Medicine®

OPEN

The combined therapy of fecal microbiota transplantation and laxatives for functional constipation in adults
A systematic review and meta-analysis of randomized controlled trials

Sijia Fang, MM[a], Shan Wu, MM[a], Lina Ji, MM[a], Yongsheng Fan, PhD[a], Xinchang Wang, PhD[b], Kepeng Yang, PhD[b],* ID

Abstract

Objective: Functional constipation is a prevalent, burdensome gastrointestinal disorder whose treatment remains challenging. Combined therapy uniting multiple treatments may be promising. Fecal microbiota transplantation (FMT) which tends to be an etiological treatment has been increasingly investigated in its management. Meanwhile, laxatives are widely used to relieve constipation temporarily, but their overall efficacy is poor. Therefore, we performed meta-analyses of randomized controlled trials to evaluate the joint efficacy of FMT and laxatives in functional constipation.

Methods: We performed a systematic literature search of 6 electronic databases as of August 11, 2020. Randomized controlled trial of FMT together with laxatives vs laxatives alone in functional constipation in adults were included. Two reviewers independently performed the screening, data extraction, and bias assessment. Dichotomous outcome data were synthesized by risk ratio, and measurement data by weighted mean difference (WMD).

Results: A total of 1400 records were identified, of which 5 were eligible (409 patients). Overall, compared to laxatives alone, combined therapy of FMT and laxatives more significantly improved total effective rate (risk ratio: 1.35; 95% confidence interval [CI]: 1.14, 1.60; $I^2 = 13\%$), Bristol stool form scale score (WMD: 1.04; 95% CI: 0.57, 1.51; $I^2 = 76\%$), reduce Wexner score (WMD: −3.25; 95% CI: −5.58, −0.92; I2 = 92%), Knowles-Eccersley-Scott-Symptom (KESS) score (WMD: −5.65; 95% CI: −7.62, −3.69; $I^2 = 0\%$) and patient assessment of constipation quality of life score (WMD: −18.56; 95%; CI: −26.43, −10.68; $I^2 = 78\%$). No serious adverse events were reported. The majority of included studies had poor methodological quality.

Conclusion: Combined therapy of FMT and laxatives may be a reasonably effective and safe treatment for people with functional constipation. However, caution is needed with the interpretation of these data due to the small sample size, high heterogeneity, and low quality of the studies. Besides, we expect that more studies will be performed exploring the efficacy and safety of combined therapy for functional constipation.

Keywords: combined therapy, constipation, fecal microbiota transplantation, meta-analysis

1. Introduction

Functional constipation is a symptom-based gastrointestinal disorder without an organic origin (e.g. bowel obstruction).[1] Besides reduced stool frequency, a range of symptoms is described, such as hard or small stool, excessive straining, feelings of incomplete evacuation, abdominal discomfort, or a requirement for digital manipulation to assist defecation.[2] Rome III is the most widely accepted diagnostic criteria of functional constipation.[3] The diagnosis can be established as the presence of 2 or more of the following symptoms for at least 3 months: straining in at least 25% defecations; lumpy or hard stool in at least 25% defecations; sensation of incomplete evacuation in at least 25% defecations; sensation of anorectal obstruction/ blockade in at least 25% defecations; manual maneuvres to facilitate at least 25% defecations (e.g. digital evacuation, pelvic floor support); fewer than 3 defecations per week; loose stools are rarely present without the use of laxatives; insufficient criteria for irritable bowel syndrome.

Constipation is 1 of the most common clinical problems, which greatly impairs patients' health and quality of life. The prevalence of constipation in the worldwide general population ranged from 0.7% to 79% (median 16%).[4] A study including 3,359,653 US

veterans indicated that 237,855 (7.1%) were identified as having constipation; further research showed that constipation status and laxative use are independently associated with a higher risk of all-cause mortality and incident coronary heart disease and ischemic stroke.[5] Constipation is also associated with other functional gastrointestinal disorders such as chest pain, gastro-esophageal reflux disease and functional dyspepsia, as well as an increased prevalence of psychological distress such as anxiety, depression, obsessive-compulsive traits and somatization.[6] Moreover, constipation consumes considerable healthcare resources. In the USA, 821 million dollars is spent annually on over-the-counter laxatives alone.[7]

Functional constipation is a complicated condition, the pathogenesis of which involves various factors, such as type of diet, genetic predisposition, colonic motility, absorption, social-economic status, daily behaviors.[8] The management of functional constipation remains challenging. The first steps that should be taken to relieve symptoms are diet and lifestyle modifications, and if unsuccessful, laxative therapy among which osmotic and stimulant laxatives are recommended as first treatment strategies should be initiated.[8–10] However, laxatives tend to relieve constipation temporarily, failing to fundamentally solve patients' long-term problems. Besides, the overall efficacy of these drugs is poor.[11,12] Thus, new therapies are in need. Besides, given the need for temporary relief of constipation symptoms and long-term control of the disease, combined therapy uniting multiple treatments may have more advantages than a single treatment.

Growing Evidence indicates that dysbiosis of gut microbiota may contribute to functional constipation.[13–16] A meta-analysis in 2014 reported that probiotics which modify the gastrointestinal microbiota may improve whole gut transit time, stool frequency, and stool consistency.[1] Fecal microbiota transplantation (FMT) involves administration of fecal material containing distal gut microbiota from a healthy individual (donor) to a patient with a disease or condition related to dysbiosis, or an alteration in their "normal" gut microbiota; the goal of FMT is to treat disease by restoring phylogenetic diversity and microbiota more typical of a "healthy" individual.[17] FMT has been recommended by a number of clinical medical guidelines for the treatment of recurrent or refractory Clostridium difficile infection. In addition, FMT seems to be useful in the treatment of functional constipation.

We aimed to investigate the joint effect of FMT and laxatives in adults with functional constipation by comparing a combined treatment of FMT and laxatives to laxative treatment alone via a meta-analysis of randomized controlled trials (RCTs).

2. Methods

This systematic review was carried out in line with the relevant criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[18] and the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions.[19,20]

2.1. Data sources and search strategy

The following data sources were searched up to August 11, 2020: English data sources included MEDLINE, EMBASE, Cochrane Library, and Web of Science; Chinese data sources included Chinese Biomedical Literature Database (CBM), CNKI, and WANFANG.

