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Long-term safety of fecal microbiota transplantation in Chinese children from 2013 to 2023: a single-center retrospective study

Pei Xiao[1†], Youran Li[1†], Xiaolu Li[1], Ting Ge[1], Dan Li[1], Qiao Xu[1], Yangming Ruan[1], Fangfei Xiao[1], Yongmei Xiao[1] and Ting Zhang[1,2*]

Summary

Background The gut microbiome plays a vital role in influencing various health conditions. Fecal Microbiota Transplantation (FMT) has emerged as a rapid, safe, and effective method for modifying the microbiome. However, there is a lack of long-term safety data regarding FMT in children. This study presents the largest single-center analysis of the long-term safety outcomes of FMT in pediatric patients in China, featuring a substantial sample size and an extended follow-up period to thoroughly examine its safety in children.

Methods A retrospective study was conducted on 813 patients who underwent FMT treatments at our hospital from December 2013 to December 2023. All FMT procedures adhered to standardized protocols. The safety of these treatments was retrospectively assessed, focusing on adverse events (AEs) and serious adverse events (SAEs). AEs associated with FMT were categorized as short-term (within 48 h post-FMT) and long-term (within 3 months). Various potential influencing factors for AEs, including sex, age, route of administration, disease type, and consanguineous donor, were examined as independent variables. Significant independent factors and their associated risk ratios with 95% confidence intervals (CI) were determined through multivariate logistic regression analysis. A *p*-value of less than 0.05 was considered statistically significant.

Results A total of 813 patients underwent FMT, with a median age of 93 months (range 4-215) and 68.0% being males. The average follow-up time was 32.3 months (range 1-122). All short-term AEs resolved within 48 h, with an overall occurrence rate of 5.8% (47/813). The most common short-term AEs included vomiting (2.0%), abdominal pain (1.6%), diarrhea (0.9%), fever (0.7%), dysphoria (0.4%), and nausea (0.4%). Multivariable analysis revealed that patients with inflammatory bowel disease (IBD) (OR: 3.98, 95% CI: 1.78–8.92, $P=0.001$) and those who received FMT via capsules (OR: 0.09, 95% CI: 0.03–0.27, $P=0.000$) were independent risk factors for FMT-related AEs. All 813 patients were followed up for at least 1 month, with 78.8% followed for more than 12 months. No long-term AEs occurred during the longest follow-up period of 122 months.

†Pei Xiao and Youran Li have contributed equally to this work.

*Correspondence:
Ting Zhang
zhangt@shchildren.com.cn

Full list of author information is available at the end of the article

Conclusions FMT is a promising treatment option that appears to be safe and well tolerated. This study stands out for its substantial sample size, making it's the largest reported series in pediatrics, as well as for having the longest follow-up period for FMT in this population.

Clinical trial number Not applicable.

Keywords Fecal microbiota transplantation, Safety, Pediatrics

Introduction

Fecal Microbiota Transplantation (FMT) is a technique that involves transferring gut microbiota from a healthy donor to a patient, with the aim of establishing or restoring a stable microbial community in the gut. FMT is already widely recommended as a highly effective treatment for recurrent or refractory *Clostridioides difficile* infection (CDI) [1–3]. In 2013, the U.S. Food and Drug Administration (FDA) approved FMT in children and included it in the guide lines for the treatment of recurrent CDI (rCDI) [4]. FMT has been successfully used in pediatric patients for CDI, with the first reported use in 2010 [5]. A growing body of research is exploring the potential of FMT in treating various health conditions associated with the intestinal microbiome. The most extensively documented applications of FMT involve gastrointestinal diseases and infections, followed by its use in neuropsychological, hematological, and liver diseases [6]. Gastrointestinal diseases where FMT has been widely reported include inflammatory bowel disease (IBD) [7, 8], irritable bowel syndrome (IBS) [9], constipation [10] and pouchitis [11]. Infectious diseases where the use of FMT is being explored include multidrug-resistant organisms (MDROs) [12], urinary tract infections (UTIs) [13], antibiotic associated diarrhea (AAD) [14] and hepatitis B [15]. Based on the well-known microbiota gut-brain axis, gut dysbiosis has been implicated in various neuropsychiatric disorders, including parkinsonism [16], autism spectrum disorders (ASD) [17], bipolar disorder [18] and anorexia nervosa [19]. In addition to the aforementioned diseases, there is an increasing number of studies indicating the use of FMT in the treatment of metabolic diseases, hematological diseases, and various other conditions [6]. While the benefits of FMT are recognized, concerns remain regarding its long-term potential adverse events (AEs) associated with the procedure. However, most studies about safety of FMT have primarily focused on the adult population [20–22], leaving the pediatric population less well understood. All pediatric FMT data currently come from small case series and case reports, with the largest study to date including 74 patients who underwent a total of 508 FMT courses at a single center [23]. In addition, since most studies were small and retrospective, the risk of underreporting may limit these findings. Therefore, this study represents the largest retrospective cohort analysis to date, with the longest follow-up in the pediatric population, evaluating the safety and factors associated with FMT treatment.

