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Systematic review: faecal transplantation for the treatment of *Clostridium difficile*-associated disease

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SUMMARY

Background
Management of recurrent *Clostridium difficile*-associated disease (CDAD), particularly in elderly patients, remains clinically challenging. Faecal transplantation (FT) may restore normal microbiota and break the cycle of recurrent CDAD.

Aim
To critically appraise the clinical research evidence on the safety and effectiveness of FT compared with standard care in the treatment of patients with CDAD.

Methods
A comprehensive literature search was conducted by a research librarian to identify relevant studies published between 2000 and 2011. The Cochrane Library, PubMed, EMBASE, CINAHL, Biological Abstracts, BIOSIS Previews and Web of Science were searched using the following Medical Subject Headings (MeSH) terms and keywords, alone or in combination: Clostridium infections/Clostridium difficile/pseudomembranous/colitis/faeces/rectal/colon flora/gastrointestinal/nasogastric tube/enema/donor/transplant/infusion/bacteriotherapy/human probiotic infusion. Methodological quality of the included case series studies was assessed in terms of patient selection criteria, consecutive recruitment, prospective data collection, reporting of lost to follow-up, and follow-up rates.

Results
No controlled studies were found. Based on the weak evidence from seven full-text case series studies of 124 patients with recurrent/refractory CDAD, FT appears to be a safe and effective procedure. In most cases (83%) symptoms improved immediately after the first FT procedure, and some patients stayed diarrhoea free for several months or years.

Conclusions
Although these results appear to be promising, the treatment effects of faecal transplantation cannot be determined definitively in the absence of a control group. Results from randomised controlled trials that compare faecal transplantation to oral vancomycin without or with a taper regimen will help to better define the role of faecal transplantation in the management of recurrent CDAD.

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INTRODUCTION

Healthcare-associated infections, defined as infections that patients acquire during the course of receiving treatment for other conditions,[1] are an important global public health problem. *Clostridium difficile* (*C. difficile),* Gram-positive, spore-forming bacteria, is the most important and common nosocomial pathogen of healthcare-associated diarrhoea in hospitalised patients in developed countries and causes millions of human infections worldwide annually. It is the cause of at least 25% of all cases of antibiotic-associated diarrhoea and accounts for nearly all cases of pseudomembranous colitis. *C. difficile*-associated disease (CDAD) covers a broad spectrum of patient conditions, ranging from mild diarrhoea to life-threatening complications, such as ileal perforation, fulminant colitis, toxic megacolon, or brain empyema.[2] *C. difficile* produce enterotoxin (toxin A), cytotoxin (toxin B), and binary toxin.[3]

During the past several years, CDAD has become more frequent and severe, more refractory to standard therapy, and more likely to relapse.[4, 5] This pattern is widely observed in Canada, the United States, and Europe and is attributed to a new hypervirulent strain of *C. difficile* called NAP1/BI/027.[6, 7] Since 2002, an epidemic of this new strain has spread to as many as 30 hospitals in Quebec, with a 30-day mortality rate of 23.0% compared with 7.0% of matched control patients.[8]

In the United States, the number of hospital discharges with CDAD more than doubled from 2001 to 2005.[9] CDAD primarily affects elderly patients; about 49% of CDAD patients were aged 65–84 years and 19% were 85 years or older. CDAD patients were associated with more severe and complex conditions, longer hospital stay (nearly three times higher than average), and higher mortality rate (about 4.5 times higher than average). A Canadian national survey also revealed that 70% of 1493 CDAD cases identified between 2004 and 2005 were 65 years or older.[7]

