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Treatment approaches including fecal microbiota transplantation for recurrent *Clostridium difficile* infection (RCDI) among infectious disease physicians

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ABSTRACT

Background: *Clostridium difficile* infection (CDI) was the most common nosocomial infection in the U.S. in 2010. Most cases of CDI respond to a standard course of antibiotics, but recurrent *C. difficile* infections (RCDI) are increasingly common. Given the lack of randomized clinical trials, it is important to understand how infectious disease physicians are managing RCDI to inform future clinical research.
Methods: An electronic survey was conducted among members of the Emerging Infections Network (EIN) in October 2012. Respondents were asked to answer specific questions about their treatment approaches toward patients with CDI, including fecal microbiota transplantation (FMT).
Results: The overall response rate was 621/1212 (51%). The vast majority of respondents had cared for small to moderate numbers of patients with CDI over the prior 6 months, and reported recurrence rates were consistent with published data. Preferred treatment regimens for RCDI showed significant variance from recommendations published in national guidelines. Eighty percent (424/527) of the respondents would consider FMT for patients with RCDI, and of 149 who had FMT available at their institution, 107 (72%) had actually treated >1 patient with FMT in the preceding year. However, significant barriers to institutional adoption of FMT remain for many respondents, despite very good success rates with its use.
Conclusions: Physicians who regularly care for patients with CDI use a variety of treatment approaches for treating severe or recurrent CDI cases. The results of our survey demonstrate that FMT is used by a growing number of infectious disease providers as an effective and safe treatment alternative for patients with multiple recurrences of *C. difficile* infection.

1. Background

Clostridium difficile infection (CDI) is a nosocomial infection that has steadily increased in incidence and severity during the last decade [1]. CDI was reported as the leading nosocomial infection in the United States in 2011 [2]. The spectrum of CDI ranges from mild watery diarrhea to fulminant pseudomembranous colitis associated with significant morbidity and mortality [3]. Most cases are a consequence of a preceding treatment with antimicrobial agent(s), and fluoroquinolones, cephalosporins, and clindamycin are associated with the highest risk for CDI [3,5]. Factors that predispose to CDI recurrence include age older than 65 years, low serum albumin concentration, recent abdominal surgery, prolonged hospitalization and stay in the intensive care unit [1,3–5]. Patients who have suffered one recurrence of CDI after antibiotic treatment are at increased risk for subsequent episodes of diarrhea [6,7].

CDI usually responds to treatment with oral metronidazole or vancomycin, but between 5 and 35% of treated patients experience recurrent diarrhea in spite of appropriate therapy [3,4]. Unfortunately, alternative treatment strategies with new antimicrobials (e.g., rifaximin, nitazoxanide, tolevamer, and fidaxomicin) have failed to consistently demonstrate a significant benefit in the treatment of recurrent *C. difficile* infections (RCDI) [3,4]. Due to the limited treatment effectiveness of many therapeutic approaches to RCDI, fecal microbiota transplantation (FMT, previously known as fecal transplantation therapy) has been used to successfully treat

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RCDI [7–10]. Despite the apparent success of FMT, there has been limited enthusiasm for this treatment modality among medical providers in North America.

Because infectious disease (ID) specialists are often asked to manage or help manage more complex patients infected with *C. difficile*, we surveyed ID practitioners about their approaches to treating adult patients with recurrent CDI. Specifically, they were asked to describe: 1) their use of antimicrobials to treat CDI recurrences or severe disease; 2) their use of non-antimicrobial therapies such as IVIG, probiotics or fecal microbiota transplantation; and 3) their views and experience regarding fecal microbiota transplantation for the treatment of CDI.

2. Materials and methods

2.1. Survey recipients

The 1212 members of the Infectious Diseases Society of America's (IDSA) Emerging Infections Network (EIN) who practice adult infectious disease medicine were sent a survey in October 2012 about their therapeutic or preventive approaches to CDI and RCDI. The EIN is a voluntary network of infectious disease physicians who regularly engage in clinical activity. The network is funded through a cooperative agreement between the Centers for Disease Control and Prevention (CDC) and the IDSA. The initial survey request was sent by either weblink or facsimile, and was followed by two subsequent reminders for non-responders one week apart.

