World Journal of

Gastroenterology

World Journal of Gastroenterology

Contents

ABOUT COVER

Editorial board member of *World Journal of Gastroenterology*, Haruhiko Sugimura, MD, PhD, Professor, Department of Tumor Pathology, Hamamatsu University School of Medicine, Hamamatsu 431-3192, Japan

AIMS AND SCOPE

World Journal of Gastroenterology (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. *WJG* was established on October 1, 1995. It is published weekly on the 7th, 14th, 21st, and 28th each month. The *WJG* Editorial Board consists of 642 experts in gastroenterology and hepatology from 59 countries.

The primary task of *WJG* is to rapidly publish high-quality original articles, reviews, and commentaries in the fields of gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, hepatobiliary surgery, gastrointestinal oncology, gastrointestinal radiation oncology, gastrointestinal imaging, gastrointestinal interventional therapy, gastrointestinal infectious diseases, gastrointestinal pharmacology, gastrointestinal pathophysiology, gastrointestinal pathology, evidence-based medicine in gastroenterology, pancreatology, gastrointestinal laboratory medicine, gastrointestinal molecular biology, gastrointestinal immunology, gastrointestinal microbiology, gastrointestinal genetics, gastrointestinal translational medicine, gastrointestinal diagnostics, and gastrointestinal therapeutics. *WJG* is dedicated to become an influential and prestigious journal in gastroenterology and hepatology, to promote the development of above disciplines, and to improve the diagnostic and therapeutic skill and expertise of clinicians.

INDEXING/ABSTRACTING

World Journal of Gastroenterology (*WJG*) is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central and Directory of Open Access Journals. The 2018 edition of Journal Citation Reports® cites the 2017 impact factor for *WJG* as 3.300 (5-year impact factor: 3.387), ranking *WJG* as 35th among 80 journals in gastroenterology and hepatology (quartile in category Q2).

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Yan Huang*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Xue-Jiao Wang*
Proofing Editorial Office Director: *Ze-Mao Gong*

ORIGINAL ARTICLE

Retrospective Cohort Study

Five years of fecal microbiota transplantation - an update of the Israeli experience

Sharon A Greenberg, Ilan Youngster, Nathaniel A Cohen, Dan M Livovsky, Jacob Strahilevitz, Eran Israeli, Ehud Melzer, Kalman Paz, Naomi Fliss-Isakov, Nitsan Maharshak

Sharon A Greenberg, Nathaniel A Cohen, Naomi Fliss-Isakov, Nitsan Maharshak, Department of Gastroenterology and Liver Diseases, Tel Aviv Sourasky Medical Center, affiliated with the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv 6423906, Israel

Nitsan Maharshak, Bacteriotherapy Clinic, Tel Aviv Sourasky Medical Center, affiliated with the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv 6423906, Israel

Ilan Youngster, Assaf Harofe Medical Center, Zerifin 70300, Israel

Dan M Livovsky, Kalman Paz, Digestive Diseases Institute, Shaare Zedek Medical Center, Jerusalem 91031, Israel

Jacob Strahilevitz, Department of Clinical Microbiology and Infectious Diseases, Hadassah-Hebrew University, Jerusalem 91120, Israel

Eran Israeli, Department of Gastroenterology and Liver Diseases, Hadassah-Hebrew University, Jerusalem 91120, Israel

Ehud Melzer, Gastrointestinal and Liver Diseases Institute, Kaplan Medical Center, Rehovot 76100, Israel

ORCID number: Sharon A Greenberg (0000-0001-7346-1746); Ilan Youngster (0000-0001-5233-1213); Nathaniel A Cohen (0000-0002-3997-4174); Dan M Livovsky (0000-0002-8212-9638); Jacob Strahilevitz (0000-0002-9192-7164); Eran Israeli (0000-0001-8679-4363); Ehud Melzer (0000-0002-3021-6684); Kalman Paz (0000-0001-5357-1593); Naomi Fliss-Isakov (0000-0003-4849-0291); Nitsan Maharshak (0000-0002-9324-0024).

Author contributions: All authors helped to perform the research; Greenberg SA contributed to collecting data, data analysis and writing the manuscript; Youngster I, Livovsky DM, Melzer E and Paz K contributed to performing procedures and data collection; Cohen NA contributed to data collection and writing the manuscript; Strahilevitz J contributed to data collection; Israeli E contributed to performing procedures; Fliss-Isakov N contributed to data analysis; Maharshak N contributed to drafting conception and design, performing procedures, writing the manuscript and data collection.

Corresponding author to: Nitsan Maharshak, MD, Chief Doctor, Director, Doctor, Senior Lecturer, Department of Gastroenterology and Liver Diseases, Tel Aviv Sourasky Medical Center, 6 Weizmann St., Tel Aviv 6423906, Israel. nitsanm@tlvmc.gov.il
Telephone: +972-3-6947305
Fax: +972-3-6974184

Abstract

AIM
To evaluate and describe the efficacy of fecal microbiota transplantation (FMT) for *Clostridium difficile* infection (CDI) in a national Israeli cohort.

METHODS
All patients who received FMT for recurrent (recurrence within 8 wk of the previous treatment) or refractory CDI from 2013 through 2017 in all the five medical centers in Israel currently performing FMT were included. Stool donors were screened according to the Israeli Ministry of Health guidelines. Clinical and laboratory data of patients were collected from patients' medical files, and they included indications for FMT, risk factors for CDI and disease severity. Primary outcome was FMT success (at least 2 mo free of CDI-related diarrhea post-FMT). Secondary outcomes included initial response to FMT (cessation of diarrhea within 7 d) and recurrence at 6 mo.

RESULTS
There were 111 FMTs for CDI, with a median age of 70 years [interquartile range (IQR): 53-82], and 42% (47) males. Fifty patients (45%) were treated *via* the lower gastrointestinal (LGI, represented only by colonoscopy) route, 37 (33%) *via* capsules, and 24 (22%) *via* the upper gastrointestinal (UGI) route. The overall success rate was 87.4% (97 patients), with no significant difference between routes of administration (P = 0.338). In the univariant analysis, FMT success correlated with milder disease (P = 0.01), ambulatory setting (P < 0.05) and lower Charlson comorbidity score (P < 0.05). In the multivariant analysis, only severe CDI [odd ratio (OR) = 0.14, P < 0.05] and inpatient FMT (OR = 0.19, P < 0.05) were each independently inversely related to FMT success. There were 35 (32%) patients younger than 60 years of age, and 14 (40%) of them had a background of inflammatory bowel disease.

CONCLUSION
FMT is a safe and effective treatment for CDI, with capsules emerging as a successful and well-tolerated route. Severe CDI is less likely to respond to FMT.

Key words: *Clostridium difficile* infection; Capsules; Israel; Fecal microbiota transplantation

Core tip: Fecal microbiota transplantation (FMT) emerged as a promising treatment for *Clostridium difficile* infection (CDI). Our aim was to summarize the national Israeli experience in FMT. One-hundred and eleven patients with CDI underwent FMT, 37 (35%) of which *via* oral capsules and 50 (45%) *via* colonoscopy. The overall success rate was 87.4%, with no difference between administration routes. Success was independently related to mild disease and an ambulatory setting. One-third of the patients were younger than 60 years. 14 of which (40%) also suffered from inflammatory bowel disease. FMT is an effective treatment for recurrent CDI. FMT *via* capsules was shown to be a successful alternative to endoscopy.

