

Systematic review with meta-analysis: the Efficacy of Faecal Microbiota Transplantation for the treatment of recurrent and refractory *Clostridium difficile* infection

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**Systematic review with meta-analysis: the Efficacy of Faecal
Microbiota Transplantation for the treatment of recurrent
and refractory Clostridium difficile infection**

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3 1 **Systematic review with meta-analysis: the Efficacy of Faecal Microbiota Transplantation for the**
4 **treatment of recurrent and refractory Clostridium difficile infection**
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7
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26
27 16 **Background:**
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30 17 Clostridium difficile infection (CDI) is the commonest nosocomial cause of diarrhoea. Faecal
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32 18 microbiota transplantation (FMT) is an approved treatment for recurrent or refractory CDI but there
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34 19 is uncertainty about its use.
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37 20 **Aim:**
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40 21 Evaluate the efficacy of FMT in treating recurrent and refractory CDI and investigate outcomes from
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42 22 modes of delivery and preparation.
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45 23 **Methods:**
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48 24 A systematic review and meta-analysis was performed. MEDLINE, EMBASE, CINAHL, Cochrane
49
50 25 Library, trial registers and conference proceedings were searched. Studies on FMT in recurrent and
51
52 26 refractory CDI were included. The primary outcome was clinical resolution with subgroup analyses of
53
54 27 modes of delivery and preparation. Random effects meta-analyses were used to combine data.
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3 29 **Results:**
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6 30 37 studies were included; 7 randomised controlled trials and 30 case series. FMT was more effective
7
8 31 than vancomycin (RR: 0.23 95%CI 0.07 to 0.80) in resolving recurrent and refractory CDI. Clinical
9
10 32 resolution across all studies was 92% (95%CI 89% to 94%). A significant difference was observed
11
12 33 between lower GI and upper GI delivery of FMT 95% (95%CI 92% to 97%) versus 88% (95%CI 82% to
13
14 34 94%) respectively (p=0.02). There was no difference between fresh and frozen FMT 92% (95%CI 89%
15
16 35 to 95%) versus 93% (95%CI 87% to 97%) respectively (p=0.84). Administering consecutive courses of
17
18 36 FMT following failure of first FMT resulted in an incremental effect. Donor screening was consistent
19
20 37 but variability existed in recipient preparation and volume of FMT. Serious adverse events were
21
22 38 uncommon.
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26 39 **Conclusion:**
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29 40 FMT is an effective treatment for recurrent and refractory CDI independent of preparation and route
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31 41 of delivery.
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3 51 **Background**
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6 52 *Clostridium difficile* infection (CDI) is the most important cause of nosocomial diarrhoea usually
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8 53 related to antibiotic use. It is associated with significant morbidity, mortality and cost worldwide.¹
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10 54 UK National Institute for Health and Care Excellence (NICE) guidelines published in March 2014
11
12 55 recommend the use of faecal microbiota transplantation (FMT) for patients with recurrent CDI that
13
14 56 have failed to respond to antibiotics and other treatments.² However, a recent survey across
15
16 57 England revealed that only just over 25% of hospital trusts perform FMT for this indication.³ This
17
18 58 poor uptake has been attributed by physicians in part to paucity of randomised controlled trial (RCT)
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20 59 data, the lack of a standard treatment protocol, and uncertainty about long-term safety of FMT.³
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24 60 CDI occurs mainly in the elderly and those with significant chronic illnesses.¹ The long-term cure rate
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26 61 from standard first line antibiotics (metronidazole or vancomycin) is low with CDI re-occurring after
27
28 62 apparent resolution in about 35% of patients.⁴ Recurrent CDI is defined as complete recovery
29
30 63 without symptoms followed by at least one further episode of diarrhoea confirmed to be secondary
31
32 64 to CDI. Recurrent attacks of CDI expose patients to risk of complications such as toxic dilatation of
33
34 65 the colon and septicaemia, which are associated with high mortality. Commonly, tapering doses of
35
36 66 vancomycin are used for recurrent and refractory CDI although the effectiveness of this therapy is
37
38 67 uncertain with sustained cure rates reportedly ranging widely between 49% and 100%.⁵ While
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40 68 fidoxamicin has been shown to be more effective than vancomycin in the resolution of CDI as a first-
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42 69 line agent, this agent has not been tested in recurrent CDI.^{6,7}
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46 70 FMT for the treatment of CDI was attempted first in the modern era by Eiseman et al in 1958 in a
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48 71 small number of patients.⁸ Over the past decade or so, FMT has been studied by several centres
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50 72 worldwide for management of recurrent and refractory CDI. However, uncontrolled studies make up
51
52 73 the bulk of the supporting evidence. Previous systematic reviews and meta-analyses either have
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54 74 methodological limitations as they have a restrictive selection criteria, do not have a comprehensive
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56 75 search strategy or do not consider the effect of different modalities of preparation or delivery of
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3 76 FMT. Moreover, they do not include the most recent evidence, which to date includes more than
4
5 77 five randomised controlled trials.⁹⁻¹² In this systematic review and meta-analysis we therefore aim to
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7 78 address these issues to bring the evidence on FMT in recurrent and refractory CDI up to date.^{13,14}
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10 **Methods**

13 **Objectives**

16 81 To systematically evaluate the effectiveness of FMT as treatment for recurrent and refractory CDI.

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19 82 The review and meta-analysis were undertaken in line with guidance from the Cochrane Handbook
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21 83 of Systematic Reviews of Interventions, and reported in line with preferred reporting items for
22
23 84 systematic reviews and meta-analysis.^{13,14}
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26 **Search strategy**

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29 86 The databases MEDLINE, EMBASE, CINAHL, and Cochrane Library were searched from
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31 87 commencement of databases to October 2016 for relevant articles. Free text and index terms for
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33 88 faecal microbial transplantation and Clostridium difficile were combined and no study design or
34
35 89 language of publication filters were used. The MEDLINE and EMBASE strategy are shown in Appendix
36
37 90 1. Details of ongoing trials and studies yet to be fully published were sought from trials registers
38
39 91 (controlled-trials.com, clinicaltrials.gov), and microbiology, infection, and gastroenterology
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41 92 conferences proceedings (Digestive Diseases Week, British Society of Gastroenterology Conference,
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43 93 United European Gastroenterology Week) from September 2014 to October 2016. Reference lists of
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45 94 existing systematic reviews and articles included in this review were checked for additional studies.
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49 95 Search results were entered into a bibliography manager and duplicate entries removed.
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52 **Study Selection**

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55 97 Titles and abstracts of each article were screened for relevance. Copies of relevant articles were
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57 98 obtained and assessed for inclusion in the review using the criteria below. Screening and selection
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3 99 were undertaken independently by two reviewers and any disagreements resolved through
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5 100 discussion. The reason for not-selecting studies for review was recorded.
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8 101 Type of studies:
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11 102 RCTs, non-randomised trials and case series with 10 or greater participants were included. Studies
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13 103 published in abstract only format (for example from conference supplements) were only included if
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15 104 they were RCTs.
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18 105 Type of participants:
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21 106 Studies recruiting patients of all ages with refractory or recurrent CDI were included. Patients
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23 107 include those with ongoing diarrhoea without resolution of symptoms despite standard
24
25 108 antimicrobial therapy. Recurrent and refractory CDI was taken as defined by the authors.
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28 109 Comparator:
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31 110 For comparative study designs there was no restriction on the type of comparator
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34 111 Primary outcome:
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37 112 Studies reporting clinical resolution of CDI based on improvement of symptoms or negative
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39 113 Clostridium difficile stool culture or toxin were included.
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42 114 **Data extraction**
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45 115 Data were extracted using a predesigned collection form on characteristics of study design,
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47 116 participants, type of CDI (recurrent and/or refractory) and outcomes. In addition data were
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49 117 extracted on donor screening, procedural aspects (FMT preparation, pre-medications and number of
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51 118 infusions) to establish variation of practice. Data on adverse events were also collected.
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55 119 There was no missing data or unclear information that necessitated contacting study authors for
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57 120 clarification. For papers not published in English partial translations were undertaken (in one case).
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3 121 Data extraction and risk of bias assessment were undertaken by two reviewers independently. If
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5 122 there were any discrepancies, a third reviewer was consulted (in one case).
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8 123 **Risk of Bias**

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11 124 RCTs were assessed with the Cochrane Collaboration's risk of bias tool.¹³ For non-randomised trials
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13 125 the same tool was to be used without application of criteria related to randomisation. Case series
14
15 126 were assessed using the Centre for Reviews and Dissemination guidance.¹⁵
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18 127 **Data assessment and analysis**

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20
21 128 The effect of FMT on clinical resolution of recurrent and refractory CDI was evaluated by analysing
22
23 129 studies with direct comparison against a non-FMT arm. The overall effect of FMT was analysed using
24
25 130 data from all studies (including the FMT arm data from RCTs).
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28
29 131 The author's definition of outcome of CDI resolution was used at the time point specified by the
30
31 132 author following the delivery of FMT. In order to study the effect of multiple infusions, the data was
32
33 133 analysed to compare rate of clinical resolution if only a single infusion was administered and if more
34
35 134 than one infusion was delivered.
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38 135 Analysis was carried out to study the effects on FMT efficacy of mode of FMT delivery (upper GI
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40 136 (foregut) versus lower GI (colonic)) and different preparations of donor stool (fresh versus frozen).
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42 137 These comparisons were performed first with RCTs (if any) and then on subgroups of case series for
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44 138 each assessment. As it was anticipated that studies on the whole would not clearly differentiate
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46 139 between patients with recurrent and refractory CDI, no separate analyse on these subgroups was
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48 140 undertaken. A descriptive analyses of adverse event data was performed.
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51 141 Statistical analysis

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55 142 For the primary outcome pooled estimates of relative risk from the RCTs, and response rates from
56
57 143 case series, were estimated with a random effect model using the method of DerSimonian &
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3 144 Laird.^{16,17} For the latter the pooled estimate was calculated after the Freeman-Tukey Double Arcsine
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5 145 Transformation was applied to stabilise the variances facilitating synthesis of studies with 100%
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7 146 response rate.¹⁸ Exact confidence intervals were calculated for the individual studies.
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10 147 Heterogeneity was assessed using the I^2 statistic and calculation of 95% prediction intervals for the
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12 148 response proportion in a new study.^{19,20} The latter were calculated using a logistic regression model
13
14 149 with a random intercept. In interpreting I^2 we describe values from 0%-30% as being likely minimal,
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16 150 values from 30-60% as likely moderate, and values from 60%-100% as likely substantial
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18 151 heterogeneity. The possibility of small study effects was assessed by asymmetry of funnel plots if 10
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20 152 or more studies contributed to a meta-analysis and the potential impact quantified using the Duval
21
22 153 and Tweedie nonparametric "trim and fill" method.²¹
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26 154 Confidence intervals for relative risks from individual RCTs were calculated assuming the sampling
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28 155 distributions of the log-relative risk are normally distributed. All analyses were performed in STATA
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30 156 version 14.
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33 157 **RESULTS**

34 158 **Study characteristics**

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39 159 The initial search identified 2097 publications. Of these, 1179 duplicates were excluded and an
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41 160 additional 615 were removed after screening titles and abstracts. Consequently, 303 papers were
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43 161 retrieved in full text. Of these 19 were systematic reviews from which no additional papers were
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45 162 identified. From the remaining 284 papers, 102 were overviews, summaries, opinion pieces and
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47 163 narrative reviews, 83 were case reports or case series with a sample size of less than 10 patients and
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49 164 62 were case series published only as an abstract. Therefore 37 papers reporting studies met the
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51 165 selection criteria (Figure 1).
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55 166 The 37 included studies are summarised in Table 1 and Supplement 1. Supplement 1 elaborates on
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57 167 the primary response rate data and assessment of study quality. Seven studies were RCTs (of which
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3 168 two were only published in abstract form) and 30 were case series. The different arms of the RCT
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5 169 data are summarised in Table 2. The included studies included a total of 1973 patients with 428
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7 170 enrolled in RCTs (360 in the donor FMT arm and 68 in the non-donor FMT arm) and 1545 described
8
9 171 in case series. Two RCTs were open label comparisons of vancomycin and FMT (van Nood et al and
10
11 172 Cammarota et al).^{22,23} Both were ended early following interim analysis by the respective data and
12
13 173 safety monitoring boards due to observed efficacy of FMT. One RCT compared autologous versus
14
15 174 donor FMT (Kelly et al), and the remaining RCTs compared different forms of FMT or modes of
16
17 175 delivery: Fresh and frozen FMT (Lee et al), capsule versus colonoscopic delivery (Kao et al), low dose
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19 176 versus high dose FMT (Allegretti et al), nasogastric versus colonoscopic delivery (Youngster et al).²⁴⁻²⁸
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23 177 Of the case series, 25 performed FMT solely using fresh stool, two studies solely used frozen stool,
24
25 178 two studies performed FMT with both fresh and frozen and one did not report on FMT preparation.
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27 179 Eight studies delivered FMT via the upper GI route, 18 studies delivered FMT via the lower GI route
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29 180 and one study delivered FMT via both routes. The remaining studies used a combination of both
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31 181 routes but did not report on data separately. Almost all the 30 studies had similar cohorts with
32
33 182 regard to age and gender and similar response rates were observed in older and younger groups and
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35 183 those with male or female predominance as shown in Table 1 and Supplement 1. There was a female
36
37 184 preponderance in the studies with a male: female distribution of 2:3. No studies solely used toxin
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39 185 negativity to define clinical resolution. Prior endoscopic evaluation was undertaken in six studies.
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43 186 Donor screening protocol

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46 187 Donors were a mixture of spouses, intimates, relatives and healthy volunteers. Most studies used a
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48 188 screening procedure to exclude individuals with known exposure to transmissible viruses, sexually
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50 189 transmitted disease, those involved in high-risk sexual behaviours and those with a history of drug
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52 190 abuse. Those with known gastrointestinal co-morbidity were excluded as were those who had
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54 191 recently taken antibiotics. With regard to donor screening there was considerable standardisation in
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56 192 screening for blood-borne viruses with screening for common transmissible agents such as hepatitis
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3 193 A, B, C, HIV 1&2, *Helicobacter pylori* and Treponema in blood. This also applied to stool pathogens
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5 194 including *Clostridium difficile* toxin, common pathogens including *Cryptosporidium* and *Giardia* and
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7 195 the majority of studies also reported microscopic examination for ova, cysts and parasites in stool
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10 196 samples.

11
12 197 Procedural aspects

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15 198 i) FMT preparation

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18 199 In eight studies the solvent was water, saline in 20 and glycerol was used as a cytoprotectant in the
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20 200 three studies using frozen stool preparations. The remaining studies did not describe the diluent
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22 201 used to make up the transplant material. Where stated, time from collection to administration
23
24 202 varied from 1 hour to 8 weeks for frozen stool whilst the median time was six hours for studies using
25
26 203 fresh stool samples. Quantity and volume of FMT material was very variable. In the studies using the
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28 204 upper route of delivery, the volume of material varied from 25ml to 500ml and the mass of faecal
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30 205 material also varied widely from 6g up to about 140g (median 40g). In the studies reporting on the
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32 206 lower GI route of delivery the volume of FMT was reported in 19 and this ranged from 100ml to
33
34 207 1000ml with a mean volume of about 450ml. The fresh mass of faecal matter used was variably
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36 208 reported from 30g to 152g (median of 86g). Two RCTs used capsulated forms of stool however
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38 209 further details on the preparation of these capsules was not available as the data was only published
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40 210 in an abstract form.^{26,32}

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45 211 ii) Pre-medication

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48 212 Standard colonoscopy bowel preparation was used in all studies undertaking FMT via the lower GI
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50 213 route. Proton pump inhibitors were given in most studies using the upper route with the exception
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52 214 of the Van Nood randomised controlled trial.²² The use of anti-diarrhoeals to prolong retention of
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54 215 the faecal suspension in the colon was also reported in two studies. Antibiotics were generally
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3 216 stopped 1-2 days before FMT with the exception of the van Nood RCT where antibiotics were
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5 217 continued until the day of the treatment.²²
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8 218 iii) Number of infusions
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11 219 24 studies allowed more than one infusion / treatment of FMT in the event of failure of response. Of
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13 220 the 13 studies that only performed a signal infusion of FMT 9 were done using the lower GI route, 3
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15 221 used only the upper GI route and one used either route.^{26,27,33-43} Twelve studies used only fresh
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17 222 stool, and one used either fresh or frozen and 1 performed FMT also using a capsulated form. In the
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19 223 remaining studies FMT was administered up to 4 times for recurrent or unresolved symptoms.
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22 224 **Assessment of study quality**

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25 225 The seven RCTs were assessed to have a low risk of bias and demonstrated adequate randomisation
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27 226 with concealed automated allocation and performed an intention to treat analysis. For case series,
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29 227 although selection criteria were defined in most of these studies, all mentioned or implied
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31 228 consecutive recruitment of patients. Patients were followed up till achievement or failure of the
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33 229 primary outcome. Consequently, few studies reported long term outcomes and adverse events.
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35 230 Follow up ranged from 10 weeks to 8 years.
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39 231 **Efficacy of FMT**

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42 232 Most studies differed in their definition / criteria for resolution of CDI. Hence the author's definition
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44 233 of outcome of CDI resolution at their specified time point following the delivery of FMT was used.
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46 234 Based on the variability of definitions used in the literature it was not possible to clearly separate
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48 235 data on "recurrent" versus "refractory" CDI. There were no true placebo controlled trials
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50 236 investigating the efficacy of FMT.
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53 237 Response to FMT - RCTs

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3 238 There were 3 RCTs that compared FMT to a non-FMT intervention. In the two RCTs comparing FMT
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5 239 to vancomycin, the pooled relative risk of treatment failure of FMT against vancomycin was 0.23
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7 240 (95% CI 0.20 to 0.80) with moderate heterogeneity ($I^2 = 41%$) indicating the superiority of FMT.^{22,23}
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9 241 The relative risk against vancomycin and bowel lavage in the RCT by Camorotta et al was 0.08 (95%
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11 242 CI 0.01 to 0.05).²³ The overall response rate from the two RCTs comparing FMT to vancomycin was
12
13 243 90% in the FMT arm while the response rate was less than 30% in the antibiotic arms. The RCT by
14
15 244 Kelly compared single infusion of donor versus autologous FMT.²⁷ In the intention-to-treat analysis,
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17 245 20 of 22 patients (90.9%) in the donor FMT group achieved clinical cure at 8 weeks compared with
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19 246 15 of 24 (62.5%) in the autologous FMT group ($P = 0.042$).
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23 247 The RCT by Lee and colleagues (comparing fresh versus frozen FMT) reported an overall combined
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25 248 clinical resolution rate with FMT of 72% in the intention-to-treat analysis, and 84% in the per
26
27 249 protocol analysis across both arms.²⁴ This was 52% for a single infusion but increased to 96% in
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29 250 patients who received more than two FMTs in the 13 week period. The RCT by Youngster (comparing
30
31 251 nasogastric versus colonic FMT) reported a primary response rate (one infusion) of 70% across both
32
33 252 arms and this increased to 90% with a second infusion in those that failed to respond to the first.²⁸ A
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35 253 further two RCTs published in abstract form comparing efficacy with capsule versus colonic delivery
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37 254 and low dose versus high dose capsulated FMT both showed a response rate of 95% across both
38
39 255 FMT arms.^{26,32} Kao demonstrated a cure rate of 100% versus 92% in colonoscopy and capsule
40
41 256 delivered FMT respectively.²⁶ In the Allegretti study presented at the Digestive Diseases Week in San
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43 257 Diego 2016, the authors reported on encouraging remission in 14 out of 19 patients treated with
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45 258 either a low or high dose of capsules.³² The abstract reports the 5 non-responders at 8 weeks were
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47 259 all given a high dose of capsules with cure in 4.
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55 261 Response to FMT – all studies
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3 262 The mean pooled overall response for FMT in recurrent and refractory CDI based on all the included
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5 263 37 studies regardless of the number of infusions was 92% (95% CI 89% to 94%) with likely moderate
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7 264 heterogeneity ($I^2 = 59%$) (figure 2). From the 34 studies that presented efficacy data for a single FMT
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9 265 infusion, the mean pooled response rate was 84% (95% CI 79% to 89%) with a likely high degree of
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11 266 heterogeneity ($I^2 = 84%$). For a single infusion a 95% prediction interval for the response proportion
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13 267 in a new study is 49% to 96%. On analysis by funnel plot, studies were not symmetrically distributed
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15 268 about the pooled estimate possibly indicating an absence of some smaller and medium sized studies
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17 269 with findings that, although favourable, are not as favourable as other small studies. There are many
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19 270 possible reasons for this including chance, small study effects and publication bias. When this funnel
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21 271 plot asymmetry was adjusted for, the efficacy of one or more FMT infusions was only reduced by a
22
23 272 small amount to 79% (95% CI 73% to 84%) (supplement 2).
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27 273 The case series had cure rates ranging from 68 – 100% with only one study having an overall
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29 274 response rate of under 75% and eight case series demonstrating a response rate of 100% (although
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31 275 there was incomplete follow up in some of these studies).
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34 276 Only one study addressed the efficacy of FMT for treatment of CDI in immunocompromised patients.
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36 277 ³⁰ This study included a series of patients with IBD, solid organ transplants on immunosuppression,
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38 278 HIV and cancers. The CDI cure rate observed after a single FMT was 78%, with an overall cure rate of
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40 279 89% following a second transplant.
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44 280 Comparison between upper GI and lower GI routes of delivery

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47 281 The RCT that compared nasogastric (upper GI) versus colonic delivery of FMT reported a cure rate of
48
49 282 60% at 8 weeks with a single infusion and an overall cure rate 80% after second infusion when
50
51 283 delivered via NG.²⁸ The cure rate with colonic delivery was 80% with a single infusion at 8 weeks and
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53 284 an overall cure rate of 100% after a second infusion.
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3 285 Of the remaining studies, 25 case series and 7 RCTs had separate outcome data for modes of FMT
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5 286 delivery. 22 delivered FMT by the lower GI route (colonoscopy or retention enema) and 11 delivered
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7 287 FMT by the upper gastrointestinal route (upper GI endoscopy, nasogastric tube or naso-jejunal
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9 288 tube). Results are displayed in figure 3. The pooled response of CDI to lower GI-delivered FMT was
10
11 289 95% (95% CI 92% to 97%) with likely moderate heterogeneity between the studies ($I^2 = 48\%$). When
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13 290 adjusted for funnel plot asymmetry overall response was 90%. This compared to the overall pooled
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15 291 response rate to upper GI FMT of 88% (95% CI 82% to 94%) with moderate observed heterogeneity
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17 292 between the studies and adjusting for funnel plot asymmetry revealed a response rate of 83%. There
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19 293 was evidence of a difference between the delivery methods with respect to response to FMT
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21 294 ($p=0.02$). Analysis of cure rate with a single infusion did not show a significant difference with route
22
23 295 of delivery with a response of CDI of 81% (95% CI 73% to 88%) to lower GI-delivered FMT and of 87%
24
25 296 (95% CI 79% to 94%) for upper GI-delivered FMT ($p=0.20$).

