A Retrospective Comparison of Fecal Microbial Transplantation Methods for Recurrent *Clostridium Difficile* Infection

Nathaniel A. Cohen MD[1]*, Dan M. Livovsky MD[6], Shir Yaakobovitch BSc[2], Merav Ben Yehoyada PhD[2], Ronen Ben Ami MD[4], Amos Adler MD[3], Hanan Guzner-Gur MD[1], Eran Goldin MD[6], Moshe E. Santo MD[2], Zamir Halpern MD[2], Kalman Paz MD[6]* and Nitsan Maharshak MD[2,5]*

Departments of [1]Internal Medicine B, [2]Gastroenterology and Liver Diseases and [3]Clinical Microbiology, [4]Infectious Disease Unit, and [5]Bacteriotherapy Clinic, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
[6]Digestive Diseases Institute, Shaare Zedek Medical Center, Jerusalem, Israel

ABSTRACT:

Background: Antibiotic treatment of *Clostridium difficile* infection (CDI) has a high failure rate. Fecal microbiota transplantation (FMT) has proven very effective in treating these recurrences.

Objectives: To determine which method of fecal microbiota transplantation (upper or lower gastrointestinal) and which type of donor (a relative or unrelated) is superior.

Methods: This is a retrospective analysis of treatment protocols and outcomes in 22 patients with refractory or recurrent CDI who underwent FMT at two Israeli facilities. Each center used a different donor type, stool preparation and method of delivery. The Tel Aviv Sourasky Medical Center used unrelated fecal donors and frozen stool samples and delivered them primarily (92%) via the lower gastrointestinal (GI) tract. Shaare Zedek Medical Center used fresh donor stool of relatives and delivered them primarily (90%) via the upper GI tract.

Results: FMT had an overall 2 month cure rate of 89%. Patients treated with FMT that was executed through the lower GI tract recovered faster from the infection (1.6 ± 1.08 vs. 2.4 ± 1 days for the upper tract, $P = 0.03$). The results also showed that patients who received lower GI tract FMTs were more likely to be cured of CDI (100% vs. 75% for upper tract FMTs, $P = 0.16$). Five patients (22%) died of CDI/FMT-unrelated causes and two (10%) died of CDI/FMT-related causes during the study period.

Conclusions: Lower GI tract FMT is a safe and effective treatment for refractory and recurrent CDI, and yields quicker results than upper GI tract FMT.

IMAJ 2016; 18: 594–599

KEY WORDS: fecal microbiota transplantation (FMT), *Clostridium difficile*, diarrhea, bacteriotherapy, colonoscopy, gastroscopy

For Editorial see page 623

Antibiotic-associated diarrhea caused by *Clostridium difficile* is the most common cause of hospital-acquired diarrhea. Since 2000 there has been a significant increase in the incidence and severity of health care-associated *C. difficile* infection (CDI) worldwide, particularly in patients over 65 years of age [1]. This increase is largely attributed to the widespread use of antibiotics, which raise the risk of CDI by eight- to tenfold during use and for one month afterwards [2]. Current treatment regimens are primarily based on antibiotic therapy [3], but up to 20% of patients will suffer from CDI recurrence after treatment of an initial episode and 40–65% after treatment of a second episode [4]. New therapies are being sought for the treatment of CDI as a result of this significant failure rate and its associated burden on both the patient and the health care system.

Fecal microbiota transplantation (FMT) has been shown to have an 80–95% success rate with long-term durability in numerous well-conducted studies [5-7]. It was also found to be highly acceptable among patients and their families [5]. The aims of the current study were to assess the success rate and side effects of FMT for CDI in two Israeli medical centers – Tel Aviv Sourasky Medical Center in Tel Aviv, and Shaare Zedek Medical Center in Jerusalem – and evaluate whether two different protocols for donor selection, FMT preparation and routes of FMT administration yielded different results.

