Experience of a gastroenterology center in fecal microbiota transplantation in the treatment of *Clostridioides Difficile*

Experiência de um centro de gastroenterologia em transplante de microbiota fecal no tratamento de *Clostridioides difficile*

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ABSTRACT

Background: The treatment of *Clostridioides difficile* is based on an antibiotics cycle, but for individuals who have more than two recurrences, fecal microbiota transplantation can be considered as a therapeutic option. **Objective:** To describe the technique and results of fecal microbiota transplantation performed for recurrent infection by *Clostridioides difficile*. **Methods:** Retrospective, cross-sectional study based on a review of medical records of patients undergoing transplantation of fecal microbiota. Data were obtained on the criteria used to select the donor, the preparation of stools in the laboratory and the method of delivery of the material offered, as well as information regarding the characteristics of the recipient, such as: gender, age, comorbidities, hospitalizations, use of antibiotics prior to infection, clinical presentation, diagnosis and treatments performed for Clostridioides difficile. After transplantation, data on efficacy, outcome, follow-up time and procedure complications were considered. **Results:** Between 2012 and 2019, 11 patients underwent fecal microbiota transplantation. The use of antibiotics prior to infection occurred in 9 patients, no patient was hospitalized in the previous 6 months due to another etiology. All had at least 2 cycles of vancomycin for recurrent disease. Of the total of 11 patients, 2 required 2 infusions and 1 patient required 3, totaling 15 fecal microbiota transplants. The success rate was 81.8% with only one infusion and 90.9% resolution considering patients who needed more than one infusion. **Conclusion:** Fecal microbiota transplantation is a feasible therapy with resolution in 90.9% of cases as a treatment for recurrent Clostridioides difficile infection.

Keywords: Clostridioides difficile; Clostridium infections; Fecal microbiota transplantation; Diarrhea/drug therapy; Dysbiosis; Anti-bacterial agentes/therapeutic use; Observational study

RESUMO

Contexto: O tratamento do Clostridioides difficile é baseado em ciclo antimicrobiano, mas para os indivíduos que apresentam mais de duas recorrências, pode-se considerar o transplante de microbiota fecal como opção terapêutica. **Objetivo:** Descrever a técnica e os resultados do transplante de microbiota fecal realizados para infecção recorrente por Clostridioides difficile. **Métodos:** Estudo retrospectivo, transversal, baseado em revisão de prontuários de pacientes submetidos ao transplante de microbiota fecal. Foram obtidos dados sobre os critérios empregados para seleção do doador, o preparo das fezes e o método de entrega do material, além de informações referentes às características do receptor, como: sexo, idade, comorbidades, internamentos, uso de antimicrobiano prévio à infecção, apresentação clínica, diagnóstico e tratamentos realizados para o Clostridioides difficile. Após o transplante, dados sobre eficácia, desfecho, tempo de seguimento e complicações do procedimento foram considerados. **Resultados:** Entre 2012 e 2019, 11 pacientes foram submetidos ao transplante de microbiota fecal. O uso de antimicrobiano prévio à infecção ocorreu em 9 pacientes, nenhum paciente internou nos 6 meses anteriores por outra etiologia. Todos fizeram pelo menos 2 ciclos de vancomicina para doença recorrente. Do total de 11 pacientes, 2 necessitaram de 2 infusões e 1 paciente necessitou de 3, totalizando 15 transplantes de microbiota fecal. O sucesso foi de 81,8% com apenas uma infusão e resolução de 90,9% considerando pacientes que necessitaram de mais de uma infusão. Conclusão: O transplante de microbiota fecal é uma terapia factível e com resolução em 90,9% dos casos como tratamento de infecção recorrente por Clostridioides difficile.

Descritores: Clostridioides difficile; Infecções por clostridium; Transplante de microbiota fecal; Diarreia/tratamento farmacológico; Disbiose; Antibacterianos/uso terapêutico; Estudo observacional

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INTRODUCTION

Clostridium difficile infection, reclassified as *Clostridioides difficile*[1], is the leading cause of antibiotic-associated diarrhea in hospitalized patients. The bacterium is present in the human intestinal flora and is capable of generating clinical manifestations when there is dysbiosis in the microbiota. The clinical state may be mild/moderate, severe, fulminant or recurrent, increasing morbidity and mortality, which can reach 58% in critically ill patients. The mild/moderate form is characterized by leukocytes below 15 thousand cells/mL and creatinine below 1.5mg/dL. The clinically severe, by leukocytes above 15 thousand cells/mL or creatinine above 1.5mg/dL. In case of hypotension, shock, paralytic ileus or megacolon, the clinic is fulminating. In addition, we define recurrence as the return of symptoms with a positive Clostridioides difficile test within 8 weeks of a previous episode. Endoscopically, it may present as pseudomembranous colitis[2-4].

