Safety of fecal microbiota transplantation in Chinese children: A single-center retrospective study

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Abstract

BACKGROUND
Fecal microbiota transplantation (FMT) is the administration of fecal bacterial liquid from healthy donors to a recipient’s digestive tract, which is recommended as a therapeutic method for recurrent Clostridium difficile infection (CDI). Many clinical trials focusing on different diseases are in progress. To date, scarce research and long-term follow-up have been conducted on FMT in children or on the proper guidelines. Our center first performed FMT to treat a 13-month-old boy with severe CDI in 2013. Until February 2018, our center had performed 114 pediatric FMT procedures in 49 subjects.

AIM
To investigate the safety of FMT in children.

METHODS
A retrospective study was conducted on 49 patients...
who underwent 114 FMT treatments at our hospital. All FMT processes followed uniform standards. Adverse events (AEs) related to FMT were divided into short-term (48 h post-FMT) and long-term (3 mo). All potential influencing factors for AEs, such as gender, age, time of FMT infusion, route of administration, disease type, immune function state, and donor relative genetic background, were analyzed as independent factors. The significant independent factors and risk ratio with 95% confidence interval (CI) were assessed by multivariate logistic regression analysis.

RESULTS
Forty-nine patients (mean age 68.1 mo, range 4 to 193 mo) were recruited. Their average follow-up time after the first FMT was 23.1 mo. The incidence of short-term AEs was 26.32% (30/114). The most common short-term AEs were abdominal pain, diarrhea, fever, and vomiting, which were all self-limited and symptom-free within 48 h. Two severe AEs occurred, and one patient died in the fourth week after FMT. All-cause mortality was 2.04%. As independent factors, age (P = 0.006) and immune state (P = 0.002) had significant effects. Age greater than 72 mo seemed to be correlated with more AEs than age 13 to 36 mo (P = 0.04). In multivariate logistic regression analysis, immune state was an independent risk factor for AE occurrence (P = 0.035), and the risk ratio in immunodeficient patients was 3.105 (95% CI: 1.080-8.923).

CONCLUSION
Although FMT was proven to be tolerated in children, we need to be more cautious with immunodeficient patients. The effect on children’s long-term health is unpredictable.

Key words: Safety; Fecal microbiota transplantation; Pediatrics; Adverse event; Immune system diseases; Age factors

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Core tip: A retrospective study was conducted on 49 patients who underwent 114 fecal microbiota transplantation (FMT) treatments at our hospital. The safety of FMT was evaluated by short-term, long-term, and severe adverse events (AEs). The incidence of short-term AEs was 26.32% (30/114). The most common short-term AEs were abdominal pain, diarrhea, fever, and vomiting. Age and immune state had significant effects, and immune state was an independent risk factor for AEs occurrence. The risk ratio in immunodeficient patients was 3.105. Pediatricians need to be more cautious when FMT is applied to immunodeficient patients.

INTRODUCTION
Fecal microbiota transplantation (FMT) is the administration of fecal bacterial liquid from healthy donors to a recipient’s digestive tract. FMT can quickly adjust, restore, and rebalance the recipient’s intestinal microbiota, repair the intestinal mucosal barrier, settle the inflammatory response, and regulate the immune system[1,2]. FMT is recommended as a therapeutic method for recurrent *Clostridium difficile* (*C. difficile*) infection (CDI) by various guidelines[3,4]. There is also much clinical research focusing on FMT to treat different diseases, such as inflammatory bowel disease, constipation, irritable bowel syndrome, autism, allergy, and metabolic syndrome[1,5,6].

To date, scarce research has been conducted on FMT in children or on the proper guidelines. As safety is uncertain and there is a lack of long-term follow-up data, the pediatricians’ attitude has been relatively conservative. The safety of FMT has been confirmed in adults[7-9]. A clinical trial for 7- to 21-year-old children and young adults with ulcerative colitis (UC) showed that FMT was well tolerated and safe[10].

Our center first performed FMT to treat a 13-month-old boy with severe CDI in 2013[11]. Until February 2018, our center had performed 114 pediatric FMT procedures in 49 subjects. We here retrospectively evaluated the safety of these procedures and analyzed the adverse events (AEs).

MATERIALS AND METHODS
Study population
Forty-nine pediatric patients who underwent FMT at Shanghai Children’s Hospital from November 2013 to February 2018 were recruited into our retrospective analysis. These patients included children with the diagnosis of recurrent CDI (with or without inflammatory bowel disease), chronic intractable diarrhea, functional gastrointestinal disorder, metabolic syndrome, non-alcoholic steatohepatitis, severe eczema, systemic juvenile rheumatoid arthritis (sJIA), hemophagocytic lymphohistiocytosis with Epstein-Barr virus (EBV) infection, and Okuda syndrome with severe constipation (Table 1). Written informed consent was obtained from parents or legal guardians of all pediatric subjects. This study was approved by the Regional Ethical Review Board in Shanghai Children’s Hospital (2014RY015-E02).

