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Fecal microbiota transplantation through transendoscopic enteral tubing for inflammatory bowel disease: High acceptance and high satisfaction

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Key words

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Ethical approval: Our study was conducted following the Declaration of Helsinki. Ethics approval was granted by the Second Affiliated Hospital of Nanjing Medical University institutional review board for this study (I2022 KY14501).

Abstract

Background and Aim: Fecal microbiota transplantation (FMT) has been shown to positively affect the treatment of inflammatory bowel disease (IBD). However, the safety and efficacy of FMT may depend on the route of microbiota delivery. This study investigates the acceptance, satisfaction, and selection preference of a new delivery route, transendoscopic enteral tubing (TET), for treating IBD.

Methods: A survey was conducted among patients with IBD from five medical centers across China. The objective was to assess their acceptance, subjective feelings, and major concerns regarding two types of TET: colonic TET and mid-gut TET. In addition, the survey also analyzed the factors affecting the selection of TET and TET types among these patients.

Results: The final analysis included 351 questionnaires. Up to 76.6% of patients were willing to accept TET and preferred to choose colonic TET when they first learned about TET. Patients with longer disease duration, history of enema therapy, or enteral nutrition were more open to considering TET among IBD patients. After treatment, 95.6% of patients were satisfied with TET, including colonic TET (95.9%) and mid-gut TET (95.1%). Patients with a history of enema therapy and ulcerative colitis preferred colonic TET. In contrast, those with a history of enteral nutrition and Crohn's disease were willing to choose mid-gut TET. However, some patients hesitated to accept TET due to concerns about efficacy, safety, and cost.

Conclusions: TET was highly accepted and satisfied patients with IBD. Disease type and combination therapy influenced the choice of colonic or mid-gut TET.

Informed consent: All patients had signed the informed consent.

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¹Jue Lin and Jinlei Xiong contributed equally to this work.

Introduction

Inflammatory bowel disease (IBD), a modern refractory disease, presents significant therapeutic challenges.¹ Fecal microbiota transplantation (FMT), a method of reconstructing the gut

microbiota with the fecal microbiota from a healthy donor, has been approved as a standard therapy for recurrent *Clostridioides difficile* infection (CDI).^{2,3} In addition, compelling evidence suggests that FMT can be an effective treatment option for many conditions. A comprehensive systematic review of 782 studies found

that FMT had positive outcomes in the treatment of 85 specific diseases, including infections, gut diseases, microbiota-gut-liver axis, microbiota-gut-brain axis, metabolic diseases, oncology, hematological diseases, and other diseases.⁴ Research indicates that FMT could be a potential therapy for ulcerative colitis (UC) and Crohn's disease (CD).^{5–9} The methodology of FMT based on the automatic washing process and the related delivery since 2014 was named washed microbiota transplantation (WMT), which represented more safety and a promising efficacy compared with FMT.^{10–12}

Routes of microbiota transplantation can be identified as the upper, mid, and lower gut. Having these different delivery options provides more flexibility in the treatment of patients. A systematic review of the global incidence of adverse events for FMT conducted over the last decades has shown that the delivery route is a critical influencing factor.¹³ Lower gut delivery routes are superior to mid-gut and upper gut delivery routes, which have also been demonstrated in the case of IBD.¹⁴ However, it should be noted that the optimal route for WMT is still uncertain, and further research in this area is needed to determine the best delivery method.

Since 2014, We have explored a new delivery route named transendoscopic enteral tubing (TET),^{15,16} which means inserting a slender, soft tube into the colon or mid-gut and fixing it onto the intestinal wall with endoscopic clips under endoscopy. The tube will be kept in the gut for repeat delivery of microbiota solution (Fig. 1).^{8,15,17,18} TET, which includes colonic TET and mid-gut TET, has been shown to reduce the occurrence of microbiota transplantation-related adverse events.¹⁹ The rate of the TET procedural success was 98.8–100%.^{16,18,20} Our recent clinical

study has validated that cap-assisted colonoscopy for colonic TET can save the second operating time of difficult colonoscopies, increase patient safety,¹⁷ and reveal that two to four endoscopic clips could retain TET for 7–11 days.¹⁵ Due to its efficacy and safety advantages, TET is becoming a promising delivery route for patients with IBD who undergo FMT.¹⁰