PATIENTS AND METHODS

We performed a retrospective analysis of the data and outcomes in patients with recurrent or refractory CDI who were treated with FMT at the two centers from July 2013 through August 2015. Written consent was obtained from the patients or their surrogates before FMT. The study was approved by the ethics committees of both medical centers. Patients were

---

*These authors contributed equally to this study

followed routinely at 48 hours, 2 months and 6 months after the procedure for assessment of side effects and treatment outcome at the Bacteriotherapy Clinic of the Department of Gastroenterology and Liver Diseases at both medical centers.

DEFINITIONS

CDI was defined as the presence of ≥ 3 unformed stools per day for at least 2 days and a positive test for toxigenic *Clostridium difficile* [8]. Recurrent CDI was defined as another episode of CDI within 8 weeks of the previous one [8]. FMT was performed after the third recurrence. Refractory CDI was defined as disease that did not respond to medical therapy. We defined the initial response to FMT (assessed within one week post-procedure) as a decrease in the number of bowel movements to < 3 unformed stools/day. A cure associated with FMT was defined as no recurrence of CDI-related diarrhea within a 2 month period post-transplantation [9,10].

RECIPIENTS

All the patients who were treated with FMT for refractory or recurrent CDI in both centers were included in the study. Their clinical data were obtained from digital medical records and included epidemiologic information, risk factors for CDI, Charlson Co-morbidity Index [11], and information on symptoms and disease recurrence post-FMT for up to 6 months.

DONOR SELECTION

The preferred Tel Aviv Sourasky donors were healthy individuals unrelated to the patient and who had not been recently exposed to health care facilities. If such donors were not available, a healthy relative or friend with no history of intestinal disease or usage of antibiotics within the 6 months prior to donation was selected. Donors were excluded if they had been or were currently at high risk of a transmissible infectious disease (similar to blood donors). Most of the Shaare Zedek donors (90%) were healthy relatives who fulfilled the same criteria. Those donors underwent blood and stool tests to exclude undiagnosed metabolic, hematologic, infectious and inflammatory/immune diseases [12].

DONOR STOOL PREPARATION

Donor stool was delivered to the institution within a few hours of evacuation in a clean, closed, plastic container. Stool was immediately diluted with sterile saline (NaCl 0.9%) and blended into a homogenous liquid. The liquid was then filtered to remove particulate matter. The stool dosage was 60 g at Sourasky, and ranged between 35 and 75 g (depending on the amount provided by the donor) at Shaare Zedek. Stool donations were processed and kept frozen at -80ºC until use at Sourasky, while fresh donor stool was delivered to Shaare Zedek on the day of FMT for processing and transplantation.

FECAL MICROBIOTA TRANSPLANTATION PROCEDURE

- *Patient preparation.* If the transplantation was performed via colonoscopy, the patients received oral bowel preparation (3 L of a polyethylene glycol with electrolytes solution) before the procedure and all antibiotics were discontinued for at least 12 hours prior to the procedure. They received loperamide on the morning of the procedure to promote retention of the FMT. Patients whose transplantation was performed via the upper GI received a dose of proton pump inhibitor the evening before and on the morning of the procedure, and metoclopramide was administered prior to the procedure to prevent nausea and vomiting of the fecal transplant matter.

- *Fecal transplantation.* At Sourasky, the frozen stool donation was thawed at 4ºC and a 250 ml portion was instilled via colonoscopy or gastroscopy into the recipient's ileocecum or distal duodenum, respectively. In the colonoscopy procedure, 200 ml of the fecal transplant solution was instilled in the cecum or terminal ileum and 50 ml was distributed along the colon. At Shaare Zedek, the quantity of preparation varied since saline was added gradually to the stool until the desired consistency for the transplant was obtained. Patients who underwent FMT via the upper GI tract (either by direct instillation through the scope into the distal duodenum or through a nasoduodenal tube placed under direct endoscopic vision) were administered 100–300 ml of stool solution. Those who underwent FMT via the lower GI tract were administered up to 500 ml of stool solution that was distributed evenly, starting at the terminal ileum and continuing down to the sigmoid colon.