Mature colonic bacterial microbiota in a healthy adult is generally resistant to *C. difficile* colonisation. Any factors associated with the alteration of normal intestinal microbiota increases the risk of *C. difficile* colonisation after exposure to the bacteria.[10] The most common risk factor is the use of broad-spectrum antibiotics, or concomitant use of multiple and prolonged antimicrobials.[10–12] Other recognised risk factors for CDAD include advanced age (65 years or older), recent transplantation or gastrointestinal surgery, use of immunosuppressive drugs or proton pump inhibitors, prolonged hospitalisation, malnutrition, nasogastric tube feeding and presence of multiple co-morbidities.[3, 13–16] However, the host immune response is considered the major determinant of outcome following exposure to *C. difficile*.[17]

Standard treatment of CDAD includes: discontinuation of the offending/inducing antibiotics and *C. difficile* targeted antibiotic therapy with oral metronidazole, or vancomycin (the only US FDA approved drug for CDAD).[18–22] Although generally effective in the majority of patients in achieving clinical improvement, the use of antibiotics (e.g. vancomycin) does not restore intestinal microbiota, nor does it reduce the exposure to *C. difficile* in the environment, co-morbidities or other host risk factors.[23, 24]

The major problem in treating CDAD is the high recurrence rate,[25, 26] and the emergence of the new strain of *C. difficile* (BI/NAP1/027) which complicates matters.[27] Despite the fact that more than 90% of patients respond to the treatment initially, 20% to 60% of patients will experience at least one recurrence within a few weeks of completion of the vancomycin treatment.[20, 24, 28, 29] Important and consistently reported risk factors for recurrent CDAD include inadequate antitoxin antibody response, persistent disruption of the colonic microbiota, advanced age, continuation of non-*C. difficile* antimicrobial therapy, prolonged hospital stay, concomitant use of antacid medications, and long-term dialysis.[27, 30]

Optimal management of multiple relapses remains clinically challenging. Strategies such as additional courses of oral metronidazole or vancomycin, pulsed/tapered antibiotics, nitazoxanid, rifaximin, alone or in combination, the administration of probiotics and intravenous immunoglobulin, toxin binding, faecal transplantation, have been used with varying degrees of success.[21, 31–33]

Faecal transplantation (FT), also known as faecal bacteriotherapy, faecal microbiota transplantation, faecal microbiota reconstitution, or human probiotic infusion, refers to the process of instilling a liquid suspension of stool from a healthy donor into the patient's upper gastrointestinal tract through a nasogastric/nasoduodenal catheter or gastroscopy, or into the colon through a colonoscopy or a rectal catheter.[18]

The precise mechanisms of FT in the treatment of CDAD remain unclear, but may involve the re-colonisation of microbiota with missing components to generate colonisation resistance or direct antagonistic activity of the normal microbiota to *C. difficile*.[34] Unlike the transient use of antibiotics (e.g. vancomycin) for *C. difficile*, implanted microbiota may provide a prolonged presence

of 'antagonistic' activity, break the cycle of antimicrobial use, and prevent future colonisation by *C. difficile*.[34]

The use of human faecal microbiota to treat gastrointestinal disorders is not a novel concept. FT has been used sporadically in one form or another since the mid-1950s, primarily for antibiotic-associated diarrhoea and severe *C. difficile*-related diarrhoea. One recent review[35] observed a trend of increased interest in this procedure as demonstrated by the increased volume of clinical studies published since 2005 and reported promising results from 22 publications in a total of 239 patients with various gastrointestinal disorders.

The objective of this systematic review is to critically appraise the best available clinical research evidence on the safety and efficacy/effectiveness of FT compared with standard care in the treatment of patients with CDAD. This review is an update of an earlier evidence assessment report on the safety and effects of FT for the treatment of CDAD or ulcerative colitis[36] and focuses on CDAD only.