The colonic TET has been recommended for IBD patients who require multiple WMTs or colon drug delivery in the first WMT consensus.¹⁰ Studies have shown that the colonic TET is as effective as the mid-gut TET and is considered a safe and feasible option, particularly for young patients between the ages of 3 and 7 years.²⁰ Compared with the mid-gut TET (23.3%), colonic TET (6.0%) has a lower incidence of adverse effects and better compliance.⁸ When treating IBD, which may be complicated by strictures, fistula, and colonic mucosal ulcers, selecting the appropriate delivery route based on the patient's lesion characteristics is important.

TET is a flexible treatment that offers various benefits, such as facilitating the administration of multiple doses of microbiota and serving multiple purposes.²¹ Mid-gut TET is particularly useful for enteral nutrition in patients suffering from severe duodenal stasis, esophageal diseases, gastric surgery, or pancreatitis. Colonic TET is highly effective for administering drugs to the entire colon. It can also be used for colonic drainage to rescue endoscopy-associated perforation and collect intestinal specimens in real-time.²²

This study investigates patient acceptance, satisfaction, and preference for TET in IBD. The results will guide clinicians in selecting appropriate therapies for individual patients.

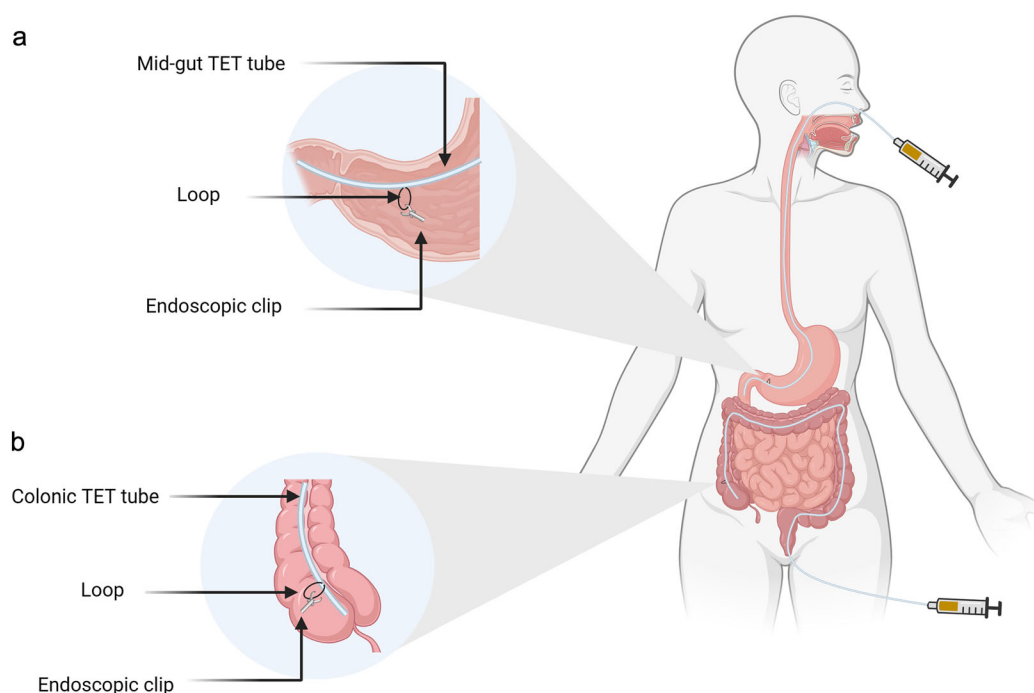


Figure 1 The diagram of transendoscopic enteral tubing (TET): (a) Mid-gut TET, the TET tube was inserted into mid-gut with the assistant with gastroscop, and the loop on the tube was fixed in the antrum mucosa near the pylorus with a clip; (b) colonic TET, the TET tube was inserted into cecum through the channel of colonoscope, and was fixed on the intestinal wall using endoscopic clips.