STATISTICAL ANALYSIS

Continuous variables were analyzed using a two-sided *t*-test and the non-parametric Mann-Whitney test, as appropriate. The chi-square test was used to explore categorical variables. Kaplan-Meier estimates were used to assess time to response to FMT, and the difference in response between the two groups was compared using the log rank test (SPSS® Statistics software version 19). A *P* value < 0.05 was considered significant for all analyses.

RESULTS

FMT was performed on 22 patients with recurrent or refractory CDI at the two tertiary medical centers during the study period. Twelve patients from the Tel Aviv Sourasky Medical Center and 10 patients from Shaare Zedek Medical Center were included in this study. Patient demographics, epidemiological data and risk factors for CDI are listed in Table 1.

Most of the patients (n=16, 73%) presented with mild-to-moderate disease and the rest were diagnosed with severe

Table 1. Study population characteristics according to FMT delivery route

| | Method of FMT | | | |
	Upper GI	Lower GI	Overall	*P* value
Patients, no. (% of total)	10 (45)	12 (55)	22 (100)	
Male gender, no. (%)	8 (80)	5 (42)	13 (59)	0.1
Age, median (range)	73.3 (16–92)	70 (18–89)	71.5 (16–92)	0.74
Expected survival at 1 year (Charlson Co-Morbidity Index)	75 ± 9	91 ± 8	77.8 ± 8.5	0.52
Hospitalization in past 3 months, no. (%)	8 (80)	6 (50)	14 (64)	0.2
Use of antibiotics in past 3 months, no. (%)	6 (60)	6 (50)	12 (55)	0.69
PPI usage, no. (%)	4 (40)	7 (58)	11 (50)	0.67
Chemotherapy, no. (%)	0	2 (17)	2 (9)	0.48
Inflammatory bowel disease, no. (%)	0	1 (8)	1 (5)	NS
Previous episodes of CDI, median (range)	2 (0–5)	1.2 (0–4)	1.6 (0–5)	0.23
Previous CDI treatments				
Metronidazole, no. (%)	9 (90)	10 (83)	19 (86)	n/s
Vancomycin, no. (%)	10 (100)	12 (100)	22 (100)	n/s
Combination antibiotics (metronidazole + vancomycin), no. (%)	7 (70)	6 (50)	13 (59)	0.41
CDI characteristics at time of FMT				
Severe disease, no. (%)	4 (40)	2 (17)	6 (27)	0.35
Refractory, no. (%)	3 (30)	6 (50)	9 (41)	0.41
Recurrent, no. (%)	7 (70)	6 (50)	13 (59)	0.41
Treated as outpatient, no. (%)	3 (30)	7 (58)	10 (45)	0.23

FMT = fecal microbiota transplantation, GI = gastrointestinal tract, PPI = proton pump inhibitors, CDI = *Clostridium difficile* infection, NS = not significant

Table 2. FMT outcome and patients' follow-up

| | Method of FMT | | | |
	Upper GI	Lower GI	Overall	*P* value
No. of patients	10	12	22	
Response within 7 days, no. (%)	9 (90)	10 (83)	19 (86)	NS
Days to response, median (range)	2.4 (0–5)	1.6 (0–3)	2 (0–5)	0.03
No. of patients at 2 months follow-up	7	11	18	
Cure at 2 months, no. (%)	5 (71)	11 (100)	16 (88)	0.16
No. of patients at 6 month follow-up	7	5	12	
Cure at 6 months, no. (%)	5 (71)	5 (100)	10 (83)	0.45
Total deaths, no. (%)	5 (50)	2 (17)	7 (32)	0.17
CDI/FMT unrelated	3 (60)	2 (100)	5 (23)	NS
CDI related	1 (20)	0 (0)	1 (5)	NS
FMT related	1 (20)	0 (0)	1 (5)	NS
No. of adverse events (%)	2 (20)	4 (33)	6 (27)	0.6