Patients with advanced age, severe underlying disease, inadequate immune response to Clostridioides difficile and use of other antibiotics during or after Clostridioides difficile treatment are at increased risk of recurrence. Furthermore, it is observed that these patients have a smaller amount of bacterial population, as well as their diversity, which may be due to repeated cycles of antibiotics[2].

Epidemiologically, in the United States, there has been an increase in the number of cases of recurrent infection of 188% since the 2000s, resulting in prolonged hospitalizations, use of antibiotics and high health costs[5]. In Brazil, there are few studies on the epidemiology of the infection. Regionally, in the southern region, a study with 351 patients observed that 17.7% of diarrhea associated with antibiotics were due to *Clostridioides difficile*[6].

Among the diagnostic methods, the detection of toxins A and B in feces or the detection of *Clostridioides difficile* via polymerase chain reaction (PCR) are the most available methods[7,8].

The treatment consists of a cycle of metronidazole and/or vancomycin, depending on the patient's clinical severity and previous treatments. However, for those with more than 2 recurrences, fecal microbiota transplantation can be considered as a therapeutic option[2,7,9,10].

Transplantation of fecal microbiota was first described in 1958 for the treatment of pseudomembranous colitis, a form of presentation of *Clostridioides difficile* infection[11]. Its objective is to correct intestinal dysbiosis, restoring the healthy flora. This procedure has a cure rate above 80%, a good safety profile, cost-effectiveness and an average time to resolution of symptoms of 3 days[4,10,12].

There are several possible routes for the administration of fecal transplant: high route through upper digestive endoscopy, nasoenteral tube, upper enteroscopy or capsule; lower route through colonoscopy or enema. There is no consensus on the most indicated route and cure rates were similar among them[9,13]. Ideally, antibiotics should be discontinued 48 hours before the procedure in order to avoid the residual effect after microbiota transplantation[14,15].

Several mechanisms are believed to play a role in the success of fecal microbiota transplantation. The reconstitution and biodiversity of the intestinal flora are essential by themselves, but also by acting on non-bacterial components capable of helping suppression of *Clostridioides difficile*. Healthy microbiota is capable of forming secondary bile acids and short-chain fatty acids, with immunomodulating and antimicrobial effects. Furthermore, the presence of bacteriophage bacteria, production of bacteriocins and antimicrobial peptides inhibit the growth and activity of the toxin[16].

The aim of the study is to describe the technique and results of fecal microbiota transplantation performed for recurrent infection by *Clostridioides difficile* in a gastroenterology service in southern Brazil.

METHODS

Study design

This is a retrospective, observational, cross-sectional study based on a review of medical records of patients who underwent fecal microbiota transplantation from September 2012 to June 2019 at a tertiary service in Curitiba.

This study was approved by the ethics committee for research in human beings under number 3,320,554, on May 12, 2019, with the free and informed consent form being waived to the participants.

Criteria for donor selection, stool preparation and microbiota administration were identified. In addition, data regarding the recipient such as: gender, age, comorbidities, previous hospitalizations, previous use of antibiotics, clinical presentation, diagnostic examination and treatments performed. Information regarding complications, outcome and follow-up time after transplantation were also described. Based on the definition of recurrence, resolved infection was the resolution of symptoms for a period of 8 weeks after fecal microbiota transplantation.

Data were organized in an Excel table for further description.

Donor evaluation

The microbiota donor was initially selected as a possible candidate for clinical evaluation, which may or may not be a family member, excluding those who had close contact with the patient, due to the risk of being colonized by the bacteria, and those who had recently used antibiotics. After choosing the volunteers, a clinical evaluation was carried out, with a preference for healthy donors aged 18-60 years. These underwent laboratory tests with analysis of serology for HIV, viral hepatitis, syphilis, liver and kidney biochemistry, complete blood count, research for *Clostridioides difficile* (preferably by polymerase chain reaction), Strongyloides stercoralis, Giardia lamblia, coproculture and parasitology of feces.

The stool sample came from a single donor, who had normal exams. Collection flasks were made available for the storage of feces that occurred on the same day as the fecal microbiota transplantation.