INTRODUCTION

Background
The incidence of *Clostridium difficile* infection (CDI) is rising in parallel to the increased use of broad-spectrum antibiotics, with more than 500000 cases and 29000 related deaths annually in the United States alone[1]. The resistance to current treatment with metronidazole and vancomycin is also increasing, with recurrence rates of up to 20% after the first episode and 40%-65% after the second[2-4]. Fecal microbiota transplantation (FMT) has cure rates ranging between 85%-95%, and it has emerged as being a safe and promising treatment option that is widely accepted for recurrences and refractory or severe cases of CDI[5-10]. FMT is considered the most effective treatment for recurrent CDI[11,12] in both young and elderly patient populations[13]. FMT it is also a promising potential treatment for conditions other than CDI, such as inflammatory bowel diseases (IBD), irritable bowel syndrome, neuropsychiatric conditions, obesity, insulin resistance, and autoimmune diseases[14,15].

Current techniques for FMT administration vary considerably between institutions and can be performed *via* a nasogastric/nasojejunal tube, gastroscopy, oral capsules, enema, sigmoidoscopy or colonoscopy[6,15-18]. The procedure is considered safe and is mostly free of severe adverse events, although peri-procedural transient gastrointestinal (GI) symptoms may develop in some patients. The mortality cited in previous studies was attributed to the patients' pre-morbid conditions, and generally occurred in elderly and critically ill patients[5,15-17,19].

Objective
We had earlier described the initial Israeli experience of 22 patients that were treated with FMT for CDI and

experienced an overall cure rate above 89%[20]. However, during the past 5 years, the procedure has been performed in additional Israeli centers that processed feces from a wide range of donors in a significantly larger number of patients with different disease conditions, and using all acceptable transplantation routes. Therefore, our aim was to examine whether FMT continued to demonstrate efficacy despite this wider range of donors and patients, to investigate FMT-dependent variables, and to examine the efficacy of individual FMT routes.

MATERIALS AND METHODS

Study design and settings

This multi-center retrospective study included all the patients who were treated with FMT for CDI in Israel between January 2013 and October 2017. The participating medical centers were the Tel Aviv Medical Center (TLVMC), Tel Aviv; Shaare Zedek Medical Center (SZMC) and Hadassah Medical Center (HMC), Jerusalem; Assaf Harofe Medical Center (AHMC), Zerifin; and Kaplan Medical Center (KMC), Rehovot. All the patients or their legal surrogates provided written informed consent. The study was approved by the ethics committees of each medical center. Patients were followed routinely at 48 h, 7 d, 2 mo, and 6 mo after the procedure for the assessment of side effects and treatment outcome.

Following the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) practice guidelines[21], CDI was defined as diarrhea ($\geq$ 3 unformed stools per day) and a stool test that was positive for *Clostridium difficile* antigen and its toxins by either an ELISA (immunocheck™) or by PCR if the glutamate dehydrogenase antigen was positive and the toxin assessment was negative[22]. Recurrence was defined as another episode occurring within the 8 wk following the previous treatment. Refractory CDI was defined as disease that did not respond to medical therapy. Severe disease was defined by leukocytosis $\geq$ 15000 cells/μL and/or a serum creatinine level $\geq$ 1.5 times the premorbid level[21]. Initial response to FMT was defined as fewer than 3 liquid stools per day within the 7 d following FMT, and cure was defined as at least 2 mo free of CDI-related diarrhea post-FMT.

Donor stool preparation

The donor stool was delivered to the institution within a few hours of evacuation in a clean closed plastic container. It was immediately diluted with sterile saline (NaCl 0.9%) and blended into a homogenous liquid. The liquid was then filtered to remove particulate matter. Stool donations were processed and kept frozen at -80 ℃ until use at TLVMC or AHMC, while a fresh donor stool was delivered to SZMC or HMC on the day of FMT for processing and transplantation. KMC used both frozen and fresh donor stools. The preparation of

capsules was the same as that described in our previous reports[6,23].

Participants

All patients aged 10 to 92 years who were treated with FMT for refractory, recurrent, or severe CDI in all five centers were included. Donor selection, FMT procedure and patient follow-up were the same as those described in our earlier report[20], and they were carried out according to practice guidelines[24]. Capsule FMT was administrated following practice guidelines as reported elsewhere[6,7].

Variables

The primary outcome was FMT success (at least 2 mo free of CDI-related diarrhea post-FMT). Secondary outcomes included initial response to FMT (see above) and recurrence at 6 mo. The key variables were age, Charlson comorbidity score, and the risk factors for CDI in the 3 mo preceding the infection (hospitalization, exposure to antibiotics, IBD and chemotherapy).

Data sources

Clinical data were obtained from medical records, and they included epidemiologic information, risk factors for CDI, the Charlson comorbidity score[25], and follow-up information up to 6 months post-FMT. Patients were excluded if FMT was indicated for an etiology other than CDI or if follow-up was incomplete.

Statistical analysis

All continuous variables were displayed as mean [standard deviation (SD)] or median [interquartile range (IQR)], while categorical variables were displayed as number (percent) of patients within each group. Continuous variables were analyzed by the Student t test for normally distributed variables and by the Mann-Whitney U test and the Kruskal-Wallis test for non-normally distributed variables. We used the χ^2 test to assess associations among categorical variables. Statistical significance is expressed as $P \leq 0.05$ or $P \leq 0.01$. Multivariate logistic regression analysis was used to test the association between patient and FMT characteristics and successful FMT while controlling for potential confounders. The SPSS 22.0 statistical package was used to perform all statistical analyses (SSPS Inc., Chicago, IL, United States).

RESULTS

Participants

A total of 113 CDI patients were treated with FMT in five Israeli medical centers. Two patients were excluded due to insufficient follow-up. The median age of the 111 participating patients was 70 years (IQR: 53-82), 47 (42%) of them were males, and the median 1-year Charlson comorbidity score for the cohort was 6 (IQR:

	Overall		**Upper GI**[1]		**Lower GI**		**Capsules**		*P* value
	n (valid)	% (IQR)	*n*	% (IQR)	*n*	% (IQR)	*n*	% (IQR)	
Patients	111	100	24	22[2]	50	45	37	33	
Male gender	47 (111)	42	16	67[3]	19	38	12	32	
Age, median (IQR)	70 (111)	(53-82)	68	(51-86)	78	(61-83)	68	(45-75)	0.114
Charlson comorbidity score, median	6 (81)	3-7	5.5	(3-7.25)	6	(1.75-7.5)	5	(2-7)	0.734
CDI risk factors									
Prior hospitalization	80 (111)	72	18	75[3]	26	52	36	97	< 0.01
Prior antibiotics use	66 (108)	59	15	63[3]	15	30	36	97	0.012
PPI usage	37 (110)	33	8	33[3]	14	28	15	41	0.470
Chemotherapy	19 (111)	17	4	17[3]	3	6	12	32	0.005
IBD	20 (111)	18	5	21[3]	7	14	8	22	0.606
Previous CDI episode, median	2 (107)	(2-3)	2	(1-3)	2	(1-3)	3	(2-4)	0.275
Prior therapy									
Metronidazole	89 (110)	80	17	71[3]	41	82	31	84	0.365
Vancomycin	109 (110)	98	24	100[3]	48	96	37	100	0.534
Combination	31 (110)	28	10	42[3]	15	30	6	16	0.099
Severe CDI	20 (111)	18	8	33.3[3]	10	20	2	5.40	0.019
Indication									
Refractory	29 (111)	26	6	25[3]	19	38	4	11	0.017
Recurrent	82 (111)	74	18	75[3]	31	62	33	89	
Outpatient	78 (111)	70	12	50[3]	36	72	30	81	0.032

[1]Upper GI: Gastroscopy, nasogastric tube or through percutaneous endoscopic gastrostomy; [2]Percentages refer to the total number of subjects in the cohort; [3]Percentages refer to the number of subjects in the specific group. CDI: *Clostridium difficile* infection; IBD: Inflammatory bowel diseases; PPI: Proton pump inhibitor; GI: Gastrointestinal; FMT: Fecal microbiota implantation; IQR: Interquartile range; Prior hospitalization: Hospitalization in the 3 mo prior to the FMT; Prior antibiotics: Antibiotics use in the 3 mo prior to the FMT.