Materials and methods

Setup, participants, and study design. The present study surveyed patients with IBD about their acceptance and satisfaction with TET. The IBD experts carefully reviewed the questionnaire to determine the feasibility and scientificity of the details. The questionnaire was generated by Wen Juan Xing (Changsha Ranxing Information Technology Co., Ltd., Hunan, China). Then, the questionnaire was distributed on WeChat to five centers, namely, the Second Affiliated Hospital of Nanjing Medical University, the First Affiliated Hospital of Guangdong Pharmaceutical University, the Affiliated Wuxi Second People's Hospital of Nanjing Medical University, the Affiliated Huaian No. One People's Hospital of Nanjing Medical University, and Suining Central Hospital. Patients' participation were voluntary, and signed informed consent was obtained from each participant. They have only one chance to complete the questionnaire anonymously. Ethics approval was granted by the Second Affiliated Hospital of Nanjing Medical University institutional review board for this study ([2022]KY14501).

Questionnaire design. We devised an electronic questionnaire based on the advice of experts and previous studies (Table S1). It consists of three parts: single-choice, multiple-choice, and completion. After collecting basic information (age, gender, etc.), IBD characteristics, current treatments for IBD, times of WMT/FMT, and acceptance for TET were inquired. Patients were divided into two groups, according to whether they have experience with TET. To gain further insight into the subjective feelings toward treatments with TET, these patients with experience of TET were categorized into three groups: mid-gut TET, colonic TET, and both.

Statistical analysis. The statistical analysis was conducted using SPSS (IBM SPSS 21.0; SPSS Inc, Armonk., USA). Data were described using mean \pm standard deviation or median (interquartile range [IQR]), and categorical variables were expressed as percentages. χ^2 test or Fisher's exact test was used to compare the general information and attitude toward TET. Continuous variables were compared using the Mann–Whitney *U*-test or independent *t*-test nonparametric test. Using univariate and multivariate logistic regression analyses to explore the influencing factors of selecting two routes and TET, multivariate analysis was performed using variables with *P* value < 0.05 in the univariate analysis. Statistical significance was determined by *P* value < 0.05 .

Results

Basic characteristics. In total, 351 valid electronic questionnaires were qualified for analysis. The patients ranged from 29 to 46 years old, with a median of 36. The majority (57.0%) of the patients were Crohn's disease, 35.9% were UC, and 7.1% were IBD indeterminate. (Table 1).

The cognition and selection of TET for the first time. In this investigation, 88% of patients have heard or known about TET from different sources. Physicians' recommendation

Table 1 Characteristics of patients

Items	Results
Total number, n	351
Sex, male, n (%)	203 (57.8)
Age, years, median (range)	36 (29–46)
Disease type, n (%)	
UC	126 (35.9)
CD	200 (57.0)
Indeterminate IBD	25 (7.1)
Disease duration, years, median (range)	4 (2–9)
Medical or biomedical background, n (%)	
With	103 (29.3)
Without	248 (70.7)
History of enteral nutrition, n (%)	
Yes	179 (51.0)
No	135 (38.5)
Times of WMT/FMT, n (%)	
0	78 (22.2)
1–3	137 (39.0)
4–6	76 (21.7)
7–9	33 (9.4)
≥ 10	27 (7.7)
Primary selection of TET, n (%)	
Colonic TET	217 (61.8)
Mid-gut TET	134 (38.2)
History of TET, n (%)	
Yes	180 (51.3)
No	171 (48.7)
Type of TET that patients had experienced, n (%) [†]	
Colonic TET	77 (42.8)
Mid-gut TET	58 (32.2)
Both	45 (25.0)
The attitude of TET, n (%)	
Accept	269 (76.6)
Reject/uncertain	82 (23.4)

[†]The patients who had a history of TET.

CD, Crohn's disease; FMT, fecal microbiota transplantation; IBD, inflammatory bowel disease; TET, transendoscopic enteral tubing; UC, ulcerative colitis; WMT, washed microbiota transplantation.

