Fecal microbiota transplantation induces remission of infantile allergic colitis through gut microbiota re-establishment

Liu, Sheng-Xuan; Li, Yin-Hu; Dai, Wen-Kui; Li, Xue-Song; Qiu, Chuang-Zhao; Ruan, Meng-Ling; Zou, Biao; Dong, Chen; Liu, Yan-Hong; He, Jia-Yi; Huang, Zhi-Hua; Shu, Sai-Nan

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Fecal microbiota transplantation induces remission of infantile allergic colitis through gut microbiota re-establishment

Sheng-Xuan Liu, Yin-Hu Li, Wen-Kui Dai, Xue-Song Li, Chuang-Zhao Qiu, Meng-Ling Ruan, Biao Zou, Chen Dong, Yan-Hong Liu, Jia-Yi He, Zhi-Hua Huang, Sai-Nan Shu

Author contributions: Liu SX and Li YH contributed equally to this work; Shu SN and Huang ZH designed the research; Dai WK designed the follow-up plans and collected patients’ information with Li XS, Ruan ML, Zou B and Dong C after FMT; Qiu CZ, Liu YH and He JY performed bioinformatics analysis; Ruan ML and Zou B recorded patients’ and donors’ clinical data; Shu SN and Huang ZH conducted FMT.

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Abstract

AIM
To investigate the impact of fecal microbiota trans-
plantedation (FMT) treatment on allergic colitis (AC) and gut microbiota (GM).

METHODS
We selected a total of 19 AC infants, who suffered from severe diarrhea/hematochezia, did not relieve completely after routine therapy or cannot adhere to the therapy, and were free from organ congenital malformations and other contraindications for FMT. Qualified donor-derived stools were collected and injected to the AC infants via a rectal tube. Clinical outcomes and follow-up observations were noted. Stools were collected from ten AC infants before and after FMT, and GM composition was assessed for infants and donors using 16S rDNA sequencing analysis.

RESULTS
After FMT treatment, AC symptoms in 17 infants were relieved within 2 d, and no relapse was observed in the next 15 mo. Clinical improvement was also detected in the other two AC infants who were lost to follow-up. During follow-up, one AC infant suffered from mild eczema and recovered shortly after hormone therapy. Based on the 16S rDNA analysis in ten AC infants, most of them (n = 6) had greater GM diversity after FMT. As a result, Proteobacteria decreased (n = 6) and Firmicutes increased (n = 10) in post-FMT AC infants. Moreover, Firmicutes accounted for the greatest proportion of GM in the patients. At the genus level, Bacteroides (n = 6), Escherichia (n = 8), and Lactobacillus (n = 4) were enriched in some AC infants after FMT treatment, but the relative abundances of Clostridium (n = 5), Veillonella (n = 7), Streptococcus (n = 6), and Klebsiella (n = 8) decreased dramatically.

CONCLUSION
FMT is a safe and effective method for treating pediatric patients with AC and restoring GM balance.

Key words: Pediatric; Infantile allergic colitis; Fecal microbiota transplantation; Gut microbiota; Immune reaction

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Core tip: This retrospective study explored the therapeutic effects and safety of fecal microbiota transplantation (FMT) treatment in 19 allergic colitis (AC) infants who were younger than 1 year old. After FMT treatment, AC symptoms were relieved in the patients rapidly, and no patient relapsed within 15 mo. With gut microbiota (GM) analysis, six of ten patients exhibited higher microbial diversity after FMT treatment. Moreover, decreased Proteobacteria and increased Firmicutes supplied the hints of GM re-establishment in the patients after FMT treatment. Therefore, this work showed the curative effects of FMT in AC infants and its possible mechanism.
Patient selection