Criteria for choice of donors
Donors aged between 18 to 50 without smoking, alcohol, or other bad habits or digestive symptoms were
provided from rigorously screened healthy donors from a universal stool bank (OpenBiome). Eligible donors underwent serological testing for HIV type 1 and 2 antibody (Ab), hepatitis A total Ab, hepatitis B surface antigen (Ag), hepatitis B surface Ab, hepatitis B core Ab (IgM and IgG), hepatitis C Ab, syphilis Ab, CMV IgM, EBV-DNA, human parvovirus B19 IgM, TORCH, T-SPOT, hepatic and renal function, routine blood parameters, and lymphatic subgroup analysis. The participants also underwent stool testing with bacterial culture for enteric pathogens (Escherichia coli 0157, Salmonella, Shigella, Yersinia, Campylobacter, Staphylococcus aureus, Vibrio parahaemolyticus, and Vibrio cholerae), parasitic ovum and parasites; *C. difficile* toxin A/B; fecal Giardia, Cryptosporidium, and Helicobacter pylori antigens; and Norovirus and Rotavirus through enzyme immunoassays. The 16S RNA bacterial sequence was tested if necessary. Other tests included abdominal ultrasound scan and C13 breath test.

**Bacterial liquid preparation**

Fresh stool from each donor was collected and blended using 200-250 mL sterilized saline per 150 g stool at high speed for 2-3 min. The stool suspension was filtered with two layers of medical gauze to remove large particles. Stool filtrate was drawn into 50 mL syringes for immediate FMT use or collected in 50 mL tubes and frozen at -80 °C for further use.

**FMT procedure**

The bacterial liquid was resuscitated and transferred into the patients’ digestive tract. The route of administration varied and included nasojejunal tube, nasogastric tube, and enema. The time of FMT infusion was divided into single infusion (1 d) or multiple infusions (2-3 d continuously). Five millilitres of bacterial liquid per kilogram weight of the patient was used. The dose was adjusted by the age or weight of patients, and when the patient’s weight was more than 50 kg, the dose for adults was used. The patients fasted for at least 4 h before FMT, and infusion was slowly administered through a tube. After the infusion procedure, patients were asked to keep the same position (>30° semireclining position or hip-up position) for at least 2 h.

**Safety evaluation**

AEs were evaluated and assessed according to clinical manifestation, laboratory tests, and follow-up period. All AEs were divided into short-term (48 h post-FMT) and long-term (3 mo). The short-term AEs were defined as any untoward medical occurrence that did not exist before FMT or syndrome deterioration in a patient to whom FMT was administered. Short-term AEs could be clinically significant changes from baseline physical examination, laboratory tests, or other diagnostic investigations, complications related to the procedure used to administer FMT, or new events.
or pre-existing conditions that became aggravated or worsened in severity or frequency within 48 h post-FMT. The potential long-term AEs under our supervision included infection due to unrecognized infectious agents, chronic diseases based on gut microbiota alteration, restriction of growth, and changes in behavior. The intensity and severity of AEs with FMT followed the Common Terminology Criteria for Adverse Events (version 3.0), in which severe AEs (SAEs) were any adverse experience occurring during or after FMT beyond mild or moderate AEs. AEs and SAEs were determined to be related or unrelated [7].

Data analysis
IBM SPSS Statistics 20 was used for statistical analyses. The independent factors were analyzed by the Pearson/Fisher χ² test or rank sum test, while the between-group variance was determined by the Tukey’s HSD test. Values of P < 0.05 were considered statistically significant. The significant independent factors and risk ratio with 95% confidence interval (CI) were assessed by multivariate logistic regression analysis.

RESULTS
Patient and donor characteristics
The characteristics of all patients and donors are listed in Table 1. Twenty-seven male and 22 female subjects, with a mean age 68.1 mo (range 4 to 193 mo) were enrolled in this cohort. Their average follow-up time after the first FMT was 23.1 mo. The 49 subjects were divided into two major groups (gastrointestinal disorders and nongastrointestinal disorders). Fifteen patients were diagnosed as being immunodeficient (6 primary immunodeficiency and 9 inflammatory bowel disease (IBD) patients with immunosuppressive agent treatment) after FMT. Twenty patients accepted FMT once, while 29 patients had 2-11 rounds of FMT. There were 30 donors (11 of them were male), whose mean age was 32.8 years old, including 14 patients’ family members (12 of them were parents and 2 of them were sisters) and 16 volunteers.

