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BRIEF REPORT

Fecal Microbiota Transplantation for Recurrent *Clostridium difficile* Infection Reduces Recurrent Urinary Tract Infection Frequency

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Broad-spectrum antibiotics for recurrent multidrug-resistant urinary tract infections (UTIs) disrupt the gut microbiome and promote antibiotic resistance. Fecal microbiota transplantation led to resolution of recurrent *Clostridium difficile*, significantly decreased recurrent UTI frequency, and improved antibiotic susceptibility profile of UTI-causing organisms.

Keywords. *C. difficile* infection; fecal transplant; infection; microbiome; urinary tract infections.

Recurrent urinary tract infections (UTIs) are among the most common bacterial infections, especially in the elderly. UTIs pose frequent management challenges, including antibiotic choice, due to worsening resistance patterns with each infection. It is estimated that UTIs account for nearly 7 million office visits, 1 million emergency room visits, and about 100 000 hospitalizations per year and cost $1.6 billion annually [1].

Clostridium difficile infection (CDI) is the most common nosocomial infection and has been associated with significant morbidity and mortality, with an estimated 29 000 deaths annually within 30 days of infection and a high risk of recurrence [2, 3]. The most common risk factor for recurrent CDI is ongoing broad-spectrum systemic antibiotic exposure used to treat infections such as recurrent UTIs. These antibiotics disrupt the gut microbiota and not only lead to recurrent CDI but also facilitate emergence of multidrug-resistant organisms (MDROs) in the gut. These organisms are likely the major pathogens responsible for recurrent UTIs, especially in patients who have profuse diarrhea due to CDI [4].

Fecal microbiota transplantation (FMT) has emerged as an effective therapy for recurrent CDI by restoring the normal gut microbiota [5]. Interestingly, there may be additional benefits from FMT in addition to resolution of CDI. A recent study demonstrated that FMT for recurrent CDI eradicated vancomycin-resistant enterococci (VRE) colonization in 73% of VRE-positive patients [6].

We hypothesized that FMT would reduce the frequency of recurrent UTIs from antibiotic-resistant organisms by decolonization of MDROs from the gut. The institutional review board approved this study, and receipt of informed patient consent was verified.

METHODS

Patient Selection

We retrospectively identified patients with 3 or more UTIs in the year preceding FMT (for recurrent CDI) from May 2012 to September 2016. UTI was defined as the presence of urinary symptoms and urinary bacterial cultures with $>10^5$ colony-forming units/mL. Eligibility criteria for FMT included third or greater CDI episode proven by a positive *C. difficile* polymerase chain reaction stool assay in the presence of diarrhea. Donor stools were obtained after obtaining an extensive medical history and laboratory evaluation (blood and stool tests). Detailed inclusion and exclusion criteria for donors in our program have been previously published [7]. A control group of patients with 3 CDI episodes managed with antibiotics and 3 or more UTIs the year prior to the third CDI episode was also included.

Data Collection

We recorded patient demographics, CDI history, and frequency of UTIs in 1 year before and 1 year after FMT. Additionally, we collected microbiological data (causative microorganisms and their antibiotic-resistance patterns) from the positive urine samples.

Statistical Analyses

Statistical analyses were performed using JMP, version 13.0 (SAS Institute Inc.). Demographic and clinical variables were summarized using descriptive statistics. Continuous variables are reported as median (range), and categorical variables are reported as proportions. The differences in frequency of UTIs before and after FMT or the third CDI episode for the control group were analyzed using Wilcoxon signed rank test.

RESULTS

Recurrent *Clostridium difficile* Infection and Recurrent Urinary Tract Infection Patients Managed With Fecal Microbiota Transplantation

Of all patients who underwent FMT for recurrent CDI, 8 (75% female; median age 78.5 years [range, 25–86]) had 3 or more

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UTI episodes the year prior and were included in the study. Prior to FMT, the median number of CDI episodes was 4 (range, 3–7), median number of prior metronidazole courses was 1.5 (range, 1–3), and median number of prior vancomycin courses was 3 (range, 1–5).

There was a significant decrease in the frequency of UTIs, from a median of 4 (range 3–7) episodes in the year before to 1 (0–4) episode in the year after FMT ($P = .01$; Wilcoxon signed rank test; Figure 1). Three patients with a single UTI episode after FMT were managed with either nitrofurantoin or trimethoprim-sulfamethoxazole. Two patients had 4 UTI episodes after FMT and were managed with intravesical gentamicin irrigations, which is a third-generation cephalosporin or ciprofloxacin. All patients had complete resolution of CDI and had no recurrences within 1 year of follow-up despite future antibiotic exposure.

