Fecal Microbiota Transplantation Via Nasogastric Tube for Recurrent Clostridium difficile Infection in Pediatric Patients


ABSTRACT

Fecal microbiota transplantation (FMT) is a safe and effective therapy for adults with recurrent Clostridium difficile colitis, but data regarding FMT in children are limited and focus on colonoscopic administration of FMT. We present 10 consecutive children who received FMT via nasogastric tube for treatment of recurrent C difficile infection. Median age was 5.4 years, and 30% were receiving simultaneous immunosuppression. Median follow-up was 44 days, and 90% of patients resolved their C difficile infection; one patient relapsed 2 months later after receiving antibiotics. FMT via nasogastric tube appears safe, well tolerated, and effective in treating pediatric recurrent C difficile colitis.

Key Words: Clostridium difficile, fecal microbiota transplantation, pediatrics

METHODS

Study Approval

Informed consent was obtained from the parent/guardian of each patient. This retrospective case series was approved by the institutional review board of the Seattle Children’s Hospital (SCH).

Patient Selection

This series includes 10 consecutive children who received FMT at SCH between August 2011 and May 2014 for the treatment of recurrent C difficile infection using the same protocol, defined as 3 or more recurrences of C difficile diarrhea with failed treatment, including vancomycin taper. During the study period, C difficile infection was identified at SCH using 2-step testing, first with antigen and toxins A&B, and then with C difficile toxin A&B polymerase chain reaction in cases of antigen-positive but toxin-negative specimens. This recommended two-step testing scheme maximizes sensitivity and specificity (12). Some patients referred by their primary care providers had initial C difficile testing using their local protocol. Retrospective chart review was performed to describe the demographics and clinical characteristics of the population. No patients with recurrent C difficile infection managed at SCH during this period were denied the opportunity for FMT.

Donor Screening and Preparation

We considered recipients’ adult family members, household members, or adult family friends as potentially acceptable donors. The American Association of Blood Banks Donor History
TABLE 1. Exclusion criteria and screening for potential donors

1. Chronic systemic infections or risks for infection
   • Serological testing for:
     a. HIV, type 1 and 2 (HIV-1 p24 antigen and HIV-1 and HIV-2 antibody screening), performed and reviewed no more than 14 days before donation
     b. Hepatitis A virus IgM
     c. Hepatitis B virus surface antigen, core antibody (IgG and IgM), surface antibody
     d. Hepatitis C virus IgG
     e. RPR and fluorescent treponemal antibody-absorbed
     • Known HIV, hepatitis B or C infections
     • Known exposure to HIV or viral hepatitis (within the previous 12 mo)
     • High-risk sexual behaviors (eg, sexual contact with anyone with HIV/acquired immunodeficiency syndrome or hepatitis, men who have sex with men, sex for drugs or money)
     • Use of illicit drugs
     • Tattoo or body piercing within 6 mo
     • Incarceration or history of incarceration
     • Known current communicable disease (eg, upper respiratory tract infection)
     • Risk factors for variant Creutzfeldt-Jakob disease

2. Gastrointestinal infectious organisms identified through screening studies
   • Stool testing for:
     a. C difficile 2-step test (EIA for C difficile antigen and toxins A&B; C difficile toxin B PCR is used in cases of antigen-positive but toxin-negative specimens)
     b. Ova and parasites to include screening for protozoa, trophozoites and cysts, helminths and ova including Entamoeba histolytica, Microsporidia species, Dientamoeba fragilis, Blastocystis hominis, Giardia lamblia, Ascaris lumbricoides, trematodes, and tapeworms. Acid-fast staining for Cryptosporidium, Cyclospora, and Isospora
     c. Helicobacter pylori antigen
     d. Bacterial culture for enteric pathogens (includes Salmonella species, Shigella species, Campylobacter species, Staphylococcus aureus, Aeromonas hydrophila, Yersinia, Vibrio parahaemolyticus, Vibrio cholerae, E coli 0157, and Listeria species).