297 Comparison of freshly prepared versus frozen FMT

298 In the RCT by Lee patients received either FMT prepared no more than five hours earlier ($n=111$) or
299 FMT frozen for up to 30 days ($n=108$).²⁴ The clinical resolution of diarrhoea using intention to treat
300 analysis showed no evidence of a difference in outcome between preparations, with a relative risk of
301 failure to respond of 1.19 (95%CI 0.77,1.84) with a 70% response in the fresh FMT group and 75% in
302 the frozen FMT group. This increased to 85.6% and 90.7% respectively when patients were given
303 multiple infusions FMT due to lack of response.

304 Of the other studies, thirty case studies used fresh stool and 4 studies (2 case series, 2 RCTs) used
305 frozen stool to prepare FMT and a response rate was calculable for each group. For the fresh FMT
306 studies the overall response rate was 92% (95% CI 89% to 95%) with moderate heterogeneity
307 between the studies ($I^2 = 54\%$). When adjusted for funnel plot asymmetry the overall response rate
308 was 87%. The overall response in frozen FMT studies was 93% (95% CI 87% to 97%) with minimal
309 observed heterogeneity between the studies ($I^2 = 19\%$). There were insufficient studies to assess

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3 310 funnel plot asymmetry. There was no evidence of a difference in response between the two groups
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5 311 ($p=0.84$) (figure 4). Analysis of a single infusion revealed a response rate of 85% (95% CI 79% to 90%)
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7 312 for fresh FMT and a lower response rate of 68% (95% CI 47% to 86%) for frozen FMT but there was
8
9 313 only very weak statistical evidence of a difference ($p=0.10$).

12 314 Adverse Events

15 315 The RCT by Van Nood reported no significant adverse events (SAEs) in 16 patients treated with FMT,
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17 316 however there were two urinary tract infections and one patient suffered from choledocholithiasis.
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19 317 ²² No SAEs related to FMT were reported in other RCTs. Transient mild diarrhoea and cramping was
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21 318 very common in the FMT arm of three RCTs by Lee, Cammarota, Van Nood, and about 25% of the
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23 319 recruits in the RCT by Lee reported long term constipation and flatulence following FMT. Similarly,
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25 320 19% of patients in the FMT arm reported constipation in follow up period in the van Nood RCT. Mild
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27 321 abdominal pain and bloating was reported in 20% of patients treated by a frozen inoculum of FMT.²⁸
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29 322 In the RCT by Kelly et al comparing FMT with autologous vs heterologous (donor) stool administered
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31 323 by colonoscopy, chills were observed more frequently in autologous group.²⁷ Rates of other minor
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33 324 AEs did not differ significantly between groups.

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37 325 In the case series most side effects were minor and often transient: bloating, belching, abdominal
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39 326 cramps, pain or discomfort, nausea, vomiting, excess flatulence, constipation, transient fever,
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41 327 urinary tract infections, self-limiting diarrhoea, and irregular bowel movement. However, recurrent
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43 328 and refractory CDI negative diarrhoea or worsening diarrhoea following FMT was also reported
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45 329 although the duration of this adverse event was not reported.^{37,44} The data from these case series
46
47 330 did not allow an assessment of any differences in adverse events by route of treatment or use of
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49 331 fresh or frozen transplant.

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53 332 There were no reported cases of aspiration following FMT delivery via the upper GI route. In one
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55 333 case the patient vomited immediately after FMT application via nasogastric tube.⁴⁵ There was only

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3 334 one reported case of mucosal tear and micro perforation following colonoscopic delivery of FMT.
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5 335 ^{30,46} Hospitalisation with self-limited FMT related abdominal pain, was reported in one patient.³⁰
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8 336 There were 50 deaths reported in the studies reviewed, however these were almost all due to
9
10 337 critical illness of elderly patients with multiple comorbidities or unrelated illness and were not
11
12 338 directly attributed to the FMT. However, there was a death as a result of aspiration at the time of
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14 339 sedation for the colonoscopy to administer the FMT.³⁰ Two patients with recurrent diarrhoea and
15
16 340 initial response to the FMT died subsequently from complications of ileus and colonic perforation
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18 341 Four deaths in patients infected with the ribotype 027 strain who did not respond to FMT and died
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20 342 within 3 months were also reported.⁴⁷
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24 343 Of note, a case series of FMT in 80 immunocompromised patients with three month follow up did
25
26 344 not report any serious adverse events.³⁰ However, four patients with inflammatory bowel disease
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28 345 experienced a flare up of their condition after FMT. Similarly a case series of 146 elderly patients
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30 346 that were followed up for one year did not report any serious adverse events.⁴⁸
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36 348 **DISCUSSION**

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39 349 This systematic review and meta-analysis has demonstrated that FMT is a highly effective treatment
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41 350 for resolution of recurrent and refractory CDI. Even the most conservative analysis gives an estimate
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43 351 of efficacy of a 49% response rate for FMT in this setting based on the lower prediction interval for a
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45 352 single infusion. Previous systematic reviews and meta-analysis have reported the marked efficacy of
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47 353 FMT for treatment of CDI in the range of 88 to 92%, similar to our findings.^{9,10} These, however, pre-
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49 354 dated or failed to include the five recent RCTs and included far fewer case series.^{23,24} There is good
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51 355 agreement between the efficacy demonstrated in observed response rates in the seven RCTs (only
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53 356 three of which have a non-FMT comparator arm) performed to date and the reports from case
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3 357 series. The limited data on mortality and significant adverse events suggests that FMT is safe and
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5 358 generally well tolerated, even in sick immunocompromised elderly patients.³⁰
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8 359 No previous meta-analysis has compared fresh and frozen FMT in treatment of recurrent CDI, whilst
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10 360 the present study shows no difference in efficacy between these modes of stool preparation. The
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12 361 review also demonstrates that repeated infusions of FMT in non-responders resulted in a higher
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14 362 cure rate albeit with some limited data for this analysis. Previous reviews have suggested that the
15
16 363 efficacy for lower GI route is greater than upper GI route (Kassam et al, (91% vs 80% respectively
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18 364 ($p=0.046$)).¹⁰ We have however shown that this difference was no longer significant when efficacy
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20 365 with only a single infusion was analysed.
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24 366 With regard to attempting to differentiate between the efficacy of FMT for recurrent or refractory
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26 367 CDI, we found that the distinction between recurrent and refractory disease in the case series is
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28 368 often vaguely reported and not robust enough to allow for meaningful sub-group analysis. Similarly,
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30 369 previous reviewers have reported that no studies have compared refractory CDI to standard therapy
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32 370 and from the small numbers of patients being treated for solely refractory CDI meaningful analysis is
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34 371 difficult.^{11,12}
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38 372 This systematic review and meta-analysis is a comprehensive ascertainment of the available
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40 373 evidence through a detailed search strategy, and includes the seven RCTs to date. Structured
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42 374 analyses were performed to address key issues with regards to storage and administration of FMT
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44 375 that may improve wider uptake of this treatment strategy. There are, however, limitations to our
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46 376 analysis. Characterisation of initial /primary response depended on the authors' definitions, hence
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48 377 varying between studies and being sometimes poorly defined. Although almost all studies defined
49
50 378 initial response as resolution or improvement of diarrhoea, but the time to response varied from 1
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52 379 day to 90 days and the overall response varied from 7 days to 3 months. Most studies failed to
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54 380 report *C. difficile* toxin for assessment of clearance in several studies lacked long-term data. A recent
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56 381 paper has highlighted the high incidence of IBS after an attack of CDI.⁴⁸ There was significant
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3 382 variability of dose of FMT and several studies defined their clinical resolution following use of more
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5 383 than one infusion of FMT. The use of concomitant medications and other biases may be greatly
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7 384 underestimated given the retrospective nature of most of the case series included in this review.
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10 385 The data suggest that, irrespective of route of delivery or method of preparation repeated
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12 386 treatments have an incremental benefit. There are no clear strategies for this and guidelines are
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14 387 required, as well as additional RCTs to further determine the optimal dose and long-term outcomes
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16 388 and side effects of FMT are required. Finally, 'corrected' estimates calculated using the Trim and Fill
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18 389 method should be treated with great caution and as indicative as the method does not take into
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20 390 account reasons for funnel plot asymmetry other than publication bias and limited numbers to
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22 391 detect differences in subgroup analyses.¹³
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26 392 Included studies exhibited substantial heterogeneity in procedural aspects of FMT preparation and
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28 393 delivery. Donor screening appeared to be robust and studies consistently had strict exclusion criteria
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30 394 based on history of high-risk behaviours, recent antibiotic use and a comprehensive serology of
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32 395 blood borne viruses and stool cultures for pathogens. FMT was prepared using water or saline along
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34 396 with glycerol in most studies. However the quantity and volume of stool and solvent used to prepare
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36 397 the transplant was very variable.
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40 398 Patients who underwent FMT via a lower GI route received a larger amount / concentration of FMT
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42 399 compared to those who had it delivered via the upper GI route. The number of infusions prior to
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44 400 achieving clinical resolution as defined by the authors also varied significantly between studies
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46 401 although most studies only gave a single infusion. There is little uniformity of practice with regard to
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48 402 treatment protocol with respect to the triggering of subsequent treatments after the first.
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51 403 This review is focussed on FMT and, as such, we have not included emerging data from
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53 404 investigations using faecal bacteriotherapy in which the microbiota is altered or in which specific
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55 405 bacteria are infused.^{49,50}
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3 406 Short-term adverse events were reported in almost all the studies however there was lack of
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5 407 consistency in long-term follow up for adverse events in uncontrolled studies and this was often
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7 408 reported on an ad-hoc basis. Follow up was also limited to 10 -13 weeks in RCTs. Most adverse
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9 409 events were self-limiting gastrointestinal symptoms including abdominal cramps, constipation,
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11 410 diarrhoea and usually occurred within 24 hours of the procedure and resolved within a week of the
12
13 411 FMT. Deaths reported following FMT were almost always due to inter-current illness unrelated to
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15 412 CDI, FMT and overt failure to respond to FMT. On the whole the current evidence suggests a good
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17 413 short-term safety of FMT however data is limited and uncertainty remains concerning unrecognised
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19 414 long-term consequences. It should also be noted that in this review studies were selected based on
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21 415 whether they reported an outcome related to resolution of CDI and that case series with less than
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23 416 ten patients were not analysed. Thus it could be argued that this review is not comprehensive of all
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25 417 studies that might report adverse events.
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30 418 Despite uncertainty FMT for the treatment of CDI associated colitis has been adopted as the
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32 419 biological rationale for its use is compelling and the treatment is cheap. The second line antibiotic
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34 420 treatment for CDI associated colitis after standard antibiotics (metronidazole and vancomycin) is
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36 421 fidaxomicin and this is vastly more expensive than FMT.¹ Moreover, there is no current evidence for
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38 422 fidaxomicin in the treatment of recurrent CDI and as yet no direct comparison of the effectiveness of
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40 423 this antibiotic against FMT.
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44 424 In the UK NICE has approved FMT “for patients for with recurrent CDI that have failed to respond to
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46 425 antibiotics and other treatments”.² However, despite this official stamp of approval, standards of
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48 426 governance with respect to the procedure itself remain undefined. This is perhaps particularly
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50 427 pertinent now that manipulation of the microbiome is being considered in younger cohorts of
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52 428 patients for indications other than CDI associated colitis.^{51,52}
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55 429 Most studies appear to comply with the donor screening criteria outlined by the American
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57 430 Gastroenterology Association.^{53, 54} However there is no agreement as to what constitutes an
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3 431 acceptable donor with respect to, for example, relatedness to the patient, lifestyle, diet, co-
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5 432 morbidity, body mass index and there is no mandate with regard to follow up of donors. Similarly no
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7 433 consensus exists about fundamental aspects concerning the actual process of delivering FMT. Some
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9 434 investigators use the upper GI route for the administration of FMT others (the majority of published
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11 435 studies) use colonoscopy or retention enemas. There is little evidence of uniformity with respect to
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13 436 stopping other treatments prior to FMT or concomitant treatments to be used to facilitate FMT.
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15 437 However despite a lack of consistent approach the clinical efficacy for FMT is universally positive and
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17 438 much greater than that seen with antibiotics. A recent International Consensus has highlighted the
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19 439 uncertainties concerning route of delivery, donor selection (household members/healthy
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21 440 volunteers), the place of routine pre-treatment with antibiotics and bowel preparation and, in light
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23 441 of long term safety concerns, the desirability of establishing a patient registry.⁵⁵The utility of frozen
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25 442 FMT has gained significant interest as it allows the ability to deliver treatment on demand and to a
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27 443 wider population. As a result recent regulatory discussions concerning FMT provision in the
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29 444 European Union have led to the situation that FMT use in the context of clinical trials is to be
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31 445 controlled by regulatory authorities.⁵⁶
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36 446 Data is beginning to emerge regarding the association of microbiome alteration with response to
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38 447 FMT. In a recent study from the US, the authors reported specific gut microbiota signatures
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40 448 associated with response to or recurrence after FMT.⁵⁷ This raises the possibility of predicting which
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42 449 patients may not respond to primary treatment with antibiotics and those then likely to need FMT.
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44 450 In another intriguing study from this group it was reported that microbiota changes associated with
45
46 451 bile salt metabolism following FMT may also indicate patients likely to progress to recurrent CDI and
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48 452 the need for FMT.⁵⁸
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52 453 In the future it is likely that we will see further data emerging from investigators who prepare
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54 454 “designer” FMT or by culturing specific organisms in vitro particularly as we better understand
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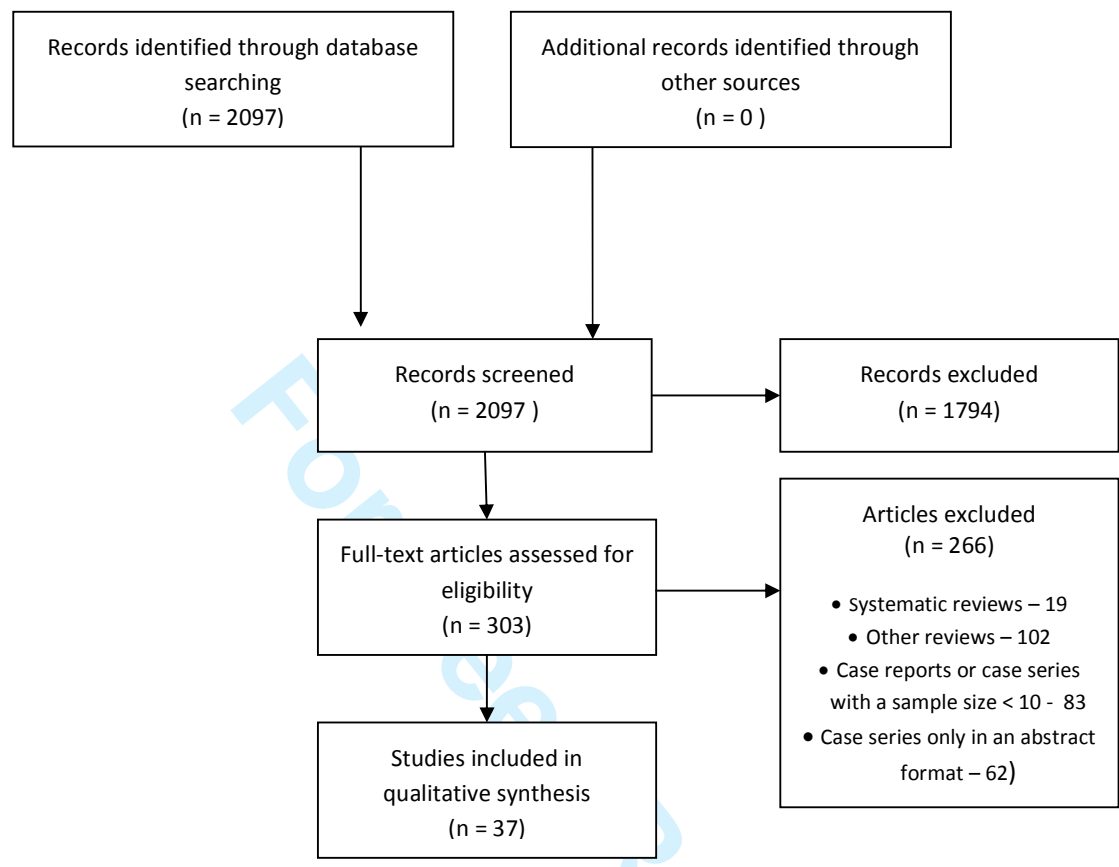
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3 455 microbiota profiles which differentiate health from disease and the profile which is associated with
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5 456 successful FMT.^{49,50}
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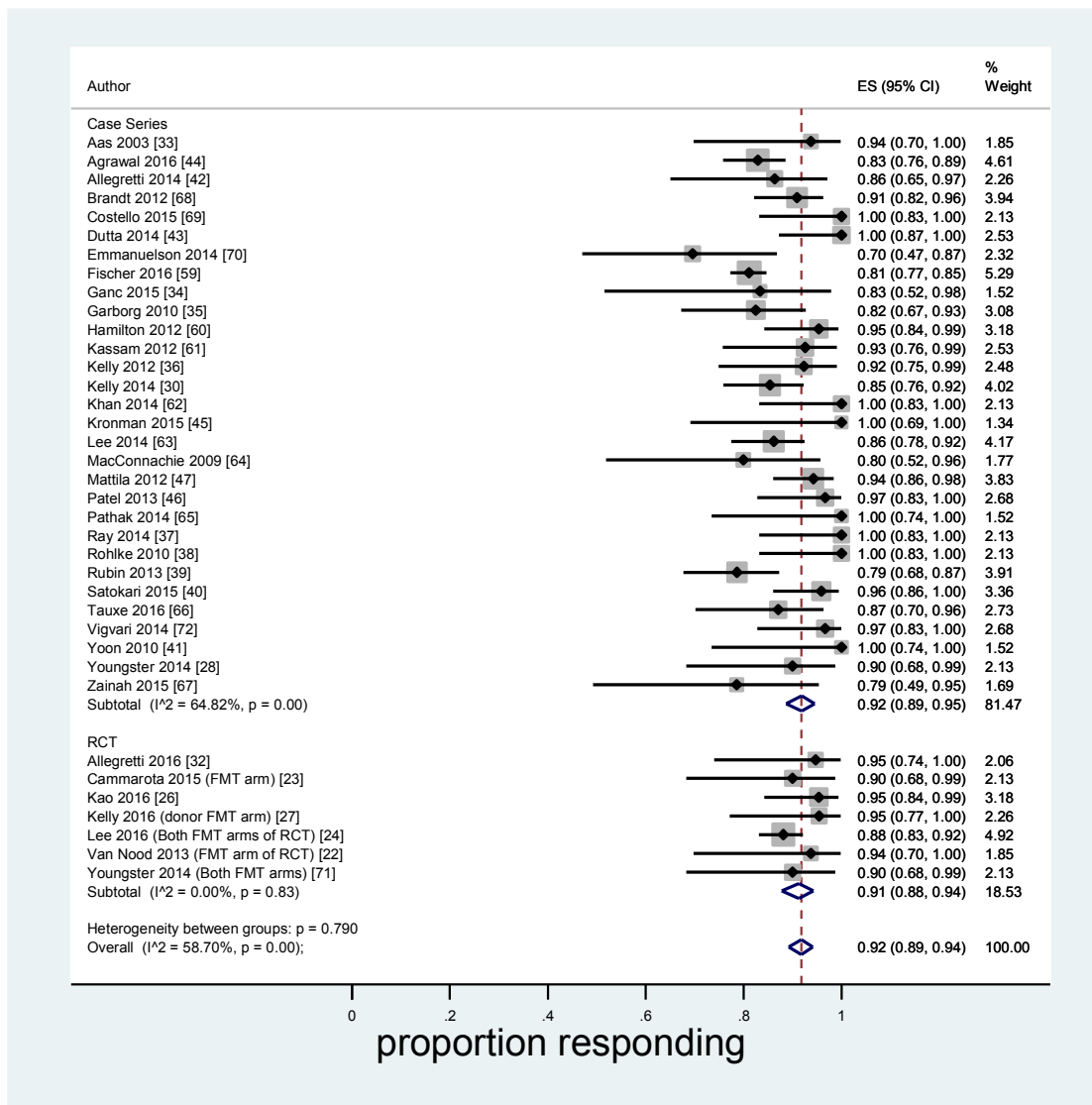
8 457 In conclusion, FMT appears to be an effective and possibly a safe treatment strategy for recurrent
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10 458 and refractory CDI. The efficacy is similar in both controlled and uncontrolled studies. The current
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12 459 data is relatively heterogeneous with regards to the methodology for transplantation and the
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14 460 outcome measure for resolution of CDI. Whilst this could be explored with the current evidence base
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16 461 to refine estimates and potentially suggest effect modifiers, the effect of FMT on resolution of
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18 462 recurrent/refractory CDI markedly evident and appears to be quantitatively in excess of that seen
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20 463 with other antimicrobial therapies such as vancomycin. Further studies should be of robust design
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22 464 and focus on determining the optimal procedures and long-term outcomes and side effects of FMT
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25 465 in order that FMT is available to help alleviate the burden of this significant iatrogenic hazard.
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467 **Figure 1. Flowchart of search**



