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## Review article: Faecal transplantation therapy for gastrointestinal disease.

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**Review article: Faecal transplantation therapy for  
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**Review article: Faecal transplantation therapy for  
gastrointestinal disease.**

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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

1  
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3  
4 fulminant and refractory *Clostridium difficile*. No adverse  
5  
6  
7 effects of faecal transplantation have been reported. However,  
8  
9  
10 there are no level 1 data of faecal transplantation and reports to  
11  
12 date may suffer from reporting bias of positive outcomes and  
13  
14 under-reporting of adverse effects. This therapy holds great  
15  
16 promise where a dysbiosis of the gut microbiota is responsible  
17  
18 for disease and further studies are necessary to explore this  
19  
20  
21 potential.  
22  
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27

## 28 **Background**

29  
30 The possibility of modifying the gut microbiota to replace  
31  
32 harmful bacteria with more favourable microbes has been  
33  
34 widely explored since Metchnikoff's observations in 1907 of  
35  
36 the potential health benefits of the "Bulgarian bacillus" (1).  
37  
38

39  
40 With the application of molecular techniques to the study of gut  
41  
42 microbiology, mounting evidence is emerging regarding the  
43  
44 relationship between a dysbiosis of the human gut microbiota  
45  
46 and a number of gastrointestinal diseases as well as diseases  
47  
48 beyond the gut including diabetes and metabolic syndrome  
49  
50  
51 (2,3,4,5).  
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53

54  
55 *In vitro* studies have demonstrated a positive effect of probiotic  
56  
57 bacteria on gut inflammation by modulating gut immune cells  
58  
59 (6,7). Probiotics have been extensively investigated in many  
60

1  
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4  
5 gastrointestinal disease states where an abnormal microbiota is  
6  
7 considered pathogenic (8,9,10). The outcomes of these studies  
8  
9 have however been variable and modest (10). One confounding  
10  
11 factor of the probiotic approach is the comparatively low  
12  
13 number and diversity of bacterial species available in a typical  
14  
15 commercial probiotic preparation in comparison with the gut  
16  
17 microbiota. Furthermore, probiotic bacterial strains may not be  
18  
19 able to compete effectively against the complex interactions of  
20  
21 an established and adapted indigenous gut microbial  
22  
23 community.  
24  
25  
26  
27  
28

29 An alternative approach is transplantation of the gut  
30  
31 microbiota. This is a concept that has been described in  
32  
33 ruminants for some time (11). Its use as therapy in humans was  
34  
35 first reported by Eiseman *et al.* in 1958 in the treatment of  
36  
37 fulminant pseudomembranous enterocolitis (12). Over the  
38  
39 subsequent decades, there have been a small number of case  
40  
41 reports and case series of faecal transplantation for *Clostridium*  
42  
43 *difficile* (13-29) and also constipation (16,30,31), irritable bowel  
44  
45 syndrome (16,30) and inflammatory bowel diseases (16,30,32,33).  
46  
47  
48 In recent years there has been a resurgence of interest in this  
49  
50 procedure and its potential to modify the gut microbiota.  
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56 Reports of the procedure have originated from Canada and the  
57  
58 United States, Australia and Northern Europe, but the methods  
59  
60 of faecal transplantation, screening of donors and patient

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3  
4 groups treated with this therapy have varied greatly. In this  
5  
6  
7 article, we review the use of faecal therapy since the 1958  
8  
9 report of Eiseman *et al.* Available articles on the use of faecal  
10  
11 transplantation in the management of human gastrointestinal  
12  
13 disorders, which were identified through a Pubmed search  
14  
15 (15.1.11) and bibliographies of review articles on the subject  
16  
17 were collated. Articles including patients that were previously  
18  
19 described or articles that were not available in English were not  
20  
21 reviewed. The included publications encompassed different  
22  
23 gastrointestinal pathologies, varying methods of treatment,  
24  
25 screening and duration of follow up. Twenty two reports of  
26  
27 faecal transplantation meeting the inclusion criteria, were  
28  
29 identified. Ten of these were published since 2005,  
30  
31 demonstrating the recently renewed interest in this area. In  
32  
33 total, there are 239 patients who have undergone faecal  
34  
35 transplantation reported.  
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### 43 **Patient Details**

44  
45  
46 The majority of patients undergoing faecal transplantation were  
47  
48 treated for *Clostridium difficile* after standard treatments had  
49  
50 failed. Borody *et al.* in 1989 (16) reported 55 patients treated for  
51  
52 constipation, diarrhoea, abdominal pain, ulcerative colitis or  
53  
54 Crohn's disease. This report did not specify the numbers of  
55  
56 patients with each condition, although out of five cases  
57  
58 described in more detail, two patients had irritable bowel  
59  
60