METHODS

Search strategy

A comprehensive search strategy was developed by a research librarian to identify any potentially relevant studies on FT for the treatment of CDAD. To keep findings contemporary, only studies published in the past 10 years (from January 2000 to October 2011) were included. Electronic databases searched included the Cochrane Library, PubMed, EMBASE, CINAHL, Biological Abstracts, BIOSIS Previews (ISI) and Web of Science (ISI). Websites of various health technology assessment agencies, regulatory agencies and guideline clearinghouses were also searched. The last search was run on 12 October 2011. The following Medical Subject Headings (MeSH) terms and keywords (including suffix variations of the root words) were used alone or in combination: Clostridium infections/Clostridium difficile/pseudomembranous/faeces/stool/rectal/colonflora/gastrointestinal/nasogastric tube/enema/donor/transplant/implant/infusion/transfusion/bacteriotherapy/human probiotic infusion. No limits were applied for study design.

The bibliographies of relevant articles were manually searched for additional references that may have been missed in the database searches. We also contacted several authors from Canada for missing information on their studies or information about ongoing clinical trials. Full details of the search strategy are available from the corresponding author upon request.

Study selection

Title and abstracts were screened and eligibility of studies was determined by one reviewer (BG) using predefined inclusion and exclusion criteria. Systematic reviews, defined by the five criteria proposed by Cook and colleagues,[37] that examined the safety and efficacy evidence from randomised or non-randomised comparative studies were included for analysis. Primary studies were included if they (1) included patients of any age with CDAD, (2) compared FT with standard care or reported safety and efficacy/effectiveness outcomes of FT in a series of patients without a control group, (3) were English full text studies published between 2000 and 2011. Studies were excluded if they (1) focused on the treatment using antibiotics or other probiotics, (2) included patients primarily with other gastrointestinal diseases, such as Crohn's disease or irritable bowel syndrome, or (3) were case reports.

Quality assessment

Methodological quality of the included case series studies was assessed by one reviewer (BG). The five most important aspects of the Centre for Reviews and Dissemination (CRD) checklist for appraising the quality (including risk of bias and quality of reporting) of case series studies[38, 39] were used to examine each study. These included: (i) Were selection/eligibility criteria adequately reported? (ii) Were patients recruited consecutively? (iii) Were patients recruited prospectively? (iv) Was loss to follow-up reported or explained? (v) Were at least 90% of those included at baseline followed up? Results of quality assessment were not used to include or exclude studies.

Data extraction and synthesis

Data from included studies were extracted by one reviewer (BG) using a predeveloped data extraction form, and cross-checked by a second reviewer (CH) for accuracy and consistency. When overlapping patient groups were reported, only the study quoting the most complete data set was used.

Information was extracted from each included study on (i) characteristics of patients (including age, gender, severity of disease and method of diagnosis); (ii) characteristics of intervention (including delivery method, dose and frequency); (iii) type of outcome measures. Safety outcomes included any adverse events associated with the FT procedure. Indicators of treatment efficacy/effectiveness included change in frequency and severity of symptoms, such as diarrhoea, testing for CD and its toxins, changes in colonoscopic or histological examinations, health-related quality of life measures, patients'

acceptance of the procedure, prevention of more aggressive therapies (such as surgery), or reduction of emergency department visits.

Data extracted from each study and quality assessment results were synthesised using a narrative approach.

RESULTS

Description of included studies

Seven full-text case series studies[31, 40–45] and abstracts of 10 case series studies[46–55] met the predefined inclusion criteria. Six studies[40, 42–44, 54, 55] were conducted in the United States, four[45, 46, 48, 50] in Canada, three[47, 51, 52] in Australia, one each in the United Kingdom,[31] Norway,[41] Netherlands,[49] and Finland.[53]

In this review, only seven full-text case series studies[31, 40–45] were included for further analysis and synthesis. Results from the 10 abstracts were not reported due to insufficient description of patients, interventions and outcomes.

No systematic reviews (based on Cook criteria[37]), randomised or non-randomised controlled trials were identified. A list of the excluded studies and the reasons for exclusion is available from the corresponding author upon request.