487 **Figure 2 Forest plot of the proportion responding to treatment for all included studies**488 **a) Multiple infusions**

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490 ES (95% CI) is the proportion responding with its 95% confidence interval.

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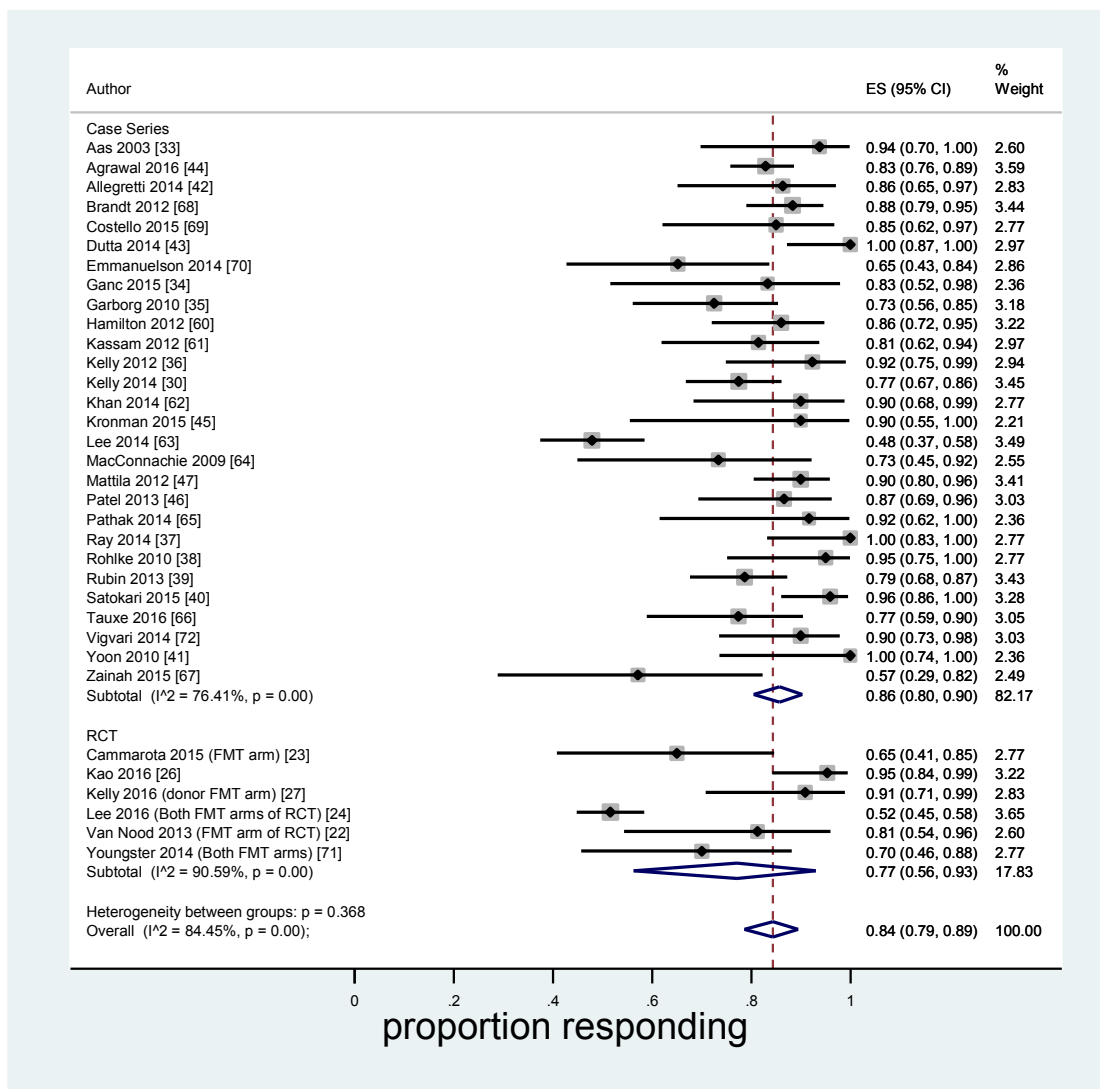
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b) Single infusion



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499 ES (95% CI) is the proportion responding with its 95% confidence interval.

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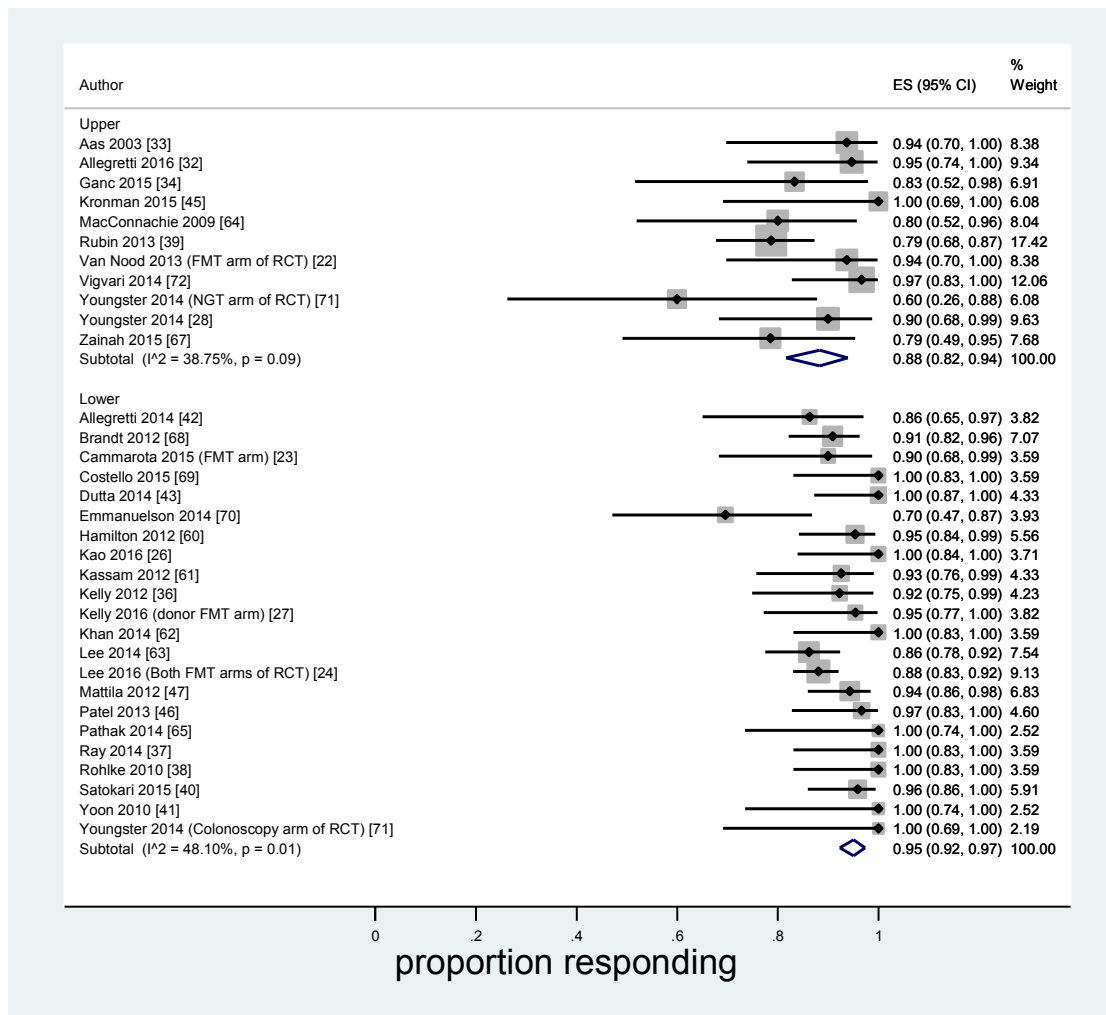
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507 **Figure 3. Forest plot of the proportion responding to treatment by Upper GI and Lower GI routes of**
 508 **delivery.**

509 **a) Multiple infusions**



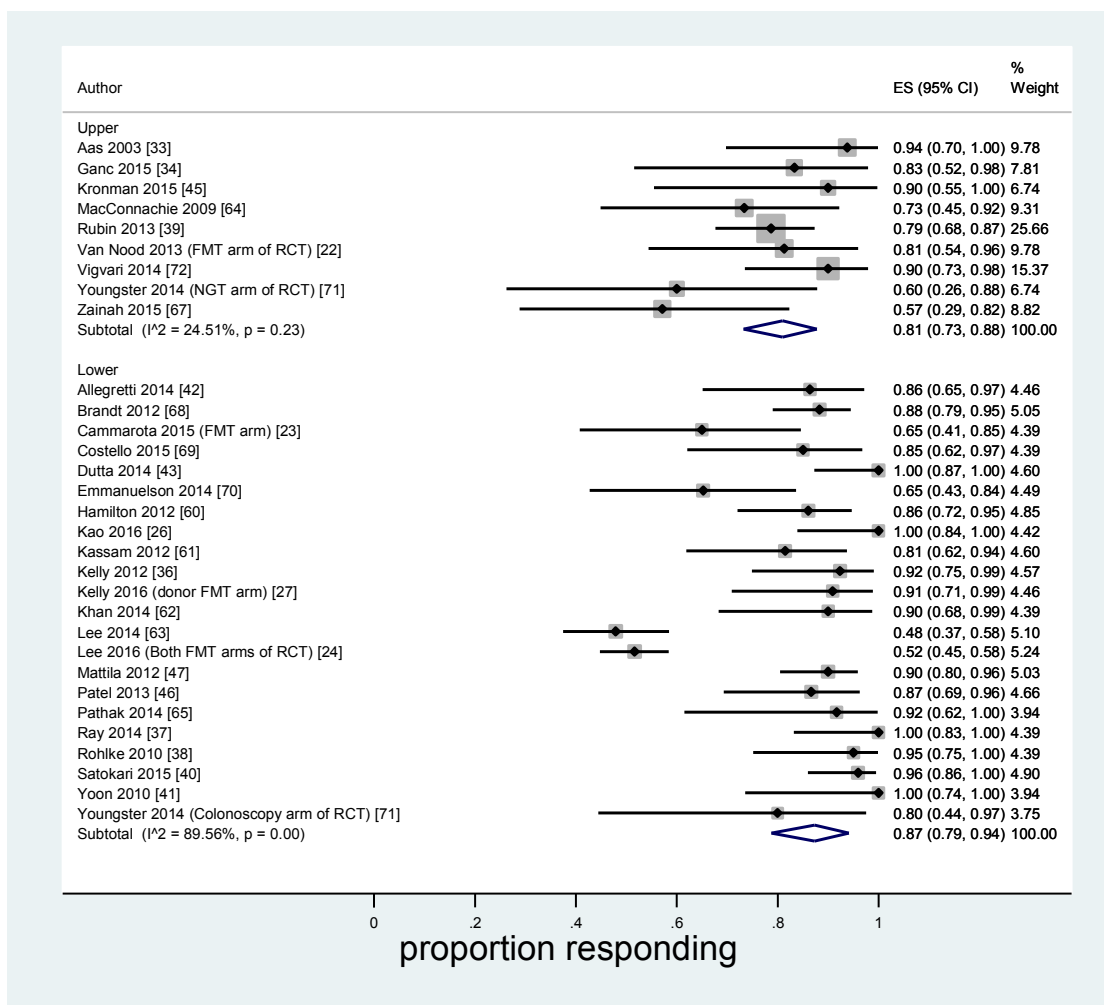
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511 ES (95% CI) is the proportion responding with its 95% confidence interval.

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514 b) Single infusion



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516 ES (95% CI) is the proportion responding with its 95% confidence interval.

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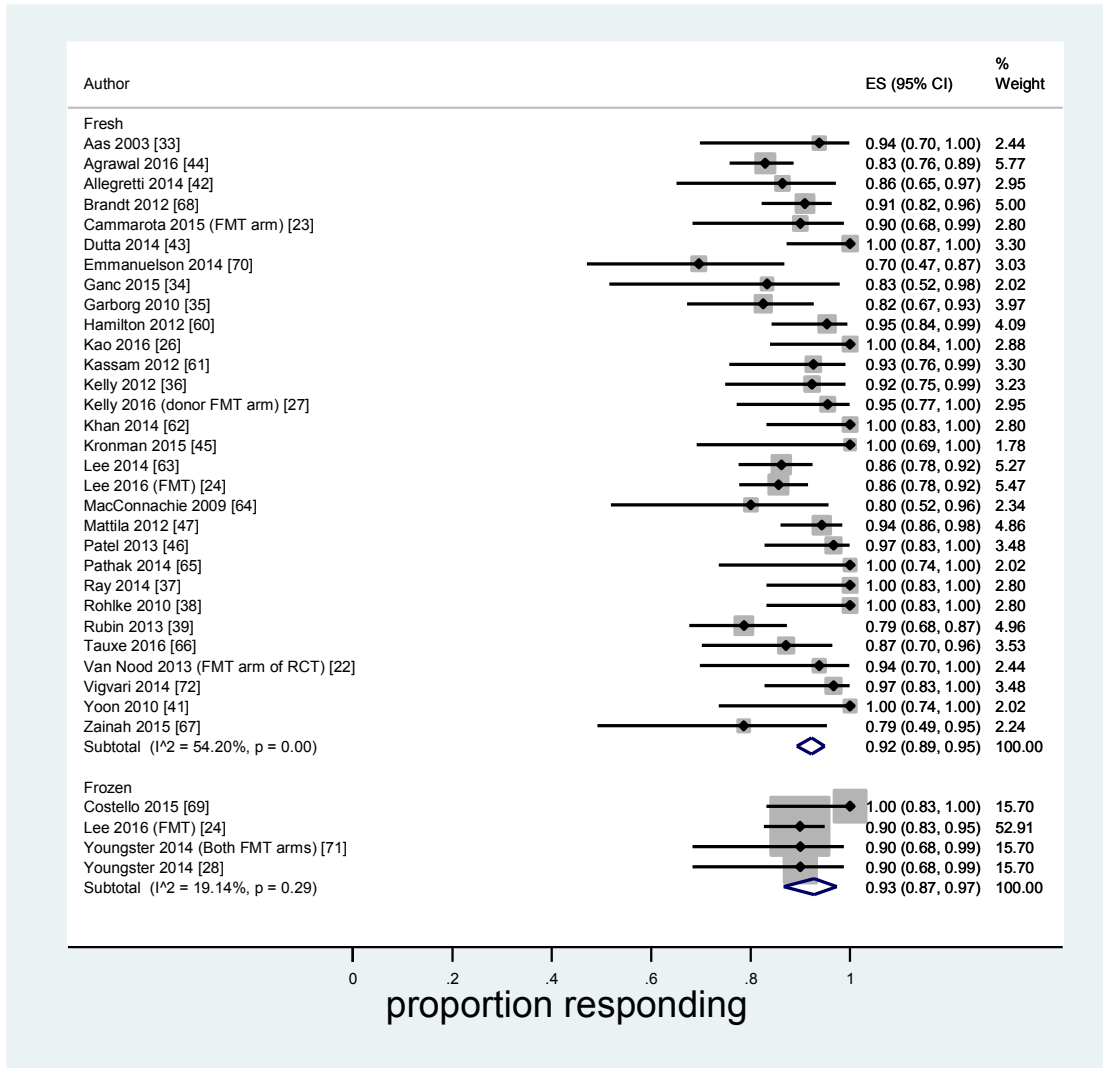
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525 **Figure 4. Forest plot of the proportion responding to treatment by freshly prepared versus frozen**
 526 **FMT.**

527 **a) Multiple infusions**



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529 ES (95% CI) is the proportion responding with its 95% confidence interval.