AEs
All short-term AEs were self-limited and symptom-free within 48 h. In total, 38.78% (19/49) of patients had AEs after FMT. Six of them had multiple AEs (2-4), and 10 of 15 immunodeficient patients had AEs. The number of AEs by different category is listed in Table 2. The total incidence of short-term AEs was 26.32% (30/114) (Table 3). The most common AEs were abdominal pain (8/114, 7.02%), diarrhea (7/114, 6.14%), fever (6/114, 5.26%), and vomiting (6/114, 5.26%). The incidence of upper gastrointestinal symptoms such as nausea, sore throat, and vomiting was 7.89% (9/114). Lower gastrointestinal symptoms such as diarrhea, abdominal pain, and mucoid stool were observed in 14.04% (16/114). Other manifestations, such as fever, appetite decrease, and chest distress, occurred in 7.02% (8/114). In all nasogastric tube ways, 80% (4/5) of AEs were vomiting and the other AEs were appetite decrease with abdominal pain. After enema, 66.7% (4/6) of AEs were the changes of stool (3 diarrhea and 1 mucoid stool), which might indicate that the different gastrointestinal symptoms were related to different routes of administration. Out of all FMT treatments,
severe AEs occurred in two cases. One UC case (PUCAI = 45) had 60 mL of blood stool 6 h post-FMT. Another UC case (PUCAI = 55) developed gastric stricture accompanied by nausea and hematemesis (30 mL) 4 h after FMT.

No relevant long-term AEs happened during 3-mo follow-up. One primary immunodeficiency patient was treated by FMT for chronic intractable diarrhea. The patient died due to sepsis and liver failure 4 wk after FMT. All-cause mortality was 2.04%.

Comparing either each individual or every FMT, the AE occurrence had no significant difference ($\chi^2$ test, $P = 0.252$, data not shown). Ten of 15 immunodeficient patients showed AEs, compared with 9 of 34 patients with normal immune function, which indicated that immunodeficient patients might have greater risk than others ($\chi^2$ test, $P = 0.008$, data not shown). All potential factors influencing AEs, such as gender, age, time of FMT infusion, route of administration, disease type, immune function state, and donor relative genetic background, were investigated through the $\chi^2$ test.

As independent factors, only age (rank sum test, $P = 0.006$, data not shown) and immune state ($\chi^2$ test, $P = 0.002$) had significant effects on AE occurrence (Table 4). Therefore, we divided the patients into different age groups to determine how age affected AEs. The data showed that four age groups had a difference in AE rate ($\chi^2$ test, $P = 0.02$), and age more than 72 mo was associated with more AEs than age 13 to 36 mo (Tukey’s HSD test between different groups, $P = 0.04$, data not shown). The reason why they had different AE rates might be the bias that older children could give a more accurate description of uncomfortable symptoms. Furthermore, we analyzed age groups and immune states by multivariate logistics regression analysis (Table 3). The results showed that immune state was an independent risk factor for AE occurrence ($P = 0.035$), and the risk ratio in immunodeficient patients was 3.105 (95%CI: 1.080-8.923).

### DISCUSSION

This retrospective analysis investigated the safety of FMT in children. We focused on the AEs in the short term and long term in FMT patients from November 2013 to February 2018 at our hospital. The results showed that only a few patients had (transient, self-limited) AEs. During the long-term follow-up, few AEs occurred.

According to our data, the immunodeficient patients had more AEs than others, so we need to be more cautious when administering FMT to immunodeficient patients. Most AEs were short-lived, self-limited, and manageable. The AEs might have occurred because their condition was more serious. Available research suggests that FMT is safe in different populations, such as immune deficiency, acute graft-versus-host disease, stem cell transplantation, and cancer patients[18-23]. Six of our patients who received FMT treatment were finally diagnosed with primary immunodeficiency. All of them were suffering severe, chronic, intractable diarrhea beyond antibiotic control with or without CDI. A definitive diagnosis had not been made before the FMT. The use of FMT aimed to improve their clinical manifestation by balancing the intestinal microbiota. Two of them accepted hematopoietic stem cell transplantation and were cured[24]. Four of them died for reasons unrelated to FMT. One was represented in the previous section. The other three died because of failure to survive with severe diarrhea and septic pyemic shock. Nine IBD patients with immunosuppressive agent treatment, such as glucocorticoid and infliximab, were diagnosed with CDI during the course of their disease. They suffered from diarrhea with mucoid blood stool with or without fever, so FMT was done to treat the CDI and repair the intestinal mucosal barrier. Two severe AEs occurred in active UC patients who had 60 mL of blood stool and 30 mL of hematemesis, respectively, and others tolerated the FMT well. Blood