Methodological quality of included studies

The five most important criteria in the Centre for Reviews and Dissemination (CRD) quality assessment checklist primarily addressed selection bias (eligible criteria, consecutive cases), attrition bias (lost to follow-up and at least 90% of patients were followed up), and detection bias (prospective design).[38, 39, 56]

Selection bias. Patient selection criteria were clearly reported in six of the seven studies. Three studies[40, 43, 44] clearly reported on the enrolment by consecutive cases, whereas in the other four studies[31, 41, 42, 45] it remains unclear whether the cases were consecutively recruited.

Attrition bias. Although the follow-up period was generally short in most studies, all seven studies followed 100% of included patients.

Detection bias. No clear description about study design was provided in two studies,[42, 45] and the other five studies were retrospective reviews of medical records of included patients.

None of the seven studies met all five criteria, thus all reached a quality rating of 'poor'.

Patient characteristics

As shown in Table 1, 124 patients were included in the seven studies, with patient number ranging from 7 to 40. Elderly patients were predominant with a mean age of over 65 years in six of the seven studies. Five studies[31, 40, 41, 43, 44] included more female patients, and in three[31, 40, 43] females accounted for more than 70% of included patients. All included patients had recurrent/refractory CDAD. Although not clearly described in one study,[42] tests for CD toxins were performed in the other six studies to confirm diagnosis. Except for three patients in one study,[41] all patients tested were CD toxin positive. Of the three patients with negative CD toxin tests, one showed characteristic pseudomembranes in the colonic mucosa on colonoscopy, and the other two were diagnosed by clinical symptoms only.[41]

Most patients developed CDAD after receiving antibiotics for various types of infections that required hospitalisation and some patients had severe comorbidities. Despite standard care with oral metronidazole or vancomycin, these patients developed a chronic pattern of repeated relapses whenever an attempt was made to discontinue the antibiotics.

Donor selection and screening

The majority of the faeces donors were family members or relatives (e.g. spouses, brothers/sisters, parents/grandparents, children/grandchildren), whereas a few were unrelated healthy volunteers or housemates. No standardised eligibility criteria were used in the seven studies. In general, donors were not eligible if they used antibiotics within the last 2–6 months, or if they had any gastrointestinal diseases.

In all studies, donors were screened for blood and stool pathogens prior to FT. The comprehensiveness of the tests varied across the studies and no standardised list of screening tests was found. Most commonly used blood tests were hepatitis virus A, B, C, human immunodeficiency virus, syphilis and most commonly used stool tests were CD toxin, ova and parasites.

Delivery methods

In all studies, fresh donor faeces were used to prepare faecal suspensions. As shown in Table 1, donor faecal suspensions were infused via nasogastric tubes,[31, 40] gastroscopy or colonoscopy,[41] colonoscopy,[42–44] or retention enema.[45] Prior to the FT procedure, all patients were treated with metronidazole or vancomycin which were then discontinued 12 h to 3 days before the procedure. Polyethylene glycol (PEG) bowel preparation was per-

Table 1 | Summary of included studies

Study	Patients				Clinical setting	Faeces suspension/ volume infused	Delivery method/ frequency	Pre-FT use of antibiotics against CD
	No.	Age, years mean (range)	Gender (M/F)	CDAD				
Aas *et al.* 2003[40] United States	18	73 (51–88)	5/13	Recurrent	Hospital or out-patient gastroenterology clinic	30 g faeces in 50–70 mL saline/25 mL	Nasogastric tube, once	Vancomycin starting $\geq$ 4 days pre-FT; discontinued the evening pre-FT
Macconnachie *et al.* 2009[31] United Kingdom	15	Median 82 (68–95)	1/14	Severe, recurrent	Hospital	30 g faeces in 150 mL saline/30 mL	Nasogastric tube, once	Vancomycin 4–51 days pre-FT; discontinued 12 h pre-FT
Garborg *et al.* 2010[41] Norway	40	75 (53–94)	19/21	Recurrent	Hospital	50–100 g faeces in 250 mL saline/200 mL	Gastroscopy (majority) or colonoscopy, once	Metronidazole or vancomycin until reduction of symptoms; discontinued the evening pre-FT.
Mellow *et al.* 2011[42] United States	13	67 (32–87)	7/6	Recurrent (12), refractory (1)	Hospital or homebound	NR/300–600 mL	Colonoscopy, once	Vancomycin or metronidazole discontinued 48 h pre-FT
Rohlke *et al.* 2010[43] United States	19	49 (29–82)	2/17	Recurrent	Medical centres	NR/200–300 mL	Colonoscopy, once	Vancomycin discontinued 1–3 days pre-FT
Yoon *et al.* 2010[44] United States	12	66 (30–86)	3/9	Recurrent	Medical centres	Unknown volume faeces in 1000 mL saline/250–400 mL	Colonoscopy, once	Vancomycin or metronidazole discontinued 3 days pre-FT
Silverman *et al.* 2010[45] Canada	7	65 (30–88)	4/3	Recurrent	Patient home	50 mL faeces in 200 mL saline/250 mL	Retention enema, once	Vancomycin or metronidazole discontinued 24–48 h pre-FT