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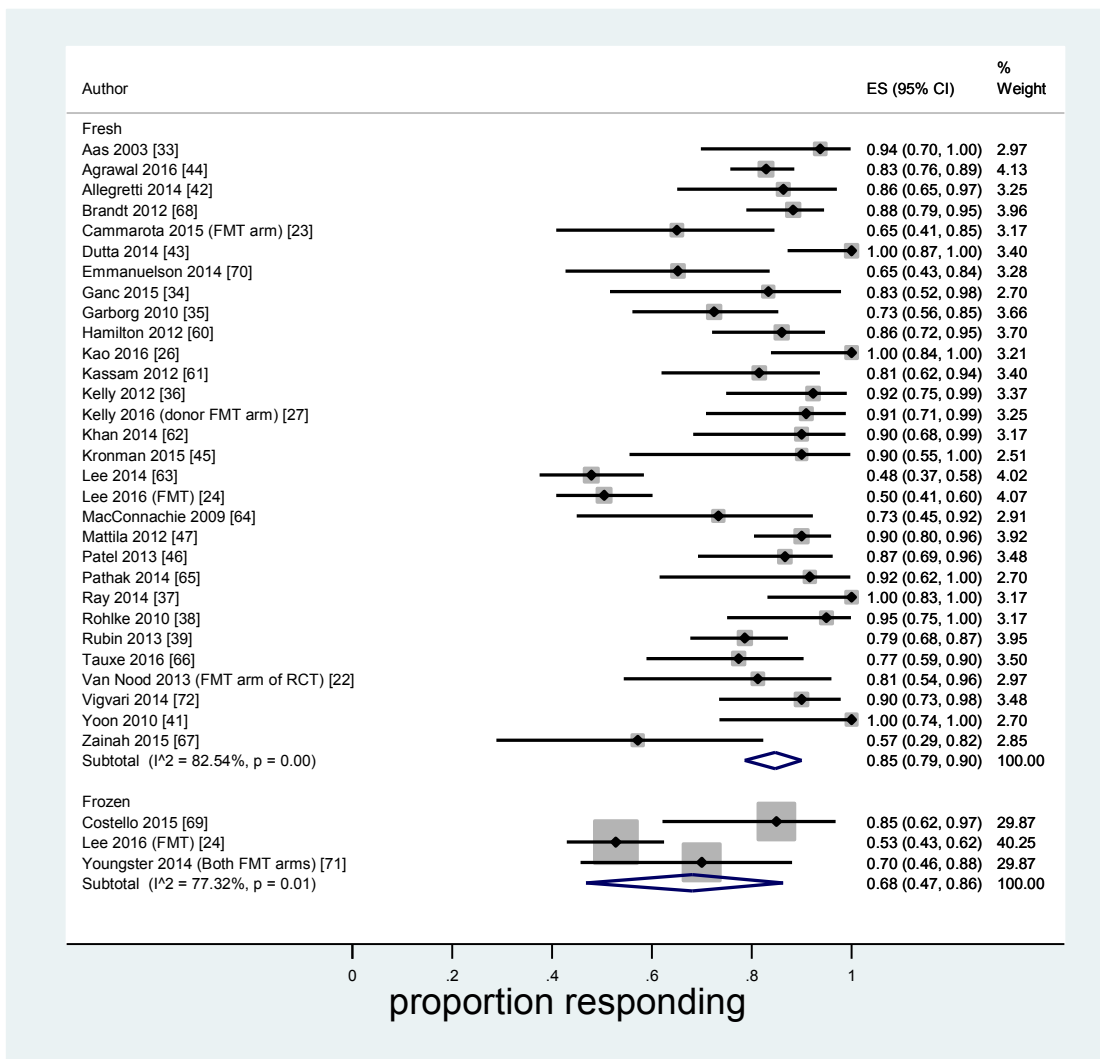
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b) Single infusion



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ES (95% CI) is the proportion responding with its 95% confidence interval.

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731 **Statement of Interests**

732 We have read and understood AP&T policy on declaration of interests and declare that we have no
733 competing interests.

734 **Authorship statement**

735 TI received a commission from APT in 2015 to undertake a systematic review and meta-analysis of
736 the literature concerning the efficacy of FMT in treating CDI. TI conceived and designed the review.
737 DM, MNQ, MP developed the review protocol. MNQ and TI performed eligibility screening, carried
738 out the data extraction and methodological quality assessment. MNQ, TI, NS and MW provided
739 advice and arbitration on the selection process, data extraction and methodological quality
740 assessment. MNQ, NS, MW and TI analysed the data. DM and MP interpreted the data. MNQ, TI, NS
741 and NB wrote the original draft, and all authors revised the draft critically for important intellectual
742 content and approved the final version of the paper, including the authorship list.

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745 of Birmingham for her help with re-designing the search strategy.

Study details			
Name, Year	Type of study i.e RCT, case control etc	No. of patients, years, location, selection criteria, Mean or median age, Gender distribution; other	Diagnosis of C.diff i.e Elisa/PCR, duration from diagnosis to transplant
Aas 2003	Case series	19 recruited over 9 years (1994-2002) at a single centre (USA); two or more lab confirmed relapses after initial specific AB treatment, adequate clin and lab documentation of post transplant course; Mean age 73 ± 9 (SEM) (Range: 51-88 years); F: 13/18 (72%); Hospitalised=5; nursing home=3; outpatient-GI clinic=10	Lab confirmed via stool sample, toxin A only, then B added from 2001. 2 or more positive test stool tests (mean 3.2, range 2-7). Mean period from diagnosis of c/diff colitis and stool transplantation 102 ± 24 (SEM) days (range 25-497)
Allegretti 2016	Open label cluster dose finding trial comparing low dose (30 pills) vs high dose (30 pills on 2 consecutive days)	19-age/gender not stated	Diagnosis method not stated
Cammarota 2015	Open label RCT	prospective RCT comparing FMT plus vancomycin to vancomycin therapy alone for recurrent CDI; 39 patients over 12 months July 2013 to June 2014; single centre; FMT group (n=20) mean age 71 years (range 29-89) F 12 (60%); Vanc group (n=19) mean age 75 (49-93) F 11 (58%)	CDI diagnosis was based on symptoms and toxin confirmed in 23/39(59%) positive culture.mean duration of CDI diagnosis prior to FMT not stated
Fischer 2016	Retrospective cohort study	Of 328 patients in the developmental cohort, 73.5% (N=241) were females with a mean age of 61.4 ± 19.3 years; 19.2% (N=63) had inflammatory bowel disease (IBD), and 23.5% (N=77) were immunocompromised. Two academic centres. 2011-2015. Of 134 patients in the validation cohort, 57% (N=77) were females with a mean age of 66 ± 18.1 years; 9.7% (N=13) had IBD, and 17.9% (N=24) were immunocompromised. Single centre. 2011-2015	Diagnosis of Cdiff if recurrent at least 3 episodes of CDI and failure of 6-8 week vancomycin taper. Severe based on albumin, elevated white cell count and abdominal pain. Severe complicated defined as admission to ITU hypotension, fever, ileus, reduced GCS, elevated white cell count and lactate with end organ dysfunction.

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<p>Ganc 2015</p>	<p>Case series, retrospective</p>	<p>12 patients. No other variables reported</p>	<p>Not reported</p>
<p>Garborg 2010</p>	<p>Case series, retrospective</p>	<p>39 patients (one had 2 FMTs). Treated single centre 1994-2008. Mean age 75y (range 53-94). F=21 (53%)</p>	<p>Toxin positivity or clinical findings (37/40 toxin positive)</p>
<p>Hamilton 2012</p>	<p>Case series</p>	<p>43 patients. Single centre. 29 non-IBD and 14 IBD patients. Non IBD cohort (mean age 64.7y SEM 3.3; F 20 (69%)); IBD cohort (mean age 44.6 SEM 5.8; F 11 (79%))</p>	<p>Inclusion criteria for FMT included a history of symptomatic, toxin-positive, infection by <i>C. difficile</i>, and at least two documented subsequent recurrences despite use of standard antibiotic therapy.</p>
<p>Kao D 2016 - abstract (FMT arm of RCT)</p>	<p>Double blind RCT (capsule vs fresh)</p>	<p>43 patients, mean 67 years, F:30/43 (70%). Two centres. 22 capsule group and 21 in colonoscopy group</p>	<p>Not reported</p>

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Kassam 2012	Case series	27 patients: the mean age was 69.4 years (range, 26-87 years) with 14 male subjects (52%) and 22 in-patients (81%).	Inclusion criteria were (1) laboratory-confirmed <i>C. difficile</i> toxin using enzyme immunoassay with no other cause for diarrhea; (2) refractory CDI (defined as ongoing diarrhea despite antimicrobial treatment) or recurrent CDI (defined as symptom resolution for at least 2 days after discontinuation of treatment with recurrence of diarrhea).
Kelly 2012	Case series	26 recruited over 28 months; single centre; at least 3 recurrences of CDI following multiple antibiotic courses; adequate clinical and lab documentation post transplant; Mean age 59 (19-86 yrs); F: 24/26 (92%)	Method of CDI diagnosis not stated; mean duration of diagnosis of CDI prior to FMT 12.6 M (range 4 to 84 M);
Kelly 2014	Case series	retrospective study of immunocompromised patients receiving FMT for CDI; 80 patients data analysed from 16 centres; eligibility assessed by 32 point questionnaire; 75 adults and 5 children; Mean age in Adults 53 (range 20-88) in children 10.9 (range 6.5-16); Adults (n=75) F:38 (48%)	4 categories; 1 recurrent/relapsing at least 3 episodes with failure of up to 8 week taper with vancomycin or at least 2 episodes of severe CDI resulting in hospitalisation and associated with significant morbidity. 2 Refractory CDI-moderate CDI not responding to standard therapy for at least a week 3 Severe CDI elevated WBC., low albumin and abdominal tenderness. 4 complicated CDI- Admission to ITU, low blood pressure, fever, ileus, mental state changes, elevated WBC, high lactate and evidence of end organ failure

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<p>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25</p>	<p>Kelly 2016</p> <p>Double blind RCT (donor vs autologous FMT)</p>	<p>46 patients . Two centres. Donor FMT group n=22, mean age=48 (SD 16); F=18 (82%); Autologous FMT group n=24, mean age = 55(SD 14), F=19 (79%).</p>	<p>≥3 unformed stools over 24 hours for 2 consecutive days and either a positive stool test result for <i>C difficile</i> or pseudomembranes on colonoscopy</p>
<p>26 27 28 29 30 31 32 33 34 35 36 37 38</p>	<p>Khan 2014</p> <p>Case series</p>	<p>retrospective analysis of 20 cases over 13 months (July 2012 to Aug 2013); selection criteria: all patients receiving FMT for CDI at their centre; single centre; adequate post transplant documentation and assessment; Demographic data presented separately for community acquired and hospital acquired CDI; Calculated Overall Mean age 66.4 years; F 13 (65%); Mean number of CDI episodes pre-FMT:5.6 community acquired and 4.6 for hospital acquired</p>	<p>Method of CDI diagnosis not stated; data presented separately for community acquired CDI and hospital acquired CDI; median duration of symptoms pre FMT for community acquired CDI was 7 months; 5 months for hospital acquired CDI</p>
<p>39 40 41 42 43 44 45 46 47 48</p>	<p>Kronman 2015</p> <p>Case series</p>	<p>retrospective study of 10 children in single centre over 3 years (between Aug 2011 and May 2014); At least 3 episodes of CDI; adequate post transplant documentation and assessment; Mean age 5.4 years; F 7/10 (70%);</p>	<p>C diff toxin A&B and/or PCR; median duration of symptoms pre-FMT 250 days (range 90-541 days);</p>
<p>49 50 51 52 53 54 55 56 57 58 59 60</p>	<p>Lee 2014</p> <p>Case series</p>	<p>retrospective analysis of 94 patients from 2008-2012; single centre; mixture of recurrent and refractory CDI definitions given; Mean age 71.8 years (range 24-95 years); F 53/94 (56.4%)</p>	<p>C diff toxin A&B and/or PCR; duration of symptoms pre-FMT not stated</p>

1 2 3 4 5 6 7 8	Lee CH 2016 (FMT arm of RCT)	FMT arm of double blind RCT (Fresh vs Frozen)	219 patients, mean 73 years, F:146/219 (67%)	Toxin and PCR
9 10 11 12 13 14 15 16 17 18 19 20 21	MacConnachie 2009	Case series	retrospective analysis of 15 patients since 2003;single centre; recurrent CDI following succesful antibiotic therapy; Median age 81.5years (range 68-95); F 14/15 (93.3%)	Method of CDI diagnosis not stated;mean duration of diagnosis of CDI prior to FMT not stated
22 23 24 25 26 27 28	Mattila 2012	Case series	70 patients over 3 years (2007-2010) all laboratory confirmed recurrent CDI refractory to standard treatment. Mean age 73(22-90) F=42(60%). 60(86%) outpatients	positive culture and toxin; strain typing . Time from diagnosis to CDI mean 133 days (46-360). 36(51%0 had ribotype 027
29 30 31 32 33 34 35 36	Patel 2013	Case series	31 patients over 2 years (2011-2013) all had recurrent (at least 2 previouslt documented CDI episodes). Mean age 61 (SD19) F=17(55%).17/31 (55%) gi comorbdiity. Diverticulitis (5), IBS (5), UC (3), CD(2), gastroparesis (1), coloanal fistula(1)	Diagnosis method not stated. Medain time(range) from index diagnosis to FMT 340 days(18-2205)
37 38 39 40 41 42 43 44 45 46 47 48	Pathak 2014	Case series	12 patients with recurrent or relapsing CDI with at least 3 episodes and failure of treatment with vancomycin +/- additional antibiotic such as fidox or patients wuth at least two episodes of severe CDI or patients with moderate CDI not responding to vanc for a week or patients with severe/fulminant CDI not responding to standar treatment for 48 h. 12 patients over 3 years. mean age 72 (SD 15) range 37-90; F 8/12 (67%)	Diagnosis method not stated
49 50 51 52 53 54 55 56 57 58 59 60	Ray 2014	Case series	20 (August 2012-November 2013) 2 recurrences as defined by diarrhoea OR positive Cdiff after antibiotics (m,v,or f). Or if life threatening and/or admission to ICU. 20 patients mean age 62 (SD 18). F 16(80%). 15 (75%) out patients. Average time from diagnosis to FMT 49.6 weeks	Diagnosis method not stated

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	Rohlke 2010	Case series	19 patients over 5 years(September 2004-July 2009). At least 3 courses or treatment included vanc amn tapered vanc over 6 months.Mean age 49 (SD 15). F17 (90%). All out-patients	Diagnosis method confirmed by lab in all cases but method not specified
	Rubin TA 2013	Case series, retrospective	74 patients (75 courses), mean age 63 years, F 49/74 (65%)	Diagnosis of CDI confirmed by lab only in a few cases. Method not specified.
	Satokari R 2015	Case series, retrospective	49 patients, mean age 56 years, F 34/49 (69)	Culture and toxin
	Tauze 2016	Case series, retrospective	31 patients, mean age 77 years, F 18/31 (58%)	Not reported
	Yoon 2010	Case series, retrospective	12 patients, mean age 66 years, F 9/12 (75%)	Toxin positivity or clinical findings
	Youngster2014	Case series, prospective	20 patients, Median age 64.5; F 9/20 (45%). Exclusion criteria - delayed gastric emptying synd, recurrent aspiration, pregnancy, significant immunocompromise, history of significant food allergy to food included in donor diet.	Toxin and ELISA, PCR if toxin negative but ELISA is positive or indeterminate
	Zainah 2015	Case series, retrospective	14 patients, mean age 73 years,	C. difficile toxin EIA and/or PCR

Brandt LJ 2012	Case series, retrospective	77 patients in 5 centres, mean age 65, F 56/77 (73%).	Not reported
Allegretti 2014	Case series, retrospective	22 patients, mean age 55, F 18/22 (82%)	C. difficile toxin EIA and/or PCR
Costello 2015	Case series, prospective	20 patients , median age 69 years, gender distribution not reported	Not reported
Agrawal 2016	multicentre, retrospective, long term follow up study	146 patients, 100 (68.5%) women; mean age (range) 79.	Not reported
Dutta 2014	Case series, prospective	27 patients, mean age 64.5y, F 22/27 (81.5%)	Cdiff toxin positivity by ELISA
Emmanuelson 2014	Case series, retrospective	23 patients, mean age 66y, F 61%	Culture and/or toxin EIA

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<p>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21</p> <p>Van Nood 2013</p>	<p>FMT arm of RCT (FMT versus vancomycin)</p>	<p>From January 2008 through April 2010, 43 patients were randomly assigned to receive donor-feces infusion (17 patients), vancomycin (13), or vancomycin and bowel lavage (13). One patient assigned to receive donor-feces infusion was subsequently excluded from further analysis. Baseline demographics per groups: Donor Feces Infusion: 16 patients; mean age +/-SD (73 +/-13); F: 8/16 (50%); Vancomycin only: 13 patients; mean age +/-SD (66 +/-14); F: 7/13 (54%); Vancomycin and Bowel Lavage: 13 patients; mean age +/-SD (69 +/-16); F: 3/13 (23%)</p>	<p>Toxin and PCR. In 39 patients, a positive toxin test before inclusion was confirmed by a positive <i>C.difficile</i> culture. PCR ribotyping was performed on strains obtained from 34 patients</p>
<p>22 23 24 25 26 27 28 29 30 31 32 33</p> <p>Youngster 2014</p>	<p>FMT arm of open-label RCT (NG versus colonic delivery of FMT)</p>	<p>37 patients were assessed for eligibility and 20 patients underwent randomisation: Colonoscopy arm: 10 patients, mean age +/-SD (50.4 +/-28.8); F:6/10 (60%); Nasogastric tube:10 patients; mean age +/-SD (58.6 +/- 19.6); F: 5/10 (50%)</p>	<p>Toxin: initial toxin/glutamate dehydrogenase (GDH) enzyme-linked immunosorbent assay, followed by PCR only if the GDH test is positive or indeterminate, and does not routinely test for the NAP-1/B1/207 strain</p>
<p>34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60</p> <p>Vigvari 2014</p>	<p>Case series, retrospective</p>	<p>30 patients, mean age 70.1 years (26-88 years), Female: 18/30 (60%)</p>	<p>Not reported</p>

Patient characteristics			Donor Ch
Pre FMT Abx +/- other therapy (M,V,Fidox,IVG)/How many courses i.e M(2), V(1), IVG(1), Fidox(1). Were abx stopped prior to FMT	Refractory / Recurrent	Flexi sigi / Colonoscopy findings	Healthy volunteer/Spouse/Related i.e mother/Other non related i.e friend
Mean 3.6 courses of abs (range 2-7) abs varied (Clm, Cm, Cpx, Ctri, Ctox, Amp, Gm, Clex, Mtz, Pen, Pip, tMp-SMZ, Taz, Lev, Tet, Vm) number of courses prior to transplant varied: 2-7; Recipients were pre-treated with vm (250mg q8h) for 4 or more days and this was discontinued the night before transplant.	recurrent (two or more lab confirmed relapses)	Not reported	15/18 were family members of recipient; no member available for remaining 3 so donors were healthy clinic staff. Hierachy of ideal donor described: intimate physical contact with patients (spouse/partner) > family household member > other healthy donor
Not stated	Not stated	Not reported	Healthy donors from OpenBiome stool bank mean age 36 years
All patients had antibiotics prior to diagnosis of CDI but specifics not stated; FMT group patients had 3 days vanc prior to FMT which stopped the day before; vanc group had 10 days of standard vanc followed by at least three weeks of pulsed vanc	recurrent with lab confirmation	6 out of 20 patients in FMT group had pseudomembranous colitis	Healthy volunteers less than 50 years old from which 16/20 donors related; 2 intimates; 2 unrelated
Not reported	split into refractory, recurrent and severe complicated	Colonoscopies done on most	Mix of healthy volunteers (319 69%) and family (143 31%)

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Not reported	Recurrent	N/A	The donor is usually a family member of the patient who meets certain criteria, such as not having used antibiotics in the previous six months, being immunocompromised, and having no history of illicit drug use, tumors or inflammatory bowel disease.
The patients were treated with metronidazole or vancomycin until reduction of symptoms. All antimicrobial therapy was discontinued on the evening prior to stool transplantation.	Recurrent	1 patient with pseudomembranous colitis	Close relatives or other household members were selected as stool donors. Individuals without symptoms of gastrointestinal disease or a history of chronic infectious disease were considered suitable for stool donation.
At least one failed antibiotic regimen had to include a minimum of a 6-week course of tapered or pulsed vancomycin dosage, or at least a 1-month vancomycin course followed by a minimum of 2-week rifaximin "chaser."	Recurrent	Not reported	patients were asked to self-identify potential donors. These included mothers (n=2), daughters (n = 1), sons (n = 3), wives (n = 1), husbands (n = 1), and friends (n = 2).
Not reported	Recurrent	Not reported	Unrelated volunteers