FMT = fecal microbiota transplantation, GI = gastrointestinal tract, PPI = proton pump inhibitors, CDI = *Clostridium difficile* infection, NS = not significant

Figure 1. Kaplan-Meier estimates of patient response to FMT for the two groups of patients. Response rates were significantly different between the groups (*P* = 0.02 using the log rank test) with patients receiving FMT via lower GI showing a more rapid response

disease as determined by a leukocyte count > 15,000 cells/ul and/or a serum creatinine level ≥ 1.5 times the premorbid level. Ten patients (45%), mostly those who received FMT via colonoscopy, were treated on an outpatient basis.

Twelve patients (55%) were transplanted via the lower GI (colonoscopy) and 10 via the upper GI (gastroscopy, nasogastric/jejunostomy tube) or via an existing percutaneous endoscopic gastrostomy tube. Thirteen patients (59%) received the FMT material from an unrelated donor. Eleven patients (92%) who underwent FMT via the lower GI route received the stool donation from an unrelated relative as did 2 patients (20%) in the upper GI group. The general characteristics of the patients in the upper and lower GI FMT groups were very similar [Table 1].
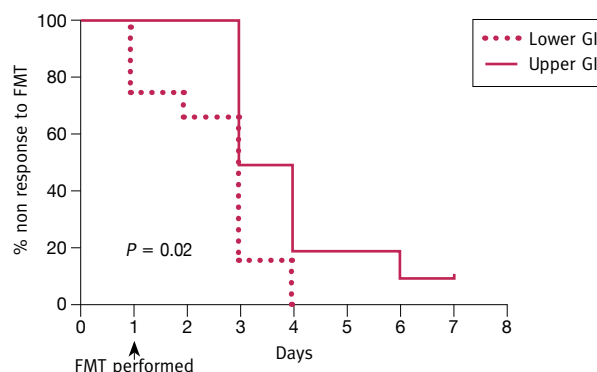
RESPONSE TO TREATMENT AND SIDE EFFECTS

An initial response to FMT was observed within 5 days of the procedure in 19 patients (86%). Among the patients who did not initially respond, two experienced an improvement manifested as a decrease in more than 50% of their bowel movements, but still more than three bowel movements per day. Both of these patients were cured of CDI by the 2 month follow-up. One patient did not initially respond to FMT and was diagnosed as having intractable CDI. Patients who underwent FMT via a colonoscopy responded in a mean of 1.6 ± 1.08 days compared to patients who underwent FMT via the upper GI who responded in a mean of 2.4 ± 1 days (*P* = 0.03) [Table 2]. The Kaplan-Meier estimates also showed a significant difference in response rates between the two groups (*P* = 0.02) [Figure 1].

At 2 months post-procedure, three patients had died of causes unrelated to FMT or CDI [Table 2], and 17 of the remaining 19 patients (89%) had been cured of CDI. One patient did not respond to FMT and one patient had a severe complication consisting of aspiration of fecal transplant matter during the procedure as detailed below. At 6 months post-FMT, 10 patients remained asymptomatic, and another 2 patients

Table 3. Patient mortality during the study period

Age (years)	Gender	Cause of death	Timing post-FMT (days)	Expected survival at 1 year (%)*	Response to FMT	Route of FMT administration	Dept. of hospitalization before FMT
87	F	CDI colitis	52	79 ± 9	No	Gastroscopy	Intensive care ward
86	M	Chronic respiratory insufficiency	40	64 ± 11	Yes	Gastroscopy	Intensive care ward
89	M	Complications of hemodialysis	30	64 ± 11	Yes	Gastroscopy	Home
92	M	Pneumonia	25	64 ± 11	Yes	Gastroscopy	Normal ward
71	M	Line sepsis post-fecal transplant aspiration	10	64 ± 11	Yes	Gastroscopy	Intensive care ward
84	M	Died at home, cause unknown+	87	79 ± 9	Yes	Colonoscopy	Normal ward
87	M	Pneumonia/*Pseudomonas* sepsis	9	64 ± 11	Yes	Colonoscopy	Intensive care ward