3. Gastrointestinal comorbidities
   • History of inflammatory bowel disease
   • History of irritable bowel syndrome, idiopathic chronic constipation, or chronic diarrhea
   • History of gastrointestinal malignancy or known polyposis

4. Factors that can or do affect the composition of the intestinal microbiota
   • Antibiotics within the preceding 3 mo
   • Major immunosuppressive medications, for example, calcineurin inhibitors, exogenous glucocorticoids, biological agents, and so on
   • Systemic antineoplastic agents

All screening and other testing of donor stool and blood was performed and reviewed no more than 30 days before donation, except as otherwise mentioned. EIA = enzyme immunoassay; HIV = human immunodeficiency virus; Ig = immunoglobulin; PCR = polymerase chain reaction; RPR = rapid plasma reagin.

questionnaire was used to evaluate study subject donors (Table 1)(13). Donor laboratory studies were guided by those suggested by Bakken et al (14) and included hepatitis A virus immunoglobulin (IgG and IgM), hepatitis B virus serum antigen and antibody and core antibody, hepatitis C virus IgG, human immunodeficiency virus 1 and human immunodeficiency virus 2 IgG, rapid plasma reagin, Epstein-Barr virus, and cytomegalovirus IgG and IgM, as well as stool testing for C difficile, bacterial culture, and ova and parasites. Donors were not allowed to have had antibiotics within 3 months before FMT. Directed stool donors were instructed to avoid foods to which the recipient may be allergic for 5 days before the procedure. In addition, all of the donors were instructed to notify the study investigators of any symptoms of infection, such as fevers, diarrhea, or vomiting, occurring between screening and time of donation.

Fecal Microbiota Transplantation

Recipients received premedication before FMT, including vancomycin/fidaxomicin, for at least 7 days before transplant, with the last dose given 24 hours before the procedure. Recipients also received 8.5 to 17 g of polyethylene glycol in 8 oz of water 3 times per day for 2 days before FMT, and omeprazole (1 mg/kg orally) on the day before and morning of procedure. For the FMT, an NG tube was placed and its location confirmed by x-ray. Alternatively, a nasoduodenal or nasojejunal tube was placed in patients with a baseline high risk of emesis; if patients already had a nasoduodenal or nasojejunal tube in place for feeding, that tube was used to administer the FMT. Approximately 30 g of donor stool was mixed with 100 mL of normal saline and blenderized until a homogenous texture was achieved. The stool suspension was then filtered using 4 × 4 gauze. Infusion of 30 to 60 mL was slowly administered via NG tube for a 3-minute period. The tube was flushed with 15 mL of normal saline for 1 minute. After 15 minutes, the tube was removed. Subjects were discharged home after 30 minutes of observation.

Posttransplantation Follow-Up

Study subject recipients were called 2 days after transplantation. Patients from Washington State followed up in the gastroenterology clinic after FMT; patients from out of state had follow-up by telephone to collect possible adverse events, including fever, abdominal pain, abdominal distension, nausea, vomiting, and flatulence, and those that could have been the result of the NG or nasojejunal tube placement, including epistaxis and sore throat.

Statistical Methods

We report standard descriptive statistics, such as mean, median, range, and interquartile range (IQR) as appropriate. STATA 12.1 (StataCorp, College Station, TX) was used for all analyses.

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TABLE 2. Demographic and clinical information for 10 pediatric patients treated for recurrent *Clostridium difficile* with FMT

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at 1st <em>C difficile</em> infection, y</th>
<th>Age at FMT, y</th>
<th>Sex</th>
<th>Comorbid condition</th>
<th>No. <em>C difficile</em> infections before FMT</th>
<th>Antimicrobial agents used to treat <em>C difficile</em> before FMT</th>
<th>Antimicrobial agents used before <em>C difficile</em> infections</th>
<th>Immunosuppressive medications</th>
<th>FMT route</th>
<th>Outcome</th>
<th>Adverse events</th>
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<tr>
<td>1</td>
<td>6.2</td>
<td>6.5</td>
<td>F</td>
<td>IBD</td>
<td>3</td>
<td>Vm, Mtz</td>
<td>Mtz</td>
<td>AZA at the time of FMT</td>
<td>NG</td>
<td>Resolution</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>0.8</td>
<td>1.7</td>
<td>M</td>
<td>CP</td>
<td>5</td>
<td>Vm, Mtz, VmT</td>
<td>Amc</td>
<td>None</td>
<td>NG</td>
<td>Resolution</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>10.7</td>
<td>11.4</td>
<td>M</td>
<td>IBD</td>
<td>3</td>
<td>Vm, Mtz, VmT</td>
<td>None</td>
<td>Aza, MTX, Ada at the time of FMT</td>
<td>NG</td>
<td>Resolution</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>3.7</td>
<td>4.4</td>
<td>F</td>
<td>Wilms tumor</td>
<td>3</td>
<td>Vm, Mtz, VmT</td>
<td>Amp, Amc, Cfd</td>
<td>Chemotherapy 11 mo before FMT</td>
<td>NJ</td>
<td>Failure</td>
<td>2nd FMT performed</td>
</tr>
<tr>
<td>5</td>
<td>0.3</td>
<td>1.8</td>
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<td>None</td>
<td>4</td>
<td>Vm, Mtz, VmT</td>
<td>Amox</td>
<td>None</td>
<td>NJ</td>
<td>Resolution</td>
<td>Immediate post-FMT vomiting; mucoid stools for 2 days</td>
</tr>
<tr>
<td>6</td>
<td>2.4</td>
<td>2.7</td>
<td>F</td>
<td>None</td>
<td>4</td>
<td>Mtz, VmT</td>
<td>None</td>
<td>None</td>
<td>ND</td>
<td>Resolution</td>
<td>None</td>
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<tr>
<td>7</td>
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<td>13.6</td>
<td>M</td>
<td>IBD</td>
<td>3</td>
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<td>Aza, MTX at the time of FMT</td>
<td>NG</td>
<td>Resolution</td>
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<tr>
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<td>3.1</td>
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<td>Vm, Mtz</td>
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<td>NG</td>
<td>Resolution</td>
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<tr>
<td>9</td>
<td>8.2</td>
<td>9.2</td>
<td>F</td>
<td>None</td>
<td>3</td>
<td>Mtz, VmT</td>
<td>Cfx, Pen</td>
<td>None</td>
<td>NG</td>
<td>Resolution</td>
<td>None</td>
</tr>
<tr>
<td>10</td>
<td>9.6</td>
<td>10.6</td>
<td>F</td>
<td>None</td>
<td>4</td>
<td>Mtz, VmT</td>
<td>Amox</td>
<td>None</td>
<td>NG</td>
<td>Resolution</td>
<td>None</td>
</tr>
</tbody>
</table>