Search terms used for fecal microbiota transplantation were "faecal" or "fecal" or "feces" or "faeces" or "stool" or "microbiota" or "microflora" or "fecal flora" or "faecal flora," and "transplant*" or "transfusion" or "implant*" or "instillation" or "donor*" or "enema" or "reconstitution or infusion*" or "transfer*" or "FMT" or "bacteriotherapy." The results were combined with keywords for constipation. These search terms were used both as Medical Subject Headings terms and as free text. No language or date limits were used.

2.2. Study selection

All citations were imported into EndNote X9 for assessment of eligibility. Two reviewers independently scanned the titles and abstracts of retrieved database records and the full text of potentially relevant studies were further screened in a blinded standardized manner. Disagreements were resolved by a third researcher.

Inclusion and exclusion criteria following the PICOS (participants, interventions, comparators, outcomes, and study design) approach. Studies were considered for inclusion if they met the following criteria:

(1) randomized controlled trials with ≥2 study groups;
(2) adult populations aged ≥18year with functional chronic constipation defined by clinical symptoms, a physician's opinion, or the Rome I, II, or III criteria;
(3) experimental groups were intervened with FMT combined with oral laxatives, while control groups were intervened with oral laxatives alone;
(4) reports of the clinical outcomes of stool frequency, stool consistency, gut transit time, adverse effects, and so on. Studies of constipation-predominant irritable bowel syndrome or intervened with probiotics were excluded.

2.3. Data extraction and quality assessment

A data extraction spreadsheet was developed. Two reviewers assessed each study and extracted the data. Conflicts were resolved by a third researcher.

The following properties of studies were extracted: basic information (first author, publication year, and location), characteristics of participants (age, gender, duration of disease, constipation definition, sample size), details of FMT therapy (intervention therapy, fecal microbiota preparation, FMT route, and frequency and duration of FMT), details of laxative therapy, outcomes of efficacy indicator and adverse events.

To measure study quality, the two reviewers independently assessed the baseline comparability, adequacy of randomization and allocation concealment, blinding methods, complete outcome data, and selective data reporting. The Cochrane Risk Bias Tool in the Cochrane Handbook for Systematic Reviews of Interventions was used to assess the quality of included studies,[19,20] which was supplemented by Jadad score.

2.4. Data synthesis and analysis

Data manipulation and analysis were performed using RevMan Version 5.4 in conjunction with Excel (Office 365). Meta-analysis was performed where outcomes from at least 2 studies could be obtained by using standard statistical procedures.

Dichotomous data were calculated by risk ratio, and measurement data by weighted mean difference (WMD). Statistical heterogeneity was assessed by using the chi-square test and was quantified by using the I^2 statistic, with a value >50% considered to represent substantial heterogeneity. A fixed-effect model was used to produce a pooled estimate of outcomes if $I^2 \leq 50\%$. Otherwise, a random-effects model was chosen. A P value of <.05 was considered to show significance.

2.5. Ethical statement

All analyses were based on previously published studies; thus no ethical approval and patient consent were required.

3. Results

The selection process is summarized in Figure 1. The initial electronic search generated 1400 records in total. After removing duplicates, screening titles and abstracts, and further reviewing full texts, 5 trials were included in our quantitative analysis.

3.1. Study characteristics

The characteristics of the included studies are described in Table 1. The 5 studies recruited 409 participants (205 were assigned to treatment groups, whereas 204 to control groups) and were all conducted in China. Except for 1 study using colonic transit time >48 hour as diagnostic criteria, Rome III was applied

in the other 4 studies. All included studies are RCTs, which comparing combination therapy of FMT and laxatives with laxative therapy alone. Laxatives referred to lactulose in 3 studies, polyethylene glycol electrolyte powder in 1 study, and macrogol 4000 powder in 1 study. All studies mixed stool with sterile saline, with concentration fluctuating between 0.08 g/ml and 0.2 g/ml. FMT was all performed through the upper digestive tract. All the 5 studies performed periodic FMT. The single doses ranged from 100 ml to 400 ml and the frequency was 3 times or 6 times. The follow-up period varied from 4 weeks to 12 weeks.

3.2. Methodological quality

Methodological quality assessment is shown in Figure 2 (risk of bias assessed with RevMan Version 5.4) and Table 2 (Jadad scale). All included studies were randomized controlled trial studies with comparable baselines. Only 1 study reported to conceal allocation of randomization by the opaque sealed envelope system, be single blinding (the investigators were blinded to the treatment assignment but patients were not blinded to the treatment), and described withdrawals and dropouts in detail (an intention-to-treat analysis was performed), while the other 4 studies didn't mention these aspects. The Jadad scale scores varied from 1 to 7. Across studies, 1 study scored five, 4 studies scored three.

