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Review article: Faecal transplantation therapy for gastrointestinal disease.

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Review article: Faecal transplantation therapy for gastrointestinal disease.

(Short Title) **Review article: Faecal transplantation**

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Abstract

Background: Evidence is emerging regarding the relationship between a dysbiosis of the human gut microbiota and a number of gastrointestinal diseases as well as diseases beyond the gut**.** Probiotics have been investigated in many gastrointestinal disease states, with variable and modest outcomes. Faecal transplantation is an alternative approach to manipulate the gut microbiota. **Aims:** To review the use of faecal transplantation therapy for the management of gastrointestinal disorders. **Methods:** Available articles on faecal transplantation in the management of gastrointestinal disorders, were identified through a Pubmed search and bibliographies of review articles on the subject were collated. **Results:** 239 patients who had undergone faecal transplantation were reported. Seventeen of twenty two studies of faecal transplantation were in fulminant or refractory *Clostridium difficile*. Studies of faecal transplantation are heterogeneous regarding the patients, donors, screening, methods of administration, and definition of response. Faecal transplantation for *Clostridium difficile* has been demonstrated to be effective in 145/166 (87%) patients. Small numbers of patients are reported to have undergone successful faecal transplantation for irritable bowel syndrome and inflammatory bowel disease. **Conclusions:** Faecal transplantation has been reported with good outcomes for

fulminant and refractory *Clostridium difficile*. No adverse effects of faecal transplantation have been reported. However, there are no level 1 data of faecal transplantation and reports to date may suffer from reporting bias of positive outcomes and under-reporting of adverse effects. This therapy holds great promise where a dysbiosis of the gut microbiota is responsible for disease and further studies are necessary to explore this potential.

Background

The possibility of modifying the gut microbiota to replace harmful bacteria with more favourable microbes has been widely explored since Metchnikoff's observations in 1907 of the potential health benefits of the "Bulgarian bacillus" (1). With the application of molecular techniques to the study of gut microbiology, mounting evidence is emerging regarding the relationship between a dysbiosis of the human gut microbiota and a number of gastrointestinal diseases as well as diseases beyond the gut including diabetes and metabolic syndrome (2,3,4,5).

In vitro studies have demonstrated a positive effect of probiotic bacteria on gut inflammation by modulating gut immune cells (6,7). Probiotics have been extensively investigated in many

gastrointestinal disease states where an abnormal microbiota is considered pathogenic (8,9,10). The outcomes of these studies have however been variable and modest (10). One confounding factor of the probiotic approach is the comparatively low number and diversity of bacterial species available in a typical commercial probiotic preparation in comparison with the gut microbiota. Furthermore, probiotic bacterial strains may not be able to compete effectively against the complex interactions of an established and adapted indigenous gut microbial community.

An alternative approach is transplantation of the gut microbiota. This is a concept that has been described in ruminants for some time (11). Its use as therapy in humans was first reported by Eiseman *et al*. in 1958 in the treatment of fulminant pseudomembranous enterocolitis (12). Over the subsequent decades, there have been a small number of case reports and case series of faecal transplantation for *Clostridium difficile* (13-29) and also constipation (16,30,31), irritable bowel syndrome (16,30) and inflammatory bowel diseases (16,30,32,33). In recent years there has been a resurgence of interest in this procedure and its potential to modify the gut microbiota.

Reports of the procedure have originated from Canada and the United States, Australia and Northern Europe, but the methods of faecal transplantation, screening of donors and patient

groups treated with this therapy have varied greatly. In this article, we review the use of faecal therapy since the 1958 report of Eiseman *et al*. Available articles on the use of faecal transplantation in the management of human gastrointestinal disorders, which were identified through a Pubmed search (15.1.11) and bibliographies of review articles on the subject were collated. Articles including patients that were previously described or articles that were not available in English were not reviewed. The included publications encompassed different gastrointestinal pathologies, varying methods of treatment, screening and duration of follow up. Twenty two reports of faecal transplantation meeting the inclusion criteria, were identified. Ten of these were published since 2005, demonstrating the recently renewed interest in this area. In total, there are 239 patients who have undergone faecal transplantation reported.

