Title
FECAL MICROBIOTA TRANSPLANTATION FOR THE TREATMENT OF REFRACTORY RECURRENT URINARY TRACT INFECTION

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Fecal Microbiota Transplantation for the Treatment of Refractory Recurrent Urinary Tract Infection

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Precis

Fecal microbiota transplantation may reduce urinary tract infection by altering gut microbiome.

Introduction

Fecal microbiota transplantation is a treatment for recurrent *Clostridium difficile* infection. A decrease in urinary tract infection (UTI) has been observed after fecal microbiota transplantation for *C. difficile* and in a case report for treatment of recurrent UTI.[1,2] Microbiota transplantation is thought to increase gut species diversity and may reduce relative abundance of uropathogens.[2-4] We hypothesized this treatment might reduce the number of symptomatic UTIs by altering the gut microbiome.

Methods

This was a prospective case series of fecal microbiota transplantation by retention enema to treat refractory recurrent UTI. Institutional IRB approval was obtained and Investigational New Drug (#17380) was granted by the Food and Drug Administration. Enrollment occurred from February to December 2018.

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Women with recurrent UTI despite six months of suppressive antibiotics were eligible.[5] Stool donors were extensively screened. Participants discontinued antibiotics 48 hours before transplantation. The primary outcome was number of symptomatic, culture-proven, antibiotic-treated UTIs in six months pre-treatment compared to six months post. Pre-treatment UTI were determined by chart review. Urine was collected at one week, one month, three and six months post-treatment, and when symptomatic. Adverse outcomes were graded.[6]

Continuous and categorial variables were compared using Wilcoxon signed-rank and Fisher's exact tests. Fecal samples were collected for microbiome analysis from donors and four recipients at each study visit. Stool samples were processed using ZymoBIOMICS protocols and shotgun Illumina sequencing was performed.[7] Microbial composition was obtained with the Centrifuge pipeline.[8] Taxonomic composition, alpha and beta diversity were assessed and figures created using R and processed in Inkscape.[9] All code and packages can be found on GitHub (https://github.com/aoliver44/Jeney-et-al-UTI).

Results

Eleven women were transplanted and ten completed study procedures. Two participants received directed donation and nine received University-provided donation. There were no significant adverse outcomes. Median (IQR) age was 70 (67-73) years; 8 of 9 post-menopausal women used vaginal estrogen.

Appendix 1 demonstrates that in six months pre-treatment, median (IQR) number of UTIs per participant was 3 (3-4), compared to 1 (0.25–3.75) in six months post-treatment (p=0.055). Pre-treatment, six women had at least one culture containing extended spectrum beta-lactamase producing bacteria compared to one (p=0.057) at three and two (p=0.17) at six months post-treatment.

Figure 1 shows microbial composition by genus for each donor and recipient (pre- and post-FMT). Appendix 2, an NMDS ordination of Bray-Curtis dissimilarities, represents Beta diversity (differences between microbial communities). Recipient post-treatment samples (Visit2-5) do not cluster differently than pre-treatment samples (Visit1) (pairwise PERMANOVA, p=0. 247, R^2=0.06). Post-treatment samples (Visit2-5) do not cluster towards donors, indicating that recipient gut microbiomes do not become significantly more similar to donors (p=0.234, R^2=0.08). Appendix 3 shows significant differences in alpha diversity by species number and evenness between groups (LME, p=1.04x10^{-07}), (LME, p=1.04x10^{-12}).

Discussion

We show a non-significant decrease in symptomatic UTI after fecal microbiota transplant with no serious adverse events. Post-treatment, 4 women no longer met criteria for recurrent UTI and three had no UTIs. We also noted a non-significant reduction in multidrug resistant organism carriage. Microbiome analysis demonstrated greater alpha diversity following treatment, yet microbiome profiles of recipients did not skew towards the donor profile but more closely resembled themselves longitudinally. Despite limitations, these pilot data

provide a foundation for the study of fecal microbiota transplant in refractory recurrent UTI patients, particularly those with antibiotic resistance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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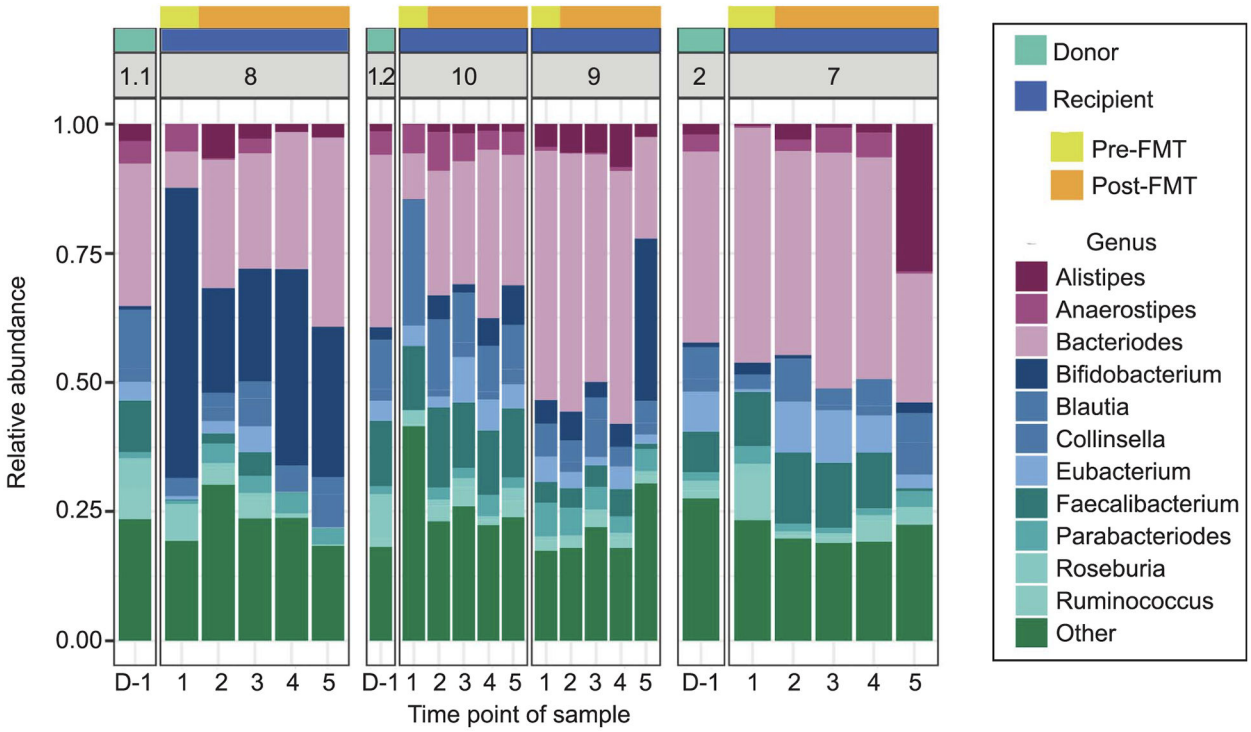

Fig. 1.

Fecal microbiome data. Relative abundance plots for donors and recipients (pre-treatment, 1 week, 1 month, 3 months, and 6 months post-treatment).

Jeney. Fecal Microbiota Transplantation for Recurrent UTIs. Obstet Gynecol 2020.