3.3. Treatment effect

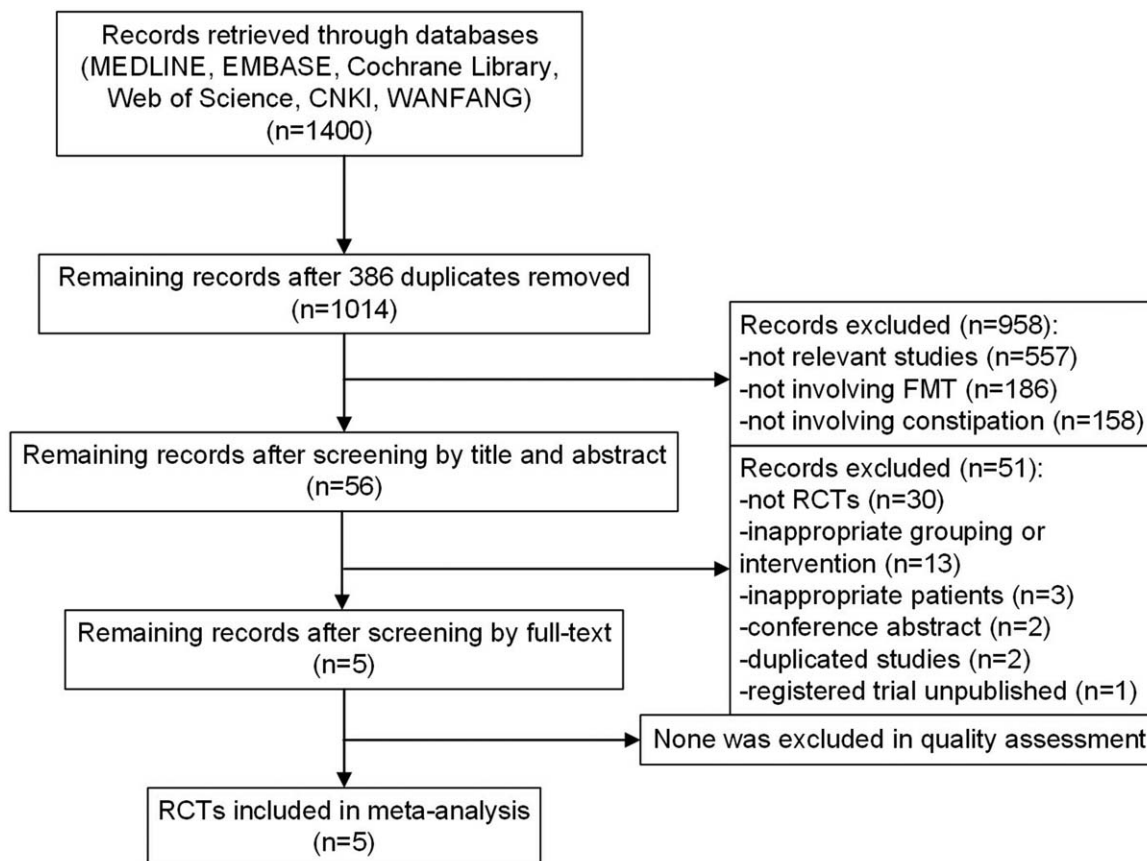Efficacy indicators included in our meta-analysis are as follows.

Figure 1. Flow chart of literature selection.

Table 1

Characteristics of included RCTs of FMT in functional constipation.

References (first author, year, location)	Participants					Intervention therapy			
	Mean age (Mean±SD)	Gender (F/T)	duration of FMT (Mean±SD)	Costipation definition	Sample size in Tr/Ct	Intervention therapy	Fecal microbiota preparation	FMT route	Frequency and duration
Tian 2017, China[21]	Tr: 53.1±10.2 Ct: 55.4±12.1	Tr: 19/30 Ct: 21/30	Tr: 9.5±2.4 Ct: 8.9±4.0	colonic transit time>48h	30/30	FMT + Macrogol 4000 powder	The stool (100g) was mixed with 500ml of sterile saline.	nasointestinal tube (placed in the proximal jejunum)	once per day (100ml)×6 d
Liu 2017, China[22]	Tr: 44.27±14.34 Ct: 47.23±13.15	Tr: 19/30 Ct: 21/30	Tr: 10.77±6.93 Ct: 9.27±7.47	Rome III criteria	30/30	FMT + PEG	The stool (80 – 100g) was mixed with 1000ml of sterile saline.	gastroscope (placed in the duodenum)	Once (300ml) every 3 d×3 times
Du 2019, China[23]	Tr: 69.21±3.58 Ct: 70.52±3.67	Tr: 19/43 Ct: 20/43	Tr: 1.35±0.24 Ct: 1.51±0.23	Rome III criteria	43/43	FMT + Lactulose	The stool (50g) was mixed with 250 ml of sterile saline.	gastroscope (placed in the duodenum)	Once (150ml) every 3 wk×3 times
Jiang 2019, China[24]	Tr: 68.4±5.3 Ct: 68.7±5.2	Tr: 26/50 Ct: 25/50	Tr: 4.7±2.2 Ct: 4.6±2.4	Rome III criteria	50/50	FMT + Lactulose	The stool (80 – 100g) was mixed with 1000ml of sterile saline.	gastroscope (placed in the duodenum)	Once (400ml) every 4 d×3 times
Ye 2019, China[25]	Tr: 71.32±4.25 Ct: 72.10±5.72	Tr: 24/52 Ct: 22/51	Tr: 23.41±3.56 Ct: 22.89±4.61	Rome III criteria	52/51	FMT + Lactulose	The stool (80 – 100g) was mixed with 1000ml of sterile saline.	gastroscope (placed in the duodenum)	Once (300ml) every wk×6 times

References (first author, year, location)	Comparison therapy	Outcome of interest		
		Follow-up	Efficacy indicator	Adverse events
Tian 2017, China[21]	Macrogol 4000 powder (up to 20g powder was permitted if patients had no defecation for ≥ 3 days)	12 wk	Total effective rate (an average increase of one or more CSBMs per week), CSBM, BSFS score, Wexner score	Tr: 50 times adverse events in total Ct: 4 times adverse events in total
Liu 2017, China[22]	PEG (a packet of agent A and a packet of agent B dissolved in 125ml water, 2 times per day)	4 wk	Total effective rate (≥ 3 defecations per week, stool characteristics were improved), BSFS score, KESS score, PAC-QOL score	Tr: abdominal distension, diarrhea, nausea and increased exhaust occurred in 1 patient, and disappeared after 2 days. Ct: tolerable abdominal distension occurred in 2 patients, and disappeared in the second week.
Du 2019, China[23]	Lactulose (15ml, 2 times per day)	4 wk	BSFS score, Wexner score, PAC-QOL score	Tr: flatulence occurred in 1 patient, and relieved spontaneously. Ct: slight abdominal pain occurred in 3 patients, and relieved spontaneously.
Jiang 2019, China[24]	Lactulose (30ml, once per day)	6 wk	KESS score, PAC-QOL score	NR
Ye 2019, China[25]	Lactulose (15ml, 3 times per day)	6 wk	Total effective rate (≥ 3 defecations per week, hard stool turns soft)	NR