2.2. Survey questions

Respondents were asked to estimate the number of patients with CDI they had treated in the preceding 6 months, the number who experienced at least one recurrence after initial drug treatment, and to indicate their preferred treatment choice for i) the primary episode of CDI, ii) the first recurrence for patients with mild disease, and iii) the second recurrence for patients with mild disease. Respondents were asked to define the duration of treatment for patients with a second recurrence and mild disease; to indicate whether their treatment choice would change after a third or subsequent recurrence; and to indicate which antibiotic regimen they would choose to treat patients with severe CDI with or without ileus (possible combinations included oral or IV metronidazole, oral vancomycin, vancomycin per rectum, fidaxomicin, rifaximin, or tigecycline). We also asked respondents if they had ever used IVIG to treat CDI or probiotics (including *Saccharomyces boulardii*) to either prevent or manage CDI. Finally, a number of questions about FMT were included, such as i) circumstances under which FMT would be recommended, ii) the number of CDI recurrences that would prompt initiation of FMT; iii) whether FMT was available at their practice location at the time of the survey, and if not, to indicate why not.

2.3. FMT subsurvey

We asked the subset of EIN members at whose primary institutions FMT was available to answer several additional questions about this treatment modality. They indicated the number of patients under their care who had received FMT in the past year, the source of the donated stool material; the screening laboratory tests typically ordered for potential stool donors; the preferred route for administering FMT; the number of FMT instillations administered; the volume of stool administered per instillation; and the estimated success rate of FMT. Data were analyzed using SAS version 9.3 (SAS Institute, Cary, NC).

Table 1
Treatment choices selected by EIN respondents for management of mild primary *Clostridium difficile* infection (CDI) and recurrent CDI. (Respondents were instructed to select all treatments choices that applied; column numbers add up to >100%).

	Primary CDI episode *N* (%)	First CDI recurrence *N* (%)	Second CDI recurrence *N* (%)
Respondents (*N*)	537	536	529
Metronidazole PO	449 (84)	215 (40)	17 (3)
Vancomycin PO fixed dose	87 (16)	347 (65)	282 (53)
Fidaxomicin	1 (0.2)	20 (4)	60 (11)
Vancomycin PO taper	0	79 (15)	290 (55)
Rifaximin "chaser"	0	9 (2)	73 (14)
Nitazoxanide	0	1 (0.2	10 (2)
Tigecycline	0	1 (0.2)	3 (0.6)
Combination (≥2 drugs)	0	127 (24)	121 (23)

3. Results

3.1. Overall response rate

Six hundred and twenty one of 1212 EIN members (51%) submitted responses to the survey. The response rates were significantly higher among members with 15 or more years of practice experience since completion of their ID fellowship than for respondents with less experience (60% vs. 43%, respectively; $p < .0001$). The response rates were not different for U.S. Census Bureau division of practice location or for employment type. Sixty-four of these respondents (10%) reported that they had not treated CDI in the prior 6 months and were omitted from further data analysis. The total numbers of responses to individual questions varied because not all respondents answered all the questions.

3.2. Volume of patients treated for CDI

The majority of respondents (392/538, 73%) had treated fewer than 25 patients with CDI during the 12 months prior to the time of the survey, but 37 respondents (7%) had treated more than 50 patients. The numbers of patients who developed recurrent CDI seemed to increase proportionally with the total number of patients treated; practitioners who treat more CDI cases appeared see more recurrent CDI. All but 22 (4%) of 538 respondents reported patients with recurrent CDI, with recurrence rates ranging between 4 and >50%.

3.3. Antibiotic choices for treatment of CDI (primary and recurrent infection)

Respondents indicated their antibiotic choices for the management of primary mild CDI as well as for subsequent mild recurrences, as shown in Table 1. Most respondents (84%) selected oral metronidazole for treatment of the initial episode of CDI. Oral vancomycin (fixed or tapered dosing schedule) became the preferred treatment of choice for patients with recurrent CDI, even with the first recurrence. Other drug choices (fidaxomicin, rifaximin and nitazoxanide) were increasingly selected, proportionate with the number of recurrences. Duration of respondents' selected therapy for patients with their second recurrence of mild CDI (primarily vancomycin), indicated by 285 respondents, ranged from 10 to 14 days (43%), 15–28 days (29%), 29–56 days (24%) to > 56 days (4%).

