PERFORMANCE AND CONSEQUENCES FOR FECAL TRANSPLANT IN THE TREATMENT OF PSEUDOMEMBRANOUS COLITIS

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ABSTRACT

Under conditions of increased consumption of antibiotics, pseudomembranous colitis has become a common condition in Romanian hospitals. Severe forms of the disease are becoming more common, recurrences are numerous, and metronidazole and vancomycin therapy has failed to prevent these recurrences. The study aims to identify the characteristics of patients who require a fecal transplant, the time for its performance and what are the short-term and possibly long-term consequences of this method.

We analyzed 26 patients who had a fecal transplant with a favorable evolution in 96%. We consider that FMT is an effective method for preventing recurrent CDI but also for those with resistance to the usual antibiotics.

Keywords: Clostridium Difficile, recurrence, fecal transplant, microbiota

Introduction

Colitis with *Clostridium difficile* or Pseudomembranous colitis is a common condition in recent years. According to the CDC (Centers for Disease Control and Prevention), more than 336,000 Americans suffer from *Clostridium difficile* infections (CDI) each year and 14,000 deaths are reported each year despite established therapy (1).

A small number of antibiotics are used in the treatment of this condition (2). Metronidazole is usually the drug of choice because of its lower price. (3). It also has the advantage that it can be administered both orally and intravenously,

with increased efficacy and is recommended in mild and moderate forms of the disease, 500 mg every 8 hours, with an indicative duration of 10 days (3). Orally administered vancomycin is a second-line drug for mild to moderate forms and is recommended by the first line for severe disease, associated with intravenously metronidazole, 125-250 mg every 6 hours, 10-14 days and with prolonged use in recurrent cases (4, 5). Rifaximin is a safe, enteric drug, effective in combination with metronidazole or vancomycin and may be considered an optimal treatment for recurrent CDI, but has low efficacy on ribotype 027 (6). Fidaxomicin is as effective as vancomycin and has been shown

to have a lower risk of recurrence compared to other antibiotics. It can be used in patients with recurrent infections or in those who have not responded to other antibiotics. Fidaxomicin orally 200 mg twice daily for 10 days may be a valid alternative (4,7,8). Tigecycline therapy 100 mg IV infusion, then 50 mg IV infusion q12hrs could be a choice in severe forms of CDI with toxic megacolon (9). The use of other antibiotics such as fusidic acid, teicoplanin or nitazoxanide has been described in the literature, but they are not currently recommended for general use (4).

Despite these treatments, recurrences are common, it is considered that after a first treatment with metronidazole or vancomycin, *C. difficile* reappears in about 20% of cases, the risk of recurrence can increase up to 40% -60% (9).

A recommended method for preventing recurrences is to recolonize the colon with saprophytic flora by transplanting enteral flora (fecal transplant) from a healthy donor (4,10). Also, this method is considered to be approximately 90% effective in patients in whom antibiotics have not worked (11). Although fecal transplant therapy remains a controversial topic, there is growing evidence that it could be an effective treatment for severe or recurrent CDI (11,12).

The aim of the study was to identify patients in need of intestinal microbiota transplantation, the favorable time to perform it and to assess the short-term and possibly long-term consequences of this method.

Material and method

In our prospective study have been identified 26 patients diagnosed with recurrent CDI in which a fecal microbiota transplantation (FMT) was performed three years before the pandemic.

Adult patients with one or more recurrences of *Clostridium difficile* colitis or patients not responsive to the usual therapy were included in the study.

Patients with severe forms of the disease with life-threatening comorbidities (neoplasms, AIDS, severe heart failure) who could not be followed for 12 weeks posttransplant were

excluded from the study.

The study was conducted within the research activity of the Doctoral School and received a favorable opinion from the Ethics Commission. All patients signed an informed consent to enter the study.

The microbiota from donors from the patients' family was transplanted. Family members who were tested for bacterial and parasitic (*C. difficile*, *Helicobacter pylori*, *Giardia*, *Cryptosporidium*) or viral (Hepatitis A, B, C and HIV) diseases were selected as donors. The specific material processed (100 ml fecal microbiota solution) was transplanted by colonoscopy after a 2-day break from antibiotic therapy. All patients were followed for 12 weeks post-transplant.

