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

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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 univariate 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 multivariate 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

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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 50 0000 cases and 29 000 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/nasoejunal tube, gastroscopy, oral capsules, enema, sigmoidoscopy or colonoscopy[16,17]. 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[16-18].

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%\textsuperscript{[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 Haroof 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\textsuperscript{[21]}, CDI was defined as diarrhea (≥ 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\textsuperscript{[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 ≥ 15000 cells/μL and/or a serum creatinine level ≥ 1.5 times the premorbid level\textsuperscript{[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 °C 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\textsuperscript{[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\textsuperscript{[20]}, and they were carried out according to practice guidelines\textsuperscript{[24]}. Capsule FMT was administered following practice guidelines as reported elsewhere\textsuperscript{[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, and the risk factors for CDI and recurrence at 6 mo. The key variables were age, 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).

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 χ² test to assess associations among categorical variables. Statistical significance is expressed as P ≤ 0.05 or P ≤ 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:
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 capsule) 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

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**Table 1** Study population characteristics according to fecal microbiota implantation route

|                | Overall | Upper GI† | Lower GI | Capsules | P value |
|----------------|---------|-----------|----------|----------|---------|
| n (valid)      | 111     | 100       | 24       | 50       | 37      | 33 |
| % (IQR)        |         |           |          |          |         |    |
| n             | 111     | 100       | 24       | 50       | 37      | 33 |
| % (IQR)        | 111     | 100       | 24       | 50       | 37      | 33 |
| P value        |         |           |          |          |         |    |
| Patients       |         |           |          |          |         |    |
| Male gender    | 47      | 111       | 42       | 16       | 19      | 12  |
| Age, median (IQR) | 70       | 53-82     | 68       | 51-86    | 78      | 61-83 |
| Charlson comorbidity score, median | 6       | 81       | 5.5      | 3-7.25   | 6       | 1.75-7.5 |
| CIDI risk factors |         |           |          |          |         |    |
| Prior hospitalization | 80     | 111       | 72       | 18       | 75      | 26  |
| Prior antibiotics use | 66     | 108       | 59       | 15       | 63      | 15  |
| PPI usage      | 37      | 110       | 33       | 8        | 33      | 14  |
| Chemotherapy   | 19      | 111       | 17       | 4        | 17      | 3   |
| IBD            | 20      | 111       | 18       | 5        | 21      | 7   |
| Bacterial last episode, median | 2      | 107       | 2        | 1-3      | 2       | 1-3  |
| P value        |         |           |          |          |         |    |
| Prior therapy  |         |           |          |          |         |    |
| Metronidazole  | 89      | 110       | 80       | 17       | 71      | 41  |
| Vancomycin     | 109     | 110       | 98       | 24       | 100     | 48  |
| Combination    | 31      | 110       | 28       | 10       | 42      | 15  |
| Severe CDI     | 20      | 111       | 18       | 8        | 33      | 10  |
| Indication     |         |           |          |          |         |    |
| Refractory     | 29      | 111       | 26       | 6        | 25      | 19  |
| Recurrent      | 82      | 111       | 74       | 18       | 75      | 31  |
| Outpatient     | 78      | 111       | 70       | 12       | 50      | 36  |