3-7 points; expected one-year survival of 79% ± 9%).

Descriptive data

The risk factors for CDI in the 3 mo preceding the infection included hospitalization (80 patients, 72%), exposure to antibiotics (65 patients, 59%), IBD (20 patients, 18%) and chemotherapy (19 patients, 17%). The patients' demographics, epidemiological data, and risk factors for CDI are summarized in Table 1.

Seventy-eight (70%) of the FMT procedures were performed in an ambulatory setting. FMT was performed through the lower GI route (LGI; only by colonoscopy) in 50 patients (45%), followed by capsules in 37 patients (33%), and through the upper GI route (UGI; gastroscopy, nasogastric tube or through their percutaneous endoscopic gastrostomy) in 24 patients (22%). The median age of the patients in the LGI group was 78 years (IQR: 61-83), which was significantly older than the median age of 68 years for the capsules group (IQR: 45-75) (*P* < 0.05). Twenty (18%) patients had severe CDI infection: they included 8 of the 24 patients (33.3%) who received FMT *via* the UGI route compared with 10 of the 50 patients [20% who received FMT *via* the LGI route (*P* = 0.21) and 5.4% (2/37) who received FMT *via* capsules (*P* = 0.004)].

Outcome data and main results

Successful FMT is more likely in ambulatory patients with milder CDI: A total of 97 (87.4%) patients achieved clinical remission (79% UGI, 88%

LGI, and 92% capsules, *P* = 0.338). Ninety-nine patients were followed-up 6 mo after FMT initiation (11 patients died, and one had not reached this endpoint by study closure). Sixteen of them (16.2%) had a recurrence of CDI: 3 in the UGI group (15.8% of the UGI group), 5 in the LGI group (11.4%), and 8 (22.2%) in the capsule group (*P* = 0.141) (Figure 1 and Table 2). Four patients required multiple FMT infusions due to recurrence: 3 underwent a second FMT infusion (of which 2 were *via* colonoscopy and 1 was *via* capsules) and one patient had 3 FMTs (all *via* colonoscopy). Only 2 had a successful FMT (1 *via* capsules and 1 *via* colonoscopy).

We further divided the cohort based on FMT success and achievement/non-achievement of clinical remission (Table 3). The 97 patients who experienced clinical remission were more likely to have undergone an ambulatory FMT (92.3% compared with 73.8% hospitalized patients, *P* < 0.05), were less likely to have a severe form of disease (14% compared with 44% of the treatment failure group, *P* = 0.01), and had a lower Charlson comorbidity score (average 4.82 ± 3.2 compared with 6.6 ± 2.3, mean difference 1.78, 95%CI: 0.02-3.55, *P* < 0.05). In addition, patients who had a successful FMT tended to be younger (mean age 63.2 ± 22.4 years compared with 73.7 ± 12.1 years; 95%CI: -1.61 to 22.6, *P* = 0.09). Finally, more patients in the FMT failure group died during the study period (37.5% *vs* 6.2% for the treatment success groups, *P* < 0.001) (Figure 2 and Table 3). Frozen stool was used in

Table 2 Fecal microbiota implantation outcome and patients' follow-up

	Overall		Upper GI		Lower GI		Capsules		P value
	n (valid)	%/IQR	*n*	%/IQR	*n*	%/IQR	*n*	%/IQR	
Patients	111 (111)		24	22[2]	50	45	37	33	
Response within 7 d	94 (111)	84.7[2]	17	71[3]	42	84	34	92	0.198
Days to response, median	2 (111)	1-2	2	1-3	1	0-2	2	2-3	0.069
No. of patients in follow-up at 6 mo[5]	99 (99)	89.2[2]	19	79[3]	44	88	36	97	
Recurrence at 6 mo	16 (99)	16.2[2]	3	15.8[3]	5	11.40	8	22.20	0.141
Total death	11 (111)	9.9[2]	5	21[3]	6	12	0	0	0.023
Death - unrelated	6 (11)	5.4[2]	4	80[3]	2	33	0	0	
Death - CDI-related	3 (11)	2.7[2]	1	20[3]	4	66	0	0	
No. of adverse events	19 (107)	17.1[1]	1	4[3]	14	28	4	11	0.006
Success[4]	97 (111)	87.4[2]	19	79[3]	44	88	34	92	0.338

[1]Upper GI: Gastroscopy, nasogastric tube or through percutaneous endoscopic gastrostomy; [2]Percentages refer to the total number of subjects in the cohort; [3]Percentages refer to the number of subjects in the specific group; [4]Success: diarrhea-free two months post-fecal microbiota implantation; [5]Eleven patients died before this endpoint, and one had not yet reached it at study closure. Patients who died before this endpoint from a reason other than *Clostridium difficile* infection (CDI) and were diarrhea-free were regarded as success, while patients who died before this endpoint from their CDI were considered as failures. CDI: *Clostridium difficile* infection; IQR: Interquartile range; GI: Gastrointestinal.
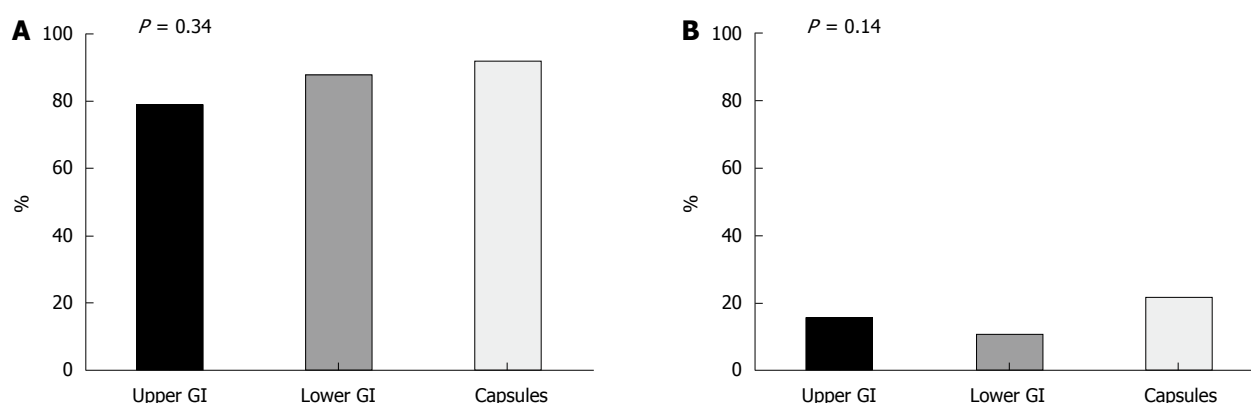
Figure 1 Comparison of success and recurrence rates of *Clostridium difficile* infection fecal microbiota transplantation treatment according route of administration. Fecal microbiota transplantation (FMT) was performed in recurrent *Clostridium difficile* infection (CDI) patients through upper gastrointestinal (GI) (*n* = 24), lower GI (*n* = 50) or capsules (*n* = 37). Success rates at 2 mo (A) and recurrence rates (B) at 6 mo post-FMT were similar between the groups. GI: Gastrointestinal.

91 of all the patients in the cohort, with slightly higher success rates than those obtained by fresh stool (89% *vs* 80%, *P* = 0.272).

