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Fecal microbiota transplantation in recurrent *Clostridioides difficile*: Is greater methodological rigor and the analysis of other populations relevant?

Trasplante de microbiota fecal en *Clostridioides difficile* recurrente: ¿es pertinente mayor rigor metodológico y el análisis de otras poblaciones?

Dear Editors,

We have read with particular interest the study by Quera et al.[1] titled ''Fecal microbiota transplantation through colonoscopy in the treatment of recurrent *Clostridioides difficile*: Experience at a university center'', whose aim was to describe the clinical results of fecal microbiota transplantation (FMT) performed as treatment for recurrent *Clostridioides difficile* infection (CDI). We would like to make the following observations.

An adequate and detailed description of the methodological aspects of the study by Quera et al.[1] should be emphasized. The use of statistical normality tests has been widely discussed. Each has its clear indications, but the Shapiro-Wilk test is recommended over the Kolmogorov-Smirnov test, given that it has been demonstrated to be more powerful and exact. However, we believe it would have been relevant to have given more statistical data on the use of the test employed and the possible limitations for its implementation. For example, for applying the Shapiro-Wilk test, probabilistic sampling is recommended, and the authors provided no further information about their sampling and selection decisions.[2]

In their study, Quera et al.[1] conducted a clinical follow-up of the patients of at least 3 months, post-FMT, and the percentage of successful FMT was defined as the absence of a new episode of CDI for 8 weeks after the procedure. In contrast, Gupta et al.[3] describe definitions for clinical and general cure, for evaluating the effectiveness of the procedure. Clinical cure is defined as diarrhea and/or *Clostridioides difficile* (*C. difficile*) toxin resolution within a period of 12 weeks or years, and general cure is defined as cure after a single or repeated FMT. One of the inclusion criteria for that study was CDI diagnosis, based on clinical symptoms and *C. difficile* confirmed through the polymerase chain reaction (PCR) test for toxins A and B, which could be considered post-management control, but is not mentioned in the study by Quera et al.[1]

Quera et al.[1] refer to the limitation in sample size, but it is important to consider special populations, such as immunocompromised patients. In the study by Alrabaa et al.,[4] a group of immunocompetent patients was compared with an immunocompromised group and found that all the immunocompetent patients achieved successful cure with FMT, whereas 3 immunocompromised patients experienced failure. A second FMT in those 3 patients was successful in one and failed in the other two. An important predictor of failure in FMT for CDI in immunocompromised patients was pre-FMT antimicrobial exposure.

In conclusion, the relevance and quality of the authors' research, their findings, and conclusions should be highlighted. We believe a collaborative effort by centers that are highly specialized in surgery and gastroenterology is necessary to develop better and more robust management guidelines in CDI and FMT. The aim of the methodological and population analyses we have made herein is to promote the ongoing implementation of methodological analyses, enabling the journal's continuous improvement and positioning in the scientific field in Latin America.

Financial disclosure

No financial support was received in relation to this letter to the editor.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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Response to ''Fecal microbiota transplantation in recurrent *Clostridioides difficile*: Is greater methodological rigor and the analysis of other populations relevant?''

Respuesta a «Trasplante de microbiota fecal en *Clostridioides difficile* recurrente: ¿es pertinente mayor rigor metodológico y el análisis de otras poblaciones?»

Dear Editors,

We appreciate that Dr. Castrillón-Lozano et al.[1] highlighted our article on fecal microbiota transplantation (FMT) results through colonoscopy in the treatment of recurrent *Clostridioides difficile* (rCDI).[2] Without a doubt, their observations enrich the critical analysis of the role of TMF as a therapeutic strategy in rCDI.

Regarding the statistical analysis, we agree with the view that the Shapiro-Wilk test is more powerful and exact than the Kolmogorov-Smirnov test, especially if a sample has < 50 individuals,[3] which was a recognized and stated limitation of our study.[2] The suggestion to delve deeper into the sampling and selection criteria are aspects we shall consider in future studies.

Concerning the clinical success definition of FMT, we utilized the absence of recurrence at 8 weeks after the procedure because it is one of the criteria utilized in the literature for evaluating the effectiveness of therapeutic FMT in CDI management,[4] and thus allows results between different studies to be compared. Nevertheless, we agree that broader definitions, such as those proposed by Gupta et al.[5] would enable a more complete and exact characterization of the therapeutic response to FMT. On the other hand, Castrillón-Lozano et al. commented that the polymerase chain reaction technique for toxins A and B could be considered a post-management control in FMT. However, the performance of stool exams for controlling CDI cure is not recommended in the literature because those tests may remain toxin-positive after treatment.[6]

We consider the need to include different scenarios in which FMT may be an effective strategy in managing CDI, as occurs in immunocompromised patients,[7] to be a very relevant observation. In our case series, the number of cases of such patients was limited, hindering the performance of conclusive sub-analyses. Nevertheless, we completely agree about the relevance of that group of patients, considering their greater clinical vulnerability. It is important to point out that, even though FMT use in immunocompromised patients is historically approached with caution, recent studies have shown its safety and efficacy in that population, with no significant increase in severe adverse events.[8] This evidence reinforces the need to develop focused research and specific guidelines for immunocompromised patients.

Lastly, we sincerely appreciate the words of recognition, in response to our study, and we fully agree about the need to generate collaborative, multicenter evidence, to strengthen the clinical recommendations regarding FMT use in rCDI.

Financial disclosure

No financial support was received in relation to this article.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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