Patient Details

The majority of patients undergoing faecal transplantation were treated for *Clostridium difficile* after standard treatments had failed. Borody *et al.* in 1989 (16) reported 55 patients treated for constipation, diarrhoea, abdominal pain, ulcerative colitis or Crohn's disease. This report did not specify the numbers of patients with each condition, although out of five cases described in more detail, two patients had irritable bowel

syndrome, one ulcerative colitis, one Crohn's disease and one *Clostridium difficile* diarrhoea. Andrews *et al.* (31) described faecal enema treatment for two patients with constipation and in the recent paper from Grehan *et al*. (32), nine patients had a diagnosis of constipation or diarrhoea predominant IBS and one patient had Crohn's disease. One patient in the series from Aas *et al.* (20) had *Clostridium difficile* diarrhoea on a background of Crohn's colitis. Seven other patients with ulcerative colitis are reported to have undergone faecal transplantation (32,33).

Faecal transplantation has been described in patients as young as two years old (24) to patients over 90 years of age (23). Several reports include patients with serious co-morbidities. Three of the four patients reported by Eiseman *et al.* (12) were in a critical condition requiring the use of vasopressors. In the patients reported by Bowden *et al.* (13), eight had a previously treated carcinoma, two chronic renal failure and two an aortic aneurysm. In the study by Aas *et al.* (20) five patients undergoing faecal transplantation were hospitalised and of those treated as outpatients, three were nursing home residents. MacConnachie *et al.* (22) described faecal transplantation in eighteen patients, eleven of whom were hospitalised with significant co-morbidity and a high proportion having hypoalbuminaemia, leucocytosis and renal dysfunction before faecal transplantation. The patient in the report of You *et al.*

(21) was treated in an intensive care unit with vasopressors and continuous veno-venous haemofiltration.

Donor Screening

The potential risk of transmission of viral, bacterial or parasitic infection during the course of faecal transplantation is a concern. No guidelines currently exist regarding screening before faecal transplantation. A number of studies have proposed screening procedures (20,24). In a recent review of faecal tranplantation for recurrent *Clostridium difficile* (34) Bakken suggests a screening process based on previous studies. However, without established guidelines or data from randomised controlled trials, ethical approval for the procedure has to date depended on physician discretion with patient and donor consent, local hospitals' or authorities' approval or occurred within the framework of ethically approved research studies.

Screening methods of stool donors are not always detailed. In the majority of reports a spouse or partner, close relative, or household member of the patient is preferred as the stool donor. However, in a number of reports, donors who are unrelated healthy individuals have been used (13,18,33). Earlier cases did not employ rigorous screening protocols, whereas more

recently, increased screening of donors' medical histories, blood and stool tests have been implemented.

Donors have been screened for a history of gastrointestinal illness, cancer or polyps, hospitalisation within the three previous months (25) and between 6 weeks (33) to 6 months (20) without the use of antibiotics. Screening blood tests have included full blood count and liver function tests (31) as well as screening of viral pathogens including HIV 1+2 (17-20,22-27,29,32), HTLV I/II (25) hepatitis A, B and C (18-20,22-25,29,33), CMV, EBV (18,33) and also for *Treponema pallidum* (20,22-24,32) and *Helicobacter pylori* antibody (25).

Donor faecal specimens have been screened for *Salmonella* spp., *Shigella* spp., *Campylobacter* spp., *Staphylococcus aureus*, *Aeromonas hydrophila, Yersinia* spp., *Vibrio parahaemolyticus, Vibrio cholerae, Candida albicans, Escherichia coli* O157 and *Clostridium difficile* toxins A and B (17,18,20,22-29,33). Stool microscopy has been screened for protozoa (trophozoites and cysts), helminths and ova including *Entamoeba histolytica, Giardia lamblia, Microspora* spp. (20,22-25,27,33), *Cryptosporidium* spp. (25), *Dientamoeba fragilis, Blastocystis hominis, Ascaris lumbricoides*, trematodes and tape worms (20,22-25,27,33).