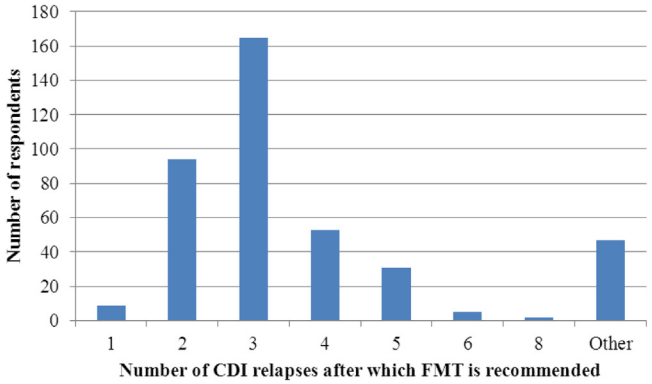

Fig. 1. Distribution of survey responses on the timing of fecal microbiota transplantation (FMT) vs. the number of *Clostridium difficile* infection (CDI) recurrence (*X*-axis) among 359 EIN respondents (*Y* axis) who would consider using FMT for treatment of laboratory confirmed CDI. "Other" refers to indicated range of 1–8 or more recurrences.

3.4. Antibiotic choices for treatment of severe CDI and testing for NAP1/027 strains

When asked which antibiotic regimen they used for treatment of severe CDI without ileus, oral vancomycin alone was selected by the single largest group of respondents (224/533, 42%), and 96% used oral vancomycin either alone or in combination with another agent(s). When treating severe CDI with ileus, the largest group of respondents selected the combination of oral vancomycin, intravenous metronidazole and vancomycin per rectum (160/533, 30%). Ninety percent of respondents used intravenous metronidazole either alone (by 16) or in combination with other agent(s) (by 465).

The majority of respondents (404/538, 75%) reported that their institutions either did not offer testing for the NAP1/027 strain of *C. difficile* or they were not sure if testing was available. When asked if their treatment choices would change if a patient was known to carry the NAP1/027 strain, 30% said yes, 42% said no and 28% were not sure.

3.5. Alternative treatments for CDI

IVIG for treatment of CDI had been recommended by about half of the respondents at least once during their years of practice. A majority (77%) of those who had recommended its use had done so less than 5 times, 16% had recommended IVIG between five and ten times, and only 19 (7%) total respondents had used it more than 10 times.

Respondents were also asked about probiotic use, including *S. boulardii* for "management of current CDI" and for "prevention of CDI (pt on antibiotics)". Approximately one-third (37%) of respondents do not recommend probiotics for either management or prevention of CDI. The largest group of respondents reported using probiotics for both treatment and prevention (218, 40%), while 23% reported using probiotics for either treatment or prevention, but not both. The majority of respondents using probiotics for either indication reported rare or occasional use; only 12% and 17% reported routine use of probiotics for either prevention or management, respectively.

3.6. Physician attitudes towards FMT

When asked to select all circumstances under which they would recommend FMT, 424 of 527 respondents (80%) indicated that they would consider FMT for recurrent disease, and 125 respondents (24%) would consider it for severe disease. Forty-seven respondents (9%) would under no circumstances recommend FMT. Most of the respondents would recommend FMT for patients who had suffered at least two recurrences of CDI (Fig. 1).

3.7. Availability of FMT in North America

One hundred and fifty six respondents (29%) indicated that FMT was available in their institution at the time of the survey, and an additional 127 respondents (24%) reported that plans for implementing FMT in their institution were underway. The remaining respondents (249, 47%) indicated that FMT was not available at the time of the survey. The most common reasons cited for the lack of an FMT program by 330 respondents included: difficulties with the logistics of the preparation and/or delivery of the fecal donor sample (265, 80%), the complexity and cost of donor screening (147, 45%), compensation/reimbursement issues (84, 26%) and patient refusal (15, 5%). Additional reasons cited in an open-text field were: local legal issues and lack of IRB approval (16, 5%), resistance to FMT by hospital administration (9, 3%), and conflicts of interest with local gastroenterology consultants (15, 5%). Nineteen respondents (6%) stated that they had not needed to consider FMT for the management of patients with CDI.