(51.9%) was the most prominent source, and mass media (23.3%) was the second most preferred source of information for TET (Fig. 2a). Only 12.0% of patients heard the TET for the first time. Meanwhile, the vast majority (76.6%) of the patients received supportive WMT/FMT through TET when they first learned about this treatment modality. At the same time, the remaining 82 patients were indecisive regarding the efficacy and safety of this method (Fig. 2b).

Of all patients, 61.8% and 38.2% would be willing to accept colonic TET and mid-gut TET, respectively. Figure 3 presents the reasons that influenced the selection of TET for the first time they learned about it. The physician's recommendation was the foremost reason. Of them, three factors (age ≥ 36 years, multivariate analyses, odds ratio [OR] = 1.760, 95% confidence interval [CI]: 1.140–2.719, *P* = 0.011; UC patients, multivariate analyses, OR = 3.143, 95% CI: 1.257–7.858, *P* = 0.014; history of enema,

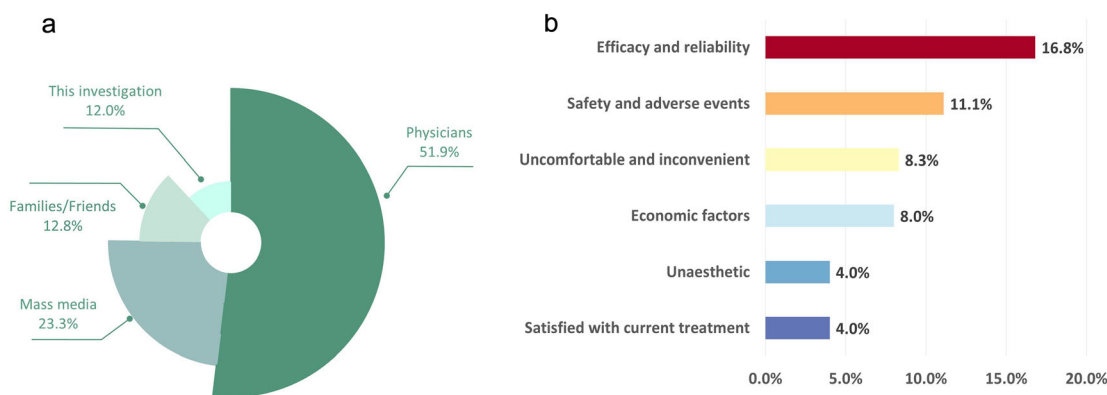


Figure 2 (a) Approaches to learning about transendoscopic enteral tubing (TET) for the first time. (b) The reasons for the negative attitude of patients with inflammatory bowel disease (IBD) toward TET when they first learned about this treatment modality.

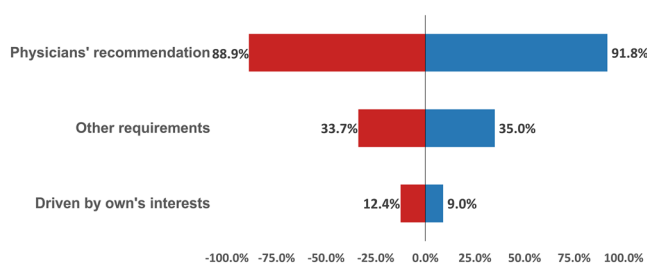


Figure 3 The reasons that influenced the selection of two routes of transendoscopic enteral tubing (TET) for the first time. ■, Colonic TET; ■, Mid-gut TET.