CDAD, *Clostridium difficile*-associated disease; FT, faecal transplantation; h, hour; No., total number; NR, not reported.

formed in two studies[42, 43] in which faecal suspensions were delivered by colonoscopy.

For most patients FT was performed by clinical specialists either in hospitals or outpatient clinical centres, whereas in the Canadian study[45] patients or their family members administered the procedures in their homes.

Volume and frequency

Volumes of faecal suspension delivery varied across the studies depending on the method of delivery used. In two studies[31, 40] a small amount (25–30 mL) faecal suspension was infused through a nasogastric tube, once only, whereas in other studies a larger amount of faecal suspensions (200–600 mL) were delivered via gastroscopy, colonoscopy, or rectal retention enema, once only. The majority of patients received a single FT procedure.

EVIDENCE OF SAFETY AND TREATMENT EFFECTS OF FAECAL TRANSPLANTATION

Table 2 presents a summary of safety and treatment effect outcomes reported in the seven studies.

Adverse events

As shown in Table 2, one study[43] did not report safety outcomes and four studies[41, 42, 44, 45] observed no adverse events associated with the FT procedure. One study[31] that used nasogastric tubes for faeces delivery reported an incident of upper gastrointestinal haemorrhage which appeared unlikely to relate to the FT procedure. Another study of 18 patients[40] reported a death following the development of peritonitis after FT using a nasogastric tube, and the authors could not exclude the possibility that the use of the nasogastric tube might have contributed to the death.

Freedom from diarrhoea

Prior to FT, all included patients experienced multiple CDAD episodes despite standard treatment for recurrent CDAD. Some patients had three to seven recurrent CDAD episodes over a span of several months to 2 years.

As shown in Table 2, two studies measured outcomes at a fixed time point, that is, at 80 days (2.7 months)[41] and 90 days (3 months)[40] after the FT procedure. One study[44] followed 12 patients for 3 weeks to 8 years, but no information was available about the mean or median follow-up period or length of follow-up for each individual patient. The other four studies followed patients for a mean or median time period of 4–27 months. Overall, the majority of patients were followed for more than 2 months but less than 1 year; only in one study of 19 patients[43] more than half were followed for 2 years or longer.

Most patients (83%) experienced resolution of diarrhoea immediately following the first FT procedure, within 24 h[41] to 7 days[42] post-FT, and remained diarrhoea free during the follow-up period. Freedom from diarrhoea was achieved in more than 70% of patients in all seven studies (ranging from 73% to 100%). In the study with a follow-up of 3 weeks to 8 years,[44] all 12 patients experienced immediate and durable freedom from diarrhoea, cramps and fever. The study with the longest mean follow-up period (27 months)[43] reported 95% freedom from diarrhoea after the first infusion and 100% after the second infusion; these patients remained diarrhoea-free for a prolonged period. Three patients developed new diarrhoea episodes after taking antibiotics for unrelated infections immediately before the onset of symptoms, thus these cases were considered reinfection rather than relapse. Table 2 indicated that a small number of patients were able to respond to the second FT procedure when the first FT failed[41, 43] or symptoms reoccurred[31] after the initial success.

