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Editorial

Faecal microbiota trasplant: Current status and perspectives beyond *Clostridioides difficile* infection

Trasplante de microbiota faecal: Situación actual y perspectivas más allá de la infección por *Clostridioides difficile*

Faecal Microbiota Transplantation (FMT) is a technique by which the microbiota present in the faeces of a healthy donor is transferred to a recipient who presents structural or functional alterations in their intestinal ecosystem. There is controversy over the denomination and some authors have proposed using the alternative terms Faecal Microbiota Transfer or Intestinal Microbiota Transfer.[1] The publication in 2013 of the first randomised clinical trial comparing the efficacy of FMT with that of vancomycin in patients with recurrent *Clostridiodides difficile* infection (rCDI) prompted its incorporation into clinical practice and significantly stimulated research into this procedure.[2] FMT requires considerable organisational effort, given that it requires the participation of multidisciplinary groups willing to select appropriate donors, handle sample processing, and prepare and administer the product once the correct indication has been established, all while ensuring donor–recipient traceability. There are still few publications by Spanish groups that have implemented FMT,[3–5] and in this issue of EIMC, Ferre-Aracil et al.[6] report their experience with 13 patients diagnosed with rCDI who were followed for more than two years. Their work helps us understand the organisational and logistical challenges involved in offering an FMT programme for rCDI, particularly in terms of how related donor samples are used and how the FMT is prepared in the hours prior to its infusion via colonoscopy. In recent years, notable advances have facilitated better organised and more efficient FMT procedures. The use of unrelated donors does not reduce efficiency[7] and makes it possible to create a stool bank. Freezing, encapsulating, and lyophilising stool make it possible to create a permanent stock and thereby simplify administration by using a small number of capsules. Despite these advances in Spain and in the rest of Europe, there is as yet no commercialised product, and few centres can offer FMT, which means few patients can access the procedure.

There are many unresolved questions surrounding FMT in rCDI. The evidence for its efficacy is not as strong as one might think; there have been few randomised clinical trials and the comparator has almost always been suboptimal (only one trial compared the efficacy of FMT with fidaxomicin).[8] Moreover, in most centres, patients receive FMT after full or partial treatment with an antibiotic targeting *C. difficile*, implying that at least some patients could have been cured without FMT.[9] Nevertheless, the North American and European guidelines recommend FMT from the third episode of rCDI onwards, and several meta-analyses demonstrate an efficacy of 80–90%.[10,11] It is generally accepted that FMT works by repopulating an intestinal microbiota devastated by previous antibiotic treatments. However, a provocative study suggests that it is not microorganisms but certain substances or metabolites from faeces that inhibit a *C. difficile*,[12] which shows that we do not yet know the ultimate mechanism by which FMT works in rCDI. Reports of infections with antibiotic-resistant microorganisms and Shiga toxin-producing *E. coli* after FMT have raised concerns about safety.[13] The emergence of SARS-CoV2 and the simian smallpox virus have forced donor screening procedures to be updated and is a good example of the risk of unsuspected transmission of pathogens (https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/safety-alert-regarding-use-fecal-microbiota-transplantation-and-additional-safety-protections-0). The interaction of a foreign microbiota with the recipient's microbiota raises the question of possible adverse physiological effects in the medium to long term. Careful selection of healthy donors does not ensure that the infused microbiota is also healthy, nor does it rule out the possibility that this microbiota could exert deleterious effects on the recipient. Certainly, recent studies of long-term follow-up of cohorts suggest the safety of FMT,[14] but given that they are mostly non-controlled studies, they do not guarantee it, and even hint at certain risks that must be examined.[15]

Should FMT be considered a "drug" and therefore, its production and distribution be subject to the same regulatory conditions as for any other pharmaceutical product? Should it be considered an organ or tissue and its management regulated by the corresponding norms?[16] In many countries there is a lack of specific regulations (in Spain they are currently being developed), while in certain countries various regulatory solutions are being adopted.[17,18] Lastly, there is a conceptual debate of interest: must we infuse a complete microbiota or can we achieve a similar therapeutic effect with species-specific bacterial consortia? The answer to this question might be different in the case of rCDI than for other diseases for which the potential utility of FMT is being investigated, such as those detailed next.