AC was diagnosed based on the following clinical symptoms: (1) rectal bleeding with/without mucus and diarrhea; (2) exclusion of infectious colitis, anal fissure, lymphoid nodular hyperplasia, and uncommon conditions such as necrotizing enterocolitis, Hirschsprung’s enterocolitis, IBD\(^{[15]}\), and IBS\(^{[16]}\); (3) clinical remission after milk exclusion and recurrence after milk re-challenge\(^{[3,17]}\); and (4) histological examination indicated that the intestinal mucosa exhibited chronic inflammation with eosinophils infiltration and colonic lesions (Supplementary File 1). Pediatric AC patients meeting the following criteria were selected as FMT candidates: (1) the patients had no complete remission after routine therapy, the patients cannot adhere to the therapy thoroughly, or their parents had strong intention to receive the treatment of FMT; (2) free from contraindications for FMT, such as intestinal obstructions, perforations, and bleeding, or severe immunodeficiency diseases; and (3) colonoscopic inspection indicated no mucosal congestion, edema, multiple spot-like erosion, or lymphoid granular nodes (four cases included in Figure 1). As a result, 19 AC patients were enrolled in the study between September 2015 and December 2015 (Table 1).

Donor screening

Patients’ mothers were considered to be donors of the highest priority, followed by fathers and healthy peers. Adult donors were screened as follows\(^{[18-20]}\): (1) no infectious diseases history (e.g., tuberculosis and hepatopathy); (2) no metabolic diseases history (e.g., obesity and diabetes); (3) no gastrointestinal diseases (e.g., diarrhea, constipation, IBD, IBS, colorectal polyps, and gastrointestinal tumors); (4) no allergic diseases (e.g., food allergy, eczema, and allergic gastroenteritis); (5) no antibiotic exposure in the last 3 months; (6) no mental disorders or autoimmune diseases; and (7) no drug abuse history, amenorrhea (for mother donors), or psychological imbalance.

Candidate donors of the same age were selected with the following criteria\(^{[18-20]}\): (1) preferred relatives with breast milk fed and same gender; (2) no antibiotic treatment in the last 3 months; (3) no allergic disease (e.g., food allergy, eczema, and allergic gastroenteritis); (4) no gastrointestinal disease (e.g., diarrhea, constipation, IBD, IBS, colorectal polyps, and gastrointestinal tumors); (5) no metabolic disease history (e.g., obesity and diabetes); and (6) no infectious disease history (e.g., tuberculosis, hepatopathy, and measles), and normal health and development. Tests for serum biochemistry and stool were performed for donors to ensure subject safety (Table 2).

FMT procedure

The application of parenteral nutrition and probiotics was stopped as soon as FMT began in the patients. No bowel preparation (cleanout or antibiotic pretreatment) was used prior to FMT, but pre-FMT clinical tests were performed as described in Table 3. Donor stool, collected 2 h before FMT, was diluted and mixed with sterile saline (1 mg of stool was diluted with 3 mL of saline). Samples were filtered through sterile gauze and 30-50 mL fecal suspension was prepared for FMT. FMT was administered over 5-10 min via a rectal tube into the left colon. The rectal tube was removed 15 min after administration and the fecal suspension was retained in the recipients’ gut for 4-6 h. Multi-FMT was given for patients with severe symptoms (Table 1).

Follow-up

Clinical symptoms, stool frequency, symptom remission time, and adverse events (e.g., abdominal pain, gastrointestinal infection, constipation, fever, and allergic disease) were recorded at the end of FMT (Table 1). Follow-up was conducted at $\geq 15$ mo after FMT, except for two cases with 0.3 and 0.5 mo follow-up (AC17 and AC19), to evaluate FMT efficacy and safety (Table 1). The remission of AC was defined as the cease of rectal bleeding and decreased stool frequency (no more than two times/d) in the patients. The primary endpoint was the improved AC symptoms and sustained clinical remission at 12 mo. Secondary endpoint was the safety of FMT which was implied by the occurrence of adverse events.