Preparation of feces for fecal microbiota transplantation:

The sample was delivered to the laboratory's microbiology sector, for dilution in saline, at the rate of 30g of feces to 70ml of 0.9% saline solution. The mixture was homogenized, filtered through gauze and stored in a refrigerated container until the time of infusion. For fresh stools, the infusion must take place within 6 hours of preparation.

Delivery method of fecal microbiota:

The administration of fecal microbiota was performed through colonoscopy in all patients with an infusion of approximately 60mL of the material in the cecum and ascending colon.

Hospital admission was not necessary exclusively for the procedure.

The cleasing agent for bowel preparation was mannitol or sodium picosulfate.

After the procedure, patients were clinically monitored for complications and released after a period of 1 to 2 hours of observation.

RESULTS

The sample consisted of 11 patients who underwent fecal microbiota transplantation for the treatment of recurrent diarrhea caused by *Clostridioides difficile* between September 2012 and June 2019. Of these, 9 are female and age ranged between 31 and 89 years, with a mean of 58.6 years.

Regarding comorbidities, 1 patient was healthy, 1 had a diagnosis of inflammatory bowel disease and the other diagnoses were: systemic arterial hypertension, hypothyroidism, rheumatoid arthritis, depression, peptic ulcer disease, gastroesophageal reflux disease, cured esophageal adenocarcinoma, hepatitis C chronic, chronic kidney disease, glaucoma, dyslipidemia and coronary artery disease.

As for the risk factors for infection by *Clostridioides difficile*, 9 patients used antibiotics previously and 2 did not. Of these, one of them attended a hemodialysis clinic. No patient required hospitalization for other diseases in the 6 months prior to the condition, but 6 patients were hospitalized due to the current diarrheal condition.

The diagnosis was mostly due to positivity in the investigation of toxin for *Clostridioides difficile* (8 patients). One diagnosis was by detection of the bacteria in feces by PCR and the other 2 were empirical.

The clinical presentation was mild/moderate in 8 patients and severe in 3.

The initial treatment was carried out with metronidazole in 9 patients and only 2 started directly with vancomycin. One hundred percent of patients took at least 2 courses of vancomycin, due to infectious recurrence, before microbiota transplantation (Table 1).

Table 1. Profile of patients undergoing fecal microbiota transplantation

Risk factors	Number	Variation or percentage (%)
Patients	11	
Men	2	18.18%
Women	9	81.81%
Average Age	58.6	31 - 89
Risk factors		
Antibiotic use	9	81.81%
Previous hospitalization for another illness	0	0%
Hospitalization due to diarrhea	6	54%
Diagnostic Method		
Toxin	8	72.72%
Stool PCR	1	9.09%
Empirical	2	18.18%
Clinical manifestations		
Mild/moderate	8	72.72%
Severe	3	27.27%
Treatments performed		
Metronidazole	9	81.81%
Vancomycin	11	100%

PCR: Polymerase Chain Reaction

Patients treated with metronidazole used a dosage of 500mg every 8 hours for 10 days. Initial vancomycin cycles were used at dosages of 125 – 500mg every 6 hours for 10 days. For cases of recurrence, vancomycin was used in a tapered and pulsed regimen.

As for fecal donors, in 5 cases, they were family members and in 1, unrelated. No data regarding other donors were found.

With just one fecal microbiota transplant administration, the infection was resolved in 9 patients (81.8%) and, considering those who required more than one infusion, the success rate was 90.9%. The interval between transplants was 2 months in the patient who received 2 microbiota infusions, and 2 and 9 months in the patient who required 3 infusions. Both received new cycles of vancomycin between procedures. None of the patients who were empirically diagnosed required retransplantation.

No complication related to the procedure technique was described. However, one patient developed post-infectious irritable bowel syndrome and two others died: one patient died of sepsis of a pulmonary focus, despite the resolution of the diarrheal condition, and unrelated to microbiota infusion. The patient who received 3 microbiota transplants, had multiple recurrences of the infection, daily use of vancomycin due to failure to respond to transplants, evolution to toxic megacolon, indication for total colectomy, sepsis and death after surgery (Table 2).

Patients were followed for a period varying from 2 months to 5 years after transplantation. This time was influenced by clinical improvement, presence of other gastroenterological comorbidities that required follow-up or the patient's desire.

DISCUSSION

The treatment of *Clostridioides difficile* through fecal microbiota transplantation has been increasingly studied and made feasible in clinical practice. This study demonstrates that this procedure can be performed in any service that has colonoscopy and laboratory support available.