Methods

Study population

A total of 831 pediatric patients who underwent FMT as part of their treatment at Shanghai Children's Hospital between December 2013 and December 2023 were retrospectively reviewed. These patients comprised children with various conditions such as rCDI, MDROs, AAD, chronic active Epstein-Barr virus infection, hepatitis B infection, chronic intractable diarrhea, ulcerative colitis (UC), Crohn's disease (CD), functional gastrointestinal disorder, pouchitis, chronic intestinal pseudo-obstruction, eosinophilic gastroenteritis, ASD, attention-deficit hyperactivity disorder (ADHD), anorexia nervosa, metabolic syndrome, non-alcoholic steatohepatitis, systemic juvenile rheumatoid arthritis (sJIA) and other diseases (Table 1). Numerous studies have provided evidence that FMT exhibits efficacy and safety for indications beyond CDI [24–26]. Written informed consent was obtained from the parents or legal guardians of all pediatric subjects. The study was reviewed and approved by the Ethics Review Committee of Shanghai Children's Hospital, Shanghai Jiao Tong University (Approval number: 2022R166-E02).

Criteria for choice of donors

Donors aged between 7 and 40 years were rigorously screened healthy individuals who did not smoke, consume alcohol, or exhibit any other bad habits or digestive symptoms. 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.

Table 1 Participant demographic characteristics

Characteristic		*n* (%)	Nasogastric tube (*n*)	Nasal jejunal tube (*n*)	Enema (*n*)	Capsule (*n*)	Colonoscopy (*n*)
Age (mo)							
< 36		101 (12.4)	25	31	34	4	7
> 36		712 (87.6)	25	90	44	521	32
Sex							
Males		553 (68.0)	23	64	46	393	27
Females		260 (32.0)	27	57	32	132	12
Diseases							
Infectious diseases	rCDI	175 (21.5)	19	54	35	62	5
	MDROs	6 (0.7)	3	1	2	0	0
	AAD	5 (0.6)	0	3	0	2	0
	Hepatitis B	1 (0.1)	0	0	0	1	0
	CAEBV	2 (0.3)	0	0	2	0	0
Gut diseases	Chronic intractable diarrhea	75 (9.2)	9	34	20	12	0
	CD	47 (5.8)	0	7	3	37	0
	Functional gastrointestinal disorder	41 (5.0)	6	9	3	23	0
	UC	29 (3.6)	2	9	2	11	5
	Pouchitis	9 (1.1)	0	1	6	2	0
	Chronic intestinal pseudo-obstruction	3 (0.4)	0	3	0	0	0
	Eosinophilic gastroenteritis	1 (0.1)	0	0	0	1	0
Psychiatric diseases	ASD	403 (49.6)	2	14	0	356	31
	ADHD	18 (2.2)	0	0	0	18	0
	Anorexia nervosa	9 (1.1)	0	1	0	8	0
Metabolic diseases	Metabolic syndrome	1 (0.1)	0	1	0	0	0
Immune diseases	Rheumatoid arthritis	12 (1.5)	0	2	0	1	0
	Allergic eczema	9 (1.1)	1	2	9	4	0
Others		13 (1.6)	9	0	0	4	2

Abbreviations: rCDI: recurrent *Clostridioides difficile* infection; MDROs: multidrug-resistant organisms; AAD: antibiotic associated diarrhea; CAEBV: chronic active epstein-Barr virus; UC: ulcerative colitis; CD: Crohn's disease; ASD: autism spectrum disorder; ADHD: attention deficit hyperactivity disorder