†Upper GI: Gastroscopy, nasogastric tube or through percutaneous endoscopic gastrostomy; †Percentages refer to the total number of subjects in the cohort; †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.
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 multivariate 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     | 14     | 12.6    |
| Male gender | 111 | 47     | 40     | 14     | 7       |
| Ambulatory | 111 | 78     | 72     | 6      | 7.7     |
| Hospitalized | 111 | 33     | 25     | 8      | 24.2    |
| CDI risk factors |   |         |        |        |         |
| Prior hospitalization | 111 | 80     | 68     | 12     | 85.7    |
| Antibiotics use | 108 | 89     | 77     | 12     | 92.3    |
| PPI usage | 110 | 37     | 32     | 5      | 35.7    |
| Chemotherapy | 111 | 19     | 17     | 2      | 14.3    |
| IBD | 111 | 20     | 18     | 2      | 14.3    |
| Steroid usage | 111 | 17     | 13     | 4      | 28.6    |
| Route: Lower GI FMT | 111 | 50     | 45     | 5      | 12.0    |
| Upper GI FMT | 111 | 24     | 19     | 5      | 20.8    |
| Capsules FMT | 111 | 37     | 34     | 3      | 8.1     |
| Frozen stool | 111 | 91     | 81     | 10     | 11.0    |
| Fresh stool | 111 | 20     | 16     | 4      | 20.0    |
| 0-1 Previous CDI | 107 | 24     | 23     | 1      | 8.3     |
| 2+ previous CDI | 107 | 83     | 72     | 11     | 78.6    |
| Indication |   |         |        |        |         |
| Refractory | 111 | 29     | 25     | 4      | 13.8    |
| Recurrent | 111 | 82     | 72     | 10     | 12.2    |
| Prior therapy |   |         |        |        |         |
| Metronidazole | 110 | 89     | 80     | 9      | 64.3    |
| Vancomycin | 110 | 109    | 95     | 14     | 100.0   |
| Combination | 109 | 31     | 27     | 4      | 30.8    |
| Valid |   | Mean     | SD     | Mean   | SD     |
| Age (yr) | 111 | 63.2    | 22.4   | 73.7   | 12.1   |
| Charlson comorbidity score | 81 | 4.82   | 3.18   | 6.6    | 2.32   |
| Previous CDI episodes (n) | 107 | 2.47   | 1.7    | 2.38   | 0.9    |
| Time from 1st CDI (d) | 89 | 140.4   | 200.8  | 108.56 | 120.3  |
| Creatinine (mg/dL) | 71 | 1.33   | 1.2    | 2.19   | 2.6    |
| Albumin (mg/L) | 54 | 3.32   | 2.8    | 2.76   | 0.5    |
| WBC (10³/dL) | 76 | 13.6   | 18.7   | 15.6   | 10.4   |

1Upper GI: Gastroscopy, nasogastric tube or through percutaneous endoscopic gastrostomy; 2Percentages referral is the total number of subjects in the cohort; 3Percentages referral is the number of subjects in the specific group. CDI: *Clostridium difficile* infection; 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 | 1.04 (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 ± 5.8 years compared with 62.4 ± 21.6 years, mean difference 21.6 years, 95%CI: 8.6-34.7, 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  |
| Male gender | 111 | 47 | 15 | 32 | 42.1 | 0.941 |
| Ambulatory | 111 | 78 | 30 | 85.7 | 48 | 63.2 | 0.011 |
| CDI risk factors | | | | | | |
| Prior hospitalization | 111 | 80 | 22 | 62.9 | 58 | 76.3 | 0.142 |
| Antibiotics use | 108 | 89 | 28 | 80.0 | 61 | 83.6 | 0.649 |
| PPI usage | 110 | 37 | 9 | 25.7 | 28 | 37.3 | 0.230 |
| Chemotherapy | 111 | 19 | 7 | 20.0 | 12 | 15.8 | 0.584 |
| IBD | 111 | 20 | 14 | 40.0 | 6 | 7.9 | 0.000 |
| Steroid usage | 111 | 17 | 9 | 25.7 | 8 | 10.5 | 0.039 |
| Fever | 76 | 21 | 7 | 35.0 | 14 | 25.0 | 0.391 |
| Severe | 111 | 20 | 3 | 8.6 | 17 | 22.4 | 0.079 |
| Route | Lower GI | 111 | 50 | 12 | 34.3 | 38 | 50.0 | 0.254 |
| Upper GI | 111 | 24 | 8 | 22.9 | 16 | 21.1 | |
| Capsules | 111 | 37 | 15 | 42.9 | 22 | 28.9 | |
| 0-1 Previous CDI | 107 | 24 | 8 | 22.9 | 16 | 22.2 | 0.941 |
| 2+ previous CDI | 107 | 83 | 27 | 77.1 | 56 | 77.8 | |
| Indication | Refractory | 111 | 29 | 8 | 22.9 | 21 | 27.6 | |
| Prior therapy | 111 | 82 | 27 | 77.1 | 55 | 72.4 | |
| Metronidazole | 110 | 98 | 29 | 82.9 | 69 | 80.0 | 0.722 |
| Vancomycin | 109 | 109 | 35 | 100.0 | 74 | 98.7 | 0.495 |
| Combination | 109 | 31 | 12 | 34.3 | 19 | 25.7 | 0.332 |
| Outcomes | Success | 111 | 97 | 33 | 94.3 | 64 | 84.2 | 0.137 |
| Recurrence by 6 m | 99 | 16 | 7 | 20.0 | 9 | 14.1 | 0.443 |
| Death | 111 | 11 | 0 | 0 | 11 | 100.0 | 0.018 |
| Adverse events | 107 | 19 | 5 | 14.3 | 14 | 19.4 | 0.512 |
| Mean | 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 (10³/dL) | 76 | 11.33 | 90.36 | 14.78 | 19.86 | 0.468 |