1  
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3  
4 syndrome, one ulcerative colitis, one Crohn's disease and one  
5  
6  
7 *Clostridium difficile* diarrhoea. Andrews *et al.* (31) described  
8  
9 faecal enema treatment for two patients with constipation and  
10  
11 in the recent paper from Grehan *et al.* (32), nine patients had a  
12  
13 diagnosis of constipation or diarrhoea predominant IBS and one  
14  
15 patient had Crohn's disease. One patient in the series from Aas  
16  
17 *et al.* (20) had *Clostridium difficile* diarrhoea on a background  
18  
19 of Crohn's colitis. Seven other patients with ulcerative colitis  
20  
21 are reported to have undergone faecal transplantation (32,33).  
22  
23  
24

25  
26  
27 Faecal transplantation has been described in patients as young  
28  
29 as two years old (24) to patients over 90 years of age (23).  
30

31 Several reports include patients with serious co-morbidities.

32  
33  
34 Three of the four patients reported by Eiseman *et al.* (12) were  
35  
36 in a critical condition requiring the use of vasopressors. In the  
37  
38 patients reported by Bowden *et al.* (13), eight had a previously  
39  
40 treated carcinoma, two chronic renal failure and two an aortic  
41  
42 aneurysm. In the study by Aas *et al.* (20) five patients  
43  
44 undergoing faecal transplantation were hospitalised and of  
45  
46 those treated as outpatients, three were nursing home residents.  
47  
48

49  
50 MacConnachie *et al.* (22) described faecal transplantation in  
51  
52 eighteen patients, eleven of whom were hospitalised with  
53  
54 significant co-morbidity and a high proportion having  
55  
56 hypoalbuminaemia, leucocytosis and renal dysfunction before  
57  
58 faecal transplantation. The patient in the report of You *et al.*  
59  
60



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5 (21) was treated in an intensive care unit with vasopressors and  
6  
7 continuous veno-venous haemofiltration.  
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9

### 10 11 12 13 **Donor Screening** 14

15  
16 The potential risk of transmission of viral, bacterial or parasitic  
17 infection during the course of faecal transplantation is a  
18 concern. No guidelines currently exist regarding screening  
19 before faecal transplantation. A number of studies have  
20 proposed screening procedures (20,24). In a recent review of  
21 faecal transplantation for recurrent *Clostridium difficile* (34)  
22 Bakken suggests a screening process based on previous studies.  
23 However, without established guidelines or data from  
24 randomised controlled trials, ethical approval for the procedure  
25 has to date depended on physician discretion with patient and  
26 donor consent, local hospitals' or authorities' approval or  
27 occurred within the framework of ethically approved research  
28 studies.  
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48 Screening methods of stool donors are not always detailed. In  
49 the majority of reports a spouse or partner, close relative, or  
50 household member of the patient is preferred as the stool donor.  
51 However, in a number of reports, donors who are unrelated  
52 healthy individuals have been used (13,18,33). Earlier cases did  
53 not employ rigorous screening protocols, whereas more  
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4 recently, increased screening of donors' medical histories,  
5  
6 blood and stool tests have been implemented.  
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9  
10 Donors have been screened for a history of gastrointestinal  
11  
12 illness, cancer or polyps, hospitalisation within the three  
13  
14 previous months (25) and between 6 weeks (33) to 6 months (20)  
15  
16 without the use of antibiotics. Screening blood tests have  
17  
18 included full blood count and liver function tests (31) as well as  
19  
20 screening of viral pathogens including HIV 1+2 (17-20,22-  
21  
22 27,29,32), HTLV I/II (25) hepatitis A, B and C (18-20,22-25,29,33),  
23  
24 CMV, EBV (18,33) and also for *Treponema pallidum* (20,22-  
25  
26 24,32) and *Helicobacter pylori* antibody (25).  
27  
28  
29

30  
31 Donor faecal specimens have been screened for *Salmonella*  
32  
33 *spp.*, *Shigella spp.*, *Campylobacter spp.*, *Staphylococcus*  
34  
35 *aureus*, *Aeromonas hydrophila*, *Yersinia spp.*, *Vibrio*  
36  
37 *parahaemolyticus*, *Vibrio cholerae*, *Candida albicans*,  
38  
39 *Escherichia coli* O157 and *Clostridium difficile* toxins A and B  
40  
41 (17,18,20,22-29,33). Stool microscopy has been screened for  
42  
43 protozoa (trophozoites and cysts), helminths and ova including  
44  
45 *Entamoeba histolytica*, *Giardia lamblia*, *Microspora spp.*  
46  
47 (20,22-25,27,33), *Cryptosporidium spp.* (25), *Dientamoeba*  
48  
49 *fragilis*, *Blastocystis hominis*, *Ascaris lumbricoides*, trematodes  
50  
51 and tape worms (20,22-25,27,33).  
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58