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<p>1 2 3 4 5 6 7 8 9 10 11 12 13</p> <p>All had at least metronidazole; 19 had subsequent vancomycin monotherapy. 8 had combination metronidazole and vancomycin therapy.</p>	<p>Recurrent or refractory</p>	<p>Not reported</p>	<p>Two healthy volunteers served as donors and were evaluated for transmissible pathogens. The donors took no antibiotics for 6 months prior to stool donation.</p>
<p>14 15 16 17 18 19 20 21 22</p> <p>antibiotics prior to CDI diagnosis- clind, cipro, metro, moxiflox, levoflox, azithro, cefurox, amox, augmentin; treatment for CDI-all had metronidazole, Sacchromyces bouladaii, 4 had lactobacillus, 2 had IV IG, 19 had had rifaximin; pre-FMT all had 2 weeks of metronidazole or vanc, discontinued 2-3 days before FMT</p>	<p>recurrent at least 3 episodes (lab confirmation not stated)</p>	<p>11 had diverticular disease; 3 had colitis; 8 normal; 2 polyps; 2 haemorrhoids; 2 previous surgery</p>	<p>25/26 family members; 1 friend</p>
<p>23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60</p> <p>79/80 had been treated with vancomycin. 55/80 had metronidazole, 23 had fidaxomicin, 13 had rifaximin and 30 had probiotics</p>	<p>recurrent CDI (at least 3 episodes and failure of vanc taper for 6-8 weeks); refractory (no improvement after 1 week of vanc); Severe CDI or complicated (definitions given)</p>	<p>Not reported</p>	<p>Not reported</p>

<p>3 or more recurrences of CDI and received a full course of vancomycin for their most recent acute episode.</p>	<p>Recurrent</p>	<p>Colonoscopies done on all</p>	<p>All prospective donors underwent a medical interview and physical examination and were excluded if they had a known communicable disease, features of the metabolic syndrome, a diarrheal disorder, an autoimmune or atopic disease, a tumor, a neurologic disorder, or chronic pain syndrome or if they had used antibiotics for any indication within 3 months. Potential donors also completed a modified AABB full-length donor history questionnaire, and those with risk factors for infectious agents were excluded (Supplement).</p>
<p>Antibiotic treatment for CDI: metronidazole (1 patient had 1 course; 7 patients had 2 courses; 12 patients had 3 courses); vancomycin (2 patients had 1 course; 12 patients had 2 courses; 4 patients had 3 courses; 2 patients had pulsed vanc); 9 had fidaxomicin; all antibiotics stopped 48 hours before FMT</p>	<p>not explicitly stated but patients had a mean of 4.6-5.6 episodes of CDI prior to FMT</p>	<p>Not reported</p>	<p>5/20 from spouse/partner; 14/20 family member; 1 non-relative</p>
<p>Antibiotics used prior to CDI diagnosis- metronidazole, augmentin, ampicillic, amoxicillin, cefdinir, cefuroxime, penicillin; CDI treatment all had metronidazole, 6/10 had vancomycin, 8/10 had vancomycin taper; pre-transplant all had vanc or fidaxomicin for 7 days, last dose given 24 hours pre-transplant</p>	<p>recurrent CDI; mean of 3.2 episodes pre-FMT</p>	<p>Not reported</p>	<p>9/10 parents; 1 sibling</p>
<p>Mean of 2,1 courses of antibiotics for CDI prior to FMT (metronidazole 79.3%, vancomycin 75%, vancomycin taper 15.2%, combination metro and vanc 17.4%, 3 patients had IVIG); pre-transplant all antibiotic therapy for Cdi was discontinued 24 hours before FMT</p>	<p>recurrent (recurrent diarrhoea after at least 2 days of resolution following antibiotic therapy) or refractory (ongoing diarrhoea despite at least 5 days of oral vancomycin)</p>	<p>Not reported</p>	<p>2 unrelated donors</p>

1 2 3 4 5 6 7 8	Metronidazole and Vancomycin	Both	Not reported	Unrelated volunteers
9 10 11 12 13 14 15 16 17 18 19 20 21	Antibiotics prior to CDI diagnosis not stated; 15/15 received metronidazole; 15/15 received vanc, 3 received iVIG; vanc given pre-procedure but length of course not stated; stopped 12 hours before FMT	recurrent CDI defined as recurrence of diarrhoea after successful antibiotic therapy typically within 7 days of stopping antibiotics;	Not reported	related donors specifics not given
22 23 24 25 26 27 28 29	mean 4.5 courses of antibiotics. Metro, vanc, rifax, 1 IVIG Stopped 36 hours before FMT	recurrent (two or more lab confirmed relapses)	Not reported	61(87%) family members; 9(13%) healthy donors
30 31 32 33 34 35 36	Stopped (usually vanc) 4 hours before bowel prep. Loperamide 4mg either before or immediately after FMT	recurrent (two or more lab confirmed relapses)	Not reported	"Mostly" family. 14 spouses, 9 children, 5 siblings, 3 parents, 1 niece, 1 friend
37 38 39 40 41 42 43 44 45 46 47 48	Antibiotics stopped 24 hours prior to procedure	Refractory / Recurrent and severe	8 colitis, 1 Cdiff, 1 haemorrhoid, 1 pseudomembranous colitis, 1 diverticulosis	10 family, 2 spouses
49 50 51 52 53 54 55 56 57 58 59 60	Antibiotics stopped 48 hours prior to procedure	16 recurrent; 4 severe/complicated	Not reported	10 family, 8 spouses, 2 healthy donors

Antibiotics stopped 1-3 days before FMT	recurrent	Not reported	4 family, 14 partner, 1 housemate
Vancomycin and / or metronidazole	Recurrent	Not reported	Healthy household members
Not reported	Refractory	Not reported	Frozen stool: 2 unrelated donors. Fresh stool: Family members, healthy volunteers, or the same universal donors.
Combinations of Vancomycin, Metronidazole, Fidoxamicin, Rifaximin	Both	Not reported	7 were from family members, rest were volunteers
Combination of metronidazole, vancomycin, rifaximin, bacitracin, nitazoxanide	Both	9/12 normal colonic mucosa, 3/12 had pseudomembranes	All family members (partner:8; child or grandchild:4)
Failed vancomycin taper and or fidaxomicin.	Refractory or recurrent. Defined 3 episodes of mild to moderate CDI or failure of 6-8 week taper with vancomycin, or atleast two episodes of severe CDI resulting in hospitalisation and associated with significant morbidity. Active CDI defined as more than 3 loose stools per day with a positive stool test.	Not reported	Unrelated adult volunteers
Vancomycin and / or metronidazole	Both	Not reported	12 from family members, 1 from unrelated volunteer

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<p>Failed on average of five conventional antimicrobial regimes; including metronidazole (81%), vancomycin (99% standard and pulsed) and/or tapered regime with or without rifaximin (22%) or probiotics (77%).</p>	<p>Recurrent CDI (unresponsive to standard therapy)</p>	<p>Not reported</p>	<p>60% partners/spouses; 27% were either first degree relatives or otherwise related to the patient. ; one case - unknown person. In all, 56 of 77 donors resided in the same household as patient.</p>
<p>Several but eligibility included starting vancomycin for 7 days before procedure and stopping day before</p>	<p>Both. Relapsing defined as three or more episodes of CDI or refractory disease that is unresponsive to traditional antibiotics.</p>	<p>Not reported</p>	<p>Patient identified donors-spouse, family, friend. My co-inhabit</p>
<p>Not reported</p>	<p>Recurrent disease</p>	<p>Not reported</p>	<p>Healthy volunteers</p>
<p>Conventional therapy with met, van and/or fidaxomicin had failed in all. Some takinh probiotics. Om average</p>	<p>Recurrent defined as recurrence of diarrhoea after completion of treatment. Severe CDI defined as low</p>	<p>Not reported</p>	<p>Donors usually identified by patient. One healthy volunteer not identified by patient</p>
<p>Most patients received metronidazole and/or vancomycin Other antibiotics included fidaxomicin, rifaximin.</p>	<p>Recurrent (>2 recurrences)</p>	<p>Active colitis seen in 26/27 patients with pseudomembranes in 2</p>	<p>Healthy donors selected via thorough clinical evaluation to exclude any transmissible disease. 10 spouse, 12 son or daughter, 1 parent, 4 friends.</p>
<p>Metronidazole and/or Vancomycin</p>	<p>Relapsing and recurrent</p>	<p>Not reported</p>	<p>Spouse or close relative of good health</p>

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<p>At least one course of adequate antibiotic therapy (≥ 10 days of Vancomycin at a dose of ≥ 125mg four times a day or ≥ 10 days of Metronidazole at a dose of 500mg three times per day). In FMT group: patients received an abbreviated regimen of Vancomycin (500mg orally four times per day for 4 or 5 days), followed by bowel lavage with 4 liters of macrogol solution (Klean-Prep) on the last day of antibiotic treatment and the suspension of donor feces through a nasoduodenal tube the next day</p>	<p>Recurrent</p>	<p>Not done</p>	<p>Healthy volunteers < 60 years of age (faces from 15 donors were used for 43 infusions in the infusion group and for patients who had a relapse after vancomycin treatment)</p>
<p>Patients had a median of 4 (range, 2-16) relapses prior to study enrollment, with 5 (range, 3-15) antibiotic treatment failures of a 6- to 8-week taper with Vancomycin (95% of patients) with or without an alternative antibiotic, including Fidaxomicin (70% of participants). Patients were required to discontinue all antibiotics at least 48 hours prior to the procedure</p>	<p>Relapsing or recurring (having at least 3 episodes of mild-to-moderate CDI OR at least 2 episodes of severe CDI resulting in hospitalization and associated with significant morbidity)</p>	<p>Not reported</p>	<p>Healthy volunteer donor: nonpregnant adults, 18-50 years of age, on no medications, with a normal body mass index</p>
<p>Not clear from paper, but it appears most patients had vancomycin</p>	<p>Refractory and recurrent</p>	<p>Not reported</p>	<p>Donors were relatives in 22 cases (73.3%) and unrelated volunteers in 8 cases (26.7%).</p>

aracteristics	FMT characteristics		
Screening and abx cessation	Fresh/Frozen, Route administered	Sample preparation Transplant sample sourcing, screening, preparation; , volume, mixing solution, storage and time from collection to transplant	Procedure: Bowel Prep/Drugs used prior to FMT i.e Moviprep 2 sachets/PPI (dose), prokinetic (dose), Loperamide FMT administration Follow up method
<p>Within 30 days before donation (usually 7 days) screened: Blood:HAV (HAV ab (IgM and IgG), HBV (ab to HepB surface antigen and core antigen), HCV (HCV ab RIBA-II), HIV-1 & 2 (EIA), Treponema pallidum (rapid plasma reagin test).</p> <p>Stool: C diff (Toxin A or B (cytotoxin) detection), enteric bacterial pathogens (selective stool culture), ova/parasites (light microscopy)</p> <p>No antimicrobial therapy in previous 6 months</p>	<p>Fresh nasogastric, with tube placement on morning of transplant and tube tip placement confirmed by radiography</p>	<p>Stool obtained 6 or less hours prior to transplant. Approx 30g or 2cm³ preferably soft stool selected and homogenised in 50-70ml 0.9N sterile saline (household blender - slow speed setting initially, rising gradually to maximum and continued then for 2-4 min) until sample smooth. Filtered through coffee paper filter x2 allowing adequate time for slow filtration to end.</p>	<p>20mg omeprazole evening before and morning of transplant. 25ml of stool suspension administered then tube flushed with 25ml sterile 0.9N saline. Tube removal. Normal diet and physical activities allowed immediately. Follow up by telephone or clinic visit and stool specimens examined for c.diff toxin A in most patients.</p>
<p>open Biome Criteria followed</p>	<p>Frozen pills</p>	<p>Not stated</p>	<p>Not described</p>
<p>no antibiotics for 6 months; stool tested for C. diff , enteric pathogens, ova and parasites, MDR gram nehgatives, MRSA, VRE; Serum tested for Hep A, Hep B, Hep C, HIV 1 and 2, strongyloides, treponema, Entamoeba. High risk lifestyle, FH of GI cancer, IBD, systemic diseases, personal GI disease</p>	<p>fresh via colonoscopy</p>	<p>Mean time from donation to infusion was 3.8 hours;mass of donation not stated but mixed with 500mls saline and blended and strained; delivered to right colon through colonoscope</p>	<p>2 groups FMT group received 4L of macrogol bowel cleansing solution for 1-2 days on the last 2 days of vancomycin followed by FMT. The other group had bowel cleansing and vancomycin standard treatment.</p>
<p>Sporicidal disinfection was performed in patient rooms as per institutional protocols; specific instructions with handouts regarding sporicidal home cleaning were provided to patients to prevent reinfection.</p>	<p>Fresh or frozen via Colonoscopy and NG tube</p>	<p>Not reported</p>	<p>Not reported</p>

<p>Some tests are performed for screening: serology for hepatitis A, B and C, human immunodeficiency virus (HIV), fecal parasitology, fecal test for <i>Clostridium difficile</i>, and fecal culture.</p>	<p>Fresh via enteroscope</p>	<p>Mixed in N. Saline. Volume and other variables not stated</p>	<p>Not reported</p>
<p>Donors were screened for hepatitis A, B and C and HIV infection, as well as enteric bacterial pathogens including <i>Salmonella</i>, <i>Shigella</i>, <i>Campylobacter</i> and <i>Yersinia</i> species.</p>	<p>Fresh via Gastroscopy or colonoscopy</p>	<p>A fresh stool sample of 50–100 g was obtained from the donor on the day of the instillation procedure. The stool sample was spread out onto a gauze pad which was then placed in a strainer. The gauze was flushed with 250 ml sterile 0.9% NaCl and the resulting suspension was collected and aspirated into syringes. A flexible videogastroscope was introduced into the distal duodenum. Approximately 200 ml of sample solution was introduced</p>	<p>No bowel prep given to colonics delivered FMT</p>
<p>The donor had to submit their medical records and underwent serologic testing for HIV and Hepatitis B and C, and stool testing that included screening for routine enteric pathogens, <i>C. difficile</i> toxin B, and examination for ova and parasites, and <i>Giardia</i> and <i>Cryptosporidium</i> antigens. Donors were excluded if they had GI co-morbidities or had used antibiotics within 3 months.</p>	<p>Fresh or frozen via Colonoscopy</p>	<p>Approximately 50g of fecal material was placed into a standard commercial blender (Oster, Subeam, Rye, NY) and homogenized in 250 ml of sterile, non-bacteriostatic normal saline. Fecal suspension, if stored, was put in 10% glycerol and stored at -80 for up to 8 weeks. The frozen preparation was diluted in 250ml saline before infusion.</p>	<p>Patients were maintained on full dose of vancomycin (125mg, four times daily by mouth) until 2 days before the FMT procedure. The day before the procedure, the patients were prepped using a split dosage polyethylene glycol purge (GoLYTELY or MoviPrep), which is standard in our endoscopy unit, before colonoscopies to wash out residual antibiotic and fecal material.</p>
<p>Not reported</p>	<p>Oral capsules vs colonoscopy</p>	<p>Not reported</p>	<p>Not reported</p>

<p>1 2 3 4 5 6 7 8 9 10 11 12 13</p> <p>Blood was screened for hepatitis B surface antigen, hepatitis C antibody, Helicobacter pylori and syphilis serologic markers, human immunodeficiency virus types 1 and 2, and human T-lymphotropic virus types I and II. Stool was processed for enteric bacterial pathogens, C difficile toxin, and ova and parasites.</p>	Retention enema	Approximately 150 g of fresh stool collected was emulsified in 300 mL of sterile water. The supernatant component was administered rectally by en-ema.	All CDI therapy was discontinued at least 24 hours prior to FT.
<p>14 15 16 17 18 19 20 21 22</p> <p>no antibiotics in preceding 90 days; blood for HAV, HBV, HCV, HIV 1&2, Treponema pallidum; stool for culture for bacteria, stain for ova and parasites, C. diff. toxin A and B</p>	Fresh via colonoscopy	stool obtained 6 hours or less prior to transplant 6-8 tablespoons of donor stool added and shaken in 1litre of sterile water passed through gauze. Aliquoted in 60ml syringes.	polyethelene glycol bowel prep night before transplant; 500-960mls administered via scope mainly to rightcolon; Avoid defecating for 30-45 mins
<p>23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60</p> <p>Not reported</p>	fresh or frozen not stated; 12 of 16 centres used colonoscopy route	Not reported	prep not stated; questionnaire sent out to 16 centres to retrospectively collect data; method of follow up at each centre not stated but had to have data for at least 12 weeks to be eligible for inclusion

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25	Testing for HIV-1 and HIV-2 was performed within 2 weeks before donation for FMT. Other serologic and stool testing was performed within 1 month before FMT and included testing for hepatitis A, B, and C viruses; testing for <i>Treponema pallidum</i> ; polymerase chain reaction (PCR) testing for detection of <i>C. difficile</i> toxin; culture for enteric pathogens (<i>Escherichia coli</i> , <i>Salmonella</i> , <i>Shigella</i> , <i>Yersinia</i> , <i>Campylobacter</i> , <i>Listeria monocytogenes</i> , <i>Vibrio parahaemolyticus</i> , and <i>V. cholerae</i>); testing for fecal <i>Giardia</i> and <i>Cryptosporidium</i> antigens; acid-fast stain for detection of <i>Cyclospora</i> and <i>Isospora</i> ; ova and parasite testing; and enzyme immunoassay for detection of Rotavirus.	Fresh via colonoscopy	The protocol specified a "dose" of 100 g of stool diluted in 500 mL of nonbacteriostatic 0.9% normal saline immediately before the procedure, but the study relied on fresh stool, which has unpredictable weight and volume, and most provided specimens were less than 100 g.	Donors took an osmotic laxative (magnesium hydroxide) the evening before and provided fresh stool the day of FMT. All donor specimens were transported on ice and processed within 6 hours of collection. Patients were given a standard bowel purge (sodium sulfate, potassium sulfate, and magnesium sulfate oral solution) the evening before the procedure. For patient convenience, sodium sulfate, potassium sulfate, and magnesium sulfate oral solution was substituted for the polyethylene glycol (PEG) bowel purge described in the study protocol.
26 27 28 29 30 31 32 33 34 35 36 37 38	no antibiotics for 3 months; stool tested for <i>C. diff</i> toxin PCR, enteric pathogens, ova and parasites, <i>Cryptosporidium</i> , <i>Microspora</i> ; Serum tested for Hep A, Hep B, Hep C, HIV 1 and 2; <i>H. pylori</i> Human T lymphotropic virus	fresh via colonoscopy	stool obtained within 30 mins of transplantation; 50g of stool into 200mls of saline and blended; Aspirated into single 60ml syringe for delivery	4 litres polyethelene glycol bowel prep; 60mls administered via scope into right colon; follow up combination of clinic, telephone and questionnaires
39 40 41 42 43 44 45 46 47 48	no antibiotics for 3 months; stool tested for <i>C. diff</i> , enteric pathogens, ova and parasites; Serum tested for Hep A, Hep B, Hep C, HIV 1 and 2; CMV, EBV, high risk behaviours, systemic antineoplastic drugs, immunosuppressives, history of GI disease. Directed donors to avoid foods which recipient may be allergic to for 5 days prior.	fresh via NGT	time from collection to transplant not stated; 30g stool added to 100mls saline and blended; filtered through gauze; 30-60mls infused	8.5g-17g polyethylene glycol in 8oz of water 3 times a day for 2 days prior to FMT; omeprazole 1mg/kg orally day before and on day of FMT; follow up all patients called 2 days after FMT, further follow up combination of clinic, telephone and repeat <i>C. diff.</i> testing
49 50 51 52 53 54 55	no antibiotics for 6 months; stool tested for <i>C. diff</i> , enteric pathogens, ova and parasites, norovirus, enterovirus; Serum tested for Hep A, Hep B, Hep C, HIV 1 and 2, human T-cell lymphotropic virus 1&2, <i>treponema</i>	retention enema	time from collection to transplant not stated; 150g stool added to 300mls water and homogenised with spatula 100mls infused	no bowel prep stated; 100mls infused via enema; follow up methods not stated but retrospective analysis extracted from clinical record

1 2 3 4 5 6 7	Questionnaire. Pathogens, HIV, HABC, CMV, EBV, syphilis, strongyloides, entamoeba. Screening every 4 months	Fresh and Frozen. Lower GI route	100g of stool homogenised and mixed in 300mls of water. If frozen kept for 30 days at -20C. If fresh administered within 24hrs.	Nil
8 9 10 11 12 13 14 15 16 17 18 19 20 21	Within 30 days before donation (usually 7 days) screened: Blood:HAV (HAV ab (IgM and IgG), HBV (ab to HepB surface antigen and core antigen), HCV (HCV ab RIBA-II), HIV-1 & 2 (EIA), Treponema pallidum (rapid plasma reagin test). Stool: C diff (Toxin A or B (cytotoxin) detection), enteric bacterial pathogens (selective stool culture), ova/parasites (light microscopy) No antimicrobial therapy in	Fresh via NGT	time between stool collection and transplant not stated; 30g of stool blended with 150mls saline and filtered; 30mls infused via NGT	no bowel prep stated;30mls infused via NGT;omeprazole given prior to FMT; follow up methods not stated but retrospective analysis extracted from clinical record
22 23 24 25 26 27 28	No antibiotics for 6 months. Blood for FBC, CRP, protein,creatinine, LFTs, HBV, HCV, HIV 1 &2, treponema. Stools for Cdiff, pathogens, OCP,	Fresh, within 6 hours colonoscopic	Stool obtained 6 or less hours prior to transplant. Homogenised in 100-200ml water.	Colonic lavage ith 4l PE solution.
29 30 31 32 33 34 35 36	No antibiotics for 3 months. Excluded chronic gastrointestinal condirions, active peptic ulcer disease, GERD, IBS,IBD,polyps, mlaignancy. Blood for HABC, HIV, Treponema, stool for culture, OCP, cryptosporidium, microsporidia, Cdiff	Fresh, colonoscope	Donors given 30ml MgOh evening before donation. Stools within 6 hours of passage blended with 100ml Nsaline and sieved for delivery.	Bowel prep for colonoscopy (not stated which), 4mg operamide either before or after FMT
37 38 39 40 41 42 43 44 45 46 47	High risk behaviours, no antibiotics for 3 months, Blood for HIV, HABC, STDs, stooll for bacterial culture, OCP, Cdiff	Fresh, colonoscope (11); 1 nasoduodenal	Donor given mg citrate before. stool collected within 6 hours of precedure. 6-8 tablespoons to 1l tap water, shaken.	PEG bowel prep, 400-500 ml to Tl/Right colon. Patients given 2 tablets of diphenoxylate/atropine. A week later 2 month course of Saccharomyces boulardii
48 49 50 51 52 53 54 55 56 57 58 59 60	3 unscreened. High risk behaviours, antibiotics in 3 months, blood for HIV, HABC, terponema, stool for Cdiff, bacterial culture, OCP, Giardia, Cryptosporidium,	Fresh, colonoscope	Time between donation and colonoscopy not stated	On day of treatment patients given 2 imodium tablets 2 hours prior and 1 after. Bowel prep not recorded.