(Table 1).

Route of Administration

The initial report of Eiseman *et al.* described administration of faecal enemas (12), which has been replicated in other studies (13-15,17,18,21,25,30-33). Others subsequently have used instillation via a colonoscope to the right colon (19,26-30) or instillation of donor faeces via nasogastric tube (20,22-24) or duodenal (29) or nasojejunal intubation (13,30). The study of Grehan *et al.* employed a combination of colonoscopic instillation followed by enemas or nasojejunal tube (30). The majority of studies entailed a single administration of donor faeces. Some studies used repeated infusions over 2 to 15 days (12-15,17,31,33). In the study by Garborg *et al.* (29), six patients underwent a second infusion of donor faeces having not responded to the initial transplantation.

Patient preparation

Preparation of the patient prior to faecal transplantation has varied depending on the method of administration of the donor stool. Studies in which donor stool is instilled at colonoscopy or via rectal enemas include patient preparation with bowel lavage treatments. Bennet and Brinkmann describe a bowel sterilisation procedure (32) prior to transplantation of donor

stool. Persky and Brandt described the use of prior bowel lavage with polyethylene glycol (19). The series of Borody *et al.* in six patients with refractory ulcerative colitis, gave seven to ten days of treatment with vancomycin, metronidazole and rifampicin prior to bowel lavage (33). This protocol was repeated in the study by Grehan *et al.* (32). Two recent studies stopped treatment with metronidazole or vancomycin 24-48 hours prior to faecal transplantation (27,29). The study by Silverman *et al.*, included prior treatment with *Saccharomyces boulardii* which was continued up to 60 days after the procedure (25). Patients treated at one centre in the study by Rholke *et al.* (26) were treated with loperamide immediately following the procedure and again 6 hours later in order maximise contact time of the donor faeces with the colonic mucosa.

Studies of faecal transplantation administered into the upper gastrointestinal tract, do not report the use of prior bowel lavage. The method described by Aas *et al.* in 2003 and followed by those of MacConnachie, Rubin and Russell *et al.*, includes pre-treatment with more than four days of vancomycin and 20mg of omeprazole the evening before and the morning of the faecal transplantation procedure (20,22-24).

Preparation of donor stool

The interval between obtaining donor stool and its administration to the patient has varied between studies, from 24 hours before, 6 hours before (20,22-24) or immediately. One study homogenised donor stool in pasteurised cow's milk and filtered the solution which was then stored at -20°C and thawed in water at 37°C 30-60 minutes prior to administration as an enema (18). Some studies have described the homogenisation of the stool and filtering to remove debris. The use of between 10 to 200g of stool, diluted in 20-500ml sterile saline, has been reported depending on the method of administration. Studies using an upper gastrointestinal protocol for faecal transplantation instilled between 30 and 50g of stool homogenised with 50-250ml sterile saline. (Table 2).

Outcomes

In many reports of faecal transplantation response is not clearly defined. Resolution of symptoms is most commonly stated. Some papers include absence of *Clostridium difficile* toxin. In the 1989 paper by Borody *et al.,* the indication for faecal transplantation in 50 of 55 patients treated was not stated. In this study however, 20 patients were cured, 26 responded and 9 patients did not respond to faecal transplantation (16). In the paper by Grehan *et al.*, outcomes were not stated (30).

Excluding these studies, faecal transplantation for *Clostridium difficile* has been demonstrated to be effective in 145/166

(87%) patients. Time to response is often not stated, although "immediate", "prompt" or "rapid" response is often reported. Where time to response is stated, this has been recorded to occur within 24 hours to twelve days (13,18,24,18,29,33). Response appears durable with follow up of patients up to 8 years following faecal transplantation (27).