1Upper GI: Gastroscopy, nasogastric tube or through percutaneous endoscopic gastrostomy; 2Percentages refer to the total number of subjects in the cohort; 3Percentages 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 | 90.1⁴ | 11 | 9.9 | 0.005 |
| Male gender | 111 | 47 | 38 | 38.0⁶ | 9 | 81.8 | 0.030 |
| Ambulatory | 104 | 75 | 74 | 77.9⁵ | 1 | 10.0 | 0.000 |
| CDI risk factors | | | | | | |
| Prior hospitalization | 111 | 80 | 69 | 69.0⁷ | 11 | 100.0 | 0.030 |
| Antibiotics use | 108 | 89 | 81 | 82.7⁷ | 8 | 80.0 | 0.834 |
| PPI usage | 110 | 37 | 31 | 31.3⁶ | 6 | 54.5 | 0.122 |
| Chemotherapy | 111 | 19 | 19 | 19.0⁶ | 0 | 0 | 0.112 |
| IBD | 111 | 20 | 20 | 20.0⁶ | 0 | 0 | 0.101 |
| Steroid usage | 111 | 17 | 16 | 16.0⁶ | 1 | 9.1 | 0.546 |
| Fever | 76 | 21 | 15 | 23.1⁶ | 6 | 54.5 | 0.031 |
| Severe | 110 | 20 | 13 | 13.0⁶ | 7 | 63.6 | 0.000 |
| Adverse events | 107 | 19 | 15 | 15.5⁷ | 4 | 40.0 | 0.053 |
| Route | | | | | | |
| Lower GI | 111 | 50 | 44 | 44.0⁷ | 6 | 54.5 | 0.023 |
| Upper GI¹ | 24 | 19 | 19.0⁶ | 5 | 45.5 | 0.010 |
| Capsules | 37 | 37 | 37.0⁶ | 0 | 0 | 0.000 |
| 0-1 previous CDI | 107 | 24 | 19 | 19.8⁶ | 5 | 45.5 | 0.053 |
| ≥2 previous CDI | 83 | 27 | 77 | 77.0⁶ | 6 | 62.3 | 0.043 |
| Indication | 111 | | | | | |
| Refractory | 23 | 19 | 19.0⁶ | 4 | 36.4 | 0.306 |
| Recurrent | 82 | 76 | 76.0⁶ | 6 | 54.5 | 0.000 |
| Prior therapy | | | | | | |
| Metronidazole | 110 | 89 | 80 | 80.8⁵ | 9 | 81.5 | 0.936 |
| Vancomycin | 110 | 109 | 98 | 99.0⁶ | 11 | 100.0 | 0.738 |
| Combination | 109 | 31 | 25 | 25.5⁵ | 6 | 54.5 | 0.043 |
| Outcomes | | | | | | |
| Adverse events | 107 | 19 | 15 | 15.5⁷ | 4 | 40.0 | 0.053 |
| Response to FMT | 111 | 94 | 88 | 88.0⁷ | 6 | 54.5 | 0.003 |
| Mean | Mean | Mean | 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 | 63.056 | 0.493 |
| Creatinine (mg/dL) | 76 | 1.44 | 1.507 | 1.74 | 1.195 | 0.482 |
| Albumin (mg/L) | 54 | 3.34 | 0.782 | 2.4 | 0.408 | 0.010 |
| WBC (10³/dL) | 76 | 13.65 | 18.87 | 15.64 | 78.62 | 0.564 |

¹Upper GI: Gastroscopy, nasogastric tube or through percutaneous endoscopic gastrostomy; ²Percentages refer to the total number of subjects in the cohort; ³Percentages 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 FMTs²⁸,²⁹. 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 Ianiero et al²⁸ 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 al²⁹ 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 report¹³, 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
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 Olmsted 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. 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\(^{[11]} \)), 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\(^{[22]} \) 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, different routes of FMT administration, and predictors of failure (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 χ² 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% ± 5%). 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.

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