran T, Sauk J, Hohmann EL. Oral, capsulized, frozen fecal microbiota transplantation for relapsing Clostridium difficile infection. JAMA 2014; 312:1772-8; PMID:25322359; http://dx.doi.org/10.1001/jama.2014.13875

[40] Postigo R, Kim JH. Colonoscopic versus nasogastric fecal transplantation for the treatment of Clostridium difficile infection: a review and pooled analysis. Infection 2012; 40:643-8; PMID:22847629; http://dx.doi.org/10.1007/s15010-012-0307-9

[41] Li Q, Wang C, Tang C, He Q, Zhao X, Li N, Li J. Successful treatment of severe sepsis and diarrhea after vagotomy utilizing fecal microbiota transplantation: a case report. Crit Care 2015; 19:738; PMID:25881250

[42] Mattila E, Uusitalo-Seppala R, Wuorela M, Lehtola L, Nurmi H, Ristikankare M, Moilanen V, Salminen K, Seppala M, Mattila PS, et al. Fecal transplantation, through colonoscopy, is effective therapy for recurrent Clostridium difficile infection. Gastroenterology 2012; 142:490-6; PMID:22155369; http://dx.doi.org/10.1053/j.gastro.2011.11.037

[43] Peng Z, Xiang J, He Z, Zhang T, Xu L, Cui B, Li P, Huang G, Ji G, Nie Y, et al. Colonic transendoscopic enteral tubing: A novel delivering way for fecal microbiota transplantation. Endoscopy International Open 2016; In press

[44] `Borody TJ, Warren EF, Leis S, Surace R, Ashman O. Treatment of ulcerative colitis using fecal bacteriotherapy. J Clin Gastroenterol 2003; 37:42-7; PMID:12811208; http://dx.doi.org/10.1097/00004836-200307000-00012

[45] Kelly CR, Ihunnah C, Fischer M, Khoruts A, Surawicz C, Afzali A, Aroniadis O, Barto A, Borody T, Giovanelli A, et al. Fecal microbiota transplant for treatment of Clostridium difficile infection in immunocompromised patients. Am J Gastroenterol 2014; 109:1065-71; PMID:24890442; http://dx.doi.org/10.1038/ajg.2014.133

[46] Kunde S, Pham A, Bonczyk S, Crumb T, Duba M, Conrad H, Jr., 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; http://dx.doi.org/10.1097/MPG.0b013e318292fa0d