The pathology in which the most efforts have been made to elucidate the potential role of FMT is in inflammatory bowel disease,

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particularly ulcerative colitis. A recent meta-analysis of double-blind, placebo-controlled clinical trials has shown benefit in terms of clinical and endoscopic remission.[19] While these results are promising, long-term results are scarcely available and it is not known, for example, whether any maintenance or additional doses are necessary.

Irritable bowel syndrome is one of the most frequent digestive pathologies, but it is also one of the most heterogeneous, in which multiple entities probably coexist. Various studies have revealed an alteration in the composition of the microbiota, which is probably related to the numerous therapeutic strategies that have been unsuccessfully attempted by these patients. A recent systematic review of FMT including 254 patients has not demonstrated superiority over placebo.[20] However, some authors suggest that the response could be conditioned by the route of administration of FMT and could also be donor dependent.[21]

The use of FMT to optimise the response to the immunomodulatory treatment of cancer is an area of extraordinary interest. The interactions of the gut microbiota with anticancer drugs are complex and include both pharmacokinetic (metabolism or enzymatic degradation) and pharmacodynamic (immunomodulation) aspects, thus the term *pharmacomicrobiome* has been coined.[22] The translation of this basic science to the clinic is beginning to be tested with, for example, the response to reinduction recently reported in some patients with metastatic melanoma refractory to anti-PD-1.[23]

The description of the eradication of multidrug-resistant bacteria after FMT for rCDI has prompted the use of this strategy in several research projects and clinical trials. Although isolated cases and series permit some optimism, there are few trials (usually involving the use of nonabsorbable antibiotics prior to FMT) with modest results.[24] In the coming years, we await the results of randomised trials such as KAPEDIS[25] to answer the questions that arise around this strategy, such as the duration of the effect, whether to administer nonabsorbable antibiotics beforehand, and the most convenient route of administration.[26]

The so-called "gut-brain axis" has been the subject of numerous studies in recent years. Several studies suggest an important role of the intestinal microbiota in the pathophysiology of many neurological disorders in which gastrointestinal alterations are frequent. Indeed, a different composition of the human gut microbiota compared with healthy controls has been found in several neurological disorders such as Parkinson's disease, autism spectrum disorders, epilepsy, and neuromyelitis optica, among others.[27] However, these associations obviously do not imply causality. As a recent narrative review shows, the evidence on the potential usefulness of FMT in neurological pathologies is still preliminary and only a few clinical trials with clear results are available.

Several experimental models have revealed various mechanisms linking the intestinal microbiota to obesity and metabolic disorders, including increased energy utilisation, which favours fat deposition, affect satiety, and promotes systemic inflammation.[28] There is therefore enormous interest in therapies that modify the intestinal microbiota as a means of correcting these disorders. Again, evidence on the efficacy of FMT in obesity and metabolic syndrome remains sparse. A recent meta-analysis of 6 trials has shown reductions in glycosylated haemoglobin and increases in HDL cholesterol at 6 weeks, but without achieving weight reduction in patients.[29]

Lastly, it has been reliably demonstrated that the intestinal microbiota plays an important role in liver cirrhosis and its complications, especially hepatic encephalopathy, which makes modification of the intestinal microbiota an attractive therapeutic target. Several preliminary studies have been encouraging, showing improvements in cognitive aspects in patients and a reduction in episodes of hepatic encephalopathy.[30] Larger studies are needed to confirm these results and to answer the questions that arise, including safety, the optimal route of administration and the necessary dosage.

In summary, at present FMT is uniquely indicated for the treatment of rCDI because of its high cure rates. Making this technique available implies logistical and management efforts that will need to be solved by the pharmaceutical industry or by national or regional public institutions supported by specific regulations. The multiple physiological functions of the microbiota and its associations with specific pathologies have generated extraordinary interest in the possible usefulness of FMT in other areas in which we are currently in the purely experimental stages. For some entities, such as hepatic encephalopathy, the possible beneficial effect of FMT appears closer to being demonstrated than in many other conditions for which the evidence is still weak. While for rCDI "any" microbiota appears to be effective, we do not know if donors or microbiota with specific characteristics would be needed for other processes, nor do we know the impact of FMT in the long term and, therefore, the necessary "dosage". In short, the road ahead for FMT in the treatment of rCDI is as exciting as it is challenging to travel.

Conflict of interest

The authors of this editorial letter, Rosa del Campo and Javier Cobo, have no conflicts of interest regarding the work we present.

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