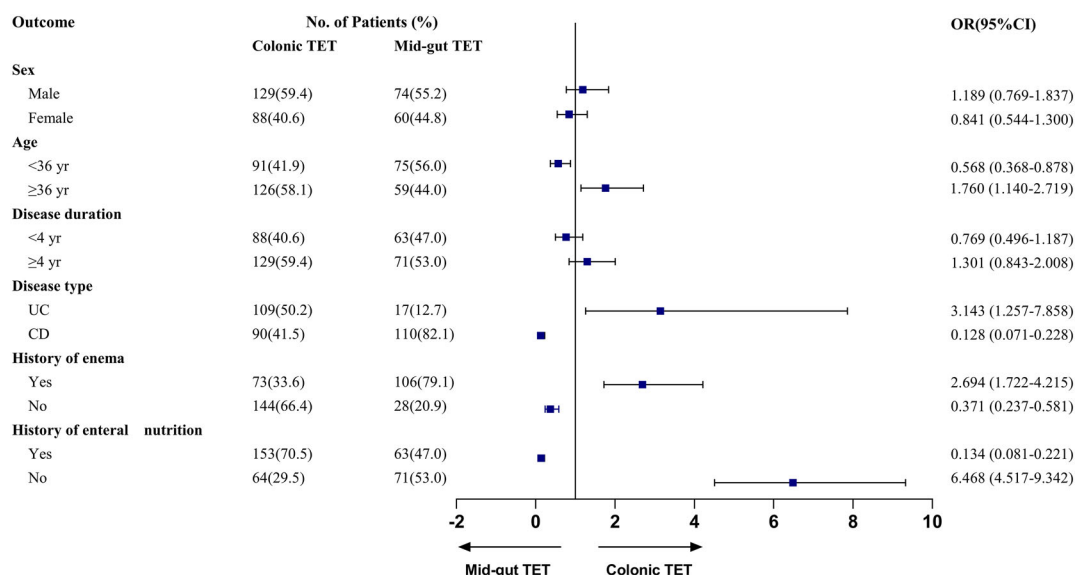


Figure 4 Subgroup analysis for selection on two routes of transendoscopic enteral tubing (TET). The forest plot of the odds ratio [OR] of the selected feature. Forest plot was used for outcome in logistic regression analysis. The X-axis displays the odd ratio and 95% confidence interval [CI] of each subgroup.

multivariate analyses, OR = 2.694, 95% CI: 1.722–4.215, $P < 0.001$) were found to have associations with the selection for colonic TET. No significant differences were detected in sex, disease duration, and current treatments (Fig. 4).

Regarding the willingness to recommend TET, 96% of patients preferred to recommend it. Encouragingly, TET was considered one of the efficient strategies for 143 (83.6%) patients for their following treatment plans.

Subjective feelings of TET post-treatment and impact factors. As shown in Figure S1, in multiple regression analysis, disease duration (OR = 1.790, 95% CI: 1.168–2.744; $P = 0.008$), times of WMT (OR = 5.944, 95% CI: 3.666–9.654; $P < 0.001$), the history of enema (OR = 1.641, 95% CI: 1.064–2.531; $P = 0.025$), and the history of enteral nutrition (OR = 2.958, 95% CI: 1.916–4.566; $P < 0.001$) were independent factor influencing the desire of patients for TET treatment.

Among the two routes of TET, overall satisfaction was 95.6%, and no noticeable difference was observed between colonic TET (95.9%) and mid-gut TET (95.1%). We also assessed the impact of TET on daily life by considering the patients' subjective feelings. "No affected" is the absence of discomfort or inconvenience. "Mild affected" is defined as experiencing some inconvenience in daily life that the patient can tolerate. "Severe affected" is defined as significantly disrupting daily life, and the patient cannot endure it. Overall, the rate of severe effects was more significant in patients who had undergone mid-gut TET (11.7%) compared with colonic TET (4.1%) ($P = 0.033$). However, the vast majority believe that TET has no or mild impact on daily life, and most patients (colonic TET 98.4%, mid-gut TET 93.2%) can tolerate these discomforts (Table 2). The most reported discomfort was the occurrence of pharynx discomfort for mid-gut TET and anal discomfort for colonic TET. No severe adverse event was observed after the treatment of TET and during it.

Most of the patients who were treated with only one single route for TET were reluctant to change to another TET route because the initial treatment can "improve quality of life" and "improve comfort" (Fig. 5). However, patients with experience with both TET routes were more willing to choose colonic TET than mid-gut TET because of the improved quality of life and aesthetics with colonic TET (Fig. 6).

