



Fecal microbiota transplantation: understanding from holistic integrative view

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Abstract: Increasing evidence has shown the role of fecal microbiota transplantation (FMT) in the treatment of dysbiosis related diseases. We need different way for understanding this special therapy concept. The remodeling of microbiota might initiate cascade reactions between bacteria and host. Yin-Yang theory in traditional Chinese medicine could be helpful for us to deeply think the complex mechanism. Importantly, FMT should be managed as a system involving with donor screening, quality control of lab process, safety monitoring, delivering way, frequency, clinical work flow and other aspects. Auto-purification of microbiota from healthy stool by GenFMTer in lab with good manufacturing practice level, one-hour protocol of FMT and step-up FMT strategy are the dominant parts of the current leading FMT system. In conclusion, understanding from the view of holistic integrative medicine is the basic step to practice FMT and move it into medicine mainstream.

Keywords: Fecal microbiota transplantation (FMT); holistic integrative medicine; one-hour protocol; step-up FMT strategy; microbiome; inflammatory bowel disease (IBD)

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A large microbial ecosystem housing several trillion microbial cells inhabits in the humans' gastrointestinal tract (1), which plays a critical role in daily physiological function, such as maturation and continued education of the host immune response, protect against pathogen invasion, regulate intestinal endocrine functions, provide a source of nutrition, metabolize bile salts, and eliminate exogenous toxins (1,2). Because of the diverse functional repertoire of the ecosystem, the dysbiosis of gut microbiota is considered to be related to a wide spectrum of chronic diseases, including atherosclerosis, metabolic syndrome, asthma, autism spectrum disorder, autoimmune disease, and inflammatory bowel disease (IBD) (1).

Fecal microbiota transplantation (FMT), is a therapeutic strategy for remodeling gut microbiota by delivering the microbiota from healthy donors into the patients' intestine. The concept of FMT was originated from traditional

Chinese medicine at least 1,700 years ago (3); however, it was populated in recent years for the better understanding of the physiological function of gut microbiota. The reports of FMT indications are expanding quickly from *Clostridium difficile* infection (CDI) (4) to IBD (5-7), and other dysbiosis related diseases (8). Emerging studies on cost-effectiveness analysis of FMT have been reported in CDI (9,10) and IBD (11) in recent three years. However, the question on how to understand the FMT practice in the current era still faces great challenge.

FMT: from single microbe to holistic integrative view

CDI is defined as the acute onset of diarrhea with documented toxigenic *C.difficile* or its toxin. The rate of CDI is increasing quickly in United States and costed more

than \$3.2 billion per year. FMT has been recommended for the treatment of recurrence CDI for the highest rate of success (>90%) compared with the other therapies (4). However, the mechanism of how FMT works is still unclear. In recent study, Yin-Yang theory in traditional Chinese medicine was helpful for us to deeply think the complex ecosystem of gut microbiota (12). According to this theory, a balance is established between the harmful and beneficial bacteria in the intestine, which describes how seemingly opposite or contrary forces may actually be complementary, interconnected, and interdependent in the natural world, and how they may give rise to each other as they interrelate to one another. The disruption of the balance leads to pathogen invasion, inflammation, and diseases. The long-time exposure to antibiotics will disrupt the intestinal hemostasis, which make the ecosystem fragile to be colonized by pathogenic bacteria such as *C.difficile* (1). A review (13) had summarized the potential mechanism including the direct interaction of donor gut microbiota with *C.difficile* bacteria and microbiota mediated effects on host physiology and immune defences that are detrimental to *C.difficile*. Commensal microbiota delivered by FMT helps to reconstruct a healthy ecosystem and compete with *C.difficile* for nutritional resources and product bacteriocins to fight against *C.difficile*. Besides direct competition, restoration of secondary bile acid metabolism in the colon and repair of the gut barrier by stimulation the mucosal immune system are also considered as the plausible mechanism of FMT (13). Inconsistent with conventional opinion in modern medicine, the effect of FMT for CDI was not to focus on one molecule, one protein, single microbe or one signaling pathway, but a system, including nutrition and immune system, dysbiosis and homeostasis, which represented a holistic integrative academic thought (14). FMT has been reported to treat IBD, functional gastrointestinal disorder (15), hepatitis B virus infection (16), autism (17), epilepsy (18), hepatic encephalopathy (19), and metabolic syndrome (20). These studies opened new window for this novel concept of therapy based on the reconstruction of gut microbiota for the infectious, autoimmune, gut-brain axis and metabolic diseases.

Our previous study presented a concept of holistic integrative therapeutics, named “step-up FMT” strategy (21,22), which combined one or more FMTs with regular cause of steroids therapy. Half of the patients with ulcerative colitis under steroids dependent status achieved clinical improvement with steroid-free after step-up FMT therapy, while these patients were failing to respond to previous

regular medication or only single FMT therapy (21,22), which indicated a synergetic effect based on the FMT and followed regular medication.

Synthetic microbiota transplantation in lab seemed to show the attractive response in trials (23). However, FMT still remains in an irreplaceable situation for the treatment of CDI and some of other microbiota-related diseases. This inspires us to rethink mechanism of FMT, the evaluation of single species of microbes, specific singling pathway and even the pure microbiome might not provide right understanding on the mechanism of FMT if we cannot think from a holistic integrative view on microbiome-host interaction or homeostasis. Since we have no better ‘composition’ at present, the best way is to utilize FMT better now from the holistic integrative view (not the alternative medicine).

FMT: not a point on methodology, but a system on therapeutics

FMT was used very limited in the world, which might be mainly related to the methodology of FMT, the difficulty on recognition and the limited reported evidence. From 2012, we started to make efforts to move standardized FMT forward, because of the methodology of FMT might determine its efficacy. The standardized FMT includes below major steps: (I) multidimensional screening of donors; (II) laboratory preparation of microbiota; (III) microbiota status; (IV) delivering of microbiota; (V) dosage and frequency of FMT; (VI) safety and quality control. The detail description had been listed in our previous studies (5,21,22). Each step should be operated very strictly to keep the quality of microbiota and efficacy of FMT, and to control the potential risk.

FMT should not be considered a simple technology, but rather an evolving technology or management system which needs to consider many aspects, such as safety, efficacy, cost, convenience, aesthetics, lab procedure, lab condition, equipment and devices. For example, the standard lab based on the automatic machine (GenFMter, FMT medical, Nanjing, China) for purification of microbiota from stool (21) should make FMT preparation easier. The novel delivering way through colonic transendoscopic enteral tubing made possible for convenient frequent FMTs or fresh FMT through the lower gastrointestinal tract at any time (24). One-hour FMT protocol (25) might be helpful for saving functional microbiota and improve clinical efficacy.

In conclusion, FMT as a therapeutic strategy to reconstruct intestinal microbiota is opening a new era of therapeutics revolution, we need a holistic view to understand the mechanism, to expand indication, and to perform the clinical practice, though it is facing a lot of challenges. It is time to move FMT into mainstream based on standardized therapeutics system and then bring clinical benefits to more patients.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/amj.2017.11.13>). B Cui and F Zhang are inventors of the GenFMTer for FMT.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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