BSFS = bristol stool form scale, CSBM = complete spontaneous bowel movement, Ct = control group, F = female, KESS = knowles eccersley scott symptom, NR = not reported, PAC-QOL = patient assessment of constipation quality of life uestionnaire, PEG = polyethylene glycol electrolyte powder, SD = standard deviation, T = total, Tr = treatment group.
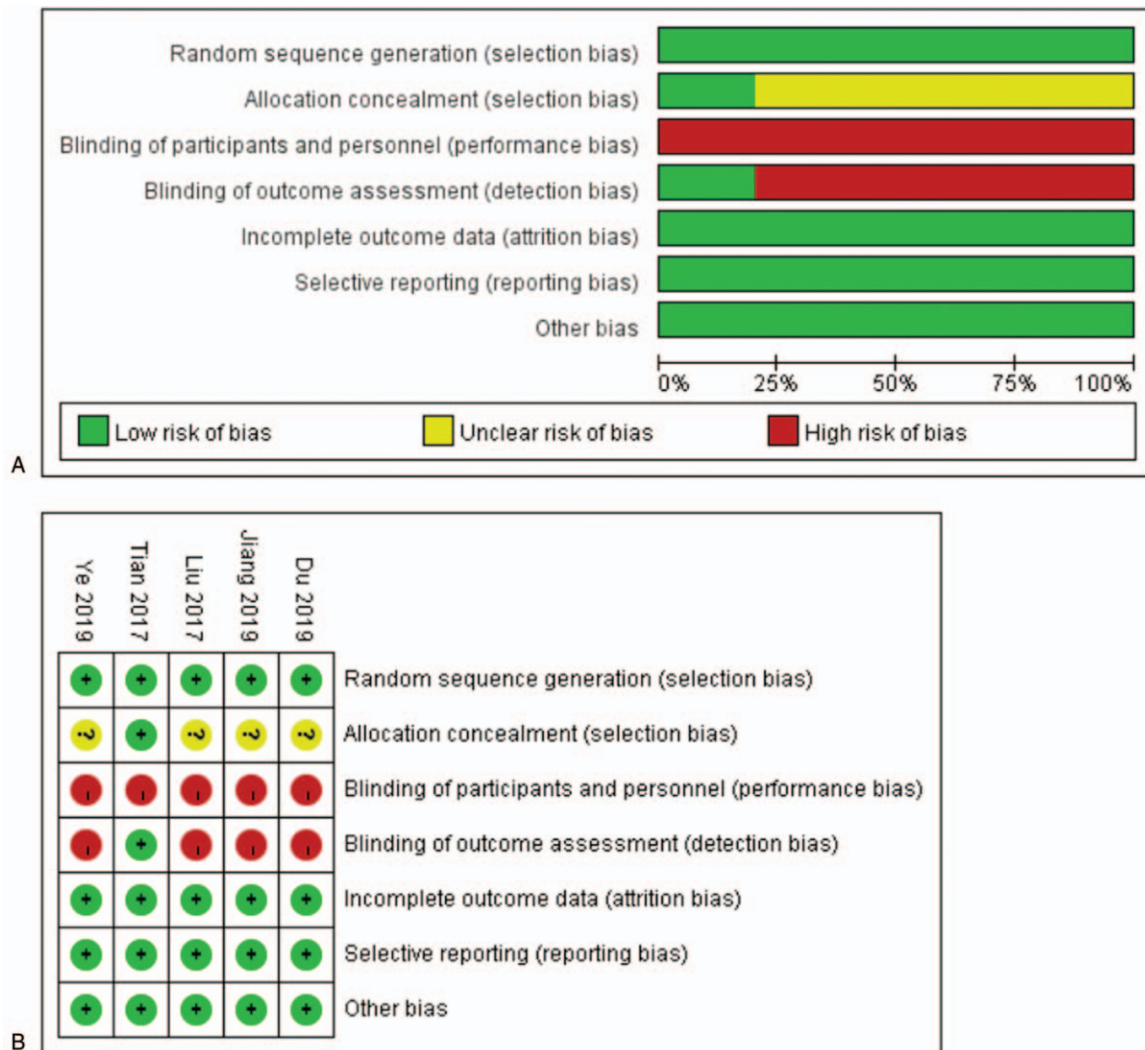
Figure 2. Methodological quality assessment of the risk of bias (A. risk of bias graph; B. risk of bias summary).

3.3.1. Total effective rate. Three of the 5 studies reported the outcome of total effective rate, which was defined as ≥3 defecations per week and improved stool characteristics and defecation difficulties in 2 studies.[22,25] However, the other 1 study[21] classified total effective rate as an average increase of 1 or more complete spontaneous bowel movements (CSBMs) per week. Thus, only the two studies with the same definition of total effective rate were included in the meta-analysis.

The meta-analysis indicated that FMT combined with laxatives showed a higher total effective rate as compared to laxatives alone (risk ratio: 1.35; 95% confidence interval [CI]: 1.14, 1.60;

$P = .0004$) (Figure 3A, Table 3). In addition, there was no significant heterogeneity under the fixed-effect model ($I^2 = 13\%$, $P = .28$).

The study which hadn't been included in the meta-analysis reported a 90.0% total effective rate in the treatment group (intervened with FMT combined with laxatives) as compared to 33.3% in the control group (intervened with laxatives alone) ($P = .0002$). Besides, the study reported the number of CSBMs per week increased both in the treatment group and control group (respectively from 1.5 ± 0.8 to 3.2 ± 1.4, and from 1.8 ± 0.7 to 2.1 ± 1.2). An intention-to-treat analysis showed a significant

Table 2

Methodological quality assessment of 5 included studies.