Microbiota analysis and statistics

Fecal microbiota was analyzed for ten patients before FMT and during follow-ups. Donor feces were also assayed for GM. Microbial DNA was extracted using a PowerSoil DNA Isolation Kit (Mo Bio Laboratories, Carlsbad, CA) according to the manufacturer’s protocol and the hyper-variable V3-V4 region was amplified using 338F (5’-ACTCCTACGGGAGGCAGCAG-3’) and 806R (5’-GGACTACHVGGGTWTCTAAT-3’) primers. Library construction and sequencing were conducted on an Illumina MiSeq platform (Illumina, San Diego, United States). Data filtration and sequencing were performed as a prior report with the RDP database as an annotation reference\(^{[21]}\). A Wilcoxon signed-rank test was used to compare samples of one patient, which were collected at different time points, and a Wilcoxon rank-sum test was used to compare donor and patient samples. Graphs were produced with R.
patients, and decreased defecation frequency with improved stool consistency was also observed (Table 1). Within more than 15 mo of follow-up, the symptoms of AC had not relapsed except two patients who were lost to follow-up (AC17 and AC19). Only one patient suffered from eczema, which appeared 2 mo after FMT and was resolved with hormone therapy. Beyond this, no other adverse event was recorded during FMT or the follow-up.

**FMT treatment associated microbiota changes**

Figures 2 and 3 depict microbiota changes of ten patients before and after FMT compared to donors. Microbiota diversity increased dramatically in five patients while it decreased in three patients after FMT (Figure 2). When sampled 1 or 2 mon after FMT, microbiota of six patients was more similar to donors’ microflora by comparison with pre-FMT samples (Figure 3).

