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Fecal microbiota transplantation may have clinical utility in reducing incidence of recurrent urinary tract infection

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ABSTRACT A critical appraisal and clinical application of Tariq R, Pardi DS, Tosh PK, Walker RC, Razonable RR, Khanna S. Fecal microbiota transplantation for recurrent *Clostridium difficile* infection reduces recurrent urinary tract infection frequency. *Clinical Infectious Diseases*. 2017 Oct 30;65(10):1745–1747. doi: 10.1093/cid/cix618.

Keywords: *Fecal microbiota transplantation, recurrent UTI, multidrug resistant organisms*

Clinical Context

A 73-year-old female with multiple chronic medical problems including obesity, type 2 diabetes, and cerebrovascular disease with a history of stroke was admitted for foul-smelling, watery diarrhea. She was accompanied by her adult daughter who was her primary caregiver and who provided the entirety of the patient's history. The daughter explained that her mother had two previous episodes of *C. difficile* infection (CDI) and that she recognized the stool consistency and smell immediately the previous night, which prompted her to bring her mother to the hospital. The patient was non-ambulatory and minimally responsive for the duration of her admission, though the daughter admitted this was not too far from baseline. She also had a gastrostomy tube and urinary catheter in place due to her chronic state.

At admission, the patient was afebrile but had a white blood cell count over 17,000. The patient's stool tested positive for *C. difficile*. The daughter reported that this was her mother's third admission CDI, and explained that doctors at her previous admission proposed it was likely secondary to extended antibiotic treatment for recurrent urinary tract infections in the setting of regular use of a urinary catheter. After discussing treatment options with the patient's daughter, it was agreed that a fecal microbiota transplant (FMT) would be the optimal treatment plan given multiple recurrences and the patient's other chronic medical problems. The patient received the FMT through her gastrostomy tube after bowel cleanout, and the daughter reported normalization of her bowel movements on day two post-transplant. The patient was discharged with her daughter five days after the transplant when her white blood cell count normalized. The daughter was instructed to have the patient follow up her primary care provider within one week.

Clinical Question

Does fecal microbiota transplant for *C. difficile* infection provide secondary benefit by reducing the incidence of urinary tract infections in at-risk patients?

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Research Article

Tariq R, Pardi DS, Tosh PK, Walker RC, Razonable RR, Khanna S. Fecal microbiota transplantation for recurrent *clostridium difficile* infection reduces recurrent urinary tract infection frequency. *Clinical Infectious Diseases*. 2017 Oct 30;65(10):1745–1747. doi: 10.1093/cid/cix618

Related Literature

Literature review began with UpToDate articles addressing fecal microbiota transplantation and recurrent urinary tract infection. This was followed by PubMed searches combining the keywords “fecal microbiota transplant” or “fecal transplant” with “multi-drug resistant organism.” Additional searches were also conducted combining “fecal microbiota transplant” or “fecal transplant” with “urinary tract infection.” These searches yielded only eleven total articles of which five were clinical studies. These searches were expanded by exploring the “similar articles” section of the PubMed pages of the articles found for more related material. Google searches with the same key worlds also yielded a clinical trial registered with the NIH examining the efficacy of FMT specifically for the treatment of recurrent urinary tract infections (UTI), though this study currently has no data yet to report.

Multiple case reports noting clearance of different multi-drug resistant organisms from the gastrointestinal tract following FMT have prompted multiple clinical studies exploring the utility of the procedure for eradication of such bacteria in patients suffering from recurrent infections.[1-2] A multicenter prospective pilot study performed by Davido et al measured the ability of FMT to successfully decolonize Carbapenem-resistant Enterobacteriaceae (CRE) or vancomycin-resistant enterococci (VRE) from a small group of 8 patients.[3] The study found clinical success eradicating CRE in 2 and VRE in 3 out of the 8 patients enrolled at one and three-month time points.[3] Dubberke et al performed a similar study examining the clearance of VRE in a group of patients receiving FMT for recurrent CDI.[4] Out of 11 patients who tested positive for VRE, 73% (n=8) became negative following FMT over the course of six-month follow up.[1] A single-center study performed by Millan et al utilized microarray analysis of gut microbiota to demonstrate a statistically significant reduction in expression of 354 known antibiotic-resistance genes in bacteria obtained from stool samples of patients following FMT for recurrent CDI.[5]

The study examined here by Tariq et al was chosen specifically because it was the only clinical study found to examine a legitimate clinical outcome (the incidence UTI) rather than just the presence of bacteria capable of causing such infections. The study identified patients with a history of three of more UTIs in the past year from a pool of patients with three or more episodes of CDI over the same time period. The experimental group was treated with FMT and were monitored for occurrence of UTI over a period of one year post-transplant.[6] Controls were obtained from the same group patients, but were monitored for occurrence of UTI over the course of one year following conventional antibiotic treatment for their third episode of CDI.[6] Bacterial speciation and susceptibilities were also collected in urine samples to evaluate changes in antibiotic resistance in the before and after time periods. Of all the studies explored, Tariq et al was the most recently published in July of 2017. It has also been cited eight times since its very recent publication indicating a high level of clinical relevance.