The multivariance analysis revealed severe disease and inpatient status as being independently inversely related to FMT success, with odd ratios (ORs) of 0.14 (*P* < 0.05) and 0.19 (*P* < 0.05), respectively (Table 4). The Charlson score did not affect FMT success or failure.

Other analysis
IBD is prevalent among young FMT patients: We next divided the cohort into one group of those below 60 years of age (mean 37.2 ± 14.7 years) and another group above 60 years of age (mean 77.1 ± 8.9 years, mean difference 39.8, 95%CI: 35.3-44.3, *P* < 0.001) (Table 5). The success rates were slightly higher in the former group, but this difference did not reach a level of significance. Forty percent (14/35) of the patients younger than 60 years of age had IBD compared to only 7.9% (6/76) of the older group (*P* < 0.001). FMT was

performed significantly earlier after diagnosis among the older patients compared to the younger ones (within 102 ± 112 d compared to 198 ± 279 d, respectively, *P* = 0.024). The elderly were less likely to be treated as outpatients (63% *vs* 86%, *P* < 0.05) and less likely to receive corticosteroids (10.5% *vs* 26%, *P* < 0.05). No patient in the younger group died during the follow-up period (Table 5).

Adverse effects: Peri-procedural side effects were recorded in 19 patients. They were mild and self-limiting in 17 of them, and included abdominal discomfort, constipation, nausea/vomiting, flatulence and decreased appetite. Most of these effects occurred in patients who underwent colonoscopy [14 (28%) compared with 4 (11%) for capsules, and 1 (4%) for UGI routes, *P* < 0.01]. There were 2 cases of post-endoscopy aspirations, one involving a patient with severe CDI who had an aspiration after FMT *via* colonoscopy and died from sepsis 12 d post-FMT, and the other involving a

Table 3 Fecal microbiota implantation success and failure

	Valid	No.	Success		Failure		*P* value
			Number	%	Number	%	
Patients	111	111	97	87.4[2]	14	12.6	
Male gender	111	47	40	41.2[3]	7	50.0	0.535
Ambulatory	111	78	72	92.3[2]	6	7.7	0.016
Hospitalized	111	33	25	75.8[2]	8	24.2	
CDI risk factors							
Prior hospitalization	111	80	68	70.1[3]	12	85.7	0.224
Antibiotics use	108	89	77	81.1[3]	12	92.3	0.318
PPI usage	110	37	32	33.3[3]	5	35.7	0.86
Chemotherapy	111	19	17	17.5[3]	2	14.3	0.764
IBD	111	20	18	18.6[3]	2	14.3	0.698
Steroid usage	111	17	13	13.4[3]	4	28.6	0.141
Fever	76	21	19	27.9[3]	2	25.0	0.86
Severe disease	111	20	14	14.4[3]	6	42.9	0.01
Death	111	11	6	6.2[3]	5	37.5	0.001
Adverse events	107	19	15	16.0[3]	4	30.8	0.19
Route: Lower GI FMT	111	50	45	88.0[2]	5	12.0	0.338
Upper GI FMT[1]	111	24	19	79.2[2]	5	20.8	
Capsules FMT	111	37	34	91.9[2]	3	8.1	
Frozen stool	111	91	81	89.0[2]	10	11.0	0.272
Fresh stool	111	20	16	80.0[2]	4	20.0	
0-1 Previous CDI	107	24	23	24.2[3]	1	8.3	0.214
2+ previous CDI	107	83	72	74.2[3]	11	78.6	
Indication							0.824
Refractory	111	29	25	86.2[2]	4	13.8	
Recurrent	111	82	72	87.8[2]	10	12.2	
Prior therapy							
Metronidazole	110	89	80	83.3[3]	9	64.3	0.09
Vancomycin	110	109	95	99.0[3]	14	100.0	0.701
Combination	109	31	27	28.1[3]	4	30.8	0.843
	Valid		Mean	SD	Mean	SD	Sigma
Age (yr)	111		63.2	22.4	73.7	12.1	0.089
Charlson comorbidity score	81		4.82	3.18	6.6	2.32	0.048
Previous CDI episodes (*n*)	107		2.47	1.7	2.38	0.9	0.864
Time from 1st CDI (d)	89		140.4	200.8	108.56	120.3	0.643
Creatinine (mgl/dL)	76		1.37	1.2	2.19	2.6	0.098
Albumin (mg/L)	54		3.32	0.8	2.76	0.5	0.053
WBC (10^3/dL)	76		13.6	18.7	15.6	10.4	0.756

[1]Upper GI: Gastroscopy, nasogastric tube or through percutaneous endoscopic gastrostomy; [2]Percentages referral is the total number of subjects in the cohort; [3]Percentages referral is the number of subjects in the specific group. CDI: *Clostridium difficile* infection; IBD: Inflammatory bowel diseases; PPI: Proton pump inhibitor; GI: Gastrointestinal; FMT: Fecal microbiota implantation; IQR: Interquartile range; WBC: White blood cells; Prior hospitalization: Hospitalization during the 3 mo prior to the FMT; Prior hospitalization: Antibiotics use in the 3 mo prior to the FMT.

Table 4 Multivariate analysis of the association between patient characteristics and a successful fecal microbiota implantation procedure

Patient characteristics	OR (95%CI)	*P* value
Hospitalized patient	0.19 (0.04-0.86)	0.032
Severe disease	0.14 (0.02-0.76)	0.023
Charlson score categories	0.82 (0.38-1.76)	0.622

Adjusted to previous hospitalization, metronidazole treatment prior to fecal microbiota implantation (FMT), previous *Clostridium difficile* infection (CDI), recurrent CDI, inflammatory bowel diseases, route of administration, stool preparation method (fresh/frozen) and FMT dosage.

severely ill patient who was hospitalized in the intensive care unit (ICU) due to fulminant CDI, with distended colon and increased intra-abdominal pressure.

Mortality: The characteristics of the 11 patients in our cohort who did not survive are compared to the rest of the cohort in Table 6. They were much older (84.0 ± 5.8 years compared with 62.4 ± 21.6 years, mean difference 21.6 years, 95%CI: 8.6-34.7, *P* < 0.001), had higher Charlson comorbidity index scores (8.0 ± 2.4 compared with 4.57 ± 2.98, mean difference 3.42, 95%CI: 1.54-5.31, *P* = 0.001), and had fewer episodes of CDI (average of 1.45 ± 1.4 compared with 2.57 ± 1.6, mean difference 1.1, 95%CI: 0.1-2.1, *P* < 0.05). None of the deceased had undergone FMT via capsules, and only one was performed on an ambulatory basis. All 11 deceased patients were hospitalized at least once within the 3 months prior to undergoing the FMT procedure. The CDI of 6 of the deceased patients had improved significantly, and they died from causes unrelated to either CDI or to the FMT procedure itself. The other 5 showed no clinical response to FMT and they died shortly after undergoing it, with continuing deterioration