1 2 3 4 5 6	Selective based on discretion. Blood from some for viruses (HABC, HIV), stool from some for Cdiff and enteric pathogens	Fresh colonoscope	Time between donation and colonoscopy not stated	PEG bowel prep. Some (not clear how many) had 2 immodium immediately after and then again 6 hours after FMT
7 8 9	Screened for occult infectious conditions and no abx use in preceding 3 months	Fresh, Upper GI (NG or PEG)	30 g of donor stool in mixed in saline. 25mls given in an infusion.	Pre-treated with 3 days of vancomycin and proton pump inhibitor prior to procedure
10 11 12 13 14 15 16	No significant medical history, no antibiotics for prior six months. Donor feces were screened for enteric pathogens and blood was screened for antibodies to hepatitis A, B, and C; HIV; and Treponema pallidum within 2 weeks of donations	Fresh: 26 patients; Frozen: 23 patients. Administered by colonoscopy	30g of stool in 200mls of saline or glycerol. If frozen stored in -80C for up to 16 weeks.	Polyethylene glycol prior to procedure
17 18 19 20 21 22 23 24 25 26	Not reported	Fresh, both routes	Not reported	Not reported
27 28 29 30 31	Donor feces were screened for enteric pathogens and blood was screened for antibodies to hepatitis A, B, and C; HIV	Fresh via colonoscopy	Stool collected morning of transplant, filtered and mixed with saline. 250 - 400mls infused into patient.	Abx stopped 3 days prior to FMT
32 33 34 35 36 37 38 39 40 41 42 43 44 45 46	Age range 18-50 years, BMI 18.5 - 25. No significant medical history, not pregnant, no antibiotics for prior six months. Donor feces were screened for enteric pathogens and blood was screened for antibodies to hepatitis A, B, and C; HIV; and Treponema pallidum within 2 weeks of donations. Donors refrain from common allergens for 5 days before donation.	Capsule (oral) frozen for mean of 113 days (range 30-252 days).	Each inoculum was prepared from the feces of a single donor. The final slurry was concentrated by centrifugation and resuspended in saline at one-tenth the volume. Fecal matter solution was pipetted into size 0 capsules (650 µL), which were closed and then secondarily sealed in size 00 capsules. Capsules were stored frozen at -80°C (-112°F) till use. A full treatment of 30 capsules contained sieved, concentrated material derived from a mean of 48 g of fecal matter (mean per capsule, 1.6 g; range, 1.0-2.05 g). Samples stored for 4 weeks without use to allow for retesting for HIV, hep B and C. (full screening and exclusion details given in appendix)	Abx stopped 48 hrs prior to FMT
47 48 49 50 51 52 53 54 55 56 57 58 59 60	Donor feces were screened for enteric pathogens and blood was screened for antibodies to hepatitis A, B, and C; HIV	Fresh. Upper GI in 13 patients, lower GI in 1 patient	Fresh stool sample (30-50 g) homogenized and mixed with water. About 120-180 ml of the suspension was instilled through NGT; 300-500 ml was administered if IMT was done via colonoscopy.	Abx stopped 24 hrs prior to FMT and given proton pump inhibitor prior to procedure

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20	Excluded if abx within preceding 3 months. Exclusion criteria also included immunosuppressive agents, including chemotherapeutic agents; had known or recent exposure to HIV, hepatitis B or C; had a current communicable disease; participated in high-risk sexual behaviors; used illicit drugs; had a history of incarceration; traveled within 6 months to areas with endemic diarrheal illnesses; or had history of inflammatory bowel disease, irritable bowel syndrome or chronic diarrhea, gastrointestinal malignancy or polyposis). Blood tested for HIV, Hep A/B/C and stool for OCP and giardia antigen and <i>cryptosporidium</i> .	Fresh (within 8 hours), colonoscopy	Suspended in saline, mixed by hand or blender, filtered and infused as 300 to 700 mls	Abx stopped 48 to 72 hrs prior to FMT. Bowel prep given before procedure
21 22 23 24 25 26 27	no abs for 3 months. No laxatives, history of constipation, no history of GI disease, travel in 3 months, not on immunosuppressives or chemo. No metabolic syndrome, autoimmune, atopic disease	Fresh (within 6 hours), colonoscopy	Fresh in blender 500ml Nsaline, strained. 60ml drawn up in 8-9 syringes per patient.	Abs stopped prior to procedure.
28 29 30 31 32	screening as per FDA guidelines 2011	Frozen stool (> 2 months in 16 patients and <2 months in 4 patients), colonoscopy route in 19, jejunal	30g in 120ml N.saline, divided into 50ml aliquots	Not reported
33 34 35	Excluded if "history of antibiotic use" (time not specified), high risk behaviour, prisoners, GI disease.	Fresh. Initial FMT in 118(81%) colonoscopy, 13(9%) OGD, 3(2%)	Milk of magnesia to donors. 60-100g stool suspended in 300-500ml nsaline, mixed, sieved. 75-200ml for upper route (OGD, enteroscopy), 250-400ml colonoscopically.	Bowel prep given. Loperamide after FMT
36 37 38 39	Blood and stool screened for transmissible diseases	Fresh, given via a combination of jejunal and colonic route	25-30g of stool given as 180mls via enteroscopy and 270mls via colonoscopy	Not mentioned
40 41 42 43 44 45 46 47	Potential donors were accepted only if serum antibodies against HIV 1 and 2, hepatitis C virus, and hepatitis B surface antigen were negative, as were stool cultures for Salmonella, Shigella, Campylobacter, enterohemolytic <i>Escherichia coli</i> , and <i>Clostridium</i>	Fresh, given as enema (lower GI)	50g of fresh faeces prepared in an anaerobic cabinet by adding and stirring small portions of pre-reduced and pre-warmed (37 °C) sterile isotonic saline, to a total of 500 ml.	Not mentioned

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<p>Questionnaire addressing risk factors for potentially transmissible diseases. Donor feces were screened for parasites, including <i>Blastocystis hominis</i> and <i>Dientamoeba fragilis</i>; <i>C.difficile</i>, and enteropathogenic bacteria. Blood was screened for HIV; human T-cell lymphotropic virus types 1 and 2; hepatitis A,B, and C; cytomegalovirus; Epstein-Barr virus; <i>Treponema pallidum</i>; <i>Strongyloides stercoralis</i>; and <i>Entamoeba histolytica</i>. A donor pool was created, and screening was repeated every 4 months. Before donation, another questionnaire was used to screen for recent illnesses.</p>	<p>Fresh via nasoduodenal tube</p>	<p>Feces were collected by the donor on the day of infusion and immediately transported to the hospital. Feces were diluted with 500mls of sterile saline 0.9%. This solution was stirred, and the supernatant strained and poured in a sterile bottle. A mean (+SD) of 141+71g of feces was infused. The mean time from defecation to infusion was 3.1+1.9 hours</p>	<p>Bowel lavage with 4 liters of macrogol solution (Klean-Prep) on the last day of antibiotic treatment. Within 6 hours after collection of feces by the donor, the solution was infused through a nasoduodenal tube (2 to 3 minutes per 50mls). The tube was removed 30 minutes after the infusion, and patients were monitored for 2 hours. Patients kept a stool diary and were questioned about stool frequency and consistency, medication use, and adverse effects. Stool tests for <i>C.difficile</i> toxin were performed on days 14,21,35, and 70 and whenever diarrhoea occurred.</p>
<p>Volunteers were excluded for any significant past medical history or any use of antibiotics in the preceding 6 months. Initial screening using the American Association of Blood Banks donor questionnaire for exposure to infectious agents. Physical examination and general laboratory screening tests (within 30 days of donations). All results had to be within normal range for age and sex. Donor feces were screened for enteric bacterial</p>	<p>Frozen via colonoscopy or NGT</p>	<p>Donors were asked to take a dose of milk of magnesia the day before fecal collections to facilitate manipulation of the sample. A fecal suspension was generated in normal saline without preservatives, using commercial blender. Materials were passed through 4 sieves to remove particulate material. The final slurry was concentrated 3-fold by centrifugation and then resuspended in sterile saline with 10% glycerol added as a bacterial cryoprotectant. Inocula were then frozen at -80 C pending use. Each sieved inoculum was calculated to have been derived from approximately 41g of fecal material. Inocula were stored frozen for up to 156 days, range, 29-156 days; frozen material was thawed in a 37 C water bath, and then kept on ice until delivery.</p>	<p>Subjects assigned to colonoscopic administration underwent a standard bowel preparation with 4 liters of PEG solution, followed by endoscopic administration to the right colon of 90 cc thawed inoculum: further diluted to 250cc for adults and 160 cc for paediatric patients. Patients were given a single oral dose of loperamide at the time of procedure. Subjects assigned to NGT delivery of FMT were</p>
<p>Pre-medical examination was carried out with a questionnaire in order to rule out high-risk individuals (such as drug use, promiscuity, known illness, taking antibiotics or trips abroad in the past six months). Stool samples</p>	<p>Fresh stool delivered via nasogastric route in 15 patients and nasoduodenal route in 15 patients</p>	<p>60 grams, it was placed in 200 mL of mortar physiological saline (0.9%) and harvested. then the homogenate of 4 x 4 cm was filtered sterile gauze pads transferred to another vessel and finally were taken from the filtrate up to 100 ml syringe and given to patient within 6 hours.</p>	<p>Antibiotics were stopped prior to transplant and patients were given laxatives. Patients received both metoclopramide and high dose proton pump inhibitor on the day of the transplant.</p>

Total no of infusions	Define primary outcome	Outcome 1 infusion	1 or more infusions	Total follow up period
not explicitly stated. Data implies a single infusion on a single occasion for each patient	Not explicitly stated, but authors report outcome based on symptom resolution and / or CDI toxin negativity	15/16 (94%)	15/16(94%)	90 days post transplantation, assessed by examination of medical records.
NA	Clinical resolution of diarrhoea at 8 weeks	NA	19/20 (95%)	Not reported
13/20 had 1 FMT; 6/20 had co-existent PMC and received infusions every 3 days until symptom resolution (4 had 2 infusions, 1 had 3 infusions and 1 had 4 infusions)	Resolution of diarrhoea 10 weeks after the end of the treatments	13/20(65%)	18/20(90%)	primary end point 10 weeks after end of treatment
Not reported	Early Failure rate defined as non-response or recurrence of diarrhoea with either toxin or PCR positive CDI within 1 month of FMT	not reported	375/462 (81.2%)	3 months

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1 infusion via enteroscopy	not defined in paper but implied symptom free to end of follow up	10/12 (83%)	10/12 (83%)	6 months
1 infusion via gastroscopy or colonoscopy	successful treatment defined as no further contact with the clinic due to CDI symptoms within 80 days of FMT	29/40 (73%)	33/40 (82.5%)	80 days
4 of 43 had repeat infusion	Not specified	37/43 (86%)	41/43 (95%)	12 months
1 infusion via colonoscopy or 1 course of capsules.	Defined as cure but no time period given	41/43 (95%)	41/43 (95%)	Not specified

1 2 3 4 5 6 7 8 9 10 11 12 13 14	Five patients underwent a second FT because of ongoing diarrhea; 3 had symptom resolution and 2 continued to experience diarrhea despite 2 FTs.	resolution of symptoms- no time period defined	22/27 (81%)	25/27 (93%)	mean follow-up at 427.3 days after transplant.
15 16 17 18 19 20 21 22	not explicitly stated but implies single infusion for all patients	Prevention of further CDI relapse and/or significant diarrhoea requiring vancomycin; time frame for outcome not stated	24/26 (92.3%)	24/26 (92.3%)	follow up mean 10.7 months ranged from 2-30 months
23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	78 patients had single infusion; 12 patients had 2 infusions	response defined as absence of diarrhoea or marked reduction in stool frequency and without need for further antibiotics within 12 weeks after 1 or more FMTs	62/80 (77.5%)	70/80 (87.5%)	minimum of 12 weeks required; mean follow up 11m (range 3-46m)

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25	1 infusion via colonoscopy	Resolution of diarrhoea without need for anti CDI therapy during 8 week follow up	20 / 22 (90.9%)	21 / 22 (90.9%)	8 weeks for efficacy, 6 months for safety
26 27 28 29 30 31 32 33 34 35 36 37 38	18 had single infusion; 2 had 2 infusions	Resolution of diarrhoea without recurrence of symptoms within 3 months of FMT	18/20 (90%)	20/20 (100%)	minimum of 6 months (range not stated)
39 40 41 42 43 44 45 46 47 48	9 patients had single infusion, 1 patient had 2 infusions	Not defined in paper but implied symptom free to end of follow up	9/10 (90%)	10/10 (100%)	median duration of follow up 44 days (range 13-700 days)
49 50 51 52 53 54 55 56 57 58 59 60	if no resolution of diarrhoea after 7 days post FMT then further enema give. Range given 1-10(46/94 had 1 FMT, 20/94 had 2 FMT, 17/94 had 3 FMT, 11/94 had 4 or more)	Cured following FMT if no recurrence of diarrhoea at 6 months follow up	45/94 (47.9%)	81/94 (86.2%)	6-24 months

1, if no response at day 4, then further FMT and if no response then FMT or abx. Primary outcome based on up to 2 FMTs.	Clinical resolution of diarrhea without relapse at 13 weeks	113/219 (52%)	193/219 (88.1%)	13 weeks
14/15 had 1 FMT; 1/15 had 2 FMT	Not explicitly stated but implied that "cure" was no symptoms at follow up after 1 FMT	11/15 (73%)	12/15 (80%)	median 16 weeks (4 weeks to 24 weeks) not predefined
67 had 1; 3 had 2	Resolution diarrhea without a positive C difficile toxin stool test at 12 weeks	63/70 (90%)	66/70 (94%)	1 year. 4 with initial favourable response had relapse after receiving antibiotics. 2 of these were successfully treated with FMT; 2 with recurrent antibiotics for CDI
28 had 1; 3 had 2	Not defined.	26/30 (87%)	29/30 (97%)	1 year 6 out of 6 maintained improvement
1 infusion in all but 1 patient who had repeat via ND route	No strict definition. Authors state: 'A successful treatment was determined by the resolution of diarrhea, a fall in white cell count, or absence of fever and an improvement in vital signs'.	11/12 (92%)	12/12 (100%)	No recurrences within 90 days of FMT. Total follow up from 2 to 29 months
1	Resolution defined as positive stools after FMT.	20/20 (100%)	20/20 (100%)	Follow up mean 3 months (range 0-10)

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1	not defined in paper but implied symptom free to end of follow up	19/20 (95%)	20/20 (100%)	6 months to 5 years
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7	Resolution of diarrhea without recurrence within 60 days of FMT	59/75 (79%)	59/75 (79%)	60 days
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11	Resolution of diarrhoea with a negative C. difficile toxin stool test at 3 months	47/49 (96%)	47/49 (96%)	All followed up for 12 weeks and 42 patients followed up for 1 year
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18	Resolution was defined as the absence of significant diarrhea (diarrhea as defined by at least three episodes per day) or a marked reduction in diarrhea not requiring antibiotic therapy.	24/31 (77%)	27/31 (87%)	Mean 9 months (range 2–24)
19	1 infusion in 27 patients, multiple infusions in 4 patients			
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28	Clinical response was defined as absence of diarrhea, cramps, and fever within 3 to 5 days of transplant	12/12 (100%)	12/12 (100%)	3 weeks to 8 years
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38	Response defined as less than 3 bowel movements in 24 hrs	NA	18/20 (90%)	Primary outcome based on 8 weeks however patients followed up for 6 months
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48	Defined as less than 3 loose bowel movements a day for 2 consecutive days after FMT and no need for further CDI therapy on day 7.	8/14 (57%)	11/14 (79%)	100 days
49	1 in 10 patients, 2 in 2 patients, and 3 in 2 patients received three FMTs			
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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19	1 infusion in 75 patients, 2 infusions in 2 patients	Resolution without recurrence within 90 days including those that needed a second infusion or antibiotics	70/77 (91%)	70/77 (91%)	Minimum 90 days, but median 17 months
20 21 22 23 24 25 26 27	1 infusion	Primary outcome not defined	19/22 (86%)	21/22 (95%)	Range 2 weeks to 17 months with ave length 3 months
28 29 30 31 32	1 infusion in 17 patients, 2 infusions in 3 patients	Resolution of diarrhoea and/or absence of CDI toxin in stool as measured by PCR after at least 3 months follow up	17/20 (85%)	20/20 (100%)	Minimum 3 months (but up to 14 months)
33 34 35	146 had one infusion, 12 out of 25 early recurrences had another	Initial Resolution of CDI symptoms with no recurrence after 12	121/146 (82.9%)	121/146 (82.9%)	mean follow up 12.3 (range 1-48) months
36 37 38 39 40	1	Resolution of diarrhoea and disappearance of stool Cdiff toxin	27/27 (100%)	27/27 (100%)	Ranged from 9.7 -34 months (mean 20.6 months)
41 42 43 44 45 46 47	1 in 22 patients and 2 in 1 patient	Resolution of diarrhoea in 3 days with no recurrence in 3 months	15/23 (65%)	16/23 (70%)	Median follow up of 18 months (range 0-201 months)

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<p>16 patients had 1 infusion; 3 who did not respond in this group had 2nd infusion.</p>	<p>Cure without relapse within 10 weeks after the initiation of therapy. For patients in the infusion group who required a second infusion of donor feces, follow up was extended to 10 weeks after the second infusion. Cure was defined as an absence of diarrhoea or persistent diarrhoea that could be explained by other causes with three consecutive negative stool tests for C.difficile toxin. Relapse was defined as diarrhoea with a positive stool test for C.difficile toxin.</p>	<p>13/16 (81%)</p>	<p>15/16(94%)</p>	<p>After first infusion at 10 weeks; follow up was extended to 10 weeks after the second infusion</p>
<p>20 patients in both study arms had one infusion (14 was cured after the first infusion (70%)). One patient in the NGT arm refused subsequent retreatment. The remaining 5 patients were given a second infusion (4 patients obtained cure after second infusion, resulting in an overall cure rate of 90%).</p>	<p>Clinical resolution of diarrhoea off antibiotics for C.difficile, without relapse within 8 weeks. For patients who required a second treatment dose, a follow-up was calculated starting at the time of the second administration.</p>	<p>14/20 (70%)</p>	<p>18/20 (90%)</p>	<p>8 weeks follow up for primary response</p>
<p>1 infusion in 27 patients and 2 infusions in 3 patients.</p>	<p>Primary cure rate was defined as resolution of symptoms without recurrence within 6 weeks after a single FMT, while secondary cure rate was calculated</p>	<p>27/30 (90%)</p>	<p>29/30 (97%)</p>	<p>6 weeks</p>