After FMT treatment, Firmicutes accounted for the greatest proportion of GM in the AC infants, followed...
<table>
<thead>
<tr>
<th>ID</th>
<th>Gender</th>
<th>Age (mo)</th>
<th>Symptom(s)</th>
<th>Duration of disease (mo)</th>
<th>Treatment(s) before FMT</th>
<th>Donor source</th>
<th>FMT times</th>
<th>Symptom remission after first FMT (d)</th>
<th>Stool frequency before and after FMT (times/d)</th>
<th>Follow-up (mo)</th>
<th>Availability of gut microbiota data</th>
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<tr>
<td>AC1</td>
<td>Female</td>
<td>7</td>
<td>Diarrhea, hematochezia sometimes; anemia, hypoproteinemia</td>
<td>&gt; 3</td>
<td>Applying amino acid formula and probiotics (C. butyricum)</td>
<td>Mother</td>
<td>2</td>
<td>1</td>
<td>3-4, 1</td>
<td>19</td>
<td>Yes</td>
</tr>
<tr>
<td>AC2</td>
<td>Male</td>
<td>10</td>
<td>Hematochezia</td>
<td>&gt; 0.5</td>
<td>Applying amino acid formula and probiotics (Bifidobacteria)</td>
<td>Healthy infants aged 10 mo old</td>
<td>2</td>
<td>1</td>
<td>2-3, 1</td>
<td>18</td>
<td>Yes</td>
</tr>
<tr>
<td>AC3</td>
<td>Female</td>
<td>11</td>
<td>Hematochezia</td>
<td>&gt; 3</td>
<td>Applying amino acid formula and probiotics (S. boulardii)</td>
<td>Healthy infants aged 8 mo old</td>
<td>3</td>
<td>1</td>
<td>5-6, 2</td>
<td>19</td>
<td>Yes</td>
</tr>
<tr>
<td>AC4</td>
<td>Male</td>
<td>9</td>
<td>Hematochezia</td>
<td>&gt; 3</td>
<td>Applying amino acid formula and probiotics (S. boulardii)</td>
<td>Mother's cousin sister</td>
<td>3</td>
<td>1</td>
<td>6-7, 1-2</td>
<td>18</td>
<td>Yes</td>
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<tr>
<td>AC5</td>
<td>Male</td>
<td>5</td>
<td>Diarrhea and hematochezia sometimes</td>
<td>&gt; 3</td>
<td>Applying amino acid formula</td>
<td>Healthy infants aged 8 mo old</td>
<td>3</td>
<td>1</td>
<td>3-4, 2</td>
<td>19</td>
<td>Yes</td>
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<tr>
<td>AC6</td>
<td>Male</td>
<td>5</td>
<td>Hematochezia</td>
<td>&gt; 3</td>
<td>Applying amino acid formula and probiotics (C. butyricum)</td>
<td>Mother</td>
<td>1</td>
<td>2</td>
<td>5-6, 1</td>
<td>18</td>
<td>Yes</td>
</tr>
<tr>
<td>AC7</td>
<td>Male</td>
<td>4</td>
<td>Hematochezia and cough sometimes</td>
<td>&gt; 2</td>
<td>Applying amino acid formula and nebulization</td>
<td>Mother</td>
<td>2</td>
<td>2</td>
<td>4-7, 1</td>
<td>15</td>
<td>Yes</td>
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<tr>
<td>AC8</td>
<td>Female</td>
<td>3</td>
<td>Diarrhea and mucoid feces sometimes</td>
<td>&gt; 2</td>
<td>Applying amino acid formula</td>
<td>Mother</td>
<td>2</td>
<td>1</td>
<td>3-4, 1-2</td>
<td>19</td>
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<tr>
<td>AC9</td>
<td>Male</td>
<td>11</td>
<td>Interval hematochezia</td>
<td>&gt; 6</td>
<td>Applying amino acid formula and probiotics (S. boulardii)</td>
<td>Mother</td>
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<td>3-4, 2</td>
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<td>AC10</td>
<td>Female</td>
<td>3</td>
<td>Hematochezia</td>
<td>&gt; 1.5</td>
<td>Applying amino acid formula</td>
<td>Healthy infants aged 10 mo old</td>
<td>4</td>
<td>2</td>
<td>5-6, 1</td>
<td>21</td>
<td>Yes</td>
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<td>AC11</td>
<td>Male</td>
<td>7</td>
<td>Diarrhea</td>
<td>&gt; 2</td>
<td>Applying amino acid formula, probiotics (Bifidobacteria), Simects and Oral Rehydration Salts (ORS)</td>
<td>Healthy infants aged 10 mo old</td>
<td>5</td>
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<td>10</td>
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<td>&gt; 1</td>
<td>Applying amino acid formula and probiotics (Bifidobacteria)</td>
<td>Mother</td>
<td>3</td>
<td>1</td>
<td>5-6, 1-2</td>
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<td>Male</td>
<td>5</td>
<td>Hematochezia and diarrhea sometimes</td>
<td>&gt; 3</td>
<td>Applying amino acid formula</td>
<td>Mother</td>
<td>1</td>
<td>1</td>
<td>3-4, 1</td>
<td>15</td>
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<td>AC14</td>
<td>Female</td>
<td>5</td>
<td>Hematochezia and then peptone shaped feces</td>
<td>&gt; 1</td>
<td>Applying amino acid formula and probiotics (Bifidobacteria)</td>
<td>Mother</td>
<td>1</td>
<td>1</td>
<td>7-8, 2</td>
<td>15</td>
<td>No</td>
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<td>AC15</td>
<td>Male</td>
<td>7</td>
<td>Diarrhea</td>
<td>&gt; 2</td>
<td>Applying amino acid formula, ORS, and probiotics (C. butyricum)</td>
<td>Mother</td>
<td>5</td>
<td>1</td>
<td>5-6, 1</td>
<td>21</td>
<td>No</td>
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<td>AC16</td>
<td>Female</td>
<td>5</td>
<td>Interval hematochezia</td>
<td>&gt; 2</td>
<td>Applying amino acid formula</td>
<td>Healthy infants aged 8 mo old</td>
<td>2</td>
<td>1</td>
<td>4-6, 1</td>
<td>21</td>
<td>No</td>
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<td>AC17</td>
<td>Male</td>
<td>7</td>
<td>Diarrhea and hematochezia sometimes</td>
<td>&gt; 3</td>
<td>Applying amino acid formula, probiotics (Bifidobacteria and C. butyricum)</td>
<td>Healthy infants aged 11 mo old</td>
<td>1</td>
<td>2</td>
<td>3-4, 1-2</td>
<td>0.5</td>
<td>No</td>
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<td>AC18</td>
<td>Female</td>
<td>8</td>
<td>Diarrhea and cough sometimes</td>
<td>&gt; 3</td>
<td>Applying amino acid formula and nebulization</td>
<td>Healthy infants aged 8 mo old</td>
<td>2</td>
<td>1</td>
<td>3-4, 2</td>
<td>17</td>
<td>No</td>
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<tr>
<td>AC19</td>
<td>Male</td>
<td>5</td>
<td>Interval diarrhea</td>
<td>&gt; 4</td>
<td>Applying amino acid formula</td>
<td>Mother</td>
<td>4</td>
<td>1</td>
<td>3-4, 1</td>
<td>0.3</td>
<td>No</td>
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</table>