| References	Baseline comparability	Randomization	Double blinding	Withdrawal or dropout	Allocation concealment	Jadad scores
Tian 2017, China[21]	Yes	Yes (random number table)	No (single blinding)	Yes	Yes	5
Liu 2017, China[22]	Yes	Yes (random number table)	No	No	Unclear	3
Du 2019, China[23]	Yes	Yes (random number table)	No	No	Unclear	3
Jiang 2019, China[24]	Yes	Yes (random number table)	No	No	Unclear	3
Ye 2019, China[25]	Yes	Yes (random number table)	No	No	Unclear	3
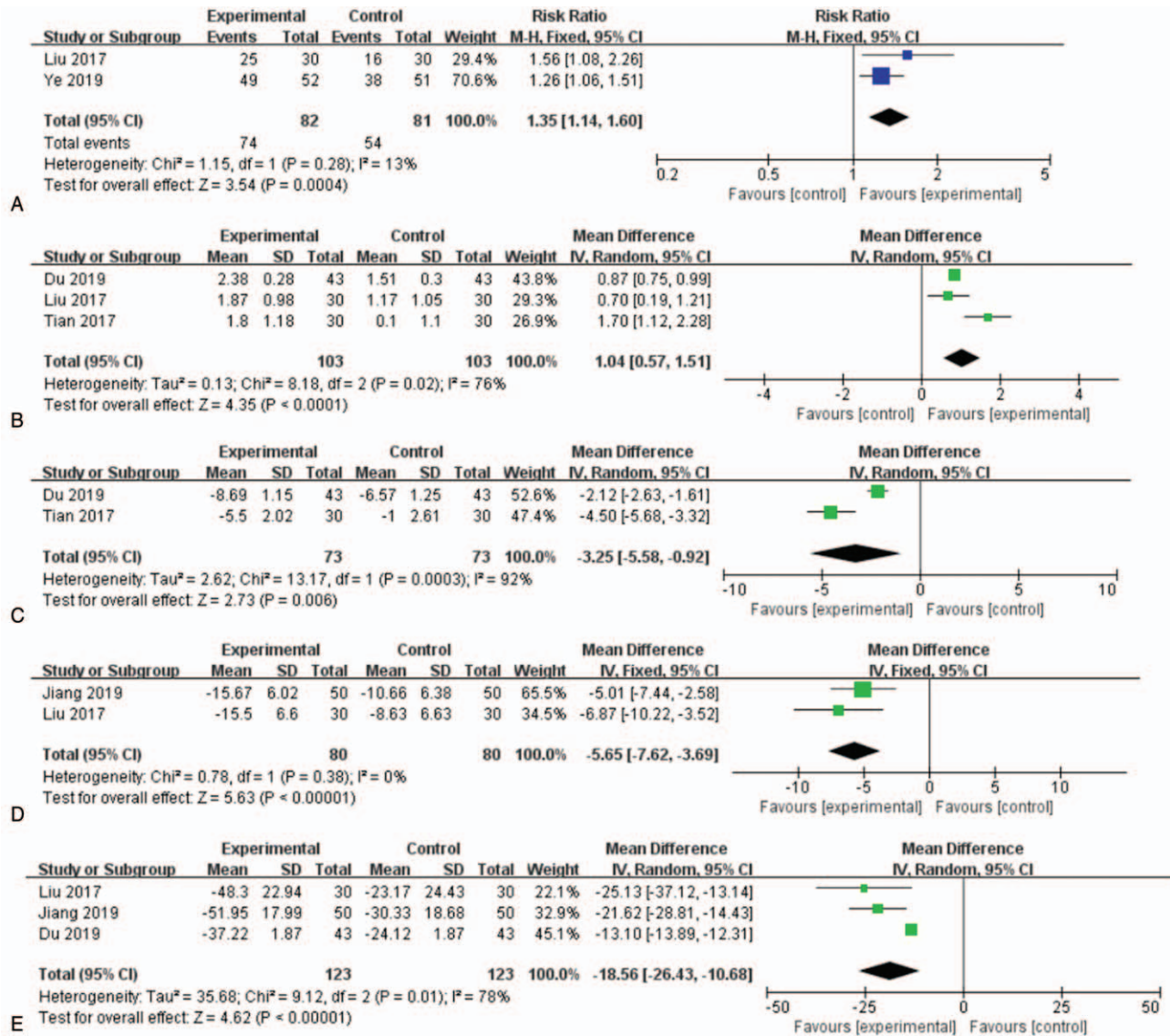
Figure 3. Forest plot of RCTs comparing a combined therapy of FMT and laxatives with laxatives for functional constipation (A. total effective rate; B. BFSF score; C. Wexner score; D. KESS score; E. PAC-QOL score).

difference of CSBMs between the 2 groups after treatment ($P=.001$).

3.3.2. Bristol stool form scale (BSFS). BSFS was measured in 3 studies[21–23] to estimate stool consistency. The BSFS scores range from 1 to 7 and the higher the scores of BSFS, the looser the

stools: stools that were rated as 1 or 2 were defined as hard, those rated 6 or 7 were defined as loose, and those rated 3, 4, or 5 were defined as normal.[26,27]

Overall, FMT combined with laxatives significantly elevated BSFS score compared with laxatives alone (WMD: 1.04; 95% CI: 0.57, 1.51; $P<.00001$) (Figure 3b, Table 3). However, there was

Table 3

Summary of meta-analysis outcomes.

Outcomes	No. of studies in meta-analysis	No. of patients (Tr/Ct)	Results		Heterogeneity	
			Overall estimate (95% CI)	P	I²	P
TER	2[22,25]	82/81	RR: 1.35 (1.14, 1.60)	.0004	13%	.28
BSFS	3[21–23]	103/103	WMD: 1.04 (0.57, 1.51)	<.00001	76%	.02
Wexner	2[21,23]	73/73	WMD: −3.25 (−5.58, −0.92)	.006	92%	.0003
KESS	2[22,24]	80/80	WMD: −5.65 (−7.62, −3.69)	<.00001	0%	.38
PAC-QOL	3[22–24]	123/123	WMD: −18.56 (−26.43, −10.68)	<.00001	78%	.01

BSFS = bristol stool form scale, CI = confidence interval, Ct = control group, KESS = knowles-eccersley-scott-symptom, PAC-QOL = patient assessment of constipation quality of life questionnaire, RR = risk ratio, TER = total effective rate, Tr = treatment group, WMD = weighted mean difference.

significant heterogeneity ($I^2 = 76\%$, $P = .02$) and the random-effects model was chosen.

3.3.3. Wexner constipation scale (also known as Cleveland constipation scoring system).

The Wexner constipation scale is a validated and internationally adopted questionnaire, which is used to quantify the severity of constipation.[21,27] This scoring system consists of 8 items with a full score of 30. Higher scores indicate a more severe condition of constipation. Only 2 studies[21,23] calculated changes of Wexner score before and after treatment in both groups.