Adverse events - mild	Adverse events - serious
no mention	2 patients died between transplant and follow up stool testing for c.diff toxin. One had end stage renal disease and was receiving peritoneal dialysis. Developed peritonitis 3 days post transplant and died shortly after. The second patient died 14 days post transplant of pneumonia complicating COPD and atherosclerosis (study authors state: " <i>the possibility that the use of the nasogastric tube contributed to the peritonitis cannot be excluded</i> ")
None reported	none reported
none in vanc group; FMT group 19/20 had transient diarrhoea, 12/20 had abdominal pain and bloating	2 deaths in FMT arm
Not reported	Not reported formally

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1 2 3 4 5 6 7 8 9 10	Not reported	None
11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37	Not reported	5 deaths; The remaining 5 patients had serious co-morbid conditions and died 3 weeks–2 months after the FDIT procedure. Two of these 5 patients were seriously weakened after long lasting diarrhoeal disease, 1 being the oldest patient in the series (94 y). Additionally, 1 patient had advanced stage Wegener’s granulomatosis with complications, 1 patient had acute myelogenous leukaemia requiring repeated antibiotic treatment for other infections, and 1 patient with advanced cardiovascular disease developed fulminant colitis and underwent subtotal colectomy, and subsequently died of complications.
38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53	Not reported	Not reported
54 55 56 57 58 59 60	Transient nausea and vomiting	None

Not reported	Not reported
mild diarrhoea post FMT in 3 patients	no serious adverse events
self limited diarrhoea in 3, fever in 1, bloating and abdo discomfort in 3, hip pain in 1, Crohn's flare in 1, Pertussis in 1, nausea in 1, minor mucosal tear at colonoscopy in 1	deaths- 1 due to pneumonia, 1 due to aspiration at time of colonoscopy; hospitalisations- 1 due to fever and encephalopathy, 1 due to abdo pain after FMT, 3 due to IBD flare, 1 colectomy, 1 hip fracture, 1 influenza, catheter infection

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<p>Chills were reported more frequently after autologous than donor FMT (P = 0.053). Rates of other solicited AEs (fever, abdominal pain, bloating, nausea, vomiting, diarrhea, flatulence, anorexia, and constipation) did not differ significantly between groups.</p>	<p>There were no SAEs related to FMT.</p>
<p>self limited diarrhoea in 4; abdominal pain in 3; nausea in 2; fatigue 13</p>	<p>none stated</p>
<p>vomiting post FMT in 1; mucooid stools for 2 days after FMT</p>	<p>none stated</p>
<p>10% had transient constipation and flatulence post FMT</p>	<p>6 deaths due to critical illness, not felt to be due to FMT or CDI directly but these 6 are included in the 8 who failed to respond overall</p>

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1 2 3 4 5 6 7 8	Transient diarrhoea (70%), abdominal cramps (10%), nausea (5%) in 24 hours post FMT; constipation (20%) and flatulence (25%) in follow up period	19 deaths in total 13 week study period (unrelated). 12 patients required hospitalization because of illnesses unrelated to FMT
9 10 11 12 13 14 15 16 17 18 19 20	none	none stated
21 22 23 24 25 26 27 28	None reported	None related to FMT
29 30 31 32 33 34 35 36	Not reported	Micro-perforation but not related to FMT. One death at 3 months afer due to ,metastatic pancreatic cancer.
37 38 39 40 41 42 43 44 45 46 47 48	None reported	None related to FMT
49 50 51 52 53 54 55 56 57 58 59 60	1 pain/nausea after colonoscopy, 1 continued diarrhoea (CDIFF neg) ? Bile salt malabsorption after cholecystectom, 2 transient bloat/ cramps	1 perforation related to colonoscopy sealed with clip

None reported	none reported
None	None
Mild transient fever in 2 (frozen FMT)	3 deaths (unrelated)
Worsening arthritis, constipation, diarrhoea, urinary tract infection.	5 deaths; not attributed to FMT. Stroke, myocardial infarction, aspiration pneumonia, hospitalisation for CDI not as a consequence of FMT.
Not reported	None
Transient abdominal cramping and bloating in 6 patients (30%) that resolved in 72 hours	1 hospitalised with a documented relapse of severe CDI after taking 15 capsules but had successful treatment after receiving the remaining 15 capsules after discharge. No other severe adverse events (grade 2 or above).
Not reported	4 deaths within 30 days of FMT unrelated to FMT.

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None reported	4 patients reported a new medical condition after FMT (peripheral neuropathy, Sjogrens, ITP and rheumatoid arthritis)
pain in one patient	none
None	None
CDI-negative diarrhoea in 7(4.8%) and constipation in 4(2.7%)	within 12 weeks-6 hospitalizations due to CDI and/or FMT. One debilitated
Low grade fever (18.5%) and bloating (11.1%)	None
Nil	Nil

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<p>1 2 3 4 5 6 94% immediate 7 diarrhoea, 31% 8 abdominal pain with 9 cramping, 19% 10 belching - resolved 11 within 3 hours. During 12 follow up 3 patients 13 had constipation (19%). 14 2 patient had 15 infections: one patient 16 with recurrent UTI had 17 UTI</p>	<p>1 hospitalisation for symptomatic choledocholithiasis (unrelated)</p>
<p>23 Mild abdominal 24 discomfort and 25 bloating in 4 patients 26 (20%). One child 27 treated 28 colonoscopically had a 29 transient fever of 38.8 30 C on day 2 that 31 resolved spontaneously</p>	<p>2 deaths (unrelated), 1 new diagnosis of malignancy (unrelated), 1 hospitalisation for Fournier gangrene (unrelated)</p>
<p>36 Nausea in one patient. 37 Nil else</p>	<p>Nil</p>

For Peer Review

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Study characteristics			
Name et al Year	RCT characteristics	Arms of RCT	No. of patients, mean or median age, Gender distribution
Lee CH 2016	Double blind RCT comparing fresh vs frozen FMT	Overall	219 patients, mean 73 years, F:146/219 (67%)
		Frozen	108 patients, mean 73 years, F:72/108 (67%)
		Fresh	111 patients, mean 73 years, F:74/111 (67%)
Kao D 2016 (abstract)	RCT comparing capsule versus colonoscopy delivered FMT	Overall	43 patients, mean 67 years, F:30/43 (70%)
		Capsule	22 patients, mean 66 years, F:17/22 (77%)
		Fresh (colonoscopy)	21 patients, mean 68 years, F:13/21 (62%)
Cammarota 2015	RCT comparing FMT versus vancomycin	FMT	20 patients, mean 71 years, F:12/20 (60%)
		Vancomycin	19 patients, mean 79 years, F:11/19 (60%)
Allegretti 2016 (abstract)	RCT comparing FMT versus vancomycin	high dose capsules FMT	9 patients demographics not stated (abstract)
		low dose capsules FMT	10 patients demographics not stated (abstract)
Kelly 2016	Double blind RCT comparing donor vs placebo (autologous) FMT	donor FMT	22 patients, mean 48 years, F:18/22 (82%)
		autologous FMT	24 patients, mean 55 years, F:19/24 (78%)
Van Nood 2013	RCT comparing FMT versus vancomycin	Vancomycin abbreviated regime (500mg orally four times per day for 4 or 5 days) with bowel lavage and FMT	16 patients; mean age +/-SD (73 +/-13); F: 8/16 (50%)
		Vancomycin standard regime (500mg orally four times per day for 14 days)	13 patients; mean age +/-SD (66 +/-14); F: 7/13 (54%)
		Vancomycin standard regime(500mg orally four times per day for 14 days) with bowel lavage on day 4 or 5.	13 patients; mean age +/-SD (69 +/-16); F: 3/13 (23%)
Youngster 2014	RCT comparing NG versus colonic	Frozen (colonoscopy)	10 patients, mean age +/-SD (50.4 +/-28.8); F:6/10 (60%)

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Youngster 2014	versus colonic delivery of FMT	Frozen (NGT)	10 patients; mean age +/-SD (58.6 +/- 19.6); F: 5/10 (50%)
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For Peer Review

Patient characteristics		
Diagnosis of C.diff i.e Elisa/PCR, duration from diagnosis to transplant	Pre FMT Abx +/- other therapy (M,V,Fidox,IVG)/How many courses i.e M(2), V(1), IVG(1), Fidox(1). Were abx stopped prior to FMT	Refractory / Recurrent
Toxin and PCR	Metronidazole and Vancomycin	Both
Not reported	Not reported	Recurrent
CDI diagnosis confirmed by toxin; in 23/39(59%) positive culture as well as toxin.mean duration of CDI diagnosis prior to FMT not stated	All patients had antibiotics prior to diagnosis of CDI but specifics not stated; Fmt group patients had 3 days vanc prior to FMT which stopped the	Recurrent with lab confirmation
Not stated	Not stated	Not stated
≥3 unformed stools over 24 hours for 2 consecutive days and either a positive stool test result for C difficile or pseudomembranes on colonoscopy	3 or more recurrences of CDI and received a full course of vancomycin for their most recent acute episode.	Recurrent
Toxin and PCR	At least one course of adequate antibiotic therapy (≥10 days of Vancomycin at a dose of ≥125mg four times a day or ≥10 days of Metronidazole at a dose of 500mg three times per day). In FMT group: patients received an abbreviated regimen of Vancomycin (500mg orally four times per day for 4 or 5 days), followed by bowel lavage with 4 liters of macrogol solution (Klean-Prep) on the last day of antibiotic treatment and the suspension of donor feces through a nasoduodenal tube the next day.	Recurrent
Toxin: initial toxin/glutamate dehydrogenase (GDH) enzyme-linked immunosorbent assay, followed by	Patients had a median of 4 (range, 2-16) relapses prior to study enrollment, with 5 (range, 3-15) antibiotic	Relapsing or recurring (having at least 3 episodes of mild-to-moderate CDI OR at least 2 episodes of severe CDI

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PCR only if the GDH test is positive or indeterminate, and does not routinely test for the NAP-1/B1/207 strain.	treatment failures of a 6- to 8-week taper with Vancomycin with or without an alternative antibiotic.	at least 2 episodes of severe CDI resulting in hospitalization and associated with significant morbidity.
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For Peer Review

Flexi sigi / Colonoscopy findings	Donor characteristics Healthy volunteer/Spouse/Related i.e mother/Other non related i.e friend
Not done	Unrelated volunteers
Not reported	Unrelated volunteers
6 out of 20 patients in FMT group had pseudomembranous colitis	16/20 donors related; 2 intimates; 2 unrelated
Not reported	Healthy donors from OpenBiome stool bank mean age 36 years
Colonoscopies done on all	All prospective donors underwent a medical interview and physical examination and were excluded if they had a known communicable disease, features of the metabolic syndrome, a diarrheal disorder, an autoimmune or atopic disease, a tumor, a neurologic disorder, or chronic pain syndrome or if they had used antibiotics for any indication within 3 months. Potential donors also completed a modified AABB full-length donor history questionnaire,
Not done	Healthy volunteers <60 years of age (faces from 15 donors were used for 43 infusions in the infusion group and for patients who had a relapse after vancomycin treatment).
Colonoscopy or NGT	Healthy volunteer donor: nonpregnant adults, 18-50 years of age, on no medications, with a normal body mass

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Colonoscopy of non	of age, on no medications, with a normal body mass index.
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For Peer Review

Characteristics		
Screening and abx cessation	Fresh/Frozen, Route administered	Sample preparation Transplant sample sourcing, screening, preparation; volume, mixing solution, storage and time from collection to transplant
Questionnaire. Pathogens, HIV, HABC, CMV, EBV, syphilis, strongyloides, entamoeba. Screening every 4 months	Fresh vs Frozen. Lower GI route	100g of stool homogenised and mixed in 300mls of water. If frozen kept for 30 days at -20C. If fresh administered within 24hrs.
Not reported	Oral capsules vs colonoscopy	Not reported
No antibiotics for 6 months; stool tested for C. diff, enteric pathogens, ova and parasites, MDR gram negatives, MRSA, VRE; Serum tested for Hep A, Hep B, Hep C, HIV 1 and 2, strongyloides, treponema,	FMT delivered fresh via colonoscopy	mean time from donation to infusion was 3.8 hours; mass of donation not stated but mixed with 500mls saline and blended and strained; delivered to
open Biome Criteria followed	Frozen pills	Not stated
Testing for HIV-1 and HIV-2 was performed within 2 weeks before donation for FMT. Other serologic and stool testing was performed within 1 month before FMT and included testing for hepatitis A, B, and C viruses; testing for Treponema, PCR detection of C difficile toxin; culture for enteric pathogens (Escherichia coli, Salmonella, Shigella, Yersinia, Campylobacter, Listeria, Vibrio, and V cholerae); testing for Giardia and Cryptosporidium, ova and parasite	Fresh via colonoscopy	The protocol specified a "dose" of 100 g of stool diluted in 500 mL of nonbacteriostatic 0.9% normal sa-line immediately before the procedure, but the study relied on fresh stool, which has unpredictable weight and volume, and most provided specimens were less than 100 g.
Questionnaire addressing risk factors for potentially transmissible diseases. Donor feces were screened for parasites, including <i>Blastocystis hominis</i> and <i>Dientamoeba fragilis</i> ; <i>C. difficile</i> , and enteropathogenic bacteria. Blood was screened for HIV; human T-cell lymphotropic virus types 1 and 2; hepatitis A,B, and C; cytomegalovirus; Epstein-Barr virus; <i>Treponema pallidum</i> ; <i>Strongyloides stercoralis</i> ; and <i>Entamoeba histolytica</i> . A donor pool was created, and screening was repeated every 4 months. Before donation, another questionnaire was used to screen for recent illnesses.	Fresh via nasoduodenal tube	Feces were collected by the donor on the day of infusion and immediately transported to the hospital. Feces were diluted with 500mls of sterile saline 0.9%. This solution was stirred, and the supernatant strained and poured in a sterile bottle. A mean (+SD) of 141+-71g of feces was infused. The mean time from defecation to infusion was 3.1+-1.9 hours.
volunteers were excluded for any significant past medical history or any use of antibiotics in the preceeding 6 months. Initial screening using the American Association of Blood Banks donor questionnaire for exposure to infectious agents. Physical examination and general	Frozen via colonoscopy or NGT	Donors were asked to take a dose of milk of magnesia the day before fecal collections to facilitate manipulation of the sample. A fecal suspension was prepared in normal saline without

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infectious agents. Physical examination and general laboratory screening tests (within 30 days of donations). All results had to be within normal range for age and sex. Donor feces were screened for enteric bacterial pathogens including rotavirus, <i>Listeria monocytogenes</i> , <i>Vibrio</i>	Frozen via colonoscopy or not	generated in normal saline without preservatives, using commercial blender. Materials were passed through 4 sieves to remove particulate material. The final slurry was
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For Peer Review

FMT Characteristics		
Procedure: Bowel Prep/Drugs used prior to FMT i.e Moviprep 2 sachets/PPI (dose), prokinetic (dose), Loperamide FMT administration Follow up method	Total no of infusions	Define primary outcome
Nil	1, if no response at day 4, then further FMT and if no response then FMT or abx. Primary outcome based on up to 2 FMTs.	Clinical resolution of diarrhea without relapse at 13 weeks
Not reported	1 infusion via colonoscopy or 1 course of capsules.	Defined as cure but no time period given
FMT group received 4L of macrogol bowel cleansing solution for 1-2 days prior to procedure; patients followed up prospectively by referring physicians;	13/20 had 1 FMT; 6/20 had co-existent PMC and received infusions every 3 days until symptom resolution (4 had 2 infusions, 1 had 3 infusions and 1 had 4	Resolution of diarrhoea 10 weeks after the end of the treatments
Not described	NA	Clinical resolution of diarrhoea at 8 weeks
Donors took an osmotic laxative (magnesium hydroxide) the evening before and provided fresh stool the day of FMT. All donor specimens were transported on ice and processed within 6 hours of collection. Patients were given a standard bowel purgethe evening before the procedure.	1 infusion via colonoscopy	Resolution of diarrhoea without need for anti CDI therapy during 8 week follow up
Bowel lavage with 4 liters of macrogol solution (Klean-Prep) on the last day of antibiotic treatment. Within 6 hours after collection of feces by the donor, the solution was infused through a nasoduodenal tube (2 to 3 minutes per 50mls). The tube was removed 30 minutes after the infusion, and patients were monitored for 2 hours. Patients kept a stool diary and were questioned about stool frequency and consistency, medication use, and adverse effects. Stool tests for C.difficile toxin were performed on days 14,21,35, and 70 and whenever diarrhoea occurred.	16 patients had 1 infusion; 3 who did not respond in this group had 2nd infusion	Cure without relapse within 10 weeks after the initiation of therapy. For patients in the infusion group who required a second infusion of donor feces, follow up was extended to 10 weeks after the second infusion. Cure was defined as an absence of diarrhoea or persistent diarrhoea that could be explained by other causes with three consecutive negative stool tests for C.difficile toxin. Relapse was defined as diarrhoea with a positive stool test for C.difficile toxin.
Subjects assigned to colonoscopic administration underwent a standard bowel preparation with 4 liters of PEG solution, followed by endoscopic administration to the right colon of 90	20 patients in both study arms had one infusion (14 was cured after the first infusion (70%)). One patient in the NGT arm refused subsequent retreatment.	Clinical resolution of diarrhoea off antibiotics for C.difficile, without relapse within 8 weeks. For patients who required a second treatment

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administration to the right colon of 50 cc thawed inoculum: further diluted to 250cc for adults and 160 cc for paediatric patients. Patients were given a single oral dose of loperamide	The remaining 5 patients were given a second infusion (4 patients obtained cure after second infusion, resulting in an overall cure rate of 90%).	who required a second treatment dose, a follow-up was calculated starting at the time of the second administration.
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For Peer Review

Results		
Primary outcome	One infusion	One or more infusion
Intention to treat: 159/219 (73%) at 13 weeks	113/219 (52%)	193/219 (88.1%)
Intention to treat: 81/108 (75%) at 13 weeks	57/108 (52.8%)	98/109 (90.7%)
Intention to treat: 78/111 (70%) at 13 weeks	56/111 (50.5%)	95/111 (85.6%)
41/43 (95%)	Not reported	41/43 (95%)
20/22 (91%)	Not reported	20/22 (91%)
21/21 (100%)	Not reported	21/21 (100%)
18/20 (90%)	13/20 (65%)	18/20 (90%)
5/19 (26%)	Not applicable	Not applicable
7/9 (77% resolution of diarrhoea at 8 weeks)	Not applicable	Not applicable
7/10 (70%) resolution of diarrhoea at 8 weeks	Not applicable	Not applicable
In the intention-to-treat analysis, 20 of 22 patients (90.9%) in the donor FMT group achieved clinical cure at 8 weeks	22/20 (90.9%)	22/20 (90.9%)
com- pared with 15 of 24 (62.5%) in the autologous FMT group (P = 0.042)	15/24 (62.5%)	15/24 (62.5%)
13/16 (81%) after first infusion at 10 weeks; overall 15/16 (94%) after second infusion, follow up was extended to 10 weeks after the second infusion	13/16 (81%)	15/16(94%)
4/13 (31%) patients at 10 weeks	15/24 (62.5%)	15/24 (62.5%)
3/13 (23%) patients at 10 weeks	15/24 (62.5%)	15/24 (62.5%)
8 out of 10 (80%) at 8 weeks primary response ; overall cure rate 100% after 2nd infusion but via NGT	8/10 (80%)	10/10 (100%)

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6 out of 10 (60%) at 8 weeks primary response ; overall cure rate 80% after second infusion via NGT	6/10 (60%)	8/10 (80%)
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For Peer Review

Adverse events - serious

19 deaths in total 13 week study period
(unrelated).

6 deaths (unrelated to FMT)

13 deaths (unrelated to FMT)

None

None

None

2 deaths (unrelated to FMT)

none

Not stated (abstract)

Not stated (abstract)

None

None

1 hospitalisation for symptomatic
choledocholithiasis (unrelated).