In the initial report of Eiseman *et al*. three of the four patients were described as terminally or critically ill. All of these had cessation of diarrhoea and were completely asymptomatic between 24 hours and ten days following faecal transplantation. The report of Bowden *et al.* describes response as a reduction in frequency of bowel motions, absence of fever, normalisation of leucocyte counts and increased general well being. Tvede and Rask-Madsen describe normalisation of bowel function as well as reduction in inflammatory markers and increased albumin levels as response to faecal transplantation. In the report of You *et al.* the patient rapidly displayed normalisation of leucocytosis, stabilisation of blood pressure enabling cessation of vasopressors and improvement in renal function allowing cessation of continuous veno-venous haemofiltration as well as normalisation of bowel function. In the reports of Schwann *et al.*, Gustaffson *et al.,* Persky and Brandt, Aas *et al.,* MacConnachie *et al.,* Khoruts *et al.,* Rholke *et al.* and Russell *et al.* cessation of diarrhoea is defined as response. Five of

these studies also document a change from a positive to a negative *Clostridium difficile* stool test.

For ulcerative colitis, of eight patients reported, all have responded and have remained in remission from 6 months to 13 years (32,33). Patients with ulcerative colitis in the series of Borody *et al*. responded within one to six weeks and were considered in remission by four months following faecal transplantation (33). Five out of the six patients reported in this series had moderate to severe disease with moderate to severe endoscopic findings. All of the patients were asymptomatic with no endoscopic evidence of active inflammation following faecal transplantation. (Table 3).

Adverse events

No studies of faecal transplantation report any adverse events related to the procedure. Some studies report patient deaths due to the underlying disease where the patient has not responded to the faecal transplantation. In one study in which donor faeces were instilled via a nasogastric tube, the patient died of peritonitis. Although considered unlikely, the nasogastric tube insertion could not be discounted to have been contributory (17). One patient in the study by Silverman *et al.* developed irritable bowel symptoms following faecal transplantation (25).

Analysis of effects of faecal transplantation on stool composition and faecal microbiota

Four studies have attempted to analyse stool before and after faecal transplantation. Using culture, Tvede and Rask-Madsen observed an absence of *Bacteroides* before bacteriotherapy and during vancomycin therapy whilst patients were symptomatic. During follow up after bacteriotherapy (including faecal enemas in two patients), *Bacteroides* were regularly cultured (15). Gustafsson *et al.* studied stool short chain fatty acid concentrations before and after faecal transplantation in nine patients. All short chain fatty acids were found to be reduced in the patient group compared with healthy adults and following faecal enema therapy the relative distribution and absolute amounts of short chain fatty acids returned to patterns similar to healthy adults (18). More recently, using modern molecular 16S rRNA gene sequencing techniques, two studies have shown a significant change in the microbiota following faecal transplantation. Khoruts *et al*. demonstrated a reduction in Bacteroidetes and Firmicutes in a patient with *Clostridium difficile* diarrhoea. Following faecal transplantation there was a rapid change in the patient's microbiota to a composition that was highly similar to that of the healthy donor for at least four weeks (the duration of follow-up stool analysis) (28). Grehan *et al.* undertook analysis on the stool of 10 patients who

underwent faecal transplantation. A dramatic change was shown in the recipients' microbiota to a composition similar to their donors' microbiota. This study analysed stool from patients up to 24 weeks following faecal transplantation demonstrating a durable change in the recipients' microbiota up to 24 weeks (30).

Conclusions

Evidence regarding the use of faecal transplantation as a means of modifying the gut microbiota and effecting cure of gastrointestinal illness is accumulating. To date the majority of studies of faecal transplantation have been in fulminant or refractory *Clostridium difficile*. However, studies of faecal transplantation to date are heterogeneous regarding the patients treated, donors used, optimal screening protocols, methods and frequency of administration, and definition of response. Furthermore, reports to date may suffer from reporting bias of positive outcomes and under-reporting of adverse effects.

Faecal transplantation, a therapy used for more than half a century, could hold great promise as a future treatment where a dysbiosis of the gut microbiota is responsible for disease. This therapy is inexpensive as well as being effective in some cases. Standardised controlled studies are necessary to ascertain the most effective regimen as well as the most acceptable method of treatment. Two randomised controlled studies of faecal

transplantation in *Clostridium difficile* are on-going in North America and Europe and results from these are eagerly awaited as well as a study of faecal transplantation in metabolic syndrome. Studies of faecal transplantation for other gastrointestinal diseases where a dysbiosis of the gut microbiota is evident are necessary. Rigorous screening of potential donors is essential as is the use of partners or close relatives as donors to minimise the potential for transmitting disease. Close monitoring and long term follow up are necessary. Combining clinical studies with molecular analysis of the microbiota and the effects on the immune response may significantly enhance our understanding of the gut microbiota and its relationship with health and disease.