Discussion

The findings of this study indicated that patients with IBD have a higher acceptance and awareness of TET compared with our previous report in 2020.²¹ This could be attributed to the recommendations made by physicians and the influence of information channels on patients' knowledge of IBD treatment options. Patients tend to trust and respect the authority and expertise of their doctors, while only a small fraction of clinicians were familiar with TET before the intervention. The mass media also played a significant role in raising awareness and shaping attitudes toward TET, although the effectiveness of this approach remains controversial. Healthcare providers must continue exploring and disseminating information through various channels, including mass media, to provide accurate and useful information about TET.

In IBD patients who had experienced TET in this study, the acceptance rate increased from 86.1% before TET experience to 97.8% after TET. As shown in previous research, TET was recommended more for patients who need multiple WMTs in a short time because a significant advantage of TET is increasing efficiency and compliance of the treatment compared with the traditional FMT.¹⁰ The type of disease and medical history influenced the choice of delivery route for TET. Patients with UC and a history of enema therapy preferred colonic TET, which could be used for enema and medication administrations, reducing treatment burden. Patients with CD preferred mid-gut TET, which was linked to enteral nutrition function. Interestingly, this study found that younger patients were more willing to choose mid-gut TET than colonic TET. This may be attributed to the inconvenience of colonic TET for defecation and anal cleaning.

The result also showed that patients who have accepted unitary TET prefer to choose the same route for their subsequent therapy.

Table 2 Subjective feeling after TET in patients with IBD

Items	Colonic TET	Mid-gut TET	<i>P</i> value
Total number, <i>n</i>	122	103	
Affected daily life, <i>n</i> (%)			0.083
No affected	37(30.3)	25(24.3)	
Mildly affected	80(65.6)	66(64.1)	
Severely affected	5(4.1)	12(11.7)	
Ability to tolerate the discomfort of TET, <i>n</i> (%)			0.830
Yes	120(98.4)	96(93.2)	
No	2(1.6)	7(6.8)	
Subjective symptom changes after TET, <i>n</i> (%)			0.358
Complete improvement	64(52.5)	48(46.6)	
Partial improvement	46(37.7)	48(46.6)	
No improvement	12(9.8)	7(6.8)	
Symptom exacerbation	0	0	
Satisfaction of TET, <i>n</i> (%)			0.776
Satisfied	117(95.9)	98(95.1)	
Unsatisfied	5(4.1)	5(4.9)	
Acceptance of TET after treatment, <i>n</i> (%)			0.726
Accept	120(98.4)	100(97.1)	
Reject/uncertain	2(1.6)	3(2.9)	
Severe adverse event	0	0	

IBD, inflammatory bowel disease; TET, transendoscopic enteral tubing.

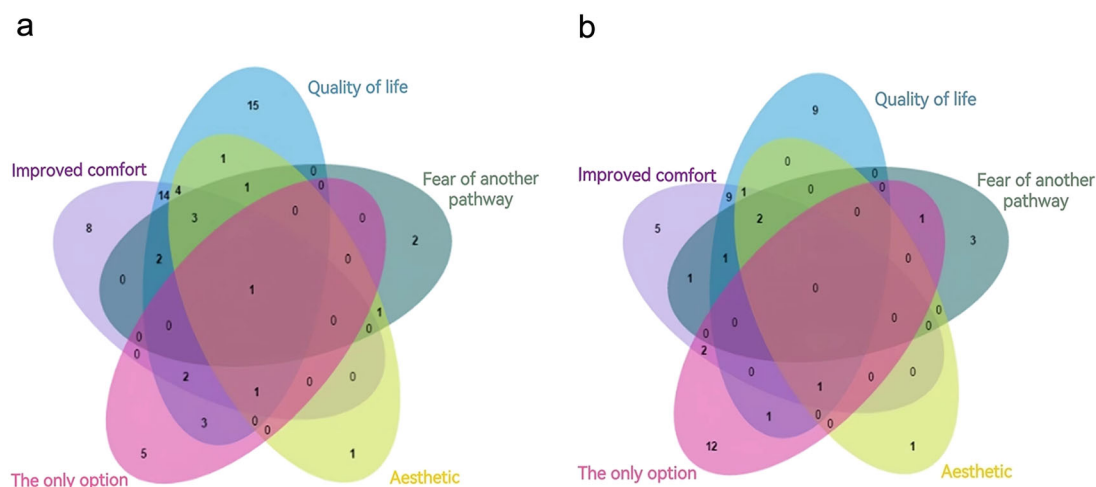


Figure 5 (a) The reasons why patients who only underwent colon transendoscopic enteral tubing (TET) choose to continue with colonic TET again at the next stage. (b) The reasons why patients who only underwent mid-gut TET choose to continue with mid-gut TET again at the next stage.

