Editorial Commentary

The real efficacy of microbiota restoration following standard of care antimicrobial in patients with recurrent *Clostridiodes difficile*

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Clostridioides difficile infection (CDI) is the most common healthcare associated infection in the United States. The treatment landscape for CDI has experienced numerous changes in recent years with standard of care for an initial episode being antibiotics such as vancomycin and fidaxomicin (1). Management of recurrence is one of the greatest current clinical challenges given the unacceptably high recurrence rates with antibiotic therapy alone (2). It is estimated that ~25% of patients with an initial episode of CDI experience recurrence despite standard of care antibiotic treatment, likely due to persistence of *C. difficile* spores and deviations from a normal intestinal microbiota (3,4). Persistent disruption of the colonic microbiota, after antimicrobial therapy leave patients susceptible to spore germination and recurrence (5). Thus, while antibiotics are necessary for all treatment of CDI, frequently, a sustained clinical response is not achieved. Microbiota restoration therapy (MRT), a form of therapeutic where we restore deficiencies in the colonic microbiota, has enabled a more physiologic, two-pronged approach to treatment of recurrent CDI (rCDI), with antibiotic use and repair of microbiota.

Over the past decade we have seen a winding path of data considering MRT in patients with CDI. Nomenclature has shifted as well, since fecal microbiota transplantation (FMT) was the term previously used to address this type of therapeutic. With this change, we have also seen an evolution in the clinical trials beginning with the most basic open label studies showing safety and efficacy for FMT in the prevention of rCDI (6) to randomized controlled trials comparing FMT with a standard of care antimicrobials (e.g., fidaxomicin) (7) to most recently, The US Food and Drug Administration (FDA) overseen randomized controlled trials for live biotherapeutic products (LBPs) (8,9). LBPs is the moniker the FDA has given for biological therapeutic that targets the microbiota. Given the consistent efficacy of FMT/MRT following standard of care antimicrobial, it has been consistently incorporated into treatment guidelines for those with second recurrence and beyond (1,10,11).

Beginning with the first meta-analyses considering open label and observational studies of FMT in patients with rCDI, this supplementary treatment approach seemed to be a very promising (12). Over the years, there have been many novel attempts to improve study design by creating better control groups including the recipients own stool and standard of care antimicrobial regimens for rCDI, such as a vancomycin taper (13,14). As we shifted away from open label studies, most thought the efficacy rates for FMT following standard of care antimicrobials in rCDI was incredibly high with one meta-analysis, including mostly open label studies estimating 92% (15). Once our study design became more rigid, and randomized controlled

trials the norm, the estimated efficacy of, now MRT, was lower. This deviation was best characterized by the initial meta-analysis from Tariq *et al.* published in 2019 (16). In this study, 13 total trials, each requiring a control group, were included showing an overall cure rate of 76.1% for MRT following standard of care antimicrobial in those with rCDI. In open-label studies, importantly, they found an efficacy of 82.7% compared with 67.7% in randomized controlled trials (RCTs) (16). This discrepancy was eye opening for many, but again, reinforced that MRT works, but better structured studies likely indicated more realistic efficacy measurements. Within this trial, they also observed significant variation in the methodologies employed for MRT, route of MRT administration and type of MRT used, which did somewhat limit the broader generalizability of these results. This study was a truly pivotal indicator that no matter what approach you take, MRT worked, but the efficacy was likely not as high as we originally thought.

The most recently updated meta-analysis considering MRT in patients with rCDI, by Tariq, Pardi and Khanna served as an update to their meta-analysis from 2019. This study included, 19 clinical trials and 1,176 patients. Here, the overall recurrence rate was 76% with rates of 72% for the randomized controlled trials and 84% for the open label studies (17). The 76% overall was very consistent with the findings from 2019 with more controlled trials included. This study, as was the previous, serves a really important purpose contextualizing the efficacy of this therapy for broader practice, but only employing studies that have control arms. There are several important points from this updated meta-analysis including heterogeneity among the trials, consideration of only a single MRT and inclusion of "any" form of FMT/MRT/LBP.

A recurring challenge when trying to compare previously conducted trials considering the efficacy for MRT is that the studies have different structures, the formulation of microbiota material used for restoration varies widely, the control groups differ (e.g., antimicrobial alone versus antimicrobial followed by placebo that mimics the active treatment), differing routes of administration and the variable times for follow up (18). The analysis by Tariq *et al.* again reinforces this heterogeneity amongst the studies (17). Despite this heterogeneity this updated meta-analysis once again shows that the concepts behind MRT, with supplementation of deficiencies in the microbiota, no matter what, or how it is administered, still works significantly better than no microbiota supplementation following antimicrobial therapy. This meta-analysis also reinforces the well-known trend for open label studies having higher efficacies than randomized controlled trials, most likely due to their inherent biases.

The Tariq *et al.* study, by design, considers MRT via a single administration following standard of care antimicrobial. This was the best and most accurate way to conduct such a meta-analysis given the variability amongst studies; however, in clinical practice, a sub-group of patients might require a second restoration of their microbiota, shortly after the initial treatment, to prevent future recurrence. The more modern trials considering LBPs included an open-label administration of the treatment if there was a recurrence, regardless of whether they received placebo or active therapy initially (8,9). This study structure shows the progress gained within our randomized controlled trials, since, if a patient received a placebo, they would be guaranteed at least one active treatment, but if they received the active treatment initially, they would receive the microbiota restoration twice. The American College of Gastroenterology guidelines recommend that if a patient fails an initial FMT within 8 weeks, a second treatment is indicated (1). Therefore, in clinical practice, the efficacy of MRT when patients are eligible for a second dose pending recurrence, is likely higher than the quoted rates we see within the reference by Tariq *et al.*

As noted previously, we are living in a new age of microbiota restoration with two FDA approved LBPs, fecal microbiota, live-jslm (RBL) and fecal microbiota spores, live-brpk (VOS). The phase 2 and phase 3 trials for these products were included within the Tariq *et al.* meta-analysis. As the present meta-analysis was designed to consider all FMT trials, it was successful, but the LBPs are different, including measured and standardized proportions of bacterial phyla, including Bacteroides amongst others with RBL and Firmicutes spores alone with VOS. This once again feeds into the heterogeneity amongst the trials included by Tariq *et al.*, but also speaks to our evolution of therapeutics in this space. These products' trials have set the standard for future studies considering MRT in patients with rCDI, and they had to be included as their efficacy should strongly influence future efficacy measurements. With FDA approval, they should be what the practicing clinician uses for MRT.

The Tariq *et al.* manuscript is a very important addition to the literature given the evolution of study design and product formulations. The totality of controlled clinical trials, including randomized controlled trials included the Tariq *et al.* manuscript, speaks to the efficacy for microbiota

restoration, largely regardless of formulation (17). We again see that the efficacy measurements in open label trials are higher than randomized-controlled trials. At this time, we no longer need to question whether FMT/MRT works, but what products and what situations might optimize outcomes. As we enter the next chapter of LBPs, the trials moving forward should have more sophisticated design and results that can be interpreted on their own helping us better understand optimal timing and situations for these treatments.

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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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