ADA = adalimumab; Amc = amoxicillin/clavulanate; Amox = amoxicillin; Amp = ampicillin; Aza = azathioprine; Cfd = cefdinir; Cfx = cefuroxime; CP = cerebral palsy; IBD = inflammatory bowel disease; INN = infliximab; MTX = methotrexate; Mtz = metronidazole; NEC = necrotizing enterocolitis; Pen = penicillin; Vm = vancomycin; VmT = vancomycin taper.
RESULTS

During the study period, 10 patients underwent FMT for recurrent *C. difficile* infection; donors included 9 parents (90%) and 1 sibling (10%). The median duration of follow-up after FMT was 44 days (IQR 21–172; range 13–700). Follow-up consisted of a combination of clinic visits, follow-up telephone calls, and repeat *C. difficile* testing.

Among these 10 patients, the median age was 5.4 years (IQR 2.7–10.6 years; Table 2) and 60% were girls. All of the subjects had 3 or more recurrences of *C. difficile* before FMT, and 40% of the patients had received immunosuppressive medications (30% with present receipt). The median duration between the identification of the first *C. difficile* infection and performing the FMT was 250 days (IQR 190–364; range 90–541).

Overall, the FMT was well tolerated. Patient 5 experienced vomiting in the outpatient clinic directly following the procedure but this resolved quickly. This patient had a nasojejunal tube placed for the FMT because of history of vomiting when upset, gastroesophageal reflex, and a strong gag reflex. In addition, this patient experienced mucoid stools for 2 days following the procedure. Otherwise, no additional adverse events were noted.

All of the patients developed initial resolution of symptoms, and 9 (90%) of the patients remained asymptomatic during follow-up. Patient 4 developed diarrhea 2 months after FMT and tested positive for *C. difficile*. The patient had received a course of cephalexin 6 days before this recurrence. The patient was treated with oral vancomycin and underwent a second FMT via nasojejunal tube 3 months after this *C. difficile* recurrence (5 months after initial FMT). Data from the patient’s second FMT are not shown. The patient again experienced recurrent *C. difficile* infection 3 months after the second FMT.

DISCUSSION

The results of this retrospective study of FMT via NG tube showed it to be safe and well tolerated in pediatric recurrent *C. difficile* colitis. Our experience with FMT for recurrent *C. difficile* infection mirrors the adult experience: FMT was safe and effective in curing recurrent *C. difficile* infection in 90% of our subjects, a rate similar to that seen among adult study subjects who received FMT via the gastric or jejunal route. Questions regarding FMT remain, such as the long-term safety of using adult microbiota for pediatric FMT, and whether pre-FMT preparation with antibiotics and laxatives has an independent effect on either *C. difficile* infection or FMT efficacy. Future studies will help elucidate both whether universal donors and frozen donated stool can streamline the FMT process by removing the necessity for donor screening for each new patient, and whether microbiota replacement can be accomplished using an oral pill, the FMT delivery method most preferred by patients in a recent attitude survey (15).

REFERENCES