AC: Allergic colitis; FMT: Fecal microbiota transplantation.
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by Bacteroidetes and Proteobacteria. Proteobacteria decreased dramatically to < 10% for most patients except four patients (Supplementary File 2). Whilst, Firmicutes increased in all patients (Supplementary File 2).

The relative abundance of *Escherichia* significantly increased in eight AC infants (Supplementary File 3). Bacteroides increased in five AC infants including three who had no Bacteroides pre-FMT (Supplementary File 3). For four patients, *Lactobacillus* was enriched after FMT, but for three subjects, it was absent even after FMT. Possible pathogens including *Clostridium* and *Klebsiella* generally decreased after FMT. *Clostridium* and *Klebsiella* decreased in five and eight AC infants respectively (Supplementary File 3). The relative abundance of *Streptococcus* was lowered in six patients. Whilst, *Veillonella* was found decreased in seven patients and its relative abundance was no more than
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8% after FMT. *Bifidobacterium* kept decreased in seven AC infants after FMT, and increased in two cases.

**DISCUSSION**

We chiefly considered the curative effects of FMT therapy in 19 AC infants and microbiota changes during treatment. Stools from both infant and adult donors suggested the same efficacy, and it was noted that all subjects had relieved symptoms of hematochezia and/or diarrhea in 2 d after the first FMT treatment. Due to the longer illness time or sever clinical symptoms, 15 patients experienced multi-FMT for the sustained clinical remission. And the multiple FMT in these patients gave us the idea that artificially modified microbiota for the specified patient might elevate the efficiency of FMT and attenuate transplantation times in the future. After being discharged from hospital, the patients were advised to take hypoallergenic milk powder instead of formula, and most patients had no relapse of colitis within more than 15 mo of follow-up. The recurrence of eczema

![Figure 3](image1.png)  
**Figure 3** Microbiota similarity between allergic colitis infants and their donors. Values in red indicate low microbiota similarity between two samples. Blue represents high microbiota similarity. The microbiota compositions of patients (AC1, AC2, AC4, AC5, AC6, AC7, AC8, and AC10) were more similar to their donors' composition after FMT treatment. One patient (AC9) had more and then less microbiota similarity and AC3 did not change in this regard. AC: Allergic colitis.