*According to Charlson Co-Morbidity Index
+This patient died at home, cause unknown but unrelated to CDI/FMT
FMT = fecal microbiota transplantation, F = female, M = male, CDI = *Clostridium difficile* infection

had died from causes unrelated to CDI/FMT. The five remaining patients who have not yet reached the 6 month follow-up point are symptom free. There were no recurrent CDI episodes among any of the patients who had a therapeutic response to FMT at the time of writing this report.

SAFETY AND ADVERSE EVENTS

Six patients (27%) experienced adverse events. Of these, five patients experienced minor and transient constipation and abdominal discomfort. One patient suffered from aspiration of the fecal transplant: he was severely ill and was hospitalized in the intensive care unit (ICU) due to fulminant CDI. He suffered from an extremely distended colon and markedly raised intra-abdominal pressures. The FMT was performed via gastroscopy in the ICU, and 300 ml of fecal transplant was instilled into the small intestine (in keeping with the amount instilled in other patients in this series). At the end of the FMT procedure, there was an entero-oral reflux of the transplant material complicated by aspiration into the airways. Immediate endotracheal intubation was performed with deep airway suction, and he was successfully weaned off mechanical ventilation in the ICU 3 days later. This patient's diarrhea ceased and a repeat toxin assay measured 7 days post-FMT was negative. However, the patient suddenly deteriorated and died during replacement of his central line, presumably from a pulmonary embolism or gram-negative sepsis cultured from his central line during his ICU admission. An additional patient did not respond to FMT and died of severe colitis. Five patients died of causes that were unrelated to CDI or FMT [Table 3].

DISCUSSION

This study summarizes the results and side effects of FMT in 22 patients with recurrent or refractory CDI. FMT was demonstrated as being a very effective treatment for CDI, with 17 of 19 patients (89%) achieving a cure after 2 months [Table 2], representing a response rate similar to that reported in previous studies [5-7]. One patient did not respond to FMT and died of severe colitis. Side effects were mostly transient and minimal, although one patient's course was complicated by aspiration of the fecal matter and he eventually died as a result of severe complications [Table 3].

These procedures were performed at two tertiary hospitals in Israel that followed two different protocols. FMT was performed at Tel Aviv Sourasky Medical Center with stool donated by unrelated healthy donors. This stool was processed and kept frozen (at -80°C) in the hospital's stool bank. Eleven patients (92%) underwent FMT via colonoscopy and one patient, who was post-total colectomy, underwent FMT via gastroscopy. The FMT procedure was performed at Shaare Zedek Medical Center with fresh stool donated by a healthy relative on the day of the procedure, and was performed via the upper GI in 9 of the 10 patients (90%). One systematic review [13] that compared various delivery methods found an 89% success rate for the colonoscopy route and a 75% success rate for nasoduodenal transplantation. Our study showed similar results, with a 100% success rate for colonoscopic FMT delivery versus a 75% success rate for upper GI delivery ($P = 0.16$). Possible reasons for the trend towards better outcome after FMT through the lower GI tract in the current study include the following:

