



EXPERT'S CORNER: A PERSONAL APPROACH

## Fecal microbiota transplantation



J. González-Altamirano<sup>a</sup>, H.J. Maldonado-Garza<sup>a</sup>, E. Garza-González<sup>a,b</sup>,  
F.J. Bosques-Padilla<sup>a,\*</sup>

<sup>a</sup> Gastroenterology Services at the "Dr. José Eleuterio González" University Hospital of the Autonomous University of Nuevo León, Monterrey, N.L., Mexico

<sup>b</sup> Department of Clinical Pathology of the "Dr. José Eleuterio González" University Hospital of the Autonomous University of Nuevo León, Monterrey, N.L., Mexico

Received 19 June 2015; accepted 19 June 2015

Available online 14 August 2015

Fecal microbiota transplantation (FMT) represents the most promising free-antibiotic therapy in the management of patients with infection by *Clostridium difficile*, recurrent or refractory to treatment with antibiotics. FMT's superiority over conventional treatment has been proven in multiple series of cases and recently in experimental prospective randomized clinical trials with a resolution of the infection in over 90% of patients.<sup>1</sup>

FMT occurs when intestinal microorganisms are infused with a suspension from a healthy donor into a sick patient for the purposes of restoring altered microbiota. The first known description of the use of human feces as a therapeutic agent comes from China. During the IV century, Ge Hong prescribed – in the emergency medicine pocket book – the intake of feces for different diseases. The success of fecal microbiota transplantation in modern medicine was first described by Eiseman et al. in 1958, administering microbiota in enemas to patients with pseudomembranous colitis.<sup>2,3</sup>

*C. difficile* is a Gram-positive spore-forming bacteria isolated in 1935 and described for the first time as a cause of diarrhea and pseudomembranous colitis in a patient in 1978.

\* Corresponding author at: Facultad de Medicina y Servicio de Gastroenterología, Hospital Universitario "Dr. José Eleuterio González" de la Universidad Autónoma de Nuevo León, Av. Francisco I. Madero y Gonzalitos s/n, Colonia Mitras Centro, C.P. 64460 Monterrey, N.L., Mexico. Tel.: +52 81 8333 3664; fax: +52 81 8333 3664.

E-mail address: [fbosques58@hotmail.com](mailto:fbosques58@hotmail.com) (F.J. Bosques-Padilla).

In the last three decades we have witnessed the increase in the incidence and severity of infectious profiles by *C. difficile*, making it a serious health issue, increasing morbidity and mortality in hospitalized patients as well as in outpatients. The incidence of infection by *C. difficile* in the community has increased 5.3 times from 1991 to 2005 and in these outpatients the disease occurs in young adults without comorbidities who lack traditional risk factors like the exposure to antibiotics and recent hospitalization. This suggests new risk factors and new forms of transmission.<sup>3,4</sup>

One of the factors which has contributed to the increase in the number of cases of infection by *C. difficile* is the presence of a new, more virulent, quinolone-resistant strain, which produces 16 times more toxin A and 23 times more toxin B, in addition to a third toxin, which has enterotoxigenic activity in vitro.<sup>5</sup> Moreover, this new strain produces more spores, conditioning a greater pollution in the environment, thereby increasing the risk of spreading. This epidemic strain is associated with a higher incidence of complicated cases and a higher mortality rate. Initially identified by a restriction endonuclease analysis and denominated as BI (1980), it is currently referred to as Type 1 (NAP1) by pulsed fields analysis or ribotype 027 by ribotyping. This NAP1 strain has spread widely in the US; nevertheless, very few clinics are aware of its presence due to its characteristics.<sup>1,4</sup>

Current recommendations to decide on a treatment for patients with infection by *C. difficile* are based on clinical severity. Patients with mild infections may be treated with metronidazole 500 mg, administered orally 3 times a day, or vancomycin 125 mg, administered orally 4 times a day for

10 days. Severe cases are treated with vancomycin 125 mg, administered orally 4 times a day for 10 days. Complicated severe cases are treated with a combination of vancomycin 500 mg, administered orally 4 times a day, plus metronidazole 500 mg IV every 8 h and rectal vancomycin (vancomycin 500 mg in 500 ml of saline solution in enema) 4 times a day in case of the presence of ileus.<sup>5</sup>

However, one of the challenging aspects in the management of patients with a *C. difficile* infection is the recurrence of the disease after a successful treatment. It is considered a recurrence when symptoms restart within the first 8 weeks after the end of treatment. Recurrence rates after treatment with metronidazole and vancomycin are similar (20.2% and 18.4%, respectively)<sup>6</sup>. For the treatment of recurrences, we recommend the same treatment that was used during the initial episode, coupled with a suspension of any antibiotics the patient may be taking to allow the restoration of the intestinal microflora. If the new episode is severe, vancomycin should be utilized. Some experts recommend giving pulses of vancomycin in the case of a second recurrence. Other antibiotics, like rifaximin and fidaxomicin, have been tested in cases of recurrence and obtained variable results and, overall, a greater cost<sup>7,8</sup>. Neither of these is currently recommended for recurring cases.

