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Treatment With Fecal Microbiota Transplantation: The Need for Complete Methodological Reporting for Clinical Trials

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The virtual explosion of research articles related to the role of the human microbiome in health and disease has opened new avenues to understanding the pathogenesis of a wide variety of conditions (1). Along with interest in potential pathogenic roles for altered structure and function of the indigenous microbiota, there is a corresponding pursuit of novel therapeutics to intentionally change the microbiota to restore health (2). Whereas various methods have been proposed to therapeutically modulate the microbiome, ranging from probiotics and prebiotics to selective antibiotics, the transfer of the intestinal microbiota from a healthy individual through fecal microbiota transplantation (FMT) has garnered significant attention in recent years (3).

Although FMT has been studied most often in the setting of recurrent infection with *Clostridium difficile* (4), it has also been investigated in conditions ranging from inflammatory bowel disease to metabolic diseases, obesity, and autism spectrum disorders (5). The published efficacy of FMT varies widely, especially when applied to conditions other than recurrent *C difficile* infection. Given this variability and considering the increasing number of studies that examine the potential utility of FMT, Bafeta and colleagues conducted a systematic review that examined 85 published reports addressing the therapeutic use of FMT (6). The authors examined the methodological details in the published reports with the assumption that understanding the differences in methods could help explain why disparate results were observed. The 85 studies were scored for inclusion of the following 7 methodological details: 1) eligibility criteria for donors, 2) delay between fecal collection and transplantation, 3) type of diluent used to prepare feces for FMT, 4) type of stool (fresh or frozen), 5) amount of stool used for FMT, 6) number of transplantations performed, and 7) method of administration.

The vast majority (84%) of the studies included in the systematic review addressed the use of FMT for treatment of recurrent *C difficile* infection or inflammatory bowel disease. A similar majority (87%) were non-randomized controlled trials. Most of the studies were relatively small, with an average of 22 patients per study (interquartile range, 10 to 43). Only 8 studies (9%) had adequate reporting of all 7 methodological components scored. Many lacked adequate reporting of the eligibility criteria for donors and key aspects of fecal collection and processing. For example, 89% of the studies did not give details on the

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methods used to prepare feces for transplantation, and 89% did not give eligibility criteria for donors, nor did they describe characteristics of the donors used.

This systematic review was conducted rigorously under the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines and points out serious shortcomings in the reporting of clinical trials of FMT. Without adequate reporting of methodological details, comparisons between trials are difficult. Insufficient reporting of methods also interferes with planning new trials. The authors also point out that the lack of detail about FMT methods used will make it difficult for clinicians to implement FMT once clinical efficacy is demonstrated.

Why is there such variability in the reporting of methodological details in studies of therapeutic FMT? Bafeta and colleagues suggest several reasons, including the complexity of the procedure itself and the relatively recent attention to performing clinical trials of FMT, which has led to a lack of consensus on some aspects of the procedure. One potential reason the authors did not discuss is that FMT does not fit well within the current regulatory framework established by agencies, such as the U.S. Food and Drug Administration. There is debate as to whether FMT should be regulated as a drug or a tissue (7). However, neither of these established regulatory schemata applies clearly to the use of feces as a therapy, as evidenced by the ongoing debate.

Regardless of the debate's outcome, it is important that future clinical studies of FMT report methodological details. As the authors note, experts have yet to agree on a standard set of technical reporting aspects for trials of FMT. They conclude by suggesting that there is "the need to develop international recommendations for standardizing FMT to facilitate reporting and implementation in clinical practice." However, it is possible that such standardization is premature. For example, the methods for FMT in recurrent *C difficile* infection may not be optimal in another condition (2). Rather than standardizing the procedure itself, it is reasonable to establish standards for the reporting of technical metadata related to the procedure in any given clinical trial. The revised 2010 CONSORT (Consolidated Standards of Reporting Trials) Statement (8) cited by Bafeta and colleagues does provide guidelines for reporting the results of randomized trials, and these principles have also been adapted for nonrandomized pilot and feasibility studies. Specific guidelines for reporting details related to interventions (a single item on the list of 25 in the CONSORT statement) have been developed for specific areas of study, and this could be done for FMT. A recently published expert consensus statement summarized the current clinical applications and methodological aspects of FMT and can serve as a starting point (9). In addition, because several studies of FMT have performed molecular analysis of the microbiota, centralized biorepositories or data repositories could be established to enable assessment of FMT's effect on the microbiota. This could facilitate an understanding of the mechanistic rationale for this treatment and lead to refinement of microbiome-based therapies.

The potential for manipulating our indigenous microbiota to maintain health and prevent or treat disease is generating appropriate excitement. The report by Bafeta and colleagues suggests that we need to temper our enthusiasm for studying procedures like FMT by establishing and adhering to standards that will permit proper development, assessment, and

refinement of these experimental treatments. This will help ensure that we realize the potential effect that an understanding of the microbiome will have on revolutionizing medical practice.

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