Table 5 Comparison of patients' characteristics by age

	Valid	No.	Below 60 yr		Above 60 yr		*P* value
			Number	%	Number	%	
Patients	111	111	35	31.5[2]	76	68.5	
Male gender	111	47	15	42.9[3]	32	42.1	0.941
Ambulatory	111	78	30	85.7[3]	48	63.2	0.011
CDI risk factors							
Prior hospitalization	111	80	22	62.9[3]	58	76.3	0.142
Antibiotics use	108	89	28	80.0[3]	61	83.6	0.649
PPI usage	110	37	9	25.7[3]	28	37.3	0.230
Chemotherapy	111	19	7	20.0[3]	12	15.8	0.584
IBD	111	20	14	40.0[3]	6	7.9	0.000
Steroid usage	111	17	9	25.7[3]	8	10.5	0.039
Fever	76	21	7	35.0[3]	14	25.0	0.391
Severe	111	20	3	8.6[3]	17	22.4	0.079
Route							
Lower GI	111	50	12	34.3[3]	38	50.0	0.254
Upper GI[1]	111	24	8	22.9[3]	16	21.1	
Capsules	111	37	15	42.9[3]	22	28.9	
0-1 Previous CDI	107	24	8	22.9[3]	16	22.2	0.941
2+ previous CDI	107	83	27	77.1[3]	56	77.8	
Indication							
Refractory	111	29	8	22.9[3]	21	27.6	
Recurrent	111	82	27	77.1[3]	55	72.4	
Prior therapy							
Metronidazole	110	98	29	82.9[3]	69	80.0	0.722
Vancomycin	109	109	35	100.0[3]	74	98.7	0.493
Combination	109	31	12	34.3[3]	19	25.7	0.352
Outcomes							
Success	111	97	33	94.3[3]	64	84.2	0.137
Recurrence by 6 m	99	16	7	20[3]	9	14.1	0.443
Death	111	11	0	0[3]	11	100.0	0.018
Adverse events	107	19	5	14.3[3]	14	19.4	0.512
			Mean	SD	Mean	SD	Sigma
Age (yr)	111		37.26	14.72	77.07	8.9	0.000
Charlson comorbidity score	81		1.29	1.95	6.35	2.3	0.000
Previous CDI episodes (*n*)	107		2.63	1.9	2.38	1.51	0.455
Time from 1st CDI (d)	89		198.75	279.04	102.68	112.19	0.024
Creatinine (mg/dL)	76		0.91	0.51	1.67	1.63	0.051
Albumin (mg/L)	54		3.51	0.99	3.17	0.69	0.153
WBC (10[3]/dL)	76		11.33	90.36	14.78	19.86	0.468

[1]Upper GI: Gastroscopy, nasogastric tube or through percutaneous endoscopic gastrostomy; [2]Percentages refer to the total number of subjects in the cohort; [3]Percentages refer to the number of subjects in the specific group. CDI: *Clostridium difficile* infection; IBD: Inflammatory bowel diseases; PPI: Proton pump inhibitor; GI: Gastrointestinal; FMT: Fecal microbiota implantation; IQR: Inter quartile range; WBC: White blood cells; Prior hospitalization: Hospitalization in the 3 mo prior to the FMT; Prior hospitalization: Antibiotics use in the 3 mo prior to the FMT.

of their general clinical condition.

DISCUSSION

Key results and interpretation

In this multi-center cohort study, we described the real-world experience of FMT procedures for CDI in a heterogeneous national Israeli population during the 5 years since the procedure was approved. We examined the distribution of the various techniques, routes and success rates in 111 FMT procedures.

There was an 85% response to treatment within the first 7 d post-FMT, and the success rates rose to 88% at 2 mo. These rates are compatible with reports and reviews of others[5,7-9,12,15-19]. Comparison of the 3 usual methods of FMT administration, UGI, LGI and capsules, revealed a higher success rates for the

capsules and LGI routes over the UGI route although not to a level of statistical significance. Nevertheless, capsules-treated patients had the highest recurrence rates (22% at 6 mo), again not reaching a level of statistical significance. These results can be interpreted in several ways. First, there were higher rates of severe CDI within the UGI group compared with the 2 other groups (Figure 1 and Table 1). Second, previous reports showed lower success rates for the UGI route compared with LGI: one systematic review of 325 cases of FMT for CDI suggested a lower success rate for upper gut administration (76%) compared with colonoscopy (89%) and enema (95%) administration[17], while Kassam *et al*[19] reported a trend for higher resolution rates through the LGI route compared with the UGI route. Cure from CDI was associated with a milder disease and undergoing treatment in an outpatient

Table 6 Mortality

	Valid	No.	Alive		Dead		*P* value
			Number	%	Number	%	
Patients			100	90.1[2]	11	9.9	
Male gender	111	47	38	38.0[3]	9	81.8	0.005
Ambulatory	104	75	74	77.9[3]	1	10.0	0.000
CDI risk factors							
Prior hospitalization	111	80	69	69.0[3]	11	100.0	0.030
Antibiotics use	108	89	81	82.7[3]	8	80.0	0.834
PPI usage	110	37	31	31.3[3]	6	54.5	0.122
Chemotherapy	111	19	19	19.0[3]	0	0.0	0.112
IBD	111	20	20	20.0[3]	0	0.0	0.101
Steroid usage	111	17	16	16.0[3]	1	9.1	0.546
Fever	76	21	15	23.1[3]	6	54.5	0.031
Severe	110	20	13	13.0[3]	7	63.6	0.000
Adverse events	107	19	15	15.5[3]	4	40.0	0.053
Route							
Lower GI	111	50	44	44.0[3]	6	54.5	0.023
Upper GI[1]		24	19	19.0[3]	5	45.5	
Capsules		37	37	37.0[3]	0	0.0	
0-1 previous CDI	107	24	19	19.8[3]	5	45.5	0.053
2+ previous CDI		83	77		6		
Indication	111						0.306
Refractory		23	19	19.0[3]	4	36.4	
Recurrent		82	76	76.0[3]	6	54.5	
Prior therapy							
Metronidazole	110	89	80	80.8[3]	9	81.8	0.936
Vancomycin	110	109	98	99.0[3]	11	100.0	0.738
Combination	109	31	25	25.5[3]	6	54.5	0.043
Outcomes							
Adverse events	107	19	15	15.5[3]	4	40.0	0.053
Response to FMT	111	94	88	88.0[3]	6	54.5	0.003
			Mean	SD	Mean	SD	Sigma
Age (yr)	111		62.37	21.656	84	5.797	0.000
Charlson comorbidity score	81		4.57	2.98	8	2.4	0.001
Previous CDI episodes (*n*)	107		2.57	1.633	1.45	1.368	0.025
Time from 1st CDI (d)	89		138.47	197.991	110.75	63.036	0.493
Creatinine (mg/dL)	76		1.44	1.507	1.74	1.193	0.482
Albumin (mg/L)	54		3.34	0.782	2.4	0.408	0.010
WBC (10[3]/dL)	76		13.65	18.87	15.64	78.62	0.564

[1]Upper GI: Gastroscopy, nasogastric tube or through percutaneous endoscopic gastrostomy; [2]Percentages refer to the total number of subjects in the cohort; [3]Percentages refer to the number of subjects in the specific group. CDI: *Clostridium difficile* infection; IBD: Inflammatory bowel diseases; PPI: Proton pump inhibitor; GI: Gastrointestinal; FMT: Fecal microbiota implantation; IQR: Inter quartile range; WBC: White blood cells; Prior hospitalization: Hospitalization within the 3 mo prior to the FMT; Prior hospitalization: Antibiotics use in the 3 mo prior to the FMT.

setup. Other factors, such as age, Charlson score, albumin levels, and creatinine levels were not significantly different between the groups, since the study was probably underpowered to detect significant differences in these variables. Multiple infusions were seldom and relatively unsuccessful in our cohort (4 patients, 50% success rate), but the numbers are too low to arrive at any conclusions and the results cannot be compared with those of recent meta analyses which showed increased success rates with multiple FMTs[26,27].