Thirty-five positive urine samples were cultured in the year before FMT (Supplementary Table 1A), and 11 positive samples were cultured in the year after FMT (Supplementary Table 1B). *Escherichia coli* was the most common organism cultured from pre- and post-FMT urine samples followed by *Klebsiella* species. A total of 15 samples were positive for *E. coli* before FMT, whereas only 4 samples had *E. coli* cultured after FMT; 9 samples were positive for *Klebsiella* before FMT and only 1 sample grew *Klebsiella* after FMT (Table 1).

Among 15 *E. coli* isolates before FMT, 4 (26.6%) were resistant to ampicillin, 3 (20%) were resistant to ciprofloxacin, and 3 (20%) were resistant to trimethoprim-sulfamethoxazole. Of the 4 *E. coli* isolates after FMT, only 1 (25%) was resistant to ampicillin, and none were resistant to ciprofloxacin and trimethoprim-sulfamethoxazole. Of the 9 *Klebsiella* isolates before FMT, 8 (88.8%) were resistant to ampicillin and 2 (22.2%) were resistant to nitrofurantoin. The only *Klebsiella* isolate after FMT was resistant to ampicillin but not to nitrofurantoin (Table 1).

Susceptibility profiling of the most recent urine cultures (UTI episode preceding FMT) from 8 patients grew *E. coli* or *Klebsiella* species (4 for each). Of the *E. coli* isolates, all 4 were resistant to ampicillin, 3 were resistant to ciprofloxacin, and 3 were resistant to trimethoprim-sulfamethoxazole. After FMT, 1 of 4 isolates was resistant to ampicillin, but all were susceptible to ciprofloxacin and trimethoprim-sulfamethoxazole. Detailed resistance patterns for *E. coli and Klebsiella* are shown in Table 1.

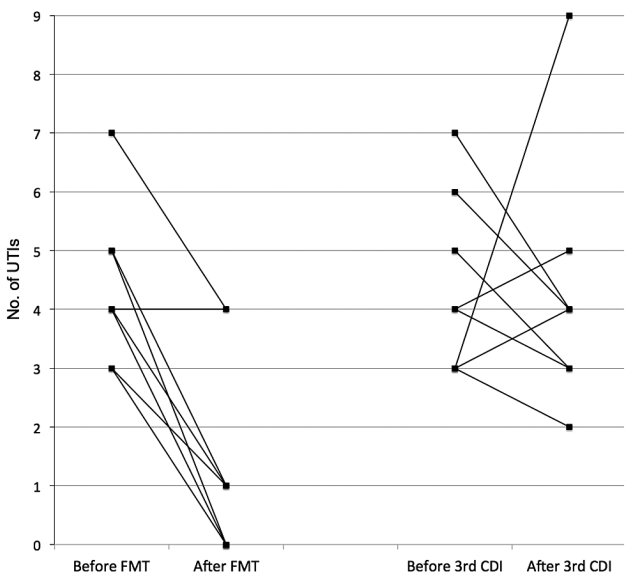

Figure 1. Frequency of urinary tract infections. Graph shows the number of infections 1 year before and 1 year after fecal microbiota transplantation and 1 year before and 1 year after the third *Clostridium difficile* infection episode in the control group. Each square and line represent 1 patient.

Recurrent *Clostridium difficile* Infection and Recurrent Urinary Tract Infection Patients Not Managed With Fecal Microbiota Transplantation

Of 8 patients in the control group (75% female; median age 85.5 years [range, 71–92]), 7 were managed with vancomycin and 1 with both vancomycin and metronidazole for their third CDI episode. Two patients had a subsequent CDI episode managed with a vancomycin taper. There was no difference in the frequency of UTI in the year before and after the third CDI episode. The median UTI frequency in the year before the third CDI was 4 (3–7) and in the year after it was 4 (2–9; $P = .55$; Wilcoxon signed rank test; Figure 1). There were no changes in antimicrobial-resistance pattern comparing 13 *E.* coli isolates before the third CDI to 9 the year after or comparing the 10 *Klebsiella* isolates before the third CDI to 13 the year after. Detailed resistance patterns are outlined in Supplementary Table 2.