The parameters followed were improving the appearance and consistency of the stools (according to Bristol Stool Scale), improvement of symptoms (nausea, vomiting, appetite, and abdominal cramps), normalization of PCR, fibrinogen, leukocyte count and absence of recurrences in the next 3 months after FTM.

Results. Patients were aged 42-77 years, with a median of 59 years, male predominated (73%).

More than half of the patients (68%) have recently had prolonged hospitalizations in various clinics such as: orthopedics (11 cases), surgery (3 cases), oncology (5 cases), hematology (6 cases), neurosurgery (1 case), all patients received antibiotic treatment with fluoroquinolones (ciprofloxacin), third generation cephalosporins or carbapenemes before the onset of *C. difficile* diarrhea, most cases (82%) had significant comorbidities.

All patients experienced treatment with metronidazole, vancomycin, rifaximin, or tygecycline during CDI episodes.

Most of the patients had multiple recurrences (20 cases), 6 patients did not respond to the usual therapy. All of these patients had mild to moderate disease at the time of transplantation (Table 1).

Table 1. Characteristics of the CDI patients

Demographic characteristics	n = 26 pts
Mean age (years)	59
Male gender	19
Risk factors	
Prolonged hospitalizations	26
Antibiotic treatment	26
Chemotherapy	11
Comorbidities	21
Hypertension	16
Diabetes	12
Inflammatory bowel disease	2
Hematological malignancies	5
Solid tumors	6
Clinical characteristics	
Average number of bowel movements	4.76
Bristol Stool Scale	type 5 (14), type 6 (10) type 7 (2)
Median Atlas score	4
Antibiotics used for the treatment of CDI	18
Fluoroquinolones	25
Third generation cephalosporins	1
Carbapenemes	
Experienced treatment during CDI	
episodes metronidazole	26
vancomycin	26
rifaximin	8
tygecycline	1
CDI ribotype 027	26
Median recurrences	3.3

Legend-pts - patients

The evolution of post-transplant patients was favorable in 25 cases, which means a cure rate of 96.1%, only in 77 year old patient recently diagnosed with non-Hodgkin's lymphoma who developed *Clostridium difficile* colitis after chemotherapy, the evolution was unfavorable, he developed toxic megacolon, requiring surgery (Table 2).

Table 2. Clinical and paraclinical outcomes

Clinical parameters (mean days)	
Improving the appearance and consistency of the stools (according to Bristol Stool Scale)	3.8 (Type 3or 4)
Nausea	3.3
Vomiting	1.2
Appetite	3.8
Abdominal cramps	1.8
Paraclinical parameters	
leukocyte count	3.3
PCR	3.8
fibrinogen	3.8
Complication after FTM	1
Absence of recurrences in the next 3 months after transplantation	25 patients

Discussions.

Regarding FTM, numerous studies have been performed in the last years in patients diagnosed with *Clostridium difficile* colitis. Vigvári et al. (13) reports a cure rate of 80-93.3% in patients who received 100 ml of fecal microbiota solution per nasogastric tube and states that the method is especially effective in patients with recurrent infection. If we refer to the administration of the fecal microbiota by colonoscopy, Khan et al. reports a cure rate of 100% in 9 patients with community-acquired CDI and only 81.8% in 11 patients with nosocomial CDI, but these patients who initially experienced failure recovered later after transplantation. (14). The study also states that after 6 months of follow-up, all patients were satisfied with this procedure and no complications or side effects were reported. In our study, the success rate was high (96.1%), comparable to the rates reported in the literature.

Also, in patients with CDI resistant to antibiotic treatment, FMT showed a therapeutic response rate of over 90% according to the Institute of Predictive and Personalized medicine (IPPM) guide (15).

A Review Article published by Jiunn-Wei Wang et al. (2019) shows an increased efficiency of FTM in patients with mild and moderate CDI, with the improvement of clinical and paraclinical parameters comparable to those observed in our study (16). In severe CDI, the authors report side effects such as complications of endoscopy (perforation, bleeding), infection and/or sepsis, therefore, recommendations are limited (16).

Conclusions

FMT represents an effective therapy in patient with recurrent CDI, is a safe method, with good results, in the short term, but also in the long term in preventing recurrences in patients with pseudomembranous colitis, especially in patients with mild and moderate forms of CDI.

Also, in patients with CDI resistant to antibiotic treatment, FMT may be an option with increased efficacy.

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