- Patients who received upper GI FMT were generally sicker: their Charlson Co-morbidity Index at 1 year predicted a 75% survival rate as compared to 91% among patients who received a lower GI FMT
- Fecal transplant directly to the disease-affected areas reaches the entire colon and terminal ileum (which may be involved in CDI) [14], without exposure of the microbiota to the hostile environment of the upper GI tract, potentially compromising the number and viability of the microbiota
- 92% of patients who underwent a lower GI FMT received stool from unrelated donors compared to 20% who underwent an upper GI FMT. A study by Hamilton et al. [15]

found that patients receiving stool from unrelated donors had a better response (91% vs. 70% for related donors), but this was not statistically significant, similar to our findings. We suggest that there is a greater difference in the microbiota between recipients and unrelated donors (thus enhancing gut microbial diversity) as compared to household/close relative donors, whose microbiome is partially shared with the recipient [14]. Furthermore, the FMT material from an unrelated donor came from a stool bank and allowed the immediate treatment of patients without the minimum one week delay of treatment required for screening a relative donor. Along with improving efficacy provided by a more timely treatment, a stool bank with pre-screened samples also reduces overall laboratory costs and can provide more standardized treatment to patients [14]

- The *C. difficile* ribotype 027 is the most common strain at Shaare Zedek [16], while the hr-02 strain predominates at Sourasky [17]. Ribotype 027 has been shown to be more resistant to metronidazole and vancomycin [17]. This may lead to more protracted disease prior to the FMT and may partially explain the poorer results in the patients treated at Shaare Zedek and hence the difference in outcome between upper and lower GI FMT. Further studies are required to determine the actual impact of FMT on the different strains of *Clostridium difficile*. While our results are in keeping with current reports of lower GI FMTs providing better cure rates, ours was a very small cohort and further studies in larger and more homogenous populations are required to validate our findings.

One significant finding of the current work was the time until an initial response. Patients who underwent a lower GI FMT responded to this treatment within an average of 1.6 days compared to 2.4 days in patients who underwent an upper GI FMT ($P = 0.03$). Numerous factors may explain this difference between the groups, most important among them is probably the immediate and direct effect of FMT through the lower GI route.

At their 2 month follow-up, 16 patients (94%) who experienced an initial response to FMT were cured, indicating that an initial response to FMT (within the first week) may be a good predictor for cure. There were no cases of CDI recurrence.

Six patients (27%) experienced adverse events, two in the upper GI group and four in the lower GI group. The most common adverse event was mild abdominal discomfort or constipation post-procedure (five patients). These findings are in keeping with the excellent safety of the procedure, as noted in other studies [6]. Of note, seven patients (32%) died during the study period [Table 3]: five deaths were unrelated to CDI or the FMT procedure, one was due to severe and unresponsive CDI and one to the FMT-related complication described above.

FMT aspiration leading to death has been previously reported by others [18]. In order to diminish chances of aspiration in upper GI FMT, fluid instillation should be performed distal to the pylorus, in a slow manner and in lower volumes [19]. Further studies are required to better define patient selection, which may reduce the mortality noted in the study.

Overall, this study supports administration of the transplant via the lower GI and the use of readily available samples from previously screened donors as the preferred method of FMT. If these conditions are not available, other methods, such as using stool from related donors and/or administration of the transplant via the upper GI tract, are safe and effective alternatives. FMT has been demonstrated to be the most effective treatment available for CDI and one that can be easily performed on an outpatient basis, as seen in this study. These successes should prompt the examination of FMT effectiveness in treating primary CDI, which may ease the burden on both the patient and the health care system in the long run [20].

Correspondence
Dr. N. Maharshak
Bacteriotherapy Service, Dept. of Gastroenterology and Liver Diseases, Tel Aviv Sourasky Medical Center, Tel Aviv 64239, Israel
Phone: (972-3) 697-4280
Fax: (972-3) 697-4622
email: nitsanm@tlvmc.gov.il

