Letter to the Editor

The need to move away from fecal transplant towards targeted, refined microbiome therapy

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Provenance: This is an invited article commissioned by the Section Editor Ming Zhong (Department of Critical Care Medicine, Zhongshan Hospital Fudan University, Shanghai, China).

Response to: Saha S, Khanna S. Microbiota replacement for Clostridium difficile by capsule is as effective as via colonoscopy. J Thorac Dis 2018;10:S1081-3.

Submitted Aug 10, 2018. Accepted for publication Sep 12, 2018.
doi: 10.21037/jtd.2018.09.80
View this article at: http://dx.doi.org/10.21037/jtd.2018.09.80

The recent editorial entitled "*Microbiota replacement for Clostridium difficile by capsule is as effective as via colonoscopy*" by Saha & Khanna provides an excellent review of the clinical efficacy, as well as the delivery options, for fecal microbiota transplantation (FMT) for patients suffering from a recurrent, *C. difficile* infection (rCDI) (1). The review also highlights the uncertainty that is relating to the optimal dose, or the delivery route for FMT (1). Admittedly, FMT is a crude and archaic method, with many drawbacks despite the high efficacy and lack of short term safety concerns. The long-term consequences remain to be determined, as the potentials for transferring infectious agents, or donor traits such as obesity, exist.

The mechanisms behind FMT's efficacy are largely unknown (2), which can prevent the development of a targeted, refined microbiome based therapy. The contents of FMT are complex, and include both live and dead bacteria as well as non-bacterial components such as viruses, bile acids and proteins (2). It is not known if some, or all of these components are necessary for the clinical efficacy of FMT. When considering the gut microbiome, it is vital to consider not only the bacteria, but also the viruses (virome), the fungal elements (mycobiome) and many small molecules, such as bile acids, and short chain fatty acids (SCFAs). These factors may be contributing to, or perpetuating gut dysbiosis, a hallmark of *C. difficile* pathogenesis.

It is assumed that live bacteria are necessary for FMT to work. Bacteriophages, which make up the majority of the gut virome, were initially thought to simply have a predator-prey relationship with microbial populations. However, recent research has demonstrated that bacteriophages have the ability to influence bacterial cell growth, virulence and favorable adaptation to changing environments (3). Previous studies have examined the possibility of treating CDI with bacteriophages alone. In an *in vitro* human colon organoid model of the CDI, although inoculation with a bacteriophage belonging to the abundant Myoviridae family, ΦCD27, led to the decrease in *C. difficile* toxin production, it was not sufficient to eradicate the *C. difficile* (4). It took a cocktail of four *C. difficile* myoviruses to eradicate the *C. difficile*, in a batch fermentation model of CDI (5). This study suggests that a combination of bacteriophages may be needed to treat CDI, and to maintain the stability of a microbial community.

In human studies, there is evidence that FMT is associated with the transfer of not just bacteria, but also bacteriophages (6). A recent study by Zhu and colleagues, has demonstrated that patients with rCDI had both bacterial, and viral dysbiosis, when in comparison with the fecal samples from healthy control groups (6). In addition, FMT led to changes in both the bacterial and

viral composition, whereas rCDI patients treated with vancomycin alone, were altered only in their bacterial composition (6). In a case report, a patient's diarrhea resolved 2 weeks after FMT but the changes in the fecal bacterial composition did not occur until 7 months later (7). However, this patient's virome was similar to the donor shortly after FMT (7), suggesting that the viral component of the FMT from the donor may be enough to induce clinical improvement. Intriguingly, Ott and colleagues used fecal filtrate, void of live bacteria, which prevented CDI recurrence in 5 patients (8). Through fecal composition analysis, again they were able to demonstrate that the bacteriophage composition of the recipient closely resembled that of the donor (8). These studies highlighted the important role that the bacteriophages potentially play in FMT.

The mycobiome is an emerging area of interest, as the composition and effect of the fungal organisms on intestinal diseases is largely unknown. In an *ex vivo* study in which diarrheal fecal samples of patients with CDI and non-CDI controls were treated with metronidazole or vancomycin, changes were observed in the relative abundances of the bacterial and fungal taxa compared with the untreated samples (9). Interestingly, the fecal samples treated with fidaxomicin, a narrow spectrum antibiotic associated with reduced CDI recurrence, had limited changes in the fungal taxa, post treatment (9). Although this study is limited by its *ex vivo* design, it highlights how *C. difficile*-directed antibiotics, are associated with distinct forms of dysbiosis comprising both bacterial and fungal communities, suggesting a trans-kingdom interaction between fungi and bacteria which may be important in the pathogenesis of *C. difficile* (9).

Furthermore, small molecules such as bile acids may also play an important role in the therapeutic actions of FMT. Pre-FMT fecal samples in patients with rCDI were reported to have a disproportionate amount of primary bile acids when compared to secondary bile acids, which are produced through the metabolism of gut commensal bacteria (2). However, the post-FMT samples had demonstrated an increase in secondary bile acids, a milieu which is inhibitory to *C. difficile* germination and growth, similar to that of the healthy donor profile (2). Thus, normalization of the bile acid metabolism is another potential mechanism. SCFAs, especially butyrate, are known to have an immune modulatory effect. Additionally, they are the preferred energy source of colonocytes (2,10). A recent study by Seekatz had found a complete recovery of the SCFA profile following a successful FMT (10). This further supported the notion, that these small molecules in donor stools, may contribute synergistically to reshape the gut microbiome (10).

Overall, the human gut is a complicated and integrated environment that is influenced by bacteria, viruses, fungal organisms, and organic compounds. With the development of metagenomics, proteomics, and complex *in vitro* models to mimic the human gut environment, we are just beginning to understand the vast intricacy between these components. New areas of research are also studying other host factors, such as the influence of inflammatory cells in the gut. The pathogenesis of *C. difficile* likely includes a combination of some or all the aforementioned components. A greater understanding of the true mechanisms of action of FMT is vital to the future development of d more targeted and refined therapies for the treatment of rCDI.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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(English Language Editor: Jeremy Dean Chapnick, AME Publishing Company).

Cite this article as: Russell L, Monaghan T, Kao D. The need to move away from fecal transplant towards targeted, refined microbiome therapy. J Thorac Dis 2018. doi: 10.21037/jtd.2018.09.80