59 (Table 1).  
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### 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

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4 stool. Persky and Brandt described the use of prior bowel  
5  
6 lavage with polyethylene glycol (19). The series of Borody *et al.*  
7  
8 in six patients with refractory ulcerative colitis, gave seven to  
9  
10 ten days of treatment with vancomycin, metronidazole and  
11  
12 rifampicin prior to bowel lavage (33). This protocol was  
13  
14 repeated in the study by Grehan *et al.* (32). Two recent studies  
15  
16 stopped treatment with metronidazole or vancomycin 24-48  
17  
18 hours prior to faecal transplantation (27,29). The study by  
19  
20 Silverman *et al.*, included prior treatment with *Saccharomyces*  
21  
22 *boulardii* which was continued up to 60 days after the  
23  
24 procedure (25). Patients treated at one centre in the study by  
25  
26 Rholke *et al.* (26) were treated with loperamide immediately  
27  
28 following the procedure and again 6 hours later in order  
29  
30 to maximise contact time of the donor faeces with the colonic  
31  
32 mucosa.  
33  
34  
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41 Studies of faecal transplantation administered into the upper  
42  
43 gastrointestinal tract, do not report the use of prior bowel  
44  
45 lavage. The method described by Aas *et al.* in 2003 and  
46  
47 followed by those of MacConnachie, Rubin and Russell *et al.*,  
48  
49 includes pre-treatment with more than four days of vancomycin  
50  
51 and 20mg of omeprazole the evening before and the morning of  
52  
53 the faecal transplantation procedure (20,22-24).  
54  
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56  
57

#### 58 **Preparation of donor stool**

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5 The interval between obtaining donor stool and its  
6  
7 administration to the patient has varied between studies, from  
8  
9 24 hours before, 6 hours before (20,22-24) or immediately. One  
10  
11 study homogenised donor stool in pasteurised cow's milk and  
12  
13 filtered the solution which was then stored at -20°C and thawed  
14  
15 in water at 37°C 30-60 minutes prior to administration as an  
16  
17 enema (18). Some studies have described the homogenisation of  
18  
19 the stool and filtering to remove debris. The use of between 10  
20  
21 to 200g of stool, diluted in 20-500ml sterile saline, has been  
22  
23 reported depending on the method of administration. Studies  
24  
25 using an upper gastrointestinal protocol for faecal  
26  
27 transplantation instilled between 30 and 50g of stool  
28  
29 homogenised with 50-250ml sterile saline. (Table 2).  
30  
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35

### 36 **Outcomes**

37  
38 In many reports of faecal transplantation response is not clearly  
39  
40 defined. Resolution of symptoms is most commonly stated.  
41  
42 Some papers include absence of *Clostridium difficile* toxin. In  
43  
44 the 1989 paper by Borody *et al.*, the indication for faecal  
45  
46 transplantation in 50 of 55 patients treated was not stated. In  
47  
48 this study however, 20 patients were cured, 26 responded and 9  
49  
50 patients did not respond to faecal transplantation (16). In the  
51  
52 paper by Grehan *et al.*, outcomes were not stated (30).  
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58  
59 Excluding these studies, faecal transplantation for *Clostridium*  
60  
*difficile* has been demonstrated to be effective in 145/166

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4 (87%) patients. Time to response is often not stated, although  
5  
6  
7 “immediate”, “prompt” or “rapid” response is often reported.  
8  
9  
10 Where time to response is stated, this has been recorded to  
11  
12 occur within 24 hours to twelve days (13,18,24,18,29,33).  
13  
14 Response appears durable with follow up of patients up to 8  
15  
16 years following faecal transplantation (27).  
17  
18