The result showed that under random-effects model, combined therapy of FMT and laxatives resulted in greater Wexner score reduction relative to controls (WMD: -3.25; 95% CI: -5.58, -0.92; $P = .006$) (Figure 3c, Table 3), with high statistical heterogeneity ($I^2 = 92\%$, $P = .0003$).

3.3.4. Knowles-eccersley-scott-symptom (KESS) score.

KESS questionnaire, an optimized version based on Wexner constipation scale, is also used to assess the severity of constipation, which contains 11 items and has the highest score of 39, and patients who get the higher score have more serious state of constipation as compared to those get the lower score.[27,28] Two studies[22,24] reported the outcome of KESS score.

Similar with the variation of Wexner score, KESS score was decreased more significantly in treatment groups (combined therapy of FMT and laxatives) than in control groups under the fixed-effect model (WMD: -5.65; 95% CI: -7.62, -3.69; $P < .00001$) (Figure 3D, Table 3), and there was no statistical heterogeneity ($I^2 = 0\%$, $P = .38$).

3.3.5. Patient assessment of constipation quality of life (PAC-QOL) questionnaire.

PAC-QOL questionnaire consists of 28 items, which are divided into 4 dimensions: worry and concern (11 items), physical discomfort (4 items), psychological discomfort (8 items) and satisfaction (5 items).[27,29] Each item is scored on a 5-point scale. The more serious the illness, the higher the score. Three studies[22–24] measured PAC-QOL score.

Overall, there was a significant effect in favor of combination therapy of FMT and laxatives improving the quality of life of patients with constipation (WMD: -18.56; 95% CI: -26.43, -10.68; $P < .00001$) (Figure 3E, Table 3). There was significant heterogeneity ($I^2 = 78\%$, $P = .01$) and the random-effects model was chosen.

3.4. Adverse events

Three of the 5 studies reported adverse events (Table 1). Two studies mainly reported gastrointestinal symptoms, such as abdominal distension, diarrhea, nausea, abdominal pain occurred in treatment or control groups, and these symptoms were mild and relieved spontaneously. Thus, no patients withdrew because of adverse events in these studies. One study reported adverse events beyond gastrointestinal symptoms. In this study, a total of 50 times adverse events were observed in the treatment group, including endoscopy related respiratory difficulty (22 times), nausea (12 times), abdominal pain (5 times), diarrhea (4 times), flatulence (4 times), transient fever (2 times) and sedation contraindication (once), compared to 4 times in control group, including abdominal pain (3 times) and flatulence (once). At last, two withdrew owing to intolerable nasointestinal tube and 1 quitted due to sedation contraindication in the treatment

group. Meanwhile, no 1 in the control group withdrew because of treatment-related adverse reactions.

4. Discussion

This meta-analysis investigated the joint efficacy of FMT and laxatives in the treatment of functional constipation in adults. To date, this is the first meta-analysis of FMT in functional constipation using RCTs. The results showed that, compared to laxatives alone, combined therapy of FMT and laxatives could better increase stool frequency (total effective rate), improve stool consistency (BSFS score), relieve the severity of constipation (Wexner score, KESS score), and promote patients' quality of life (PAC-QOL score).

Our meta-analysis was performed with the use of a robust design. Efforts were made to search various sources to minimize publication bias, and no language restrictions were applied. In an attempt to minimize clinical homogeneity, interventions in treatment and control groups were strictly qualified as described above. Besides, only RCTs were included.

Our analyses showed unstable heterogeneity fluctuating from 0% to 92%. This was likely due to the poor methodological quality of the majority of included studies, a small sample size, and clinical heterogeneity. Patients' age, course and severity of the disease, as well as the implementation methods of FMT, follow-up time and donor selection, types and doses of laxatives may lead to clinical heterogeneity. Moreover, the efficacy indicators such as BSFS, Wexner scale, KESS questionnaire and PAC-QOL questionnaire are relatively subjective indicators, and therefore intra-/inter-observer variation may exist.

This meta-analysis has several limitations. First, we tried to identify all eligible RCTs of functional constipation treated with FMT, but only 5 studies were included with small sample size, and were all conducted in China. An ongoing eligible RCT registered on the Cochrane library was found and we will stay focus on it.[31] Second, in terms of interventions, the types and doses of laxatives are not strictly unified, as well as the fecal microbiota preparation, transplantation route, frequency and duration of FMT. Third, the effect of microflora transplantation may decrease with time,[31,40] the follow-up time of all studies was not long enough to evaluate the long-term efficacy of FMT in treating functional constipation. Forth, 2 of 5 studies did not report on adverse events; therefore, the confidence in assessing safety is diminished by the absence of data in 40% of the 5 trials considered. Last but not least, we found that the methodological quality of the analyzed RCTs was unsatisfactory with no blinding, and allocation concealment is unclear for 80%. According to the Jadad scale, only 1 study was classified as high-quality RCT.

The dysbiosis of gut microbiota contributes to functional constipation. The intestinal flora of patients with chronic constipation is quite different from that of healthy people.[16,32] Changes in intestinal flora in patients with constipation are related to colonic transit time and methane production, which has been proven to slow intestinal movement.[33] FMT may work through the following ways[11]:

(i) restore the abundance and diversity of the original intestinal flora by reconstructing the patient's intestinal flora system;
(ii) increase the natural dominant flora to compete with harmful flora, thus forming a healthy intestinal micro-ecosystem;
(iii) change the metabolic level of intestinal flora, such as adjusting the metabolic process of bile acid and short-chain fatty acids;

(iv) improve the immune system of the intestinal tract to some extent.

FMT alone in the treatment of functional constipation had been proved to be effective. In a recently published study,[30] 1356 patients with constipation were treated with FMT and followed up for 3 months. The clinical cure rates (spontaneous defecation ≥ 3 times per week) of these patients at 3, 12 and 36 months after FMT were 41.3% (560/1356), 35.2% (320/909) and 31.4% (69/220), respectively. Clinical improvement rates (clinical symptoms are significantly improved as compared with that before treatment but don't reach the cure level) were 29.0% (393/1356), 27.8% (253/909) and 29.1% (64/220), respectively.