Due to the small number of patients in these studies, no clear relationship was observed between diarrhoea resolution rates and different delivery methods, volumes, or frequencies of FT procedures. One study[31] reported that one patient relapsed after receiving the first infusion of an insufficient amount of faeces, and diarrhoea was resolved after a second infusion with the correct amount of faecal suspension, which may suggest the importance of delivering a sufficient amount of faecal microbiota.

Two studies[31, 40] used similar FT protocols in terms of donor screening, faecal suspension preparation and administration method. Each of the studies reported a case who relapsed after FT; however, after receiving an additional 10-day antibiotic treatment with vancomycin or metronidazole, the patient was diarrhoea-free. In such cases, it is assumed that FT replaces sufficient gut microbiota to allow effective antibiotic treatment.[31] This treatment sequence may have important clinical implications. Another patient relapsed after receiving broad-spectrum antibiotics,[31] highlighting the need to monitor the use of broad-spectrum antibiotics in such patients.

Stool testing for CD toxins

Post-FT stool testing for CD toxins were only conducted in a small number of patients. This test may not be of clinical importance because positive CD toxins can be persistent for several weeks after clinical improvement.

Table 2 | Summary of safety and effectiveness of faecal transplantation

Study	Follow-up	Adverse events	Free of diarrhoea after 1st FT	No response/ recurrence	Testing for CD toxin post-FT	Patient acceptance
Aas *et al.* 2003[40] *N* = 18; via nasogastric tube	90 days	Two deaths: 1 after development of peritonitis (3 days post-FT); 1 of pneumonia (14 days post-FT)	15/16 survivors (94%)	1 relapsed 17 days post-FT	(−) in 13/14 pts who were tested for CD toxin	All receptive
Macconnachie *et al.* 2009[31] *N* = 15; via nasogastric tube	Median 4 (1–6) months	One upper GI haemorrhage (may be related to the use of aspirin and NSAIDs rather than FT)	11/15 (73%)	2 no responses; 2 relapsed (1 responded to the 2nd FT)	Not done for all pts, no results reported	Well tolerated, high level of acceptance
Garborg *et al.* 2010[41] *N* = 40, via gastroscopy or colonoscopy	80 days	None (5 unrelated deaths 3 weeks to 2 months post-FT)	29/40 (73%)	11 no responses; 4/6 responded to the 2nd FT	Not conducted	Well accepted and tolerated
Mellow *et al.* 2011[42] *N* = 13, via colonoscopy	Mean 5 (1–10) months	None (3 unrelated deaths 1–7 months post-FT)	11/13 (85%)	1 no response; 1 relapsed 7 months post-FT	(+) in one pt who did not respond to FT; (−) in 10/10 pts who had the test	NR
Rohlke *et al.* 2010[43] *N* = 19, via colonoscopy	Mean 27 (7–65) months	NR	18/19 (95%)	1 no response after 1st FT responded to the 2nd FT	Not conducted for pts without recurrent symptoms, (+) in 3 pts treated with antibiotics for unrelated infection (reinfections)	Pts uniformly preferred colonoscopy to enemas or the nasogastric tube
Yoon & Brandt 2008[44] *N* = 12; via colonoscopy	3 weeks to 8 years (mean value: NR)	None	12/12 (100%)	None	(−) in 6/7 pts who had the test	NR
Silverman *et al.* 2010[45] *N* = 7, via retention enema	Mean 8.6 (4–14) months	None	7/7 (100%)	None	(−) in 1 pt with irritable bowel symptom, NR for other pts	Well tolerated by this group of highly motivated outpatients

(+), positive; (−), negative; CD, *Clostridium difficile*; FT, faecal transplantation; GI, gastrointestinal tract; N, total number; NR, not reported; NSAIDs, nonsteroid anti-inflammatory drugs; pt(s), patient(s).