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<td>Hepatic and renal function examinations: Glutamic-pyruvic transaminas, glutamic oxalacetic transaminase, total protein, albumin, globulin, prealbumin, total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, gamma glutamyltranspeptidase, total cholesterol, triglycerides, high-density lipoprotein, low density lipoprotein, apolipoprotein A1, apolipoprotein B, lactic dehydrogenase, calcium, corrected calcium, phosphorus, magnesium, urea, creatinine, trioxypurine, bicarbonate radical, total bile acid, 5-nucleotidase, α-L-ducosidase, cholinesterase, cystatin C, lipase, and amylase.</td>
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<td>Food allergen examination (sIgE).</td>
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<td>Lymphocyte subpopulation examination.</td>
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<td>Detection on hepatitis A-IgM.</td>
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<tr>
<td>TORCH examinations: Detections on toxoplasmosis IgG, toxoplasmosis IgM, rubella virus IgG, rubella virus IgM, cytomegalovirus IgG, cytomegalovirus IgM, herpes simplex virus 1/2 IgG, and herpes simplex virus 1/2 IgM.</td>
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<tr>
<td>Detection on parvovirus B19.</td>
</tr>
<tr>
<td>Blood coagulation examinations: Detections on prothrombin time, prothrombin activity, international normalized ratio, fibrinogen, activated partial thromboplastin time, thrombin time, and D-dimer.</td>
</tr>
<tr>
<td>Blood type examination.</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis antibody examination (or the enzyme-linked immuno-spot assay test for tuberculosis).</td>
</tr>
<tr>
<td><strong>Stool testing</strong></td>
</tr>
<tr>
<td>Fecal routine examinations: Detections on fecal color, character, red blood cells, white blood cells, occult blood, parasite eggs, protozoan, fat ball, rotavirus antigen, and fungus.</td>
</tr>
<tr>
<td>Bacterial culture tests: Detections on Vibrio cholera, Salmonella, Shigella, Aeromonas, Plesiomonas, and pathogenic Escherichia coli.</td>
</tr>
<tr>
<td><strong>Other testing</strong></td>
</tr>
<tr>
<td>Enteroscopic examination.</td>
</tr>
<tr>
<td>Abdominal ultrasound scan (intestinal adhesion).</td>
</tr>
<tr>
<td>Electrophysiological examination.</td>
</tr>
</tbody>
</table>

8% after FMT. *Bifidobacterium* kept decreased in seven AC infants after FMT, and increased in two cases.
in one infant might be caused by the inflammatory reactions which were triggered by discontinuous intake of hypoallergenic milk powder.

Fecal microbiota was analyzed in ten patients and their donors. We noted that the microbiota diversity increased in six patients after FMT. For three other subjects, GM diversity decreased after an initial increase while all the patients demonstrated clinical improvement. Individual-specific GM changes suggested the effect of donor’s GM complexity and patient’s gut micro-ecology imbalance. Khoruts et al[10] also suggested that bacteria can be eliminated due to nutrient competition, antimicrobial peptide suppression, and immune-mediated colonization resistance during GM re-establishment.

Proteobacteria, which contain opportunistic pathogens[22], decreased in six AC infants, and their relative abundance was less than 10% after FMT. In contrast, Firmicutes increased in all AC infants. Previous work implied that Firmicutes decreased in patients with Cohn’s disease[23], and the proportion of Firmicutes was negatively associated with gastrointestinal inflammation[24].

After FMT, the relative abundances of Bacteroides and Lactobacillus increased. Prior reports showed that species in Bacteroides could secrete polysaccharide A, which promoted the number of T regulatory (Treg) cells[25,26]. Interleukin (IL)-10 produced by Treg cells also eliminated inflammatory reactions and protected against infectious pathogens[25,26]. Lactobacillus can secrete lactic acid, increase the proportion of Treg cells, and relieve symptoms of AC[8,27]. Generally, the relative abundance of opportunistic pathogens decreased, including Veillonella, Streptococcus, Clostridium, and Klebsiella. Prior reports suggested that the combination of Veillonella and Streptococcus had been found in various GM systems and can augment IL-8, IL-6, and tumor necrosis factor-α (TNF-α) responses, which were associated with inflammatory reactions[28]. Clostridium can cause diarrhea via enterotoxin secretion, and Klebsiella was positively associated with macrophage migration-inhibitory factor (MIF) and affected host immunity[29]. However, GM imbalance and post-FMT improvement need more analysis to understand the mechanisms underlying AC improvements.

This study pioneered the application of FMT in AC treatment and provided important reference to understand microbiota changes before and after FMT. Although the results favor the application of FMT for AC treatment, it is still important to clarify whether AC symptoms can be improved in our future studies with larger sample size. Also, we will explore the microbiota changes at the gene or functional level before and after FMT, to further the understanding of GM imbalance and re-configuration during FMT treatment of infantile AC.

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