In the context of treating a recurrent *C. difficile* infection, we are confronted with a grand paradigm; the recurring infection is secondary to a disruption of the colonic microflora started by the antibiotic therapy and perpetuated by metronidazole or vancomycin. The antibiotics destroy the bacteria, but also destroy the intestinal microbiota, which is vital to maintaining health, immunity and colonic metabolism. The risk of recurrence is greater in patients with a previous recurrence, increasing by 20% after the first episode, up to 40% with the first recurrence and up to more than 60% after 2 recurrences<sup>4,9</sup>.

There is a decrease in the diversity of fecal microbiota in patients with recurrent diarrhea due to a *C. difficile* infection. This decrease can be observed, for the most part, in the concentration of the specie *Bacteroides* and *Fermicutes*. Because of this, a treatment without antibiotics, preserving and restoring microbiotic diversity, can represent a new strategy to achieve the prevention and treatment of recurring *C. difficile* infections<sup>10</sup>. FMT has been demonstrated to be an effective alternative in the treatment of refractory *C. difficile* infections, and is the most radical and direct method to change the composition of the colon microbiota<sup>2</sup>.

To perform a FMT, a feces sample from a healthy person is required. In our hospital we performed a simple questionnaire looking for a person without comorbidities, with an adequate BMI, who did not have any antecedent of previous hospitalization or use of antibiotics within the last 3 months. We performed general examinations (blood count, blood chemistry) a viral profile (HBVAg, Antibodies against HCV and HIV), a coprological is conducted as well as a single stool specimen ova and parasite examination and toxins A and B for *C. difficile* in feces.

Upon deciding that the patient with a *C. difficile* infection is a candidate for FMT, the use of antibiotics was suspended for 48–72 h and a nasojejunal probe was placed and its adequate placement verified by simple X-rays. One day before the transplant, 4 packets of Nulitely (109.6 g each) were administered, each one diluted in 4 L of water.

On the day of the transplant a fecal material sample is requested from the donor in the morning, and laboratory personnel homogenize the sample in a saline solution and filter it, obtaining approximately 50 ml of microbiotic solution. The FMT is administered by means of the nasojejunal probe. In case it does not advance to the small intestine, an endoscope is used to instill the FMT directly into the duodenum. The case can be used as an alternate method of administering a colonoscopy, as the situation warrants. The therapy is considered to be effective when the diarrhea disappears after the administration of the FMT.

The superiority of the FMT over treatment with antibiotics has been demonstrated in multiple publications. The series of cases show favorable responses in more than 90% of cases<sup>11</sup>. Recently, a controlled randomized study was performed, comparing the effectiveness of FMT ( $n = 16$ ) against treatment with antibiotics, observing the resolution of the disease in 94% of cases (3 patients received a double FMT infusion)<sup>12</sup>. Now, there are studies that show its utility in seriously ill patients or immunosuppressed patients with recurring or refracting *C. difficile* infections, observing a recovery in 89% ( $n = 80$ ). In our center, we have used the FMT in refractory as well as recurring cases. For the most part, the patients are hospitalized and suffering from multiple comorbidities. We have obtained a resolution of diarrhea of 87%, and were able to avoid surgical management and reduce morbi-mortality in these patients. Recently, methods have been developed to freeze the microbiota for the FMT in capsules at  $-80^{\circ}\text{C}$  and study its effects in cases of refractory *C. difficile* infections, with an observed effectiveness of 90%<sup>13</sup>. None of the studies have reported significant side effects. Other uses that the FMT has been used for have been in patients with a *C. difficile* infection and inflammatory bowel disease (IBD), including a therapeutic proposal in cases of refractory IBD<sup>1</sup>.

By what has been documented, we can conclude that the FMT has shown its usefulness in patients with a recurrent or refractory *C. difficile* infection, and as a medical treatment even for patients that are seriously ill or with some degree of immunosuppression. With the increase in the incidence and severity of *C. difficile* infections, the FMT has a very important role to play in the combating of this disease. Our experience underlines the fact that treatment with FMT in Mexico is a reality. The requirements for its implementation and the technical process are simple, bringing the option of a cure to the majority of patients managed with this therapy, which is free of antibiotics and serious adverse effects.

## Funding

No financial support was provided.

## Conflict of interest

The authors have no conflicts of interest to declare.

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