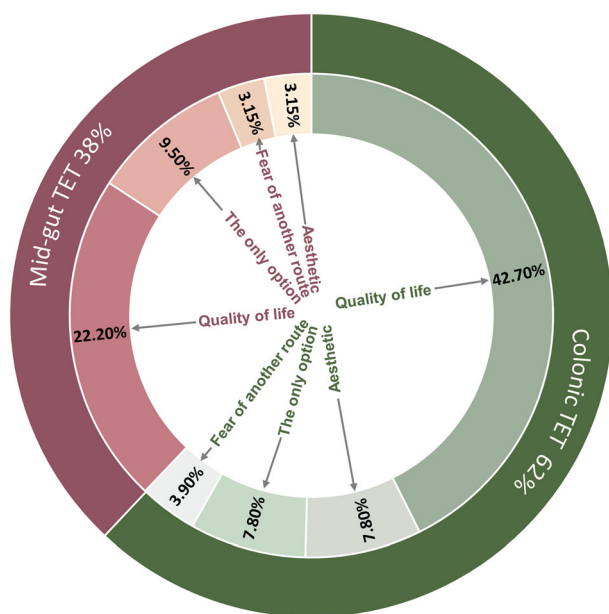


Figure 6 The rate and reason for the choice of delivery routes for patients with experience of both TET routes at the next stage. Colonic TET: ■, Quality of life; ■, Aesthetic; ■, The only option; ■, Fear of another route. Mid-gut TET: ■, Quality of life; ■, The only option; ■, Fear of another route; ■, Aesthetic.

This could be because a single method could meet their treatment demand. In addition, quality of life and comfort were also the criteria to be considered for patients who had experienced TET, particularly those who had tried two different TET routes. Mid-gut TET appeared to have a more severe impact on daily life than colonic TET, possibly due to its effect on social anxiety. However, most uncomfortable feelings were considered tolerable, such as anal and pharynx discomfort, respectively. No severe adverse events were observed during or after TET. This may explain

why overall patient satisfaction with TET was higher for colonic TET. However, no significant differences were found in subjective feelings of IBD patients between colonic TET and mid-gut TET. The unaesthetic condition was one of the significant reasons why mid-gut TET was not more prevalent. Moreover, there is evidence that colonic TET may be less psychologically challenging for patients than the mid-gut TET.²³

The questionnaire study raises concerns about the efficacy and adverse events of TET. This finding is similar to data reported for CDI, which identified efficacy (91%) and safety (62%) as the most common factors influencing preference for FMT delivery routes.²⁴ However, our questionnaire only covered subjective evaluations of symptom changes. Min Chen *et al.* conducted a study in 2020 that found that the efficacy of FMT in treating moderate to severely active UC was not significantly different between the nasojejunal tube (similar to mid-gut TET) or colonic TET delivery routes.²⁵ However, this study was an open-label prospective trial that only included nine UC patients, so further randomized controlled trials with larger sample sizes are needed to validate these observations. Meanwhile, patients with no TET experience are more concerned about economic factors, which can make them hesitant to choose the next step in their treatment.

In addition to TET, there are several other delivery routes are used for conducting WMT, including the upper gut (UG) route (gastroendoscopy and oral capsules), mid-gut (MG) (nasogastric/nasojejunal tube), and lower gut (LG) (retention enema, sigmoidoscopy or colonoscopy).^{14,26} A meta-analysis²⁷ showed that LG (28%) had a higher clinical remission rate compared with UG (14%) in UC patients, although no significant difference in the distribution was found between the two groups ($P = 0.101$, χ^2 test). However, clinical efficacy was not the most predominant factor when patients selected the delivery route for WMT. Providing tailored health guidance to IBD patients based on the evolution of the disease condition and the assessment of therapy needs is necessary. For example, in cases where the lesions are confined to the rectum/sigmoid colon or the patients are critically ill,²⁶ retention enema should be preferred. More details about different delivery routes are shown in Table 3.