Multivariant analysis revealed that severe CDI (OR = 0.14, *P* < 0.05) and inpatient FMT (OR = 0.19, *P* < 0.05) were each independently inversely related to FMT success, while patients' background illnesses as reflected by the Charlson comorbidity score were not associated with either success or failure of FMT. Similar results were reported by Ianiro *et al*[28] in their single-center cohort study that showing that severe CDI

and inadequate bowel preparation were independent predictors of FMT failure, and by Fischer *et al*[29] in their multi-center study, in which predictors for FMT failure included severe or severe-complicated CDI, inpatient status during FMT and previous CDI-related hospitalization. Taken together, this data implies that the severe form of CDI is less likely to be successfully treated with FMT, and that future studies are warranted in order to find the optimal treatment. Other factors, including the patients' comorbidities as determined by the Charlson comorbidity score, did not seem to affect the FMT outcome.

To maintain continuity with a previous report[13], we compared the outcomes of the patients below and above 60 years of age and found that almost one-third (35/111) of the patients who underwent FMT for treatment of CDI in Israel were below 60 years of age (mean age 37.2 years). These patients had much
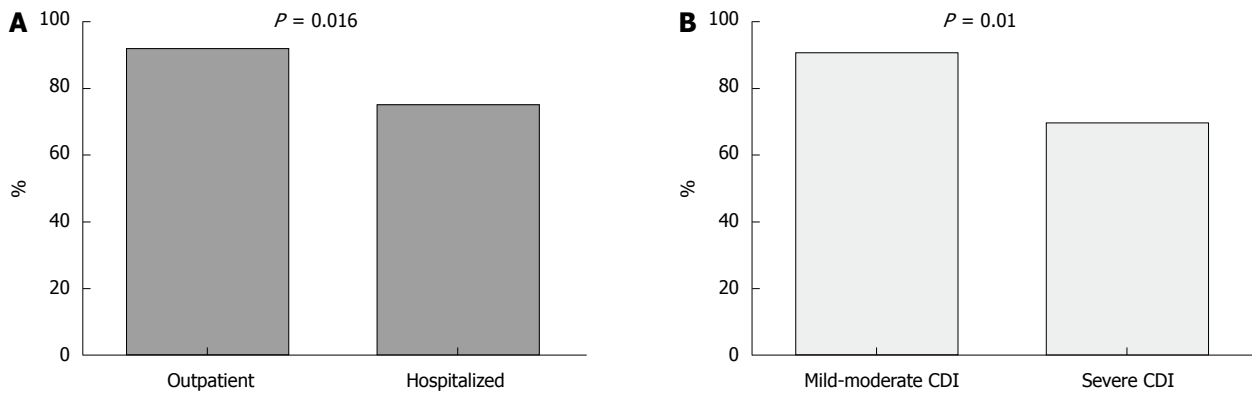
Figure 2 Comparison of fecal microbiota transplantation success rates among hospitalized and ambulatory patients. Seventy-eight patients who underwent ambulatory fecal microbiota transplantation had a success rate of 92.3% compared with 75.8% for hospitalized patients, *P* = 0.016 (A). Success rates were much lower among patients with severe *Clostridium difficile* infection compared with mild-moderate disease (B). CDI: *Clostridium difficile* infection.

lower Charlson comorbidity scores, underwent FMT on an ambulatory basis, and tended to have lower rates of severe CDI. Interestingly, there were no differences between the groups regarding hospitalizations in the 3 mo prior to the FMT. In a population-based study from Olmested county, Minnesota, United States, community-acquired CDI accounted for 41% of CDI cases and was characterized by a younger population with less severe disease, which is in line with our findings[30]. We observed a significantly higher percentage (40%) of IBD patients among this group compared to the older group (8%). Interestingly, the waiting period between the first CDI episode to undergoing FMT was longer among the younger patients compared to the older ones, possibly due to a delay in diagnosis or to a lower compliance rate to undergo the procedure, as well as a lower index of suspicion among physicians caring for younger patients with diarrhea compared to older ones leading to a delay in diagnosis. The higher rates of IBD among younger patients might also contribute to the delay in diagnosis, since diarrhea can be attributed to illnesses, such as IBD and other GI disorders other than CDI. Indeed, time to FMT from first CDI in IBD patients tended to be longer compared to non-IBD patients (207.2 and 116.9 d, respectively, *P* = 0.066). Interestingly, the IBD patients in our study experienced higher success rates than reported in the literature (90% compared to 74.4% reported by Khoruts *et al*[31]), although the group of IBD patients group in our study is much smaller (*n* = 20) compared with theirs (*n* = 272), and that might explain the difference in results.

Finally, severe CDI may be a fatal disease, especially in elderly and frail populations. The patients in our study group who died were much older, had significantly higher Charlson comorbidity scores, and much higher rates of severe CDI than the survivors. The CDI-associated diarrhea had improved significantly in 6 of them, while the condition of the others continued to deteriorate despite broad-spectrum antibiotic coverage treatment and ICU support, including mechanical ventilation and vasopressors. None of the deaths were attributed to the FMT procedure in any of them, which correlates with previous reports[13,19]. Although an approximately 10% mortality rate is quite high for FMT, it represents the natural history of weakened senior patients with multiple comorbidities in a large cohort rather than the FMT itself, as reported earlier[19,32]. Similar numbers can be found in other long follow-up studies, such as the one by Brandt *et al*[12] which reported the demise of 7 of the 77 patients in their long-term study (mean follow-up 17 mo).

Most of the adverse events were mild and self-resolving, and they included abdominal discomfort, nausea, flatulence and constipation, which can be attributed to the procedure itself (*i.e.*, most of these complications occurred in the LGI group). In addition, they are generally self-limiting and rather common post-colonoscopy events, occurring after up to 33% of colonoscopies[33]. Severe complications were recorded for 2 patients (< 2% of the cohort) who were severely ill in an ICU setting and each suffered post-endoscopy aspirations.

The strength of this study is its ability to capture real-life data from the 5 medical centers throughout Israel that perform FMT through various routes and use different donors with negligible differences in preparing donors' fecal filtrate. These are important for creating balanced data regarding the efficacy and safety of FMT.

Limitations

There were several limitations in the present study. Firstly, it is retrospective in design, warranting a prospective double blind randomized placebo-controlled study. Secondly, some of the data were collected *a posteriori* and information on laboratory findings, class of antibiotic used prior to CDI and Charlson scores of some of the patients (especially the ambulatory ones) were not available. Other limitations were the power of the study and the fact that the study population consisted only of Israeli patients.

Generalizability

The results of this study correlate with previous works regarding overall success rates[5,7,8,12,15-19], different routes of FMT administration[17,19] and predictors of failure[28,29] (see above), and reflect a multi-center data of heterogenous population from several districts in Israel and from different stool donors, making its results generalizable worldwide.

The corresponding author can provide complete data upon request.

In conclusion, FMT is a safe and effective treatment for CDI, which has been occurring in growing numbers in both older and younger populations. While both LGI and capsule administration of FMT seem to be more efficient than the UGI endoscopic route, FMT *via* capsules has emerged as a successful and well-tolerated alternative. Severe CDI and inpatient status were related to FMT failure. Prospective and well-powered studies are needed to conclusively determine the best route of administration, regarding patient safety, ease of administration, side effects and costs.

ARTICLE HIGHLIGHTS

Research background

The incidence of *Clostridium difficile* infection (CDI) is rising, and the increase is associated with significant morbidity and mortality rates. Fecal microbiota transplantation (FMT) is a promising and safe treatment. FMT has been performed in 5 medical centers in Israel since 2013, but its efficacy and safety had not yet been assessed.

Research motivation

To summarize all the FMT procedures performed in Israel for CDI between 2013-2017 and provide a detailed report on its current status, success rates, safety, and modes of administration.

Research objectives

The main objectives were to assess FMT success and failure rates as well as predictors of success with respect to mode of administration.