Statement of interests:

Dr A Hart has been a speaker for and is on the advisory board for Abbot, Shire and MSD.

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Review article: Faecal transplantation. Tables.

Table 1. Suggested screening investigations

Sample	Investigation
Blood	Full Blood Count, Liver Function Tests
	Hepatitis A,B,C
	HIV 1+2, HTLV I/II
	CMV, EBV
	Treponema pallidum
Stool	Selective stool culture
	Clostridium difficile toxin A and B
	Microscopy for ova, cysts and parasites

Table 2. Methods of faecal transplantation

	Upper Gastrointestinal Tract	Lower Gastrointestinal Tract
Donor stool collection prior to transplantation	≤ 6 hours (13,20,22,24,30)	≤ 24 hours (14,17,25-27,30,33)
Bowel cleansing	No (13,20,22,24,30)	Yes (colonic instillation) (26-28,20,32,33)
Donor stool volume	30-50g (20,22,24,29)	10-200g (15,18,19,21, 25-30,33)
Volume of dilution in saline	50-250ml (20,22,24,29)	20-500ml (15,17-19,21, 25-30,33)
Volume instilled	25-200ml (20,22,24,29)	20-500ml (15,17-19,21, 25-30,33)
Repeated instillation	No (13,20,22,24) Yes (29)	No (18,19,26,27,28) Yes (12-14,17,25,29,30,33)

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Table 3. Summary of the outcome studies of faecal transplantation

Author	Year	Indication	Number of Patients	Route of faecal instillation	Response	Stated Time to Response	Duration of Follow-up
Eiseman	1958	PMC	4	Rectal	4/4	2 days	
Bowden	1981	PMC	16	Rectal/Jejunal	14/16	1-12 days	5 days- 3years
Schwan	1984	Relapsing CDAD	1	Enema	1/1		9 months
Tvede	1989	Relapsing CDAD	2	Enema	1/2		6 months
Bennet	1989	UC	1	Enema	1/1		6 months
Borody	1989	IBS, IBD, CDAD	55	Enema	26 cure 20 response 9 no response		1-12 months
Andrews	1992	Constipation	1	Enema	1/1		18 months
Paterson	1994	Chronic CDAD	7	Enema	7/7		2 years
Gustaffson	1998	AAD/CDAD	9	Enema	9/9	6-10 days	18 months
Persky	2000	Recurrent CDAD	1	Colonic	1/1		5 years
Aas	2003	Recurrent CDAD	18	Nasogastric	15/18		90 days
Borody	2003	UC	6	Enema	6/6	1-6 weeks	1-13 years
You	2008	Fulminant CDAD	1	Enema	1/1	36 hours	
MacConnachie	2009	Recurrent CDAD	15	Nasogastric	11/15		4-24 weeks
Rubin	2009	CDAD	12	Nasogastric	10/12		90 days
Khoruts	2010	Chronic CDAD	1	Colonic	1/1	2 days	6 months
Rholke	2010	Relapsing CDAD	19	Colonic	19/19		6 months- 5 years
Russell	2010	Relapsing CDAD	1	Nasogastric	1/1	36 hours	6 months
Yoon	2010	Refractory/ Recurrent CDAD	12	Colonic	12/12		3 weeks- 8 years
Garborg	2010	Recurrent CDAD	40	Duodenal/Colonic	33/40	24 hours	
Silverman	2010	Chronic CDAD	7	Enema	7/7		

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PMC- Pseudomembranous colitis; CDAD- *Clostridium difficile* associated diarrhoea; AAD- antibiotic associated diarrhoea; IBS- Irritable bowel syndrome; IBD- Inflammatory bowel disease; UC- ulcerative colitis.