As mentioned above, the dysbiosis of gut microbiota is important pathogenesis of functional constipation. Therefore, gut flora regulation is a kind of etiological treatment, as compared to laxatives which are widely used and always indispensable to temporarily relieve the symptoms for patients with chronic functional constipation. Thus, we explored the joint efficacy of FMT and laxatives in this meta-analysis, expecting that the combination therapy can increase the curative effect. The results indicated that combination therapy may be a better choice. Moreover, there may be synergistic effects between FMT and some laxatives. Lactulose is a kind of osmotic laxatives which attracts water and keep it in the colon, to hydrate and soften stools and unblocks the system without causing harsh gastrointestinal side effects. Meanwhile, animal experiments showed that lactulose may play a role in the regulation of intestinal flora. Lactulose intervention enhanced the α-diversity of the gut microbiota of C57BL/6J mice; increased the abundance of probiotics Bifidobacteriaceae and Lactobacillaceae, which were proven to be effective for functional constipation.[1,34]

The incidence of adverse events related to FMT reported in the literature is less than 1%, mainly including 2 aspects, namely, operation-related and graft-related adverse reactions.[42] Endoscopy related respiratory difficulties and digestive system discomforts are the 2 most common adverse reactions. Compared with endoscopy and catheterization, oral bacterial capsules may be an alternative method to avoid operation-related adverse reactions which is more convenient and less expensive.[43–45] Digestive system discomfort is mostly mild and self-limited and can be given symptomatic treatment if necessary. In all, FMT has few side effects being applied alone or in combination with laxatives.

In addition, we hope that more studies will be performed to explore the combined treatment of functional constipation. For instance, the combined therapy of FMT and prebiotics may have bright prospects. Prebiotics typically refer to selectively fermented nondigestible food ingredients or substances that specifically support the growth and/or activity of health-promoting bacteria that colonize the gastrointestinal tract.[35] Probiotics had been widely used to adjust the intestinal micro-ecosystem in patients with constipation before the advent of FMT. The combination of probiotics and prebiotics is called synbiotics, which may have synergistic effects to modify microbiota composition, and play a role in gastrointestinal functions.[36,37] A randomized, placebo-controlled trial suggested that dietary supplementation with synbiotic improved evacuation-parameters-associated symptoms and colonic motility in patients with slow transit constipation.[38] Therefore, the combined therapy of FMT and prebiotics is worth expecting. Although several case-series studies indicated the efficacy and safety of the combined therapy,[39–41] high-quality RCTs are still needed for further verification.

5. Conclusion

Our meta-analysis provides evidence that, overall, the combined therapy of FMT and laxatives may be a reasonably effective and safe treatment for people with functional constipation. However, Given the limitations mentioned above, the interpretation is challenging and additional evidence is required from rigorous RCTs.

In addition, we hope related researches can optimize the methodological design. For example, the FMT should be delivered either by repeated naso-intestinal intubations, or by use of intestinal delivery or colonic delivery capsules with appropriate sham or control treatment. We also expect that more studies will be performed exploring the efficacy and safety of combined therapy for functional constipation, especially RCTs researching a combined therapy of FMT and probiotics. It would be better if these studies have a longer follow-up time to explore the regularity of the efficacy of FMT over time.

Author contributions

Data curation: Kepeng Yang.
Investigation: Sijia Fang, Shan Wu, Lina Ji.
Methodology: Sijia Fang, Shan Wu, Lina Ji, Kepeng Yang.
Software: Sijia Fang.
Supervision: Yongsheng Fan, Xinchang Wang, Kepeng Yang.
Writing – original draft: Sijia Fang.
Writing – review & editing: Yongsheng Fan, Xinchang Wang.

Correction

The funding details originally appeared incorrectly as 112123A12201/001/002 and has since been corrected to 2020YKJ03.

References

[1] Dimidi E, Christodoulides S, Fragkos KC, et al. The effect of probiotics on functional constipation in adults: a systematic review and meta-analysis of randomized controlled trials. Am J Clin Nutr 2014; 100:1075–84.
[2] Lee-Robichaud H, Thomas K, Morgan J, et al. Lactulose versus polyethylene glycol for chronic constipation. Cochrane Database Syst Rev 2010;7:Cd007570.
[3] Xin HW, Fang XC, Zhu LM, et al. Diagnosis of functional constipation: agreement between Rome III and Rome II criteria and evaluation for the practicality. J Dig Dis 2014;15:314–20.
[4] Mugie SM, Benninga MA, Di Lorenzo C. Epidemiology of constipation in children and adults: a systematic review. Best Pract Res Clin Gastroenterol 2011;25:3–18.
[5] Sumida K, Molnar MZ, Potukuchi PK, et al. Constipation and risk of death and cardiovascular events. Atherosclerosis 2019;281:114–20.
[6] Rao SS, Rattanakovit K, Patcharatrakul T. Diagnosis and management of chronic constipation in adults. Nat Rev Gastroenterol Hepatol 2016; 13:295–305.
[7] Rao SS. Constipation: evaluation and treatment of colonic and anorectal motility disorders. Gastrointest Endosc Clin N Am 2009;19:117–39. vii.
[8] Forootan M, Bagheri N, Darvishi M. Chronic constipation: a review of literature. Medicine (Baltimore) 2018;97:e10631.
[9] Black CJ, Ford AC. Chronic idiopathic constipation in adults: epidemiology, pathophysiology, diagnosis and clinical management. Med J Aust 2018;209:86–91.
[10] Shin JE, Park KS, Nam K. Chronic functional constipation. Korean J Gastroenterol 2019;73:92–8.
[11] Tian HL, Li N. Study on the application of intestinal microecological concept in the treatment of chronic constipation. J Surg Concepts Pract 2020;25:98–101.

[12] Prichard DO, Bharucha AE. Recent advances in understanding and managing chronic constipation. F1000Res 2018;7:1–10. (F1000 Faculty Rev).

[13] Ohkusa T, Koido S, Nishikawa Y, et al. Gut microbiota and chronic constipation: a review and update. Front Med(Lausanne) 2019;6:1–9.