Critical Appraisal

This was an un-blinded, controlled, pilot study evaluating the occurrence of UTI, defined by urinary symptoms and positive urine culture with $>10^5$ colony forming units per mL, in patients receiving FMT for recurrent CDI. Inclusion criteria were patients with at least three or more UTIs as well as three or more episodes of CDI confirmed with stool polymerase chain reaction over the course of the preceding year. Patients were identified retrospectively at hospital admission for a third episode of CDI and were assigned to receive either standard antibiotic therapy or FMT. Sixteen total patients were enrolled in the study with eight each being assigned to the FMT or control groups. All patients were then monitored over the following year for recurrence of UTI and CDI. Urine cultures and susceptibilities during occurrences of UTI were also compared in the one-year before and after time periods to evaluate for prevalence of antibiotic resistance.

The primary outcome of this study was the occurrence of UTI before and after treatment. The authors observed a significant decrease in the frequency of UTI in the FMT group from an average of 4 episodes in the year before, down to 1 episode in the year after ($p = 0.01$ with Wilcoxon rank test). This is in contrast to the control group, which showed no change in the average incidence of

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UTI at 4 episodes in both before and after time periods. Patients receiving FMT also showed complete resolution of CDI with no recurrences in the year after. This was despite a small subset receiving trimethoprim-sulfamethoxazole, nitrofurantoin, or gentamicin for UTI episodes. Patients in the control group received either oral vancomycin alone or oral vancomycin and intravenous metronidazole rather than FMT for their third episode of CDI. Two patients in the control group (25%) had one subsequent episode of CDI in the year after, both of which were managed with oral vancomycin taper.

A secondary outcome of the study was changes in antibiotic resistance in organisms causing UTI. This was completed by comparing antibiotic susceptibilities of *E. coli* and *Klebsiella*, the two most commonly cultured organisms found in urine cultures during episodes of UTI in enrolled patients. 35 urine samples were evaluated in the year before and 11 in the year after for patients receiving FMT versus 13 urine samples in the year before and 9 in the year after for control. Susceptibilities showed a decrease of ciprofloxacin-resistant and trimethoprim-sulfamethoxazole-resistant E. coli from 20% in the year before down to 0% in the year after in the FMT group. Likewise, nitrofurantoin-resistant *Klebsiella* moved from 22% before down to 0% after in the FMT group. There were no changes in antimicrobial resistance in the before and after time periods for controls. It should be noted that no statistical significance was noted for any of the susceptibility data described above.

The greatest strength of this study is the novelty of the clinical application, considering the paucity of data assessing possible secondary benefits of FMT outside of treatment for CDI. This is evidenced by the extremely small number of clinical studies found during initial searches on PubMed. In addition, as has been noted, this was the only related study found that examined a clinical outcome, in this case occurrence of UTI, rather than variables of more questionable clinical significance such as bacterial colonization. Another strength is the relatively objective definition of UTI, which was the primary outcome. This was particularly important in this study due to the obvious discrepancies between standard antibiotic treatment and FMT to both patients and providers, which would have made blinding impractical and near impossible.

The greatest weakness of this study was sample size, which limited both the effect size as well as the statistical significance of all outcomes. The only outcome to have noted statistical significance was occurrence of UTI in patients before and after FMT. All other outcomes, while noting trends, could not establish statistical significance. The small sample size also likely limited the authors' ability to carry out more in-depth statistical analyses between groups rather than just within them, which is another weakness. No direct analysis comparing outcomes between FMT and control was carried out. It should be noted that no mechanism of randomization was noted within the article. Additionally, the only patient population characteristics to be reported were gender (75% female in both groups) and age (78.5 years in FMT versus 85.5 years in control). No other health characteristics were evaluated. The lack of extra population statistics is again likely due to the small sample size, which might have shown skewed discrepancies between the two groups due to the low numbers.