19  
20 In the initial report of Eiseman *et al.* three of the four patients  
21  
22 were described as terminally or critically ill. All of these had  
23  
24 cessation of diarrhoea and were completely asymptomatic  
25  
26 between 24 hours and ten days following faecal transplantation.  
27  
28 The report of Bowden *et al.* describes response as a reduction  
29  
30 in frequency of bowel motions, absence of fever, normalisation  
31  
32 of leucocyte counts and increased general well being. Tvede  
33  
34 and Rask-Madsen describe normalisation of bowel function as  
35  
36 well as reduction in inflammatory markers and increased  
37  
38 albumin levels as response to faecal transplantation. In the  
39  
40 report of You *et al.* the patient rapidly displayed normalisation  
41  
42 of leucocytosis, stabilisation of blood pressure enabling  
43  
44 cessation of vasopressors and improvement in renal function  
45  
46 allowing cessation of continuous veno-venous haemofiltration  
47  
48 as well as normalisation of bowel function. In the reports of  
49  
50 Schwann *et al.*, Gustaffson *et al.*, Persky and Brandt, Aas *et al.*,  
51  
52 MacConnachie *et al.*, Khoruts *et al.*, Rholke *et al.* and Russell  
53  
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59  
60 *et al.* cessation of diarrhoea is defined as response. Five of

1  
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3  
4 these studies also document a change from a positive to a  
5  
6  
7 negative *Clostridium difficile* stool test.  
8  
9

10 For ulcerative colitis, of eight patients reported, all have  
11  
12 responded and have remained in remission from 6 months to 13  
13  
14 years (32,33). Patients with ulcerative colitis in the series of  
15  
16 Borody *et al.* responded within one to six weeks and were  
17  
18 considered in remission by four months following faecal  
19  
20 transplantation (33). Five out of the six patients reported in this  
21  
22 series had moderate to severe disease with moderate to severe  
23  
24 endoscopic findings. All of the patients were asymptomatic  
25  
26 with no endoscopic evidence of active inflammation following  
27  
28 faecal transplantation. (Table 3).  
29  
30  
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32  
33

#### 34 **Adverse events**

35  
36  
37 No studies of faecal transplantation report any adverse events  
38  
39 related to the procedure. Some studies report patient deaths due  
40  
41 to the underlying disease where the patient has not responded to  
42  
43 the faecal transplantation. In one study in which donor faeces  
44  
45 were instilled via a nasogastric tube, the patient died of  
46  
47 peritonitis. Although considered unlikely, the nasogastric tube  
48  
49 insertion could not be discounted to have been contributory  
50  
51 (17). One patient in the study by Silverman *et al.* developed  
52  
53 irritable bowel symptoms following faecal transplantation (25).  
54  
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## 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



1  
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3  
4 underwent faecal transplantation. A dramatic change was  
5  
6 shown in the recipients' microbiota to a composition similar to  
7  
8 their donors' microbiota. This study analysed stool from  
9  
10 patients up to 24 weeks following faecal transplantation  
11  
12 demonstrating a durable change in the recipients' microbiota up  
13  
14 to 24 weeks (30).  
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### 19 **Conclusions**

20  
21  
22 Evidence regarding the use of faecal transplantation as a means  
23  
24 of modifying the gut microbiota and effecting cure of  
25  
26 gastrointestinal illness is accumulating. To date the majority of  
27  
28 studies of faecal transplantation have been in fulminant or  
29  
30 refractory *Clostridium difficile*. However, studies of faecal  
31  
32 transplantation to date are heterogeneous regarding the patients  
33  
34 treated, donors used, optimal screening protocols, methods and  
35  
36 frequency of administration, and definition of response.  
37  
38 Furthermore, reports to date may suffer from reporting bias of  
39  
40 positive outcomes and under-reporting of adverse effects.  
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47  
48 Faecal transplantation, a therapy used for more than half a  
49  
50 century, could hold great promise as a future treatment where a  
51  
52 dysbiosis of the gut microbiota is responsible for disease. This  
53  
54 therapy is inexpensive as well as being effective in some cases.  
55  
56 Standardised controlled studies are necessary to ascertain the  
57  
58 most effective regimen as well as the most acceptable method  
59  
60 of treatment. Two randomised controlled studies of faecal

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3  
4 transplantation in *Clostridium difficile* are on-going in North  
5  
6 America and Europe and results from these are eagerly awaited  
7  
8 as well as a study of faecal transplantation in metabolic  
9  
10 syndrome. Studies of faecal transplantation for other  
11  
12 gastrointestinal diseases where a dysbiosis of the gut  
13  
14 microbiota is evident are necessary. Rigorous screening of  
15  
16 potential donors is essential as is the use of partners or close  
17  
18 relatives as donors to minimise the potential for transmitting  
19  
20 disease. Close monitoring and long term follow up are  
21  
22 necessary. Combining clinical studies with molecular analysis  
23  
24 of the microbiota and the effects on the immune response may  
25  
26 significantly enhance our understanding of the gut microbiota  
27  
28 and its relationship with health and disease.  
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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
	<i>Treponema pallidum</i>
Stool	Selective stool culture
	<i>Clostridium difficile</i> 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)	No (18,19,26,27,28)
	Yes (29)	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.

For Peer Review