[14] Zhao Y, Yu YB. Intestinal microbiota and chronic constipation. Springerplus 2016;5:1130.

[15] Dimidi E, Christodoulides S, Scott SM, et al. Mechanisms of action of probiotics and the gastrointestinal microbiota on gut motility and constipation. Adv Nutr 2017;8:484–94.

[16] Chen Q, Jiang J. Relationship between functional constipation and brain-gut-microbiota axis. Zhonghua Wei Chang Wai Ke Za Zhi 2017;20:1345–7.

[17] Kelly CR, Kahn S, Kashyap P, et al. Update on fecal microbiota transplantation 2015: indications, methodologies, mechanisms, and outlook. Gastroenterology 2015;149:223–37.

[18] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009;6:e1000100.

[19] Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database Syst Rev 2019;10:Ed000142.

[20] Higgins JPT GSe. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011 Available from www.cochrane-handbookorg.

[21] Tian H, Ge X, Nie Y, et al. Fecal microbiota transplantation in patients with slow-transit constipation: a randomized, clinical trial. PLoS One 2017;12:e0171308.

[22] Liu QY, Zhang S, Chao HC, et al. Effect of fecal microbial transplant on clinical outcomes and life quality in refractory functional constipation. Chin J Digest Med Imageol (Electronic Edition) 2017;7:4–8.

[23] Dun SJ, Gao HB, Li D, et al. Effect of fecal bacteria transplantation combined with lactulose in the treatment of chronic functional constipation in the elderly. J Pract Med 2019;35:2731–6.

[24] Jiang H. Effects of fecal microbiota transplantation combined with lactulose on the gastrointestinal function and quality of life in patients with intractable functional constipation. Health Med Res & Prac 2019;16:63–6.

[25] Ye JT. Clinical efficacy of fecal bacteria transplantation combined with lactulose in the treatment of functional constipation in the elderly and its effect on gastrointestinal hormone. Zhejiang Journal of Integrated Traditional Chinese and Western Medicine 2019;29:555–7.

[26] Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol 1997;32:920–4.

[27] Zhou S-Y, Liu T, Qin H-Z, et al. Characteristics of commonly used scales for diagnosis and treatment outcome evaluation in constipation. World Chin J Digestol 2013;21:2611–6.

[28] Knowles CH, Eccersley AJ, Scott SM, et al. Linear discriminant analysis of symptoms in patients with chronic constipation: validation of a new scoring system (KESS). Dis Colon Rectum 2000;43:1419–26.

[29] Marquis P, De La Loge C, Dubois D, et al. Development and validation of the Patient Assessment of Constipation Quality of Life questionnaire. Scand J Gastroenterol 2005;40:540–51.

[30] Li N, Tian HL, Chen QY, et al. [Efficacy analysis of fecal microbiota transplantation in the treatment of 2010 patients with intestinal disorders]. [Chinese]. Zhonghua Weichang Waike Zazhi 2019;22:861–8.

[31] Li XA. Fecal Microbiota Transplantation for Chronic Functional Constipation. Available at: https://clinicaltrialsgov/show/NCT03018613. 2017-01-12/2020-08-11.

[32] Gerritsen J, Smidt H, Rijkers GT, et al. Intestinal microbiota in human health and disease: the impact of probiotics. Genes Nutr 2011;6:209–40.

[33] Huang L, Zhu Q, Qu X, et al. Microbial treatment in chronic constipation. Sci China Life Sci 2018;61:744–52.

[34] Zhai S, Zhu L, Qin S, et al. Effect of lactulose intervention on gut microbiota and short chain fatty acid composition of C57BL/6J mice. Microbiologyopen 2018;7:e00612.

[35] Bindels LB, Delzenne NM, Cani PD, et al. Towards a more comprehensive concept for prebiotics. Nat Rev Gastroenterol Hepatol 2015;12:303–10.

[36] Ford AC, Quigley EM, Lacy BE, et al. Efficacy of prebiotics, probiotics, and synbiotics in irritable bowel syndrome and chronic idiopathic constipation: systematic review and meta-analysis. Am J Gastroenterol 2014;109:1547–61. quiz 6, 62.

[37] Morelli L, Zonenschain D, Callegari ML, et al. Assessment of a new synbiotic preparation in healthy volunteers: survival, persistence of probiotic strains and its effect on the indigenous flora. Nutr J 2003;2:11.

[38] Ding C, Ge X, Zhang X, et al. Efficacy of synbiotics in patients with slow transit constipation: a prospective randomized trial. Nutrients 2016;8:

[39] Ge X, Tian H, Ding C, et al. Fecal microbiota transplantation in combination with soluble dietary fiber for treatment of slow transit constipation: a pilot study. Arch Med Res 2016;47:236–42.

[40] Zhang X, Tian H, Gu L, et al. Long-term follow-up of the effects of fecal microbiota transplantation in combination with soluble dietary fiber as a therapeutic regimen in slow transit constipation. Sci China Life Sci 2018;61:779–86.

[41] Ge X, Ding C, Gong J, et al. Short-term efficacy on fecal microbiota transplantation combined with soluble dietary fiber and probiotics in the treatment of slow transit constipation. Zhonghua Wei Chang Wai Ke Za Zhi 2016;19:1355–9.

[42] Zhang XY, Chen QY, Li N, et al. Indication selection and clinical application strategies of fecal microbiota transplantation. Zhonghua Wei Chang Wai Ke Za Zhi 2020;23:509–15.

[43] Tian HL, Chen QY, Yang B, et al. Effects of fecal microbiota transplantation in different routes on the clinical efficacy of slow transit constipation. Zhonghua Wei Chang Wai Ke Za Zhi 2020;23(Z1):63–8.

[44] Kao D, Roach B, Silva M, et al. Effect of oral capsule- vs colonoscopy-delivered fecal microbiota transplantation on recurrent clostridium difficile infection: a randomized clinical trial. JAMA 2017;318:1985–93.

[45] Staley C, Kaiser T, Vaughn BP, et al. Durable long-term bacterial engraftment following encapsulated fecal microbiota transplantation to treat clostridium difficile infection. mbio 2019;10:e01586–19.