FMT Preparation

A disposable container was used to gather fresh stool samples from donors. To achieve a uniform mixture, 100 g of feces were combined with 500 ml of saline within six hours, utilizing automated microfiltration equipment (GenFMTer, Nanjing, Jiangsu Province, China). The resulting fecal suspension was then processed for filtration according to a pre-established schedule. After microfiltration, the suspension was collected into 50 ml tubes and centrifuged at 1500 g for three minutes. The supernatant was discarded, and the pellet was reconstituted in normal saline to create a fecal bacterial solution, which can be stored at -80℃ for future use. As for capsules, the lyophilized protective agent was added to the fecal bacterial solution, which was then freeze-dried into powder by low temperature freeze-drying machine. The ultimate lyophilized powder was double-encapsulated in size 00 hypromellose capsules and kept at a temperature of -80℃ for storage.

FMT procedure

The bacterial solution was revived and transferred to the patients' digestive systems. Various routes were employed for administration, including nasogastric tubes, nasal jejunal tubes, enemas, capsules and colonoscopy. The choice of different routes for each patient in the FMT procedure is mainly influenced by various factors, such as the child's age and specific disease type. A dosage with a ratio of 1 g of donor stool per kilogram of the patient's body weight was administered. The dose was adjusted according to the patient's age or weight, with the adult dosage applied if the patient weighed over 50 kg. Patients were required to fast for a minimum of 4 h before the FMT.

Safety evaluation

All AEs were categorized into short-term (48 h post-FMT) and long-term (within 3 months). Short-term AEs were described as any medical occurrence that was not

Table 2 Donor characteristics

Item	Results
Total number	49
Sex, male, n (%)	22 (44.9)
Age [mean ± SD (range), yr]	29.1 ± 7.2 (7–40)
Adult, n (%)	47 (95.9)
Children, n (%)	2 (4.1)
Consanguineous donors, n (%)	24 (49.0)

present prior to FMT or a worsening of symptoms in a patient who received FMT. These short-term AEs could include notable changes from the initial physical examination, laboratory findings, or other diagnostic tests, complications related to the FMT administration procedure, or the exacerbation of existing conditions within 48 h post FMT. Potential long-term AEs that were monitored included infections from unknown pathogens, chronic illnesses linked to changes in gut microbiota, growth restrictions, and alterations in behavior. The severity of AEs was classified according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 [27] as mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening (grade 4), and fatal (grade 5). For this study, grades 1 and 2 were considered non-serious AEs, while grades 3, 4, and 5 were categorized as SAEs.

Statistical analysis

IBM SPSS Statistics 29 was used for statistical analyses. The independent factors were analyzed by the Pearson Fisher $\chi 2$ test or rank sum test, while the between.

group variance was determined by the multivariable logistic regression analyses. Values of $P < 0.05$ were considered as 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 donors are listed in Table 2. There were 49 donors, of whom 22 were males, with a mean age of 29.2 years. This group included 24 family members of patients (21 parents, 2 sisters, and 1 brother) and 25 volunteers. A total of 553 male and 260 female subjects, with a mean age of 93.0 months (ranging from 4 to 215 months) were enrolled in this cohort. Their average follow-up time after the FMT was 32.3 months (ranging from 1 to 122 months). The 831 subjects were categorized into 6 groups, including infectious diseases, gut diseases, psychiatric diseases, metabolic diseases, immune diseases, and other diseases. These categories are listed in Table 1.

FMT related AEs

All short-term AEs were self-limited within 48 h. The total occurrence rate of short-term AEs was 5.8% (47/813). The number of AEs by different category is listed in Table 3. The most common AEs were vomiting (16/813, 2.0%), abdominal pain (13/813, 1.6%), diarrhea (7/813, 0.9%), fever (6/813, 0.7%), dysphoria (3/813, 0.4%) and nausea (3/813, 0.4%). Short-term AEs were listed in Table 3. The occurrence rate of upper gastrointestinal symptoms such as nausea, sore throat, and vomiting was 2.5% (20/813). Lower gastrointestinal symptoms such as diarrhea, abdominal pain, and mucoid stool were observed in 2.7% (22/813). Other AEs, such as fever, headache and dysphoria, occurred in 1.4% (11/813).