The main risk factors for *Clostridioides difficile* infection are well known. It is observed that the previous use of antibiotics is an important factor, being the main one found in our sample. In an Israeli study with a large sample, 59% were exposed to antibiotics and 72% had been admitted to hospital[12]. In our sample, no patient was hospitalized for any reason other than the current diarrheal condition. In this case, due to not having accurate information about the initial diarrheal clinical picture, worsening of symptoms or relapse after the use of antibiotics, we cannot presume that previous hospitalization cannot be a risk factor for 6 of our patients.

The diagnostic methods used are in accordance with recent guidelines, stressing that, in cases of high clinical suspicion despite negative diagnostic tests, we are authorized to perform the treatment empirically[7], as occurred in two cases. This may be a limitation of the study, but it does not invalidate the evaluation of the procedure and its safety.

A large part of our sample made at least one attempt at treatment with metronidazole as the first therapeutic option. This is explained by the fact that until a few years ago, metronidazole was the first option for the treatment of patients with mild to moderate disease, as well as the higher cost and difficulty of accessing vancomycin[7]. Currently, vancomycin is the first therapeutic option for new or recurrent cases[5].

The route of administration of fecal material by colonoscopy is the most used, as shown in the study by Quraishi et al.,[10]. It has the benefits of providing greater stool volume and retention, mucosal visualization, and lower risk of bronchoaspiration of fecal material. Furthermore, bowel preparation can reduce the number of spores and residual organisms in the intestinal flora[17].

A Brazilian study published by Ganc et al., in 2015, described the experience of transplanting fecal microbiota by high enteroscopy in 12 patients, with recurrence in only 1 of the cases[3]. It has the advantage of not submitting debilitated patients to bowel preparation and, like the present study, it demonstrates the applicability of fecal microbiota transplantation in the Brazi-

Table 2. Profile of patients who relapsed or had complications after fecal microbiota transplantation.

Patient	Age	Clinical state	Complications	Number of transplants	Outcome
1	68	Severe	Multiple relapses of infection Evolution to toxic megacolon Sepsis after total colectomy	3	Death
2	78	Severe	Sepsis of pulmonary origin	1	Death
3	57	Mild/ moderate	Irritable bowel syndrome	1	Resolution
4	52	Mild/ moderate	None	2	Resolution

lian population, with the exception that the possibility of enteroscopy is reserved for some centers with more resources.

There is no need for laboratory control for cure[7]. Symptom resolution within 48-72 hours is the parameter used to assess response, maintaining only follow-up and surveillance for recurrence. In our sample, those who maintained or returned to symptoms were rescreened for *Clostridioides difficile*. In some patients, more than one infusion was necessary, which is predicted by Laniro et al., considering that the success of a single microbiota infusion is around 50 to 90%, increasing up to 96% in repeated infusions[18].

The outcome highlights the success of fecal microbiota transplantation for the treatment of *Clostridioides difficile* infection. We had 81.8% resolution with one infusion and 90.9% resolution considering all infusions, which is in agreement with what is expected in the medical literature, which describes success between 80% and 95%[4,5,7,9,10,12,13].

Serious complications were related to the patient's frailty and/or comorbidities. We had no complications related to colonoscopy or microbiota infusion. This data is also in agreement with the literature, which demonstrates that most post-procedure complaints are related to colonoscopy discomfort and not complications[5].

Long-term safety data related to the infusion of new microbiota are still scarce, but patients should be informed about them[19]. There are descriptions of autoimmune diseases, weight gain, norovirus infection, sepsis by gram negative bacteria and infections by multiresistant bacteria[5,14,20,21]. Some centers already perform screening for carbapenem-resistant enterobacteriaceae, extended-spectrum β-lactamases and methicillin-resistant Staphylococcus aureus in donors[22]. So far, the risk of such complications is low and the benefit brought by the fecal microbiota transplant outweighs them[23]. Despite this, the best way to follow up after fecal microbiota transplantation is still unknown[10].

Recently, in some regions of Brazil, there is the availability of using material from a stool bank, increasing safety and access to the technique[24].

In the future, the possibility that transplantation may be a viable alternative to oral antibiotics treatment in primary infection by *Clostridioides difficile*[25] is studied, as well as the availability of capsule infusion and preparation of a stool bank, increasing the availability and accessibility of treatment[5].

CONCLUSION

Transplantation of fecal microbiota in our environment proved to be a feasible therapy for the treatment of recurrent infection by *Clostridioides difficile*, with a resolution rate of 81.8% with only one infusion and a final success of 90.9%.

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