Most stool CD toxin tests were negative in the patients who received the test, and positive in those patients who did not respond to the FT procedure.

Patient perception and satisfaction

Although not mentioned in two studies,[42, 44] five studies[31, 40, 41, 43, 45] reported that patients accepted and tolerated the FT procedure. Patients in one study[43] uniformly preferred colonoscopy to retention enema or the nasogastric tube; however, this information was not reported in the other studies.

Health-related quality of life

Although an important clinical outcome, only one study[43] reported that 16 of 19 patients who were symptom-free had resumed a more normal quality of life; however, no formal quality of life measurement was reportedly used in this study.

DISCUSSION

Summary of research findings

The present review conducted a comprehensive literature search using multiple electronic databases and other data sources, applied a set of predefined criteria to select studies, and assessed the methodological quality of the included case series studies. By using a scientific rigorous and robust method, this review attempts to identify potential biases associated with the included studies and to incorporate information about study methodological quality in the interpretation of the study results. One of the limitations of this review is the restriction to English-language publications.

No randomised or non-randomised controlled studies were located that compared the safety and efficacy/effectiveness of FT to other interventions (e.g. vancomycin) for the treatment of patients with CDAD. No study was found that compared different delivery methods of the faecal microbiota suspensions.

Results from seven small case series studies suggest that FT administered by nasogastric tube, gastroscopy, colonoscopy, or retention enema is safe. No adverse events were reported that directly related to the FT procedure. In terms of treatment effects, all studies reported promising results indicated by high response rate. Symptoms, most frequently diarrhoea, usually improved immediately following the FT procedure and this effect sometimes lasted for several months to several years.

However, these apparently promising results need to be interpreted with caution. In general, because of the lack of control groups, causal relationship between treatment interventions and observed outcomes cannot be established by case series studies.[57] Furthermore, five included studies were retrospective and in four studies it remains unclear whether cases were recruited consecutively, which can result in selective reporting of outcomes favouring the intervention.

Clinical issues

Pretransplantation use of antibiotics against C. difficile. As shown in Table 1, in all seven studies antibiotics against CDAD, such as vancomycin or metronidazole, were used prior to FT to suppress the pathogen burden and then discontinued the evening or 1–3 days before the procedure, which raises a question about the potential impact of pretransplantation antibiotic therapy on the reported high success rates. It was generally thought that this was unlikely to influence the results because these patients have failed previous courses of vancomycin/metronidazole. However, in the absence of a control group it is not possible to determine whether the observed outcomes are the results of the pretransplantation antibiotic treatment, the results of FT alone, or the results of the combined treatment.

Two proposed randomised controlled trials (RCTs), one led by the investigators in the Netherlands[58] and the other one by investigators in Canada,[59] were designed to compare FT with vancomycin in the treatment of recurrent *C. difficile* infection. Results from these ongoing RCTs will help address the above-mentioned issue and determine the most optimal procedure.

Method of faeces delivery. All but one[41] study used the same delivery method in all patients. No study compared the results of different methods of administration, thus it is not possible to determine the superiority of one delivery method over another.

There is no general agreement on the best approach to delivering faecal microbiota or optimal volume. Several advantages or disadvantages of different faeces delivery methods were proposed by authors of the included studies.