FMT related SAEs

The occurrence rate of SAEs was 0.2% (2/813), which occurred in two cases. In one case of UC, the patient experienced 60 mL of blood in their stool 6 h post-FMT. In another UC case, the patient developed gastric stricture, accompanied by nausea and hematemesis (30 mL) 4 h after FMT. The SAEs had been reported in our group in 2018 [28].

Table 3 Short-term adverse events

Category	Sub- category	Short-term AEs n (%)	Short-term AEs Rate (%)				
			Nasogastric tube	Nasal jejunal tube	Enema	Capsule	Colonoscopy
Upper gastrointestinal symptom	Sore throat	1 (0.1)	0.0	0.0	1.3	0.0	0.0
	Vomiting	16 (2.0)	12.0	3.3	0.0	0.6	2.6
	Nausea	3 (0.4)	2.0	0.0	0.0	0.4	0.0
Lower gastrointestinal symptom	Diarrhea	7 (0.9)	0.0	5.0	1.3	0.0	0.0
	Abdominal pain	13 (1.6)	2.0	4.1	1.3	1.0	2.6
	Mucoid stool	2 (0.2)	0.0	0.8	1.3	0.0	0.0
Other manifestation	Fever	6 (0.7)	0.0	2.5	1.3	0.4	0.0
	Headache	2 (0.2)	0.0	0.0	0.0	0.2	2.6
	Dysphoria	3 (0.4)	0.0	0.0	0.0	0.2	5.1
Severe adverse event	Hematemesis	1 (0.1)	0.0	0.8	0.0	0.0	0.0
	Hematochezia	2 (0.2)	0.0	0.0	1.3	0.0	0.0

Risk factors related to AEs of FMT

All potential factors influencing AEs, such as sex, age, route of administration, consanguineous donors and disease types, were investigated through the χ2 test. Disease types encompassed the presence or absence of chronic intractable diarrhea, as well as IBD and CDI. As independent factors, route of administration, consanguineous donors, chronic intractable diarrhea and IBD had significant effects on AE occurrence (Table 4). The route of administration is divided into nasogastric tube, nasal jejunal tube, enema, capsule, and colonoscopy. Capsule had a lower occurrence rate of AEs compared to other routes. Nasogastric tube (16.0%, 8/50) and nasal jejunal tube (14.0%, 17/121) exhibited higher rates of AEs compared to other routes. Cases of chronic intractable diarrhea, excluding CDI and IBD, encompassed without underlying conditions, AAD, primary immunodeficiency, IPEX syndrome, gene mutations and graft-versus-host disease (GVHD) associated chronic intractable diarrhea. Chronic intractable diarrhea and IBD were associated with a higher occurrence rate of AEs, 10.7% (8/75) and 15.8% (12/76) respectively.

Furthermore, multivariate logistics regression analysis was analyzed (Table 4). The results showed that IBD (OR: 3.98, 95% CI: 1.78–8.92, $P=0.001$) and capsules (OR: 0.09, 95% CI: 0.03–0.27, $P=0.000$) were independent risk factors for FMT-related AEs. The OR for IBD is 3.98, indicating that patients with IBD are 3.98 times more likely to experience AEs compared to those without IBD, with a 95% CI of 1.78–8.92 suggesting a significant association, while patients using the capsule method have a significantly lower likelihood of AEs, reflected by a 95% CI of 0.03–0.27, indicating a significant negative correlation between capsule use and AEs.

Follow-up

All 813 patients were followed up for at least 1 months, 641 (78.8%) for more than 12 months, 230 (28.3%) for more than 36 months, 152 (18.7%) for more than 60 months, 80 (9.8%) for more than 84 months and 2 (0.3%) for up to 10 years. One primary immunodeficiency patient was treated by FMT for chronic intractable diarrhea. The patient died due to sepsis and liver failure 4 weeks post- FMT, which has been reported by our group in 2018 [28]. No similar cases have been reported since 2018. No long-term AEs occurred during the longest follow-up period of 122 months.