| Table 4 Potential factors influencing fecal microbiota transplantation adverse event occurrence |
|----------------|----------------|--------|--------|
| **Item**       | **Sub-item**   | **$\chi^2$** | **$P$-value** | **Wald test** | **$P$-value** |
| Gender         | Male           | 0.456  | 0.499 |
|                | Female         |        |        |
| Age group (m)  | 0-12           | 9.583  | 0.02   | 4.413       | 0.22 |
|                | 13-36          |        |        |
|                | 37-72          |        |        |
|                | 73             |        |        |
| Number of fecal microbiota transplantation infusions | Single | 0.006 | 0.936 |
| Route of administration | Nasogastric tube | 2.988 | 0.224 |
|                | Nasal jejunal tube |        |        |
|                | Enema          |        |        |
| Disease type   | Gastrointestinal disorder | 2.182 | 0.14 |
|                | Nongastrointestinal disorder |        |        |
| Immune state   | Immune deficiency | 9.801 | 0.002 | 4.425 | 0.035 |
|                | Normal immune function |        |        |
| Donor genetic background | Relative | 1.119 | 0.29 |
|                | Nonrelative    |        |        |
stool might have been related to the operation process, and hematemesis should be taken as an injury to the gastrointestinal mucosa during the process of inputting the jejunal tube. In the literature, there have been five patients with fatal AEs related to FMT, which were caused by toxic megacolon with sepsis, peritonitis, two cases of fatal aspiration pneumonia, and anesthesia death under colonoscopy\(^{18,25-28}\). Our patients did not have fatal AEs. Both of our severe AE patients were stable, and no more AEs appeared during the next clinical observation.

The effect of FMT on children’s intestinal microbiota and long-term health is still unpredictable due to the microbial liquid from adults. It has been more than 3 years after the first FMT case. Throughout the follow-up, there have been no relevant AEs or special changes in growth or behavior. Another patient died outside of the 3-mo post-FMT period, but this was not considered an SAE. The patient was diagnosed with chronic active EBV infection and died more than 6 mo after FMT due to this infection.

We first performed FMT to treat a 13-mo-old boy with severe CDI in 2013\(^{11}\). The data from our group show that although the general age of the patients was young, they tolerated the FMT treatment with good safety outcomes. The use of FMT in immunodeficient patient needs to be more cautious. The complete FMT follow-up pediatric cohort was set up for further study of FMT in children. There were also some limitations to our study. Our retrospective study lacked the advantage of a randomized control trial. The bias of AEs by subjective description was inevitable. The number of cases was limited; thus, bias also existed.

**ARTICLE HIGHLIGHTS**

**Research background**

Fecal microbiota transplantation (FMT) is the administration of fecal bacterial liquid from healthy donors to a recipient’s digestive tract, which is recommended as a therapeutic method for recurrent Clostridium difficile infection (CDI). Many clinical trials focusing on different diseases are in progress. To date, scarce research and long-term follow-up data have been conducted on FMT in children or on the proper guidelines. Our center first performed FMT to treat a 13-month-old boy with severe CDI in 2013. Until February 2018, our center had performed 114 pediatric FMT procedures in 49 subjects. We here retrospectively evaluated the safety of these procedures and analyzed the adverse events (AEs).

**Research motivation**

To investigate the safety of FMT in children.

**Research objectives**

To evaluate the adverse events occurring during and after the procedure of FMT.

**Research methods**

Forty-nine patients at Shanghai Children’s Hospital from November 2013 to February 2018 were recruited into our retrospective analysis. All FMT processes followed uniform standards. AEs related to FMT were divided into short-term (48 h post-FMT) and long-term (3 mo). All potential factors influencing AEs, such as gender, age, time of FMT infusion, route of administration, disease type, immune function state, and donor relative genetic background, were analyzed as independent factors. The significant independent factors and risk ratio with 95% confidence interval (CI) were assessed by multivariate logistic regression analysis.

**Research results**

Forty-nine patients (mean age 68.1 mo, range 4 to 193) were recruited. Their average follow-up time after the first FMT was 23.1 mo. The incidence of short-term AEs was 26.32% (30/114). The most common short-term AEs were abdominal pain, diarrhea, fever, and vomiting, which were all self-limited and symptom-free within 48 h. Two severe AEs occurred, and one patient died in the fourth week after FMT. All-cause mortality was 2.04%. As independent factors, age (P = 0.006) and immune state (P = 0.002) had significant effects. Age greater than 72 mo seemed to be correlated with more AEs than age 13 to 36 mo (P = 0.04). In multivariate logistic regression analysis, immune state was an independent risk factor for AE occurrence (P = 0.035), and the risk ratio in immunodeficient patients was 3.105 (95% CI: 1.080-8.923).

**Research conclusions**

FMT was proven to be tolerable and safe in children. However, we need to be more cautious with immunodeficient patients. The effect on children’s long-term health is unpredictable.

**Research perspectives**

FMT was well tolerated and safe in children, while more data for immunodeficient pediatric patients are required.

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