A weakness of significant importance is the incomplete standardization of donor stool samples used for FMT. A clear set of guidelines for selecting healthy donors was well described by the same group, Tariq et al, in a previous publication and used in this study.[6-7] However, the guidelines primarily rely on other medical conditions in the donor including obesity, depression, pregnancy, and antibiotic exposure among others.[7] Not included in analysis of donors was evaluation of specific bacteria present in stool with exception for a few possibly virulent organisms such as *C. difficile* and VRE.[7] Subtle differences in donor microbiota could very well contribute to differences seen not only in recurrence of UTI and CDI but also in the carriage of different antibiotic resistant organisms. This issue was avoided in the study by Dubberke et al by using a standardized fecal microbiota "drug" for FMT called RBX2660 in all study subjects. Tariq et al, themselves, acknowledge the general lack of standardization in obtaining donor samples for such studies nationally and it is a factor that should be carefully considered in all similar studies moving forward.

The work conducted by Tariq et al qualifies as a level 2 study following by the Strength of Recommendation Taxonomy (SORT) guidelines. The study was the first to explore the very novel ability of FMT in reducing recurrence of UTI. However, weaknesses including sample size, statistical power, and lack of stool donor standardization limited its ability to completely describe the clinical utility FMT for such applications. Work in the future should focus on maximizing sample size and finding ways to better standardize FMTs between patients.

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Clinical Application

While limited by sample size (N=16) in addition to a handful of other factors, Tariq et al do demonstrate possible utility for FMT in reducing the incidence of recurrent UTIs in patients being treated for CDI. Our patient did meet study criteria given the incidence of both CDI and UTI in her recent medical history. Even if she had not met criteria, however, she may still have found similar benefit from FMT given her chronic state in addition to her elevated risk for UTI with the use of regular urinary catheterization.

After discussing treatment options with the patient's daughter, she agreed that FMT would be the best course of action. The daughter in fact pushed for FMT as her end goal had always been optimal comfort for her mother, who may have benefited twofold with the reduction of both CDI and UTI should the conclusions of Tariq et al hold true.

Primary learning points:

1. Repetitive or prolonged use of systemic antibiotics increases risk of developing both CDI and multidrug resistant organism carriage, which can predispose to other recurrent infections.

2. FMT is an effective treatment for recurrent CDI and may have broader clinical application in the prevention of recurrent UTI.

3. More work is needed in evaluating the utility of FMT for the treatment of recurrent UTI both independently and in the setting of CDI.

References

1. Crum-Cianflone NF, Sullivan E, Ballon-Landa G. Fecal microbiota transplantation and successful resolution of multidrug-resistant-organism colonization. *Journal of Clinical Microbiology*. 2015;53(6):1986-1989. doi: 10.1128/jcm.00820-15
2. Kronman MP, Zerr DM, Qin X, et al. Intestinal decontamination of multidrug-resistant *Klebsiella* pneumoniae after recurrent infections in an immunocompromised host. *Diagnostic Microbiology and Infectious Disease.* 2014;80(1):87-89. doi: 10.1016/j.diagmicrobio.2014.06.006
3. Davido B, Batista R, Michelon H, et al. Is faecal microbiota transplantation an option to eradicate highly drug-resistant enteric bacteria carriage? *Journal of Hospital Infection.* 2017;95(4):433-437. doi: 10.1016/j.jhin.2017.02.001
4. Dubberke ER, Mullane KM, Gerding DN, et al. Clearance of vancomycin-resistant *Enterococcus* concomitant with administration of a microbiota-based drug targeted at recurrent *Clostridium difficile* infection. *Open Forum Infectious Diseases*. 2016 May 1;3(3):ofw133. doi: 10.1093/ofid/ofw133
5. Millan B, Park H, Hotte N, et al. Fecal microbial transplants reduce antibiotic-resistant genes in patients with recurrent *Clostridium difficile* infection. *Clinical Infectious Diseases*. 2016 June 15;62(12):1479-1486. doi: 10.1093/cid/ciw185
6. Tariq R, Pardi DS, Tosh PK, Walker RC, Razonable RR, Khanna S. Fecal microbiota transplantation for recurrent *Clostridium difficile* infection reduces recurrent urinary tract infection frequency. *Clinical Infectious Diseases*. 2017 Oct 30;65(10):1745–1747. doi: 10.1093/cid/cix618
7. Tariq R, Weatherly R, Kammer P, Pardi DS, Khanna S. Donor screening experience for fecal microbiota transplantation in patients with recurrent *C. difficile* infection. *J Clin Gastroenterol*. 2018 Feb;52(2):146-150. doi: 10.1097/mcg.0000000000000768

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