References
1. Lessa FC, Gould CV, McDonald LC. Current status of Clostridium difficile infection epidemiology. *Clin Infect Dis* 2012; 55 (Suppl 2): S65-70.
2. Hensgens MP, Goorhuis A, Dekkers OM, Kuijper EJ. Time interval of increased risk for Clostridium difficile infection after exposure to antibiotics. *J Antimicrob Chemother* 2012; 67 (3): 742-8.
3. Brown WR. Fecal microbiota transplantation in treating Clostridium difficile infection. *J Dig Dis* 2014; 15 (8): 405-8.
4. McFarland LV, Surawicz CM, Rubin M, Fekety R, Elmer GW, Greenberg RN. Recurrent Clostridium difficile disease: epidemiology and clinical characteristics. *Infect Control Hosp Epidemiol* 1999; 20 (1): 43-50.
5. Brandt LJ, Aroniadis OC, Mellow M, et al. Long-term follow-up of colonoscopic fecal microbiota transplant for recurrent Clostridium difficile infection. *Am J Gastroenterol* 2012; 107 (7): 1079-87.
6. Cammarota G, Ianiro G, Gasbarrini A. Fecal microbiota transplantation for the treatment of Clostridium difficile infection: a systematic review. *J Clin Gastroenterol* 2014; 48 (8): 693-702.
7. Mattila E, Uusitalo-Seppala R, Wuorela M, et al. Fecal transplantation, through colonoscopy, is effective therapy for recurrent Clostridium difficile infection. *Gastroenterology* 2012; 142 (3): 490-6.
8. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). *Infect Control Hosp Epidemiol* 2010; 31 (5): 431-55.
9. Kelly CR, de Leon L, Jasutkar N. Fecal microbiota transplantation for relapsing Clostridium difficile infection in 26 patients: methodology and results. *J Clin Gastroenterol* 2012; 46 (2): 145-9.
10. Rubin TA, Gessert CE, Aas J, Bakken JS. Fecal microbiome transplantation for recurrent Clostridium difficile infection: report on a case series. *Anaerobe* 2013; 19: 22-6.

11. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Gastroenterol* 1994; 47 (11): 1245-51.

12. Cohen NA, Ben-Ami R, Guzner-Gur H, Santo ME, Halpern Z, Maharshak N. Fecal microbiota transplantation for *Clostridium difficile* associated diarrhea. *IMAJ* 2015; 17: 510-14.

13. Gough E, Shaikh H, Manges AR. Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent Clostridium difficile infection. *Clin Infect Dis* 2011; 53 (10): 994-1002.

14. Kassam Z, Lee CH, Yuan Y, Hunt RH. Fecal microbiota transplantation for Clostridium difficile infection: systematic review and meta-analysis. *Am J Gastroenterol* 2013; 108 (4): 500-8.

15. Hamilton MJ, Weingarden AR, Sadowsky MJ, Khoruts A. Standardized frozen preparation for transplantation of fecal microbiota for recurrent Clostridium difficile infection. *Am J Gastroenterol* 2012; 107 (5): 761-7.

16. Wiener-Well Y, Ben-Chetrit E, Abed-Eldaim M, Assous MV, Miller-Roll T, Adler A. Clinical and molecular characteristics of an outbreak caused by the pandemic (BI/NAP1/027) Clostridium difficile clone in a single center in Israel. *Infect Control Hosp Epidemiol* 2014; 35 (10): 1306-8.

17. Adler A, Miller-Roll T, Bradenstein R, et al. A national survey of the molecular epidemiology of Clostridium difficile in Israel: the dissemination of the ribotype 027 strain with reduced susceptibility to vancomycin and metronidazole. *Diagn Microbiol Infect Dis* 2015; 83 (1): 21-4.

18. Baxter M, Ahmad T, Colville A, Sheridan R. Fatal aspiration pneumonia as a complication of fecal microbiota transplant. *Clin Infect Dis* 2015; 61 (1): 136-7.

19. Bakken JS, Borody T, Brandt LJ, et al. Treating Clostridium difficile infection with fecal microbiota transplantation. *Clin Gastroenterol Hepatol* 2011; 9 (12): 1044-9.

20. Heimann SM, Vehreschild JJ, Cornely OA, et al. Economic burden of Clostridium difficile associated diarrhoea: a cost-of-illness study from a german tertiary care hospital. *Infection* 2015; 43 (6): 707-14.