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Fecal microbiota transplantation - something more than merely a therapeutic curiosity

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Intestinal microbiota likely represents the most complex organ in our body. It is estimated to include approximately 10^{14} independent living organisms comprising bacteria, archaea, fungi, and acellular forms such as viruses. In a healthy adult microbiota accounts for approximately one kilogram in weight, and plays a role in multiple homeostatic and physiological functions. These include energy and intermediary metabolism, normal immune responses, and even appropriate bowel development and nervous system functioning. Several bacterial patterns (so-called "enterotypes") exist that have been associated with appropriate, healthy intestinal functioning. The therapeutic manipulation of intestinal microbiota may seem innovative. However, early (rudimentary) examples date back to remote times such as ancient Imperial China, and have been documented across time and geography ever since.

As stated, we have increasingly more evidence available suggesting a key role of intestinal microbiota in human health and disease. Hence, its manipulation, and more specifically fecal microbiota transplantation (FMT), is currently becoming increasingly interesting because of its proven effectiveness and the myriad of possibilities it offers (1). Some of these possibilities are now fairly well established whereas others remain under study.

The primary indication of FMT is *Clostridium difficile* infection. Many clinical series have been reported in major publications (2,3). Recently, Rossen and colleagues

performed a systematic review of FMT cases thus far reported (4). After reviewing 33 series of cases and two clinical trials, they corroborated the procedure's high efficacy rate, with resolution of diarrhea by *C. difficile* in up to 90% of patients. All studies reviewed showed efficacy above 50%, even in immunosuppressed or elderly individuals, or in patients with severe conditions; furthermore, no differences in results were seen according to fecal infusion route (using colonoscopy or a nasojejunal feeding tube). Three clinical trials have been reported thus far on FMT for recurrent *C. difficile* colitis. The first one, of poor methodological quality, showed a symptom resolution rate of 81% (5). The second study, on a sample of 20 patients, compared several infusion routes with no control group, and found a cure rate of 70%, no differences being observed according to administration approach (6). The third study, with no control group and using capsules for FMT administration, found a success rate of 70% with a single dose, and up to 90% after a second dose (7). In the setting of refractory *C. difficile* colitis fewer -though highly successful- reports and no clinical trials are available. Notably, in the light of available evidence the procedure seems very safe. But for anecdotal evidence, no adverse effects have been reported, to which thorough donor assessment surely contributes. From all the above, the procedure's effectiveness in this setting is beyond doubt, which is reflected by the inclusion of FMT in the therapeutic guidelines issued by the European Society of Infectious Diseases regarding *C. difficile* infection (8). We always refer to relapsing or refractory infection because further clinical trials with quality methodology are necessary before the technique may be extended to all infections with *C. difficile*. However, the current alternative for vancomycin failures is fidaxomicin, a costly though well-tolerated and effective antibiotic. FMT might be likely positioned level with this option in the therapeutic algorithm for *C. difficile* disease.

As regards the usefulness of FMT for other indications, evidence remains preliminary. Regarding inflammatory bowel disease more data are available for ulcerative colitis, where results are heterogeneous and symptom improvements oscillate between 20% and 92% (4). Two series with a total of six patients have been reported for Crohn´s disease, with no clinical benefit demostrated thus far.

Another likely indication of FMT is obesity, an epidemic in developed countries that still lacks effective medical therapies. In a randomized, double-blind study in obese patients one arm received their own intestinal microbiota while the other received microbiota from patients with a BMI < 23. Patients transplanted with microbiota in the second arm exhibited improved insulin sensitivity at the hepatic and peripheral level (9). Furthermore, the potential role of FMT in the eradication of colonization by multi-resistant organisms has been reported of late (10).

The experience of the Portuguese group, reported in this issue of the *Spanish Journal of Gastroenterology (Revista Española de Enfermedades Digestivas)* (11), one again provides promising results for FMT in refractory and relapsing infection with *C. difficile*. This this single-center study discusses eight procedures in six patients (three with recurrent infection, three with refractory infection), all of them of advanced age and with a recent history of antibiotic therapy, that were performed over a period of 9 months. Seven of eight FMTs were administered using gastroscopy, and one using colonoscopy. Of all six patients included, five reached remission of their diarrhea with a single FMT procedure, whereas one patient required three FMTs to achieve remission. This represents excellent results with 100% overall success, similar to prior papers (12). Evidence available is insufficient to establish the number or frequency of FMTs that are needed for therapeutic success. In this study, 83.3% were cured with only one administration, these results being similar to those reported in the literature (13). However, a patient required three FMTs to resolve diarrhea, which highlights the fact that some patients will require more than just one procedure to achieve remission. As in prior studies, the resolution of diarrhea was fast (24-48 hours after FMT), and the procedure was well tolerated with no apparent adverse effects.

Despite the availability of growing information from case series and studies, FMT preparation and administration remain non-standard as of today. The detailed protocol of this study approaches a number of controversial procedure-related aspects including donor preparation with lactulose or recipient preparation with PPIs when an upper route is selected to reduce the potential adverse effect of gastric secretion on the solution instilled. Other interesting points refer to the need for donor preparation with laxatives regardless of the chosen administration route, as the density of *C.*

difficile bacteria could be reduced. This study opted to discontinue antibiotic therapy the day before FMT, but further studies are needed to establish the timing of antibiotic discontinuation. The study by Ponte et al opted for an upper administration route, as no evidence thus far has rendered any route superior over the rest (11).

All in all, this interesting study once again reveals the efficacy and safety of FMT as evidenced in prior papers in the management of refractory and recurrent infection with *C. difficile*, an emerging issue in our daily clinical practice. Notably, the center where these authors work is a "normal" hospital, and seems to us a praiseworthy effort of interest and undertaking. To implement FMT no large facilities with extraordinary means are required, but only craftsmanship and a healthy dose of scientific curiosity. Research on microbiota manipulation is a different thing, and the resources available (whether directly or in collaboration) in an academic center seem crucial when it comes to studying the composition of microbiota and starting the use of FMT for newer indications.

In medicine, novel therapeutic procedures, particularly when carrying transgressive, even bizarre connotations as in our case, elicit preoccupation and even rejection in cautious physicians. However, FMT in the setting of *C. difficile* infection should not be regarded as an experimental or reckless procedure, as it represents an evidence-based treatment that health care institutions should offer for selected patients, where it might represent the best management option available as of today.

Beyond its value for *C. difficile* diarrhea, its limits and horizons are difficult to establish. Good safety profile, attractive pathophysiological mechanism, inexpensive raw material, and widespread availability of required resources all make FMT a potential therapy for highly diverse conditions. In the short-to-mid run, our hopes lie in the treatment of ulcerative colitis (over 20 clinical trials ongoing) and type-2 diabetes mellitus, where the ability of FMT to reduce insulin resistance has become established, as described above. Multiple sclerosis, hepatic encephalopathy, acute pancreatitis, irritable bowel syndrome, metabolic syndrome, autism, and Parkinson's disease are only a small sample of the conditions FMT may have a word on. The upcoming decade, whether for the better or worse, will be the time where its true usefulness will be decided upon and defined. It is only with long-term follow-up, procedural

standardization, and clinical trial findings that FMT will be seen to substantially change patient lives and clinical practice or to become one of those unmet promises that abound in the history of medicine.

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