Table 3 Comparison among different routes of administration of WMT

Delivery routes	Delivery site	Times of WMT	Adverse events	Safety recommendations ¹³	Advantages	Shortcoming	Applicable people
Colonic TET ^{8,25,27}	Colon and distal part of ileum	Multiple	Anorectal discomfort; abdominal pain/distention	+++	AEs are lowest; multiple WMT; deliver bacteria to the colon directly; better aesthetic; more than 95% Satisfaction	Not suitable for patients with severe perianal lesions	Need multiple WMT; no colonoscopy contraindications
Mid-gut TET ^{8,25,27}	Small intestine	Multiple	Pharynx discomfort; nose bleeding; stuffy nose; sore throat; nausea; vomiting; regurgitation;	++	Multiple WMT; more than 95% satisfaction; the catheter can be used for enteral nutrition and intestinal radiography and could be retained for a long time (more than 3 months)	AEs are higher than colonic TET; poor aesthetic	Need multiple WMTs, especially for patients who need enteral nutrition
Colonoscopy ^{25,27,28}	Colon	Single	Diarrhea; constipation; abdominal discomfort; flatulence; perforation bleeding; bloating; severe cold; even death	+++	Deliver bacteria to the colon directly	Only for single WMT	Single WMT; no colonoscopy contraindications
Gastroscopy ^{14,26}	Duodenum	Single	Nausea; fever; abdominal pain; flatulence; constipation; diverticulitis; vomiting; aspiration pneumonia; even death	+	Easy to be acceptable	AEs are highest; only for a single WMT	Single WMT
Percutaneous endoscopic cecostomy ²⁹	Colon	Multiple	Catheter dislodgement, Peritonitis	+	Can be retained for a long time (more than 3 months); convenient, can be repeated at home; inexpensive	Complex operation; Risk of catheter prolapse or incision infection	Need multiple WMTs; Limited conditions
Oral capsule ^{24,26}	Small intestine	Multiple	Nausea; vomiting; Worsening colitis; bloating; flatulence; diarrhea; constipation;	+	Convenient, can be operated at home; non-invasive	Too many capsules(40)are required; expensive; AEs are higher than lower gut delivery	Normal swallowing function; poor tolerance to invasive procedures
Retention enema ²⁶	Rectum and sigmoid colon	Multiple	Patchy inflammation of the colon; rectal abscess; abdominal discomfort	++	Cheap, convenient, and can be operated at home	Limit the volume of bacterial fluid; not as effective as TET& colonoscopy; difficult to retain the bacterial liquid and prone to leakage; hard to reach the deep part of the colon.	Need multiple WMT; cannot afford endoscopy

TET, transendoscopic enteral tubing; WMT, washed microbiota transplantation.

Choosing an appropriate treatment for IBD patients is expected to bring better clinical benefits. It should be noted that the present study has some limitations. The participants were from various therapy centers with established therapeutic systems of TET, which may not be representative of all populations. In addition, the disease activity and severity of IBD were not assessed through the questionnaire forms. Therefore, further investigations with expanded samples in the future are necessary to gain a more comprehensive understanding of the acceptance and satisfaction of TET among IBD patients.

In conclusion, this study discloses the high satisfaction and acceptance of TET in the IBD population. We have also identified the different advantages of colonic and mid-gut TET. These findings can help clinicians develop individualized clinical regimens for WMT in patients with IBD, thereby advancing the microbiota medicine as clinical discipline.

Data availability statement. The data analyzed in this study are available from the corresponding author upon reasonable request.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Subgroup analysis for IBD patients with or without experience of TET. The forest plot of the OR of the selected feature. Use of forest plot for outcome in logistic regression analysis. The X-axis displays the odd ratio and 95%CI of each subgroup.

Table S1. Acceptance and satisfaction of patients with inflammatory bowel disease to fecal bacteria transplantation through TET.