Digestive Diseases and Sciences (2020) 65:3425–3427
https://doi.org/10.1007/s10620-020-06291-6

EDITORIAL

Fecal Microbiota Transplantation for *Clostridioides difficile* in High-Risk Older Adults: Treat Early, Treat Often

Gaurav Agrawal[1]

Published online: 30 April 2020

Background and Significance of the Issues

Clostridioides difficile is an increasingly prevalent infection responsible for significant morbidity and mortality. Often treated initially with oral antibiotics, relapse is frequently seen, either due to reinfection or resistance, and highlights the need for novel approaches to therapy. Recurrence of *Clostridioides difficile* infection (CDI) is defined as complete abatement of CDI symptoms while receiving appropriate therapy, followed by reappearance of symptoms within 2–8 weeks after treatment has been stopped.

On average, 20–25% of patients treated for a first episode of *C. difficile* colitis will relapse after successfully completing therapy. These patients have a greater chance for further relapses with the rate for those with ≥ 2 relapses being 65% [1]. There are a number of risk factors for recurrent CDI, with the most common being increasing age, severity of initial disease, antibiotic use, and hospital exposure. Coexisting medications also appear to contribute [2].

Relapse or reinfection is assumed to be the two explanations for recurrent disease, which in turn leads to the shedding of more spores into the environment and may spread the infection further. *C. difficile* can exist in two forms: an "environmentally-resistant" spore that is optimized and responsible for transmission of the organism and a vegetative phenotype that produces the toxins and results in pathology and disease.

Fecal microbiota transplantation (FMT) is currently given after ≥ 2 recurrences of CDI. FMT consists of the instillation of processed stool collected from healthy donor(s) into the intestinal tract of a patient, a treatment shown effective for therapy of recurrent CDI [3]. To complicate matters, however, FMT protocols vary between centers and are still evolving in their practice, utilization, and methodology in the quest to optimize responses. FMT has been used much more frequently since the van Nood report [3] and highlights its high efficacy in resolving refractory CDI.

The gastrointestinal microbiome provides a homeostatic environment for its community of microorganisms to develop and exist in symbiosis with the host. The human gut microbiota are estimated to consist of at least 10^{14} bacteria and as many as 1000–1200 bacterial species. Antibiotics alter the composition and homeostasis of the microbiome, rendering it susceptible to colonization by pathogens, such as toxigenic *C. difficile strains,* causing illness ranging in severity from mild diarrhea to pseudomembranous colitis, toxic megacolon, and sepsis. The risk for recurrence is in part contingent on whether the spores of the pathogenic bacteria have remained and colonized the human gut, despite initial treatment, and are subsequently able to germinate. The mechanism underlying the success of FMT treatment is thought to be competition for food by the introduced bacteria with the offending pathogen with subsequent repopulation by the donor microbiome, restoring the host gut flora to its former homeostasis. Nevertheless, given that the primary insult begins as an imbalance of the microbiome composition (often due to antibiotics), recurrent CDI is an increasingly encountered issue. Patients with recurrent CDI have reduced diversity of the intestinal microbiome and diminished numbers of putatively beneficial bacteria relative to healthy individuals [4].

The instillation of stool microbiota from healthy individuals to patients with recurrent CDI can generally restore these missing microorganisms and protect against further CDI recurrence and colonization. The above-mentioned mechanisms do not include niche clinical subsets, such as patients who are immunocompromised, or who have inflammatory bowel disease (IBD), especially with severe or fulminant colitis. There is also a scarcity of data on FMT effectiveness in the higher-risk elderly population with CDI recurrence and CDI-related morbidity and mortality; since the majority

✉ Gaurav Agrawal
drgagrawal@gmail.com

[1] Sydney, Australia

of CDI patients treated with FMT are elderly, this is also a focus area.

Controversies Addressed by the Article

In this issue of *Digestive Diseases and Sciences*, Luo et al. [5] reported the second-largest retrospective review of elderly adults receiving FMT for CDI. The article reveals the inherent difficulties encountered with treatment of recurrent CDI. This is principally due to microbial resistance and early relapse, even with standard FMT, raising the issue as to whether FMT, as currently practiced, is optimal. The aim of the study was to assess the efficacy and safety of FMT for CDI in a cohort that involved a significant number of "higher-risk" older adults. The 75 patients included had an adjusted primary cure rate of 67.2%. FMT was performed for recurrent CDI in 69.3% of patients and for severe or fulminant disease in 30.6% of patients. The overall recurrence rate was 26.7% in the cohort. Furthermore, the results of 34 patients in the high-risk groups are split into separate categories: immunocompromised, inflammatory bowel disease (IBD), and patients with severe or fulminant colitis. The survival rate in the severe and fulminant CDI population was, interestingly, 73.9% at 3 months, which underscores the effectiveness of FMT in this subgroup. The adjusted CDI recurrence was 29.9%; most adverse events were rehospitalizations rather than deaths.