Research methods

This multi-center retrospective study included all the patients who were treated with FMT for CDI in Israel between January 2013 and October 2017. Clinical data were obtained from medical records, and they included epidemiologic information, risk factors for CDI, Charlson co-morbidity scores, and follow-up information up to 6 mo post-FMT. The Student t test was used for normally distributed variables and the Mann-Whitney U test was applied for non-normally distributed variables. We also used the χ^2 test to assess associations among categorical variables. Multivariate logistic regression analysis tested the association between patient and FMT characteristics and successful FMT, controlling for potential confounders.

Research results

A total of 111 CDI patients were included. The median age of the 111 participating patients was 70 years [interquartile range (IQR): 53-82], 47 (42%) of the patients were males, and the median 1-year Charlson comorbidity score for the entire cohort was 6 (IQR: 3-7 points; expected one-year survival of 79% ± 9%). Seventy-eight (70%) of the FMT procedures were performed in an ambulatory setting. FMT was performed through the lower gastrointestinal route (LGI) in 50 patients (45%), followed by capsules in 37 patients (33%), and through the upper GI route (UGI) in 24 patients (22%). A total of 97 (87.4%) patients achieved clinical remission (79% UGI, 88% LGI, and 92%

capsules, $P = 0.338$). Multiple FMT infusions were rare and unsuccessful. The multi-variance analysis revealed that severe disease and inpatient status were independently inversely related to FMT success, with an OR of 0.14 and 0.19, respectively. Patients younger than 60 years ($n = 35$, 32%) had higher percentages of background inflammatory bowel disease (IBD; 14/35, 40%) compared patients older than 60 years (6/76, 8%, $P < 0.01$), and waited much longer to undergo the FMT procedure (time between diagnosis of CDI to FMT of 102 d for the older group and 198 d for the younger group, $P < 0.05$). Eleven patients who died during the study period (no death was attributed to the FMT procedure) were much older (84 years compared with 62 years, $P < 0.01$), and had higher Charlson comorbidity index scores (8 compared with 4.5, $P < 0.01$).

Research conclusions

This is the first comprehensive description of the FMT experience in Israel since the procedure was introduced in 2013. This study shows FMT success rates which are similar to other reports worldwide, and provides the information about the efficacy and safety of the procedure, with respect to different administration routes. Predictors of FMT failure were CDI-related (severe disease and inpatient status) but not patient-related (as reflected by the Charlson comorbidity score). Concomitant IBD did not affect clinical outcomes. FMT through capsules was an efficient mode of FMT administration, and emerged as being a safe and well-tolerated alternative to endoscopy.

Research perspectives

FMT is a safe and effective treatment for CDI. The association between severe CDI with higher FMT failure rates raises the need for the future investigation of other approaches. FMT through capsules seems to be at least as good as FMT by means of endoscopies and its potential as a primary route should be investigated.

ACKNOWLEDGMENTS

REFERENCES

1   **Lessa FC**, Mu Y, Bamberg WM, Beldavs ZG, Dumyati GK, Dunn JR, Farley MM, Holzbauer SM, Meek JI, Phipps EC, Wilson LE, Winston LG, Cohen JA, Limbago BM, Fridkin SK, Gerding DN, McDonald LC. Burden of Clostridium difficile infection in the United States. *N Engl J Med* 2015; **372**: 825-834 [PMID: 25714160 DOI: 10.1056/NEJMoa1408913]

2   **Kelly CP**, LaMont JT. Clostridium difficile--more difficult than ever. *N Engl J Med* 2008; **359**: 1932-1940 [PMID: 18971494 DOI: 10.1056/NEJMra0707500]

3   **Petrella LA**, Sambol SP, Cheknis A, Nagaro K, Kean Y, Sears PS, Babakhani F, Johnson S, Gerding DN. Decreased cure and increased recurrence rates for Clostridium difficile infection caused by the epidemic C. difficile BI strain. *Clin Infect Dis* 2012; **55**: 351-357 [PMID: 22523271 DOI: 10.1093/cid/cis430]

4   **Burke KE**, Lamont JT. Clostridium difficile infection: a worldwide disease. *Gut Liver* 2014; **8**: 1-6 [PMID: 24516694 DOI: 10.5009/gnl.2014.8.1.1]

5   **Cammarota G**, Ianiro G, Gasbarrini A. Fecal microbiota transplantation for the treatment of Clostridium difficile infection: a systematic review. *J Clin Gastroenterol* 2014; **48**: 693-702 [PMID: 24440934 DOI: 10.1097/MCG.0000000000000046]

6   **Youngster I**, Mahabamunuge J, Systrom HK, Sauk J, Khalili H, Levin J, Kaplan JL, Hohmann EL. Oral, frozen fecal microbiota transplant (FMT) capsules for recurrent Clostridium difficile infection. *BMC Med* 2016; **14**: 134 [PMID: 27609178 DOI: 10.1186/s12916-016-0680-9]

7   **Bakken JS**, Borody T, Brandt LJ, Brill JV, Demarco DC, Franzos MA, Kelly C, Khoruts A, Louie T, Martinelli LP, Moore TA, Russell G, Surawicz C; Fecal Microbiota Transplantation Workgroup. Treating Clostridium difficile infection with fecal microbiota transplantation. *Clin Gastroenterol Hepatol* 2011; **9**:

1044-1049 [PMID: 21871249 DOI: 10.1016/j.cgh.2011.08.014]

8   **Cammarota G**, Ianiro G, Tilg H, Rajilić-Stojanović M, Kump P, Satokari R, Sokol H, Arkkila P, Pintus C, Hart A, Segal J, Aloi M, Masucci L, Molinaro A, Scaldaferri F, Gasbarrini G, Lopez-Sanroman A, Link A, de Groot P, de Vos WM, Högenauer C, Malfertheiner P, Mattila E, Milosavljević T, Nieuwdorp M, Sanguinetti M, Simren M, Gasbarrini A; European FMT Working Group. European consensus conference on faecal microbiota transplantation in clinical practice. *Gut* 2017; **66**: 569-580 [PMID: 28087657 DOI: 10.1136/gutjnl-2016-313017]

9   **Surawicz CM**, Brandt LJ, Binion DG, Ananthakrishnan AN, Curry SR, Gilligan PH, McFarland LV, Mellow M, Zuckerbraun BS. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. *Am J Gastroenterol* 2013; **108**: 478-98; quiz 499 [PMID: 23439232 DOI: 10.1038/ajg.2013.4]

10 **Mullish BH**, Quraishi MN, Segal JP, McCune VL, Baxter M, Marsden GL, Moore DJ, Colville A, Bhala N, Iqbal TH, Settle C, Kontkowski G, Hart AL, Hawkey PM, Goldenberg SD, Williams HRT. The use of faecal microbiota transplant as treatment for recurrent or refractory *Clostridium difficile* infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines. *Gut* 2018; **67**: 1920-1941 [PMID: 30154172 DOI: 10.1136/gutjnl-2018-316818]

11 **Mattila E**, Uusitalo-Seppälä R, Wuorela M, Lehtola L, Nurmi H, Ristikankare M, Moilanen V, Salminen K, Seppälä M, Mattila PS, Anttila VJ, Arkkila P. Fecal transplantation, through colonoscopy, is effective therapy for recurrent Clostridium difficile infection. *Gastroenterology* 2012; **142**: 490-496 [PMID: 22155369 DOI: 10.1053/j.gastro.2011.11.037]