3.8. Provider-experience with FMT

A sub-survey of providers who had prescribed FMT during the previous year generated 149 responses. Forty-two responders (28%) indicated that they had not personally administered FMT, but that other members of their institution or practice group had. The majority of respondents (53%) had treated 1-4 patients, followed by 15% who had treated 5-10 patients. Six respondents (4%) had treated $>$ 10 patients, including 2 who had overseen FMT for $>$ 25 patients during the preceding 12 months.

3.9. Screening laboratory tests for fecal donors

Six of 144 respondents (4%) indicated they did not screen potential stool donors with any laboratory testing prior to the stool donation. Providers who screened donors generally adhered to previously published recommendations for donor screening [8,11]. The most common screening tests included serologic testing for HIV (88%), hepatitis B virus (85%), hepatitis C virus (78%), hepatitis A virus (74%), and syphilis (RPR) (56%). In addition, donor stool samples were tested for *C. difficile* toxin (EIA or PCR, 73%), culture for enteric pathogens (69%), and microscopic examination for ova and parasites (65%).

3.10. Source of donated stool and route of instillation

The most common source of stool donated for FMT was a household or family member (141/144, 98%). Three respondents reported that they used banked frozen fecal material collected from an unrelated donor. The most common route of instillation of the stool sample was via the lower intestinal tract, either through the colonoscope (69/143, 48%) or by enema (27/143, 19%). A nasogastric or nasoduodenal tube was reported for instillations via the upper gastrointestinal tract (47/143, 33%).

The majority of the respondents (125/137, 91%) reported that they usually administered a single fecal instillation, while the remaining 9% performed multiple instillations. The volume of feces per instillation ranged between $<$100 ml (20%), 100–249 ml (47%), 250–500 ml (27%) or 500–1000 ml (6%).

3.11. FMT success rates

The estimated success rates of FMT reported by 145 respondents were generally high, and ranged from <50% (2 respondents), 50–79% (19 respondents), 80–95% (48 respondents), to > 95% (56 respondents).

4. Discussion

Our results demonstrate that most of the responding ID clinicians routinely care for patients with CDI. How closely respondents adhere to SHEA/IDSA Treatment Guidelines [1] depends upon the features of the case. Most respondents adhere to the guidelines for mild, initial CDI cases. In contrast, a majority chose treatments at variance with guidelines for patients with the first recurrence of CDI: rather than the recommended metronidazole; alternate agents (ie, vancomycin) are frequently chosen instead or are added as second agents. When treating a second recurrence, members reported the use of antimicrobials not discussed in the guidelines, such as rifaximin and nitazoxanide, albeit in low numbers. Fidaxomicin, which was FDA-approved for the treatment of CDI [12] after the release of the 2010 SHEA/IDSA Guidelines, is used by a sizeable minority of practitioners only after patients have experienced a second recurrence. The heterogeneity of treatment approaches for recurrent CDI cases, often at variance with guideline recommendations, suggests a lack of consensus on how to manage and treat such cases. These findings also highlight the need for controlled trials using more novel agents to guide evidence-based treatment in patients with RCDI.

Although a moderate number of respondents indicated that they used IVIG or probiotics for treatment or prevention of CDI, neither modality was used consistently, and neither of these agents is recommended by the SHEA/IDSA guidelines. Compared to these other non-antibiotic therapies, much more enthusiasm was reported for FMT, despite a relative lack of experience with the approach. Eighty percent of respondents would recommend treatment with FMT for recurrent CDI, and 24% would consider FMT for treatment of severe disease. The majority of the respondents reported that FMT should be considered after the second or third recurrence. Only 9% of respondents would not recommend FMT under any circumstances.