Discussion

The human gastrointestinal tract harbors a diverse array of bacteria, estimated to be ten times the number of human somatic cells. These microorganisms proliferate in the gastrointestinal tract of newborns and undergo significant changes during the first 2–3 years of life, influenced by factors such as delivery method (cesarean section or vaginal), feeding (breast milk or formula), microbial infections, and early antibiotic use [29]. By approximately 3 years of age, the gut microbiota stabilizes, with its composition further shaped by genetics, diet, and environmental influences [30].

Regarding FMT in children, there is a paucity of available data regarding FMT-related AEs and long-term follow-up. To the best of our knowledge, this study represents the largest single-center analysis, with a sizable sample and extended follow-up period, examining the safety of FMT in pediatric patients. In terms of adult AEs statistics, Marcella [31] reviewed the global occurrence rate of FMT-related AEs from 2000 to 2020,which included 4241 patients (5688 FMT courses). FMT-related AEs were observed in 19% of FMT procedures, with the most frequently reported AEs being diarrhea (10%) and abdominal discomfort (7%). Most FMT-related AEs were mild or moderate and self-limiting. A recent systematic review [32] showed the overall AEs rate in children was 28.9%, with mild to moderate AEs at 27.7% and severe AEs at 0.9%. AEs associated with FMT in children are predominantly mild to moderate, transient and self-limiting. Consequently, the utilization of FMT in children is considered safe and warrants broad endorsement. In our study, FMT was found to be relatively safe in children. All short-term AEs were self-limited within 48 h, with a total occurrence rate of short-term AEs at 5.8%. The occurrence rate of SAEs was only 0.2%, which occurred in two cases. No long-term AEs occurred during the longest follow-up period of 122 months.

The safety of FMT is influenced by the quality of the material from the donors as well as the method of delivery utilized. Options for delivery include upper gastrointestinal routes (UGI), such as the use of a nasogastric or nasal jejunal tube, endoscopy, capsules, and lower gastrointestinal routes (LGI) like retention enema, sigmoidoscopy, or colonoscopy. The route through which FMT is administered is believed to play an important role in the occurrence of AEs. A clinical trial involving 116 patients compared FMT administered via capsule to that delivered via colonoscopy, finding that minor AEs were reported in 5.4% of the capsule group compared to 12.5% in the colonoscopy group [33]. According to our data, capsule had a lower occurrence rate of AEs compared to other routes, which included nasogastric tube, nasal jejunal tube, enema and colonoscopy. Consequently, utilizing capsules could potentially enhance the safety of the FMT procedure by mitigating procedure-related complications and facilitating long-term use. Additionally, encapsulated FMT might become accessible to a broader patient demographic, particularly for those who cannot tolerate endoscopic procedures. However, a significant challenge, lies in the fact that a single dose requires ingestion

Table 4 Different categories of fecal microbiota transplantation and potential factors influencing AEs occurrence

Category	Sub-group		n (%)	AEs	Univariate		Multivariate		
				n (%)	χ2	*p* value	OR	95% CI	*p* value
Sex	Males		553 (68.0)	30 (5.4)	0.40	0.53	0.74	0.35–1.56	0.43
	Females		260 (32.0)	17 (6.5)					
Age group (mo)	< 36		101 (12.4)	6 (5.9)	0.005	0.94	2.05	0.73–5.8	0.18
	> 36		712 (87.6)	41 (5.8)					
Route of administration	Nasogastric tube		50 (6.2)	8 (16.0)	10.21	0.000		Reference	
	Nasal jejunal tube		121 (14.9)	17 (14.0)	17.84	0.000	0.62	0.23–1.67	0.34
	Enema		78 (9.6)	5 (6.4)	0.06	0.80	0.35	0.11–1.13	0.08
	Capsule		525 (64.6)	13 (2.5)	29.72	0.000	0.09	0.03–0.27	0.000
	Colonoscopy		39 (4.8)	4 (10.3)	1.51	0.22	0.47	0.12–1.90	0.29
Donor selection	Consanguineous donors		57 (7.0)	13 (22.8)	26.45	0.000	2.71	1.16–6.31	0.021
	Non-consanguineous donors		756 (93.0)	34 (4.5)					
Disease type	Chronic intractable diarrhea	No basic illness	27 (3.3)	0 (0.0)	21.16	0.002	1.19	0.47–3.03	0.72
		Primary immunodeficiency	8 (1.0)	2 (2.7)					
		IPEX syndrome	20 (2.5)	5 (6.7)					
		Gene mutation	3 (0.4)	0 (0.0)					
		GVHD	17 (2.1)	1 (1.3)					
	Non-chronic intractable diarrhea		738 (90.8)	39 (5.3)					
	IBD		76 (9.3)	12 (15.8)	15.42	0.000	3.98	1.78–8.92	0.001
	Non-IBD		737 (90.7)	35 (4.8)					
	rCDI		175 (21.5)	11 (6.3)	0.10	0.75	0.5	0.25	1.12
	Non-rCDI		638 (78.5)	36 (5.6)					