Use of a nasogastric tube requires less patient preparation, clinical time, patient inconvenience and cost than via a retention enema or colonoscopy,[40] and it is technically easier to perform.[31] This method provides more extensive exposure of the gastrointestinal tract to donor faecal microbiota[31]; however, this may carry the risk of vomiting and potentially aspirating feculent material.[42] Delivery of faecal microbiota via a nasogastric tube may

also predispose patients to bacterial overgrowth, particularly in elderly patients who are achlorhydric (lack of gastric acid in the stomach) or have a small intestinal motility disorder.[44]

Clostridium difficile organisms reside throughout the entire colon and in the terminal ileum, where the vast majority of *C. difficile* infestation is established.[20] Colonoscopy allows delivery of a large volume of faecal suspensions throughout the entire colon and better retention over nasogastric tube or retention enema.[42, 43] Colonoscopy also allows direct simultaneous inspection of the colon mucosa, and determination of preferential sites for infusing sufficient amounts of donor faeces (e.g. in areas of diverticulosis).[44] In addition, bowel preparation itself may also decrease the patient's *C. difficile* organism and spore concentration.[42] However, manipulation with colonoscopy through an inflamed colon can be difficult and dangerous.[41] Some authors suggested that FT by colonoscopy is applicable in the majority of patients with CDAD and even severe CDAD; however, in patients with significant colonic distension and severe colitis, use of nasogastric tube or gastroscopy or even a gentle retention enema may be preferable.[20]

Compared with colonoscopy, gastroscopy is considered a fast, safe and less stressful procedure for the patient.[41] The pattern of more marked pseudomembranous changes in the proximal colonic mucosa than in the distal colon indicate that infusion of the healthy bacterial microbiota from upper gastrointestinal tract could be beneficial.[41]

The Canadian study[45] suggests that retention enema administered by patients themselves or their family members at home is a practical, simple and less invasive procedure than other methods. The 100% successful rate in the seven patients may indicate that repopulation of the rectum with donor faecal microbiota is rapidly followed by colonisation of the rest of the colon although this hypothesis needs to be tested in future studies using a tracing material.

In the absence of currently available evidence showing superiority of one method over another in terms of safety and effectiveness, selection of the appropriate delivery method may mainly rely on clinicians' experience and comfort with certain techniques, patient colon conditions and patient preferences.

Research gaps

Since its first performance in 1950s, FT has not been widely accepted and performed until recently. In addition to aesthetic and safety concerns of manipulating faecal suspensions and concerns of potential risk of transmission of infectious pathogens from the donor to the patient, the lack of controlled clinical trials that definitively demonstrate the clinical effectiveness of FT compared with standard care is an important reason for the negative attitude towards this procedure.[60] Larger scale, controlled studies are needed to bridge the evidence gap, and longitudinal studies are also needed for economic evaluation.

Future RCTs are required to evaluate various aspects of donor stool preparation, instillation techniques, post-procedure interventions, and perhaps adjuvant interventions, such as using probiotics or prebiotics.[43] Subgroup analysis may be helpful in exploring patient characteristics predicting success or failure of FT[43] and identifying patient groups who would benefit most from this procedure.

The most appropriate protocol for the FT procedure remains a clinical issue. The lack of definition of 'normal gut microbiota' makes it difficult to develop a standard FT formula that can be administered safely. Even if the presence of stool pathogens in the donor faeces is ruled out, there remain a host of potential pathogens present, most of which are uncultivable. There is a clear need for more research about the normal or protective human microbiome before a standard FT can be safely administered.

CONCLUSIONS

Management of severe, recurrent and relapse CDAD, particularly in elderly patients, remains clinically challenging. Transplantation of faecal suspension obtained from healthy donors may restore normal microbiota, breaking the cycle of recurrent CDAD, usually after treatment with pulsed/tapered vancomycin therapy has failed.

Based on the limited evidence from seven case series studies, FT appears to be a safe procedure. In most cases (83%), symptoms improved immediately after the first FT procedure and patients stayed diarrhoea free for several months or even years, indicating that FT could be an effective alternative in the treatment of patients with recurrent/refractory CDAD. Although these results appear to be promising, the treatment effects of FT cannot be determined definitively in the absence of a control group. Results from the two RCTs that are comparing FT to oral vancomycin without or with a taper regimen in patients with recurrent CDAD may help to better define the role of FT in the management of this patient population.

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