Although the treatment principle of FMT has been practiced for several centuries by farmers and veterinarians to treat infectious diarrhea-states in domestic ungulates [8], FMT was first employed in human medicine by Eiseman and colleagues in 1958 to successfully treat 4 patients with recalcitrant diarrhea [13]. During the last 60 years, FMT has gained increasing recognition as a treatment for recurrent CDI when standard treatments have failed. By the end of 2012, 37 peer-reviewed reports of single cases or case series, including more than 600 patients with relapsing CDI, had been published in the world literature documenting the successful utilization of FMT [7–10]. Recently, the first randomized controlled trial of FMT demonstrated >81% efficacy [14]. Average success rates with colonoscopy or fecal enema instillation exceed 90%, whereas rates for instillations via the upper GI tract approximate 80% [14]. The disparate success rates may be explained by the higher volume of instilled fecal material using colonic instillation. The majority of our respondents (104/145, 72%) who had recommended FMT estimated a success rate of at least 80%. These results are consistent with those previously published [7,9,14,15] and support the assertion that FMT can resolve RCDI for patients who have failed conventional therapy.

Most respondents indicated that the donated stool samples were screened for transmissible pathogens according to previously published recommendations [6–8,11]. Nevertheless, it was surprising that six of 144 respondents (4%) did not screen the stool donor prior to stool acquisition. There were no instances of a reported transmissible infectious event observed for any of the recipients following FMT, which is in accordance with the published literature [6].

Our respondents identified several barriers to FMT use. As confirmed by our study findings, reimbursement of the costs associated with screening of the stool donor and the logistics of sample preparation and delivery have been significant barriers [16]. However, the recent approval of CPT code 44705 (G-code 0455) promises to ameliorate components of these problems, and to allow at least a partial recovery of the costs associated with FMT [17]. Only rarely did respondents cite patient refusal as a barrier to FMT, in keeping with a recent survey indicating that most patients would consider this alternative treatment for RCDI [16].

Increased experience with FMT may lead to simpler processes that may make it more widely feasible. The most common current source of the fecal material (family/household members), and mode of delivery via colonoscopy may engender more intense procedural costs and provider labor. Notably, the predominant use of household/family members as donors leads to a one-time donation after screening. If protocols to test and maintain a pool of donors, bank fecal transplant materials and deliver the transplanted material in a simple fashion such as a rectal enema are documented to provide good efficacy and safety, some of the institutional barriers to FMT could be reduced. Methods to freeze and bank fecal material before FMT have been reported, with good success rates [15]. Delivery of FMT via enema has also been reported, again with success rates comparable to delivery via nasal tube or colonoscopy [18].

4.1. Limitations

Our physician survey garnered a relatively high response rate from a broad geographic area; however, results may not be appropriately generalized to all infectious diseases physicians or all hospitals. Because respondents may have been more likely to be interested in CDI than non-respondents, our findings likely overestimate the average infectious diseases consultants' activities in the treatment of CDI. We surveyed only infectious disease physicians, not gastroenterologists, who comprise another major group that manages problematic CDI. Some fraction of these patients may be jointly managed by gastroenterologists and infectious disease clinicians, whereas some may be managed exclusively by gastroenterologists. Recent media attention following the published highly successful randomized clinical trial of FMT [14] and FDA regulatory action surrounding FMT [19] could have biased responses toward greater FMT interest and utilization in particular; however, this survey was administered, and results obtained, before either of these events. Lastly, our findings are limited by the fact that we did not ask respondents to correlate their success rates with the route of instillation or the volume of fecal material administered.

4.2. Conclusions

Despite our limitations, our results clearly demonstrate that management of RCDI represents a continuing challenge to treating physicians. The survey response demonstrates wide treatment heterogeneity, underscores the need for more randomized controlled trials to assess the relative efficacy of less commonly-used agents for RCDI, and highlights the need for new therapeutic approaches. The survey also reveals the gap between reported enthusiasm for FMT and utilization rates, underscoring the non-trivial implementation barriers to FMT across large geographic

boundaries. Finally, the emerging use of FMT as a treatment modality despite the barriers should prompt additional studies to refine strategies and specifically address issues such as the optimal routes of installation, preparation and screening of donor stool, and whether simpler methods of FMT, for example synthetic or frozen stool, could play a role in the treatment of primary CDI.

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Conflict of interest

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SEB: No conflicts.
FXR: No conflicts.
JAS: No conflicts.

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