Microbiota and Associations with Treatment Outcome in Fecal Microbiota Transplantation

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Introduction

FMT has been shown to be the most effective therapy for recurrent Clostridium difficile infections (CDI) with >80% efficacy. FMT is now recommended in national and international guidelines for the management of recurrent CDI.

In this study, we evaluated changes in the gut microbiome of patients with recurrent CDI who underwent FMT by colonoscopy or who were administered 30-50 capsules of freeze dried fecal material under direct observation.

The aims of this study were to evaluate inter-donor variability in the bacterial diversity index in FMT doses for endoscopic and capsule delivery and to analyze the gut microbiome of FMT recipients who received fecal material from the donors above.

Methods

We enrolled adult outpatients aged >18 with at least 3 documented episodes of CDI and failure of standard therapy with extended vancomycin (>6 weeks)

FMT doses were prepared by the Volunteer Stool Donor (VSD) Bank in the Division of Infectious Disease, University of Pittsburgh. Doses are obtained from healthy donors, 18-50 y of age, with normal BMI who successfully completed a screening questionnaire and medical interview/physical exam. Donors were negative for HIV-1/2, HAV, HBV, HCV, syphilis, HTLV, Entamoeba histolytica, Strongyloides, stool for Salmonella Shigella Campylobacter, Yersinia, E. coli O157:H7, C. difficile by culture, and parasites, H. pylori, MRSA, VRE, and urine drug screen. Mismatches between donor and recipients for latent viruses with fecal shedding were avoided.

All recipients were treated with vancomycin or fidaxomycin 3-5 days prior to FMT. Recipients were given 250 mL of fecal slurry via endoscopy or took 30-50 capsules of freeze dried fecal microbiota.

Successful endpoint was defined as no relapse of C. difficile-associated diarrhea 12 weeks post-FMT.

Stool samples prior to and post FMTs were collected and frozen at -80°C. Bacterial composition profiles and their relationship with treatment route, outcome and donor were studied using bioinformatics and multivariate statistics on 16S rRNA gene sequences (16S). Analyses of 16S profiles included Permutational Multivariate Analysis of Variance and linear regression models applied to bacterial abundances and diversity.

Results

Table 1. FMT success rate among procedures.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Success</th>
<th>Failure</th>
<th>Total</th>
<th>% of Procedures</th>
<th>Failure Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonoscopy</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td>18.2%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Enteroscopy</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>4.5%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Capsule</td>
<td>36</td>
<td>4</td>
<td>40</td>
<td>100.0%</td>
<td>23.3%</td>
</tr>
<tr>
<td>Total</td>
<td>41</td>
<td>4</td>
<td>45</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reject differences in failure rate between procedures: p-value=0.4873; Chi-squared test

The subjects with successful FMT outcomes (n=18) had a greater pre-FMT diversity than those that had failed (n=3), no Pre sample for one of the failures.

Figure 1. Mean taxonomic composition of subjects prior to FMT procedure.

Figure 2. Time series plot of diversity over time with LOESS curve fitting.

Conclusions

Significant differences were observed between pre- and post-FMT successes and failures (p<0.01, R²=0.24). No differences were seen between route (p>0.15) or donor (p>0.29).

Profiles of failures were more similar to pre-FMT profiles by multidimensional scaling.

Of the 5 most abundant taxa, Enterobacteriaceae and Escherichia-Shigella decreased significantly in successful outcomes, while Faecalibacterium, Blautia, and Bacteroides increased.

Increases in microbiota diversity are generally achieved in successful FMT regardless of administration route, although more than one bacterial composition profile can be identified.