DISCUSSION

In this study, successful FMT for recurrent CDI was associated with a reduced UTI frequency and an improved antibiotic susceptibility profile of organisms that cause UTIs. Commensal intestinal bacteria have an important role in pathogen colonization resistance by competing for nutrients, altering gut pH, forming antimicrobial metabolites, and preventing access to binding sites on the mucosal wall [8]. The widespread use of antibiotics created a dysbiotic microbiome and impairs colonization resistance, increasing the risk of MDRO colonization and CDI [9]. The need for repeated antibiotic courses may lead to both recurrent CDI and emergence of MDROs that cause UTIs; repeated treatment with antibiotics further disrupts the microbiome, thereby perpetuating the cycle.

Microbial replacement therapies such as FMT are being investigated for treatment of conditions associated with a disrupted gut microbiome, including inflammatory bowel disease, obesity, and metabolic syndrome [9]. It has been suggested that FMT might be effective in clearing VRE and MDROs by restoring colonization resistance [10].

Repletion of healthy gut microbial communities with FMT, primarily to treat recurrent CDI, may decolonize enteric

Table 1. Antimicrobial Resistance Patterns of Most Common Bacterial Organisms 1 Year Before and 1 Year After Fecal Microbiota Transplantation

	Resistant, No. (%)					
	Escherichia coli			*Klebsiella* sp.		
	Before FMT			Before FMT		
Antimicrobial Drug	Resistance Pattern (n = 11)[a]	Most Recent Isolate (n = 4)[b]	After FMT (n = 4)	Resistance Pattern (n = 5)[a]	Most Recent Isolate (n = 4)[b]	After FMT (n = 1)
Ampicillin	0 (0)	4 (100)	1 (25)	-[c]	-[c]	-[c]
Ampicillin-sulbactam	1 (9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cefazolin	0 (0)	3 (75)	0 (0)	0 (0)	2 (50)	1 (100)
Cephalothin	0 (0)	3 (75)	0 (0)	0 (0)	0 (0)	0 (0)
Ceftriaxone	0 (0)	3 (75)	0 (0)	0 (0)	0 (0)	0 (0)
Ceftazidime	1 (9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cefepime	1 (9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ciprofloxacin	0 (0)	3 (75)	0 (0)	0 (0)	0 (0)	0 (0)
Levofloxacin	0 (0)	3 (75)	0 (0)	0 (0)	0 (0)	0 (0)
Trimethoprim-sulfamethoxazole	0 (0)	3 (75)	0 (0)	0 (0)	0 (0)	0 (0)
Nitrofurantoin	0 (0)	0 (0)	0 (0)	1 (25)	1 (25)	0 (0)

Abbreviation: FMT, fecal microbiota transplantation.

[a]Does not include resistance pattern of the most recent isolate before FMT.

[b]Reported separately to show the effect of ongoing antibiotic exposure for urinary tract infections.

[c]Due to the inherent resistance of *Klebsiella* sp. to ampicillin, resistance for ampicillin is not reported.

MDROs and decrease the risk of recurrent UTIs. Antimicrobial-resistance patterns from the isolates demonstrated an improved susceptibility to antibiotics after FMT, suggesting gut decolonization of MDROs or a reduction in concentration of these organisms below a threshold to cause UTI. Conceptually, FMT may have reduced colonization with multidrug-resistant *E. coli* clones such as ST131 sequence type in favor of less pathogenic *E. coli* clones or other, largely commensal enteric organisms.

Although patients with a history of recurrent CDI are at high risk of recurrence of CDI on exposure to systemic antibiotics, none of the patients in this series experienced CDI recurrence, even after receipt of multiple courses of antibiotics for recurrent UTIs after FMT. However, the majority who received antibiotics were considered low risk for CDI. This suggests durability of response to FMT for recurrent CDI.

Although our findings are limited by a small sample size and lack of microbiome profiling, we demonstrate that FMT may decrease the frequency of MDRO UTIs, possibly by gut decolonization through reestablishment of colonization resistance. This effect may lead to decreased antibiotic use, morbidity, and cost. A prospective clinical trial with a comparator non-FMT treatment group, microbiome data, and molecular typing of potential stool pathogens is needed to investigate the role of FMT in eradicating gut MDROs and reducing recurrent UTIs.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. S. K. has served as a consultant for Rebiotix, Summit Pharmaceuticals, and Assembly Biosciences. D. S. P. has served as a consultant for Assembly Biosciences, Merck, Seres Therapeutics, C3 Jian, Nestlé, and Salix. All other authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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