Abbreviations: rCDI: recurrent *Clostridioides difficile* infection; IBD: inflammatory bowel disease; GVHD: Graft-versus-host diseases; IPEX syndrome: Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome. AEs: adverse events

of numerous capsules, which can result in nausea and vomiting. To date, the optimal route for FMT administration remains undetermined. Comprehensive research is necessary to elucidate the interrelationships among the chosen administration route, donor type, sample nature (whether fresh or frozen), patient compliance, and cost efficiency [34].

A systematic review and meta-analysis [35] conducted in 2023 have shown that FMT can be a safe and effective treatment for the pediatric IBD population, potentially demonstrating improved safety and efficacy compared to adults. However, the results are limited by a lack of established protocol as well as long-term follow-up for FMT in a pediatric IBD population. Our research found that individuals suffering from IBD had a higher likelihood of experiencing short-term AEs, serving as an independent predictor for FMT-related AEs. This correlation may be attributed to the heightened severity of intestinal mucosal damage in IBD patients.

Donor selection is maybe even more crucial in children, who have a dynamic and developing microbiome that correlates with the development of the immune system and other physiological functions. Although gut microbiomes can differ markedly in diversity across adults, family members are often observed to have more similar microbiotas than unrelated individuals [36]. Familial similarities are usually attributed to shared environmental influences, such as dietary preference, a powerful shaper of microbiome composition [37]. However, the occurrence rate of AEs in FMT using stool from consanguineous donors is higher than that using stool from non-consanguineous donors in our study. This increased occurrence rate of AEs among consanguineous donors may be attributed to the fact that 40.4% (23/57) of the cases involving consanguineous donors were administered via nasal jejunal tube, 31.6% (18/57) via enema and 15.8% (9/57) via nasogastric tubes, indicating a potential bias.

This study has certain limitations. Firstly, it was conducted at a single center, which may lead to selection bias in patient recruitment, such as the severity of their conditions not being representative. Retrospective studies typically lack randomized control groups, making it difficult to establish causal relationships. Reports of AEs may be influenced by the subjective judgments of physicians, resulting in inconsistencies in the findings. Additionally, such studies can introduce selection and information biases, as the completeness and accuracy of medical records may affect the documentation of patients' histories and AEs. Self-reported data from patients can also result in underreporting or misreporting of AEs, impacting the reliability of the results. Therefore, we recommend that future research adopt prospective designs to minimize the potential for bias. Furthermore, other external factors, such as patients' lifestyles, may not have been adequately controlled, affecting the reliability of the results.

Conclusions

Preliminary data indicate that most AEs were mild-to-moderate, including vomiting, abdominal pain, diarrhea, fever, dysphoria and nausea, which were typically self-limited. FMT is considered a potentially safe and well tolerated treatment. The strengths of this study include a relatively large number of subjects, making it the largest reported series and the longest follow-up period of FMT in pediatrics.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12866-025-03858-z.

Supplementary material 1

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Author contributions
XP. and LYR. drafted the initial manuscript, conducted the analysis and critically revised the manuscript. LXL., GT., LD., XQ., RYM. and XFF. performed the data curation. XYM., and ZT. provided data interpretation, critical review, and commentary to the revised versions of the manuscript.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The studies involving humans were approved by Ethics Review Committee at the Shanghai Children's Hospital, Shanghai Jiao Tong University. Written informed consent was obtained from all guardians of the participants, in line with the principles outlined in the Helsinki Declaration.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Gastroenterology, Hepatology and Nutrition, Shanghai Children's Hospital, School of medicine, Shanghai Jiao Tong University, 355 Luding Road, Shanghai 200062, China
[2]Institute of Pediatric Infection, Immunity and Critical Care Medicine, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

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