12 **Brandt LJ**, Aroniadis OC, Mellow M, Kanatzar A, Kelly C, Park T, Stollman N, Rohlke F, Surawicz C. Long-term follow-up of colonoscopic fecal microbiota transplant for recurrent Clostridium difficile infection. *Am J Gastroenterol* 2012; **107**: 1079-1087 [PMID: 22450732 DOI: 10.1038/ajg.2012.60]

13 **Friedman-Korn T**, Livovsky DM, Maharshak N, Aviv Cohen N, Paz K, Bar-Gil Shitrit A, Goldin E, Koslowsky B. Fecal Transplantation for Treatment of Clostridium Difficile Infection in Elderly and Debilitated Patients. *Dig Dis Sci* 2018; **63**: 198-203 [PMID: 29134299 DOI: 10.1007/s10620-017-4833-2]

14 **Cohen NA**, Maharshak N. Novel Indications for Fecal Microbial Transplantation: Update and Review of the Literature. *Dig Dis Sci* 2017; **62**: 1131-1145 [PMID: 28315032 DOI: 10.1007/s10620-017-4535-9]

15 **Brandt LJ**, Aroniadis OC. An overview of fecal microbiota transplantation: techniques, indications, and outcomes. *Gastrointest Endosc* 2013; **78**: 240-249 [PMID: 23642791 DOI: 10.1016/j.gie.2013.03.1329]

16 **Borody TJ**, Paramsothy S, Agrawal G. Fecal microbiota transplantation: indications, methods, evidence, and future directions. *Curr Gastroenterol Rep* 2013; **15**: 337 [PMID: 23852569 DOI: 10.1007/s11894-013-0337-1]

17 **Gough E**, Shaikh H, Manges AR. Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent Clostridium difficile infection. *Clin Infect Dis* 2011; **53**: 994-1002 [PMID: 22002980 DOI: 10.1093/cid/cir632]

18 **König J**, Siebenhaar A, Högenauer C, Arkkila P, Nieuwdorp M, Norén T, Ponsioen CY, Rosien U, Rossen NG, Satokari R, Stallmach A, de Vos W, Keller J, Brummer RJ. Consensus report: faecal microbiota transfer - clinical applications and procedures. *Aliment Pharmacol Ther* 2017; **45**: 222-239 [PMID: 27891639 DOI: 10.1111/apt.13868]

19 **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**: 500-508 [PMID: 23511459 DOI: 10.1038/ajg.2013.59]

20 **Cohen NA**, Livovsky DM, Yaakobovitch S, Ben Yehoyada M, Ben Ami R, Adler A, Guzner-Gur H, Goldin E, Santo ME, Halpern

Z, Paz K, Maharshak N. A Retrospective Comparison of Fecal Microbial Transplantation Methods for Recurrent Clostridium Difficile Infection. *Isr Med Assoc J* 2016; **18**: 594-599 [PMID: 28471618]

21 **Cohen SH**, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, Pepin J, Wilcox MH; Society for Healthcare Epidemiology of America; Infectious Diseases Society of America. 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**: 431-455 [PMID: 20307191 DOI: 10.1086/651706]

22 **Ota KV**, McGowan KL. Clostridium difficile testing algorithms using glutamate dehydrogenase antigen and C. difficile toxin enzyme immunoassays with C. difficile nucleic acid amplification testing increase diagnostic yield in a tertiary pediatric population. *J Clin Microbiol* 2012; **50**: 1185-1188 [PMID: 22259201 DOI: 10.1128/JCM.05620-11]

23 **Youngster I**, Russell GH, Pindar C, Ziv-Baran T, Sauk J, Hohmann EL. Oral, capsulized, frozen fecal microbiota transplantation for relapsing Clostridium difficile infection. *JAMA* 2014; **312**: 1772-1778 [PMID: 25322359 DOI: 10.1001/jama.2014.13875]

24 **Woodworth MH**, Neish EM, Miller NS, Dhere T, Burd EM, Carpentieri C, Sitchenko KL, Kraft CS. Laboratory Testing of Donors and Stool Samples for Fecal Microbiota Transplantation for Recurrent Clostridium difficile Infection. *J Clin Microbiol* 2017; **55**: 1002-1010 [PMID: 28077694 DOI: 10.1128/JCM.02327-16]

25 **Charlson M**, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol* 1994; **47**: 1245-1251 [PMID: 7722560 DOI: 10.1016/0895-4356(94)90129-5]

26 **Quraishi MN**, Widlak M, Bhala N, Moore D, Price M, Sharma N, Iqbal TH. Systematic review with meta-analysis: the efficacy of faecal microbiota transplantation for the treatment of recurrent and refractory Clostridium difficile infection. *Aliment Pharmacol Ther* 2017; **46**: 479-493 [PMID: 28707337 DOI: 10.1111/apt.14201]

27 **Ianiro G**, Maida M, Burisch J, Simonelli C, Hold G, Ventimiglia M, Gasbarrini A, Cammarota G. Efficacy of different faecal microbiota transplantation protocols for *Clostridium difficil* infection: A systematic review and meta-analysis. *United European Gastroenterol J* 2018; **6**: 1232-1244 [PMID: 30288286 DOI: 10.1177/2050640618780762]

28 **Ianiro G**, Valerio L, Masucci L, Pecere S, Bibbò S, Quaranta G, Posteraro B, Currò D, Sanguinetti M, Gasbarrini A, Cammarota G. Predictors of failure after single faecal microbiota transplantation in patients with recurrent Clostridium difficile infection: results from a 3-year, single-centre cohort study. *Clin Microbiol Infect* 2017; **23**: 337.e1-337.e3 [PMID: 28057560 DOI: 10.1016/j.cmi.2016.12.025]

29 **Fischer M**, Kao D, Mehta SR, Martin T, Dimitry J, Keshteli AH, Cook GK, Phelps E, Sipe BW, Xu H, Kelly CR. Predictors of Early Failure After Fecal Microbiota Transplantation for the Therapy of Clostridium Difficile Infection: A Multicenter Study. *Am J Gastroenterol* 2016; **111**: 1024-1031 [PMID: 27185076 DOI: 10.1038/ajg.2016.180]

30 **Khanna S**, Pardi DS, Aronson SL, Kammer PP, Orenstein R, St Sauver JL, Harmsen WS, Zinsmeister AR. The epidemiology of community-acquired Clostridium difficile infection: a population-based study. *Am J Gastroenterol* 2012; **107**: 89-95 [PMID: 22108454 DOI: 10.1038/ajg.2011.398]

31 **Khoruts A**, Rank KM, Newman KM, Viskocil K, Vaughn BP, Hamilton MJ, Sadowsky MJ. Inflammatory Bowel Disease Affects the Outcome of Fecal Microbiota Transplantation for Recurrent Clostridium difficile Infection. *Clin Gastroenterol Hepatol* 2016; **14**: 1433-1438 [PMID: 26905904 DOI: 10.1016/j.cgh.2016.02.018]

32 **Furuya-Kanamori L**, Doi SA, Paterson DL, Helms SK, Yakob L, McKenzie SJ, Garborg K, Emanuelsson F, Stollman N, Kronman MP, Clark J, Huber CA, Riley TV, Clements AC. Upper Versus Lower Gastrointestinal Delivery for Transplantation of Fecal Microbiota in Recurrent or Refractory Clostridium difficile

Infection: A Collaborative Analysis of Individual Patient Data From 14 Studies. *J Clin Gastroenterol* 2017; **51**: 145-150 [PMID: 26974758 DOI: 10.1097/MCG.0000000000000511]

33   **Ko CW**, Dominitz JA. Complications of colonoscopy: magnitude and management. *Gastrointest Endosc Clin N Am* 2010; **20**: 659-671 [PMID: 20889070 DOI: 10.1016/j.giec.2010.07.005]

Baishideng®