Controversies arising from this article include the low primary cure rate of FMT for CDI, which is less than the > 90% reported in most studies. Another issue is that the sub-cohort of the higher-risk groups had an adjusted recurrence rate of 32.1%, higher than usually reported, that likely contributed to the overall lower than expected primary cure rate. The authors concluded that in a high-risk subpopulation of CDI patients, a lower primary cure rate and higher CDI recurrence rate can be expected.

One message to consider is that the timing of FMT may influence its effectiveness. It should be considered early, to minimize progression, severity, and recurrence, especially in those with severe and fulminant disease. Furthermore, the current report describes a single source of the microbiota product was used in the majority of cases (67.6%) with the other third of cases utilizing material from unrelated (18.9%) and related (13.5%) donors, underscoring the possible variability of efficacy dependent on the source of donor stool.

Discussion and Future Directions

The article is, to an extent, a paradox in that despite a lower primary cure rate and higher than reported recurrence, FMT nevertheless offers substantial benefits over other forms of therapy. There are many uncontrolled variables inherent and unanswered questions surrounding the use of FMT, including the number of FMT instillations used, the use of "super-donors," factors affecting the implantation of the bacteria to the colonic mucosa, the use of antibiotics pre-treatment and post-treatment, the influence of dietary adjustments, and the variabilities of efficacy in recipients with comorbidities. These questions will be difficult to answer given the current lack of understanding of the mechanism(s) of FMT.

In this susceptible group, increasing the number of FMT instillations or co-treatment with antibiotics may well yield higher cure rates. Although a single FMT instillation is customarily used, there are data showing that > 1 FMT treatment may be necessary for optimal efficacy. Support for this view was reported in one randomized trial, where 232 patients with recurrent CDI were treated with fresh or frozen donor material. The efficacy after one FMT was approximately 50%, increasing to 75% for two FMT treatments and approximately 90% for > 2 FMT administrations. These results suggest that the current guidance of using a single FMT for recurrent CDI needs to be addressed to obtain optimum efficacy and may require additional trials, particularly in the high-risk, elderly patient group [6]. Nevertheless, the study by Luo et al. has provided a research direction to further explore, with larger and focussed trials required on these "higher-risk" subgroups reported. Their results obscured the overall accuracy of the primary cure rate in the study. It is interesting that two patients in the IBD group had experienced a change in their IBD course and biologic use. It may prove a useful avenue to explore in investigating the efficacy of biologics.

FMT alteration of the colonic microbiota appears to be durable according to some reports [7]. In an observational study of FMT for recurrent CDI, durable cure, at a median of 22 months follow-up, was reported in 82% of patients [8]. Those who had a recurrence of the condition reported antibiotic exposure following FMT, highlighting the many unexplored variables that affect FMT efficacy.

FMT appears to be safe with adverse events generally mild–moderate and self-limited. One review of > 1000 patients reported the incidence of serious adverse events including death, infection, and relapse of inflammatory bowel disease was 3.5, 2.5, and 0.6 percent, respectively [9].

With the advent of modern and evolving molecular DNA techniques, implantation of the donor microbiome can now be rigorously investigated. More information on the subspecies of bacteria is available that in turn opens a more scientifically robust approach. Quantification of the extent of donor microbiome implantation, using flow cytometry of tissue samples, in order to analyze adherence of bacteria to the mucosa over time is likely superior to the current standard of simply assessing clinical response. Multiple instillations may be required in order to overcome barriers to

implantation and to maximize adherence of the introduced bacterial community to the mucosa. Furthermore, further understanding of the detailed mechanism by which FMT is successful is needed to refine this therapy. Signalling molecules, direct physical effects, and how a homeostatic environment is created are some of the details that can be investigated. From here, achievement of the optimal steps in processing and application of FMT can be achieved.

Summary and Recommendations

- Although fecal microbiota transplantation into patients with recurrent *Clostridioides difficile* infection is effective for treatment of recurrent CDI, the elderly may require modified protocols combining multiple instillations, pedigreed donors, dietary modifications, and the adjunctive use of antibiotics.
- Patients with recurrent CDI have reduced diversity of the intestinal microbiome and diminished numbers of bacteria relative to healthy individuals. Multiple FMT vs single FMT and stool transplantation from healthy individuals to patients with recurrent *C. difficile* may better restore these missing strains and prevent CDI recurrence, although ultimately stool characterization using molecular methods may eventually be required.

Take Home Points

This is the second-largest retrospective analysis for FMT in severe, fulminant *C. difficile* colitis, including a high-risk subpopulation of CDI patients. A total of 30.6% of patients had severe or fulminant disease and experienced a 3-month survival rate of 73.9%, an adjusted primary cure rate of 67.2%, and an adjusted CDI recurrence of 29.9%. FMT should be considered early in the treatment course to prevent progression of CDI severity and recurrence, especially in patients who are elderly and have severe and fulminant disease.

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