1 death (unrelated)

None

2 deaths (unrelated), 1 new diagnosis of
malignancy (unrelated)

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1 hospitalisation for Fournier gangrene
(unrelated)

For Peer Review

Study details			
Name et al Year	Type of study i.e RCT, case control etc	No. of patients, years, location, selection criteria, Mean or median age, Gender distribution; other	Diagnosis of C.diff i.e Elisa/PCR, duration from diagnosis to transplant
Aas 2003	Case series	19 recruited over 9 years (1994-2002) at a single centre (USA); two or more lab confirmed relapses after initial specific AB treatment, adequate clin and lab documentation of post transplant course; Mean age 73±9 (SEM) (Range: 51-88 years); F: 13/18 (72%); Hospitalised=5; nursing home=3; outpatient-GI clinic=10	Lab confirmed via stool sample, toxin A only, then B added from 2001. 2 or more positive test stool tests (mean 3.2, range 2-7). Mean period from diagnosis of c/diff colitis and stool transplantation 102±24 (SEM) days (range 25-497)
Allegretti 2016	Open label cluster dose finding trial comparing low dose (30 pills) vs high dose (30 pills on 2 consecutive days)	19-age/gender not stated	Diagnosis method not stated
Cammarota 2015	Open label RCT	prospective RCT comparing FMT plus vancomycin to vancomycin therapy alone for recurrent CDI; 39 patients over 12 months July 2013 to June 2014; single centre; FMT group (n=20) mean age 71 years (range 29-89) F 12 (60%); Vanc group (n=19) mean age 75 (49-93) F 11 (58%)	CDI diagnosis was based on symptoms and toxin confirmed in 23/39(59%) positive culture.mean duration of CDI diagnosis prior to FMT not stated

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<p>Fischer et al. 2016</p>	<p>Retrospective cohort study</p>	<p>Of 328 patients in the developmental cohort, 73.5% (N=241) were females with a mean age of 61.4±19.3 years; 19.2% (N=63) had inflammatory bowel disease (IBD), and 23.5% (N=77) were immunocompromised. Two academic centres. 2011-2015. Of 134 patients in the validation cohort, 57% (N=77) were females with a mean age of 66±18.1 years; 9.7% (N=13) had IBD, and 17.9% (N=24) were immunocompromised. Single centre. 2011-2015</p>	<p>Diagnosis of Cdiff if recurrent at least 3 episodes of CDI and failure of 6-8 week vancomycin taper. Severe based on albumin, elevated white cell count and abdominal pain. Severe complicated defined as admission to ITU hypotension, fever, ileus, reduced GCS, elevated white cell count and lactate with end organ dysfunction.</p>
<p>Ganc et al 2015</p>	<p>Case series, retrospective</p>	<p>12 patients. No other variables reported</p>	<p>Not reported</p>
<p>Garborg et al. 2010</p>	<p>Case series, retrospective</p>	<p>39 patients (one had 2 FMTs). Treated single centre 1994-2008. Mean age 75y (range 53-94). F=21 (53%)</p>	<p>Toxin positivity or clinical findings (37/40 toxin positive)</p>

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Hamilton et al. 2012	Case series	43 patients. Single centre. 29 non-IBD and 14 IBD patients. Non IBD cohort (mean age 64.7y SEM 3.3; F 20 (69%)); IBD cohort (mean age 44.6 SEM 5.8; F 11 (79%))	Inclusion criteria for FMT included a history of symptomatic, toxin-positive, infection by <i>C. difficile</i> , and at least two documented subsequent recurrences despite use of standard antibiotic therapy.
Kao D 2016 - abstract (FMT arm of RCT)	Double blind RCT (capsule vs fresh)	43 patients, mean 67 years, F:30/43 (70%). Two centres. 22 capsule group and 21 in colonoscopy group	Not reported
Kassam et al. 2012	Case series	27 patients: the mean age was 69.4 years (range, 26-87 years) with 14 male subjects (52%) and 22 in-patients (81%).	Inclusion criteria were (1) laboratory-confirmed <i>C difficile</i> toxin using enzyme immunoassay with no other cause for diarrhea; (2) refractory CDI (defined as ongoing diarrhea despite antimicrobial treatment) or recurrent CDI (defined as symptom resolution for at least 2 days after discontinuation of treatment with recurrence of diarrhea);
Kelly 2012	Case series	26 recruited over 28 months;single centre;at least 3 recurrences of CDI following multiple antibiotic courses;adequate clinical and lab documentation post transplant; Mean age 59 (19-86 yrs); F: 24/26 (92%)	Method of CDI diagnosis not stated;mean duration of diagnosis of CDI prior to FMT 12.6 M (range 4 to 84 M);

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<p>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26</p> <p>Kelly 2014</p>	<p>Case series</p>	<p>retrospective study of immunocompromised patients receiving FMT for CDI; 80 patients data analysed from 16 centres;eligibility assessed by 32 point questionnaire;75 adults and 5 children; Mean age in Adults 53 (range 20-88) in children 10.9 (range 6.5-16); Adults (n=75) F:38 (48%)</p>	<p>4 categories; 1 recurrent/relapsing at least 3 episodes with failure of up to 8 week taper with vancomycin or at least 2 episodes of severeCDI resulting in hospitalisation and associated with significant morbidity.2 Refractory CDI-moderate CDI not responding to standard therapy for at least a week 3 Severe CDI elevated WBC., low albumin and abdominal tenderness. 4 complicated CDI- Admission to ITU, low blood pressure, fever, ileus, mental state changes, elevated WBC, high lactate and evidence of end organ failure</p>
<p>27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60</p> <p>Kelly et al. 2016</p>	<p>Double blind RCT (donor vs autologous FMT)</p>	<p>46 patients . Two centres. Donor FMT group n=22, mean age=48 (SD 16); F=18 (82%); Autologous FMT group n=24, mean age = 55(SD 14), F=19 (79%).</p>	<p>≥3 unformed stools over 24 hours for 2 consecutive days and either a positive stool test result for <i>C difficile</i> or pseudomembranes on colonoscopy</p>

Khan 2014	Case series	retrospective analysis of 20 cases over 13 months (July 2012 to Aug 2013); selection criteria: all patients receiving FMT for CDI at their centre; single centre; adequate post transplant documentation and assessment; Demographic data presented separately for community aquired and hospital aquired CDI; Calculated Overall Mean age 66.4 years; F 13 (65%); Mean number of CDI episodes pre-FMT:5.6 community aquired and 4.6 for hospital aquired	Method of CDI diagnosis not stated; data presented separately for community aquired CDI and hospital aquired CDI; median duration of symptoms pre FMT for community aquired CDI was 7 months; 5 months for hospital aquired CDI
Kronman 2015	Case series	retrospective study of 10 children in single centre over 3 years (between Aug 2011 and May 2014); At least 3 episodes of CDI; adequate post transplant documentation and assessment; Mean age 5.4 years; F 7/10 (70%);	C diff toxin A&B and/or PCR; median duration of symptoms pre-FMT 250 days (range 90-541 days);
Lee 2014	Case series	retrospective analysis of 94 patients from 2008-2012; single centre; mixture of recurrent and refractory CDI definitions given; Mean age 71.8 years (range 24-95 years); F 53/94 (56.4%)	C diff toxin A&B and/or PCR; duration of symptoms pre-FMT not stated
Lee CH 2016 (FMT arm of RCT)	FMT arm of double blind RCT (Fresh vs Frozen)	219 patients, mean 73 years, F:146/219 (67%)	Toxin and PCR

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<p>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17</p> <p>MacConnachie 2009</p>	<p>Case series</p>	<p>retrospective analysis of 15 patients since 2003;single centre; recurrent CDI following succesful antibiotic therapy; Median age 81.5years (range 68-95); F 14/15 (93.3%)</p>	<p>Method of CDI diagnosis not stated;mean duration of diagnosis of CDI prior to FMT not stated</p>
<p>18 19 20 21 22 23 24 25 26 27</p> <p>Mattila 2012</p>	<p>Case series</p>	<p>70 patients over 3 years (2007-2010) all laboratory confirmed recurrent CDI refractory to standard treatment. Mean age 73(22-90) F=42(60%). 60(86%) outpatients</p>	<p>positive culture and toxin; strain typing . Time from diagnosis to CDI mean 133 days (46-360). 36(51%0 had ribotype 027</p>
<p>28 29 30 31 32 33 34 35 36 37</p> <p>Patel 2013</p>	<p>Case series</p>	<p>31 patients over 2 years (2011-2013) all had recurrent (at least 2 previouslt documented CDI episodes). Mean age 61 (SD19) F=17(55%).17/31 (55%) gi comorbdiity. Diverticulitis (5), IBS (5), UC (3), CD(2), gastroparesis (1), coloanal fistula(1)</p>	<p>Diagnosis method not stated. Medain time(range) from index diagnosis to FMT 340 days(18-2205)</p>
<p>38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60</p> <p>Pathak 2014</p>	<p>Case series</p>	<p>12 patients with recurrent or relapsing CDI with at least 3 episodes and failure of treatment with vancomycin +/- additional antibiotic such as fidox or patients wuth at least two episodes of severe CDI or patients with moderate CDI not responding to vanc for a week or patients with severe/fulminant CDI not responding to standar treatment for 48 h. 12 patients over 3 years. mean age 72 (SD 15) range 37-90; F 8/12 (67%)</p>	<p>Diagnosis method not stated</p>

Ray 2014	Case series	20 (August 2012-November 2013) 2 recurrences as defined by diarrhoea OR positive Cdiff after antibiotics (m,v,or f). Or if life threatening and/or admission to ICU. 20 patients mean age 62 (SD 18). F 16(80%). 15 (75%) out patients. Average time from diagnosis to FMT 49.6 weeks	Diagnosis method not stated
Rohlke 2010	Case series	19 patients over 5 years(September 2004-July 2009). At least 3 courses or treatment included vanc amn tapered vanc over 6 months.Mean age 49 (SD 15). F17 (90%). All out-patients	Diagnosis method confirmed by lab in all cases but method not specified
Rubin TA 2013	Case series, retrospective	74 patients (75 courses), mean age 63 years, F 49/74 (65%)	Diagnosis of CDI confirmed by lab only in a few cases. Method not specified.
Satokari R 2015	Case series, retrospective	49 patients, mean age 56 years, F 34/49 (69)	Culture and toxin
Tauxe 2016	Case series, retrospective	31 patients, mean age 77 years, F 18/31 (58%)	Not reported
Yoon 2010	Case series, retrospective	12 patients, mean age 66 years, F 9/12 (75%)	Toxin positivity or clinical findings

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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16	Youngster2014	Case series, prospective	20 patients, Median age 64.5; F 9/20 (45%). Exclusion criteria - delayed gastric emptying synd, recurrant aspiration, pregnancy, significant immunocompromise, history of signif food allergy to food included in donor diet.	Toxin and ELISA, PCR if toxin negative but ELISA is positive or indeterminate
17 18 19 20 21 22 23	Zainah 2015	Case series, retrospective	14 patients, mean age 73 years,	C. difficile toxin EIA and/or PCR
24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47	Brandt LJ 2012	Case series, retrospective	77 patients in 5 centres, mean age 65, F 56/77 (73%).	Not reported
48 49 50 51 52 53 54 55	Allegretti	Case series, retrospective	22 patients, mean age 55, F 18/22 (82%)	C. difficile toxin EIA and/or PCR
56 57 58 59 60	Costello	Case series, prospective	20 patients , median age 69 years, gender distribution not reported	Not reported

Agrawal 2016	multicentre, retrospective, long term follow up study	146 patients, 100 (68.5%) women; mean age (range) 79.	Not reported
Dutta 2014	Case series, prospective	27 patients, mean age 64.5y, F 22/27 (81.5%)	Cdiff toxin positivity by ELISA
Emmanuelson 2014	Case series, retrospective	23 patients, mean age 66y, F 61%	Culture and/or toxin EIA
Van Nood 2013	FMT arm of RCT (FMT versus vancomycin)	From January 2008 through April 2010, 43 patients were randomly assigned to receive donor-feces infusion (17 patients), vancomycin (13), or vancomycin and bowel lavage (13). One patient assigned to receive donor-feces infusion was subsequently excluded from further analysis. Baseline demographics per groups: Donor Feces Infusion: 16 patients; mean age +/-SD (73 +/-13); F: 8/16 (50%); Vancomycin only: 13 patients; mean age +/-SD (66 +/-14); F: 7/13 (54%); Vancomycin and Bowel Lavage: 13 patients; mean age +/-SD (69 +/-16); F: 3/13 (23%)	Toxin and PCR. In 39 patients, a positive toxin test before inclusion was confirmed by a positive <i>C.difficile</i> culture. PCR ribotyping was performed on strains obtained from 34 patients
Youngster 2014	FMT arm of open-label RCT (NG versus colonic delivery of FMT)	37 patients were assessed for eligibility and 20 patients underwent randomisation: Colonoscopy arm: 10 patients, mean age +/-SD (50.4 +/-28.8); F:6/10 (60%); Nasogastric tube:10 patients; mean age +/-SD (58.6 +/- 19.6); F: 5/10 (50%)	Toxin: initial toxin/glutamate dehydrogenase (GDH) enzyme-linked immunosorbent assay, followed by PCR only if the GDH test is positive or indeterminate, and does not routinely test for the NAP-1/B1/207 strain
Vigvari 2014	Case series, retrospective	30 patients, mean age 70.1 years (26-88 years), Female: 18/30 (60%)	Not reported

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Patient characteristics			Donor Ch
Pre FMT Abx +/- other therapy (M,V,Fidox,IVG)/How many courses i.e M(2), V(1), IVG(1), Fidox(1). Were abx stopped prior to FMT	Refractory / Recurrent	Flexi sigi / Colonoscopy findings	Healthy volunteer/Spouse/Related i.e mother/Other non related i.e friend
<p>Mean 3.6 courses of abs (range 2-7) abs varied (Clm, Cm, Cpx, Ctri, Ctox, Amp, Gm, Clex, Mtz, Pen, Pip, tMp-SMZ, Taz, Lev, Tet, Vm) number of courses prior to transplant varied: 2-7; Recipients were pre-treated with vm (250mg q8h) for 4 or more days and this was discontinued the night before transplant.</p>	<p>recurrent (two or more lab confirmed relapses)</p>	<p>Not reported</p>	<p>15/18 were family members of recipient; no member available for remaining 3 so donors were healthy clinic staff. Hierachy of ideal donor described: intimate physical contact with patients (spouse/partner) > family household member > other healthy donor</p>
<p>Not stated</p>	<p>Not stated</p>	<p>Not reported</p>	<p>Healthy donors from OpenBiome stool bank mean age 36 years</p>
<p>All patients had antibiotics prior to diagnosis of CDI but specifics not stated; Fmt group patients had 3 days vanc prior to FMT which stopped the day before; vanc group had 10 days of standard vanc followed by at least three weeks of pulsed vanc</p>	<p>recurrent with lab confirmation</p>	<p>6 out of 20 patients in FMT group had pseudomembranous colitis</p>	<p>Healthy volunteers less than 50 years old from which 16/20 donors related; 2 intimates; 2 unrelated</p>

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<p>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17</p> <p>Not reported</p>	<p>split into refractory, recurrent and severe complicated</p>	<p>Colonoscopies done on most</p>	<p>Mix of healthy volunteers (319 69%) and family (143 31%)</p>
<p>18 19 20 21 22 23 24 25 26 27 28 29</p> <p>Not reported</p>	<p>Recurrent</p>	<p>N/A</p>	<p>The donor is usually a family member of the patient who meets certain criteria, such as not having used antibiotics in the previous six months, being immunocompromised, and having no history of illicit drug use, tumors or inflammatory bowel disease.</p>
<p>30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60</p> <p>The patients were treated with metronidazole or vancomycin until reduction of symptoms. All antimicrobial therapy was discontinued on the evening prior to stool transplantation.</p>	<p>Recurrent</p>	<p>1 patient with pseudomembranous colitis</p>	<p>Close relatives or other household members were selected as stool donors. Individuals without symptoms of gastrointestinal disease or a history of chronic infectious disease were considered suitable for stool donation.</p>

<p>At least one failed antibiotic regimen had to include a minimum of a 6-week course of tapered or pulsed vancomycin dosage, or at least a 1-month vancomycin course followed by a minimum of 2-week rifaximin "chaser."</p>	<p>Recurrent</p>	<p>Not reported</p>	<p>patients were asked to self-identify potential donors. These included mothers (n=2), daughters (n = 1), sons (n = 3), wives (n = 1), husbands (n = 1), and friends (n = 2).</p>
<p>Not reported</p>	<p>Recurrent</p>	<p>Not reported</p>	<p>Unrelated volunteers</p>
<p>All had at least metronidazole; 19 had subsequent vancomycin monotherapy. 8 had combination metronidazole and vancomycin therapy.</p>	<p>Recurrent or refractory</p>	<p>Not reported</p>	<p>Two healthy volunteers served as donors and were evaluated for transmissible pathogens. The donors took no antibiotics for 6 months prior to stool donation.</p>
<p>antibiotics prior to CDI diagnosis- clind, cipro, metro, moxiflox, levoflox, azithro, cefurox, amox, augmentin; treatment for CDI-all had metronidazole, Sacchomyces bouladaii, 4 had lactobacillus, 2 had IV IG, 19 had had rifaximin; pre-FMT all had 2 weeks of metronidazole or vanc, discontinued 2-3 days before FMT</p>	<p>recurrent at least 3 episodes (lab confirmation not stated)</p>	<p>11 had diverticular disease; 3 had colitis; 8 normal; 2 polyps; 2 haemorrhoids; 2 previous surgery</p>	<p>25/26 family members; 1 friend</p>

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<p>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26</p> <p>79/80 had been treated with vancomycin. 55/80 had metronidazole, 23 had fidaxomicin, 13 had rifaximin and 30 had probiotics</p>	<p>recurrent CDI (at least 3 episodes and failure of vanc taper for 6-8 weeks); refractory (no improvement after 1 week of vanc); Severe CDI or complicated (definitions given)</p>	<p>Not reported</p>	<p>Not reported</p>
<p>27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60</p> <p>3 or more recurrences of CDI and received a full course of vancomycin for their most recent acute episode.</p>	<p>Recurrent</p>	<p>Colonoscopies done on all</p>	<p>All prospective donors underwent a medical interview and physical examination and were excluded if they had a known communicable disease, features of the metabolic syndrome, a diarrheal disorder, an autoimmune or atopic disease, a tumor, a neurologic disorder, or chronic pain syndrome or if they had used antibiotics for any indication within 3 months. Potential donors also completed a modified AABB full-length donor history questionnaire, and those with risk factors for infectious agents were excluded (Supplement).</p>

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16	Antibiotic treatment for CDI: metronidazole (1 patient had 1 course; 7 patients had 2 courses; 12 patients had 3 courses); vancomycin (2 patients had 1 course; 12 patients had 2 courses; 4 patients had 3 courses; 2 patients had pulsed vanc); 9 had fidaxomicin; all antibiotics stopped 48 hours before FMT	not explicitly stated but patients had a mean of 4.6-5.6 episodes of CDI prior to FMT	Not reported	5/20 from spouse/partner; 14/20 family member; 1 non- relative
17 18 19 20 21 22 23 24 25 26 27 28	Antibiotics used prior to CDI diagnosis- metronidazole, augmentin, ampicillic, amoxycillin, cefdinir, cefuroxime, penicillin; CDI tretament all had metronidazole, 6/10 had vancomycin, 8/10 had vancomycin taper; pre- transplant all had vanc or fidaxomicin for 7 days, last dose given 24 hours pre- transplant	recurrent CDI; mean of 3.2 episodes pre-FMT	Not reported	9/10 parents; 1 sibling
29 30 31 32 33 34 35 36 37	Mean of 2,1 courses of antibiotics for CDI prior to FMT (metronidazole 79.3%, vancomycin 75%, vancomycin taper 15.2%, combination metro and vanc 17.4%, 3 patients had IVIG); pre- tranplant all antibiotic therapy for Cdi was discontinued 24 hours before FMT	recurrent (recurrent diarrhoea after at least 2 days of resolution following antibiotic therapy) or refractory (ongoing diarrhoea despite at least 5 days of oral vancomycin)	Not reported	2 unrelated donors
38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Metronidazole and Vancomycin	Both	Not reported	Unrelated volunteers

<p>Antibiotics prior to CDI diagnosis not stated; 15/15 received metronidazole; 15/15 received vanc, 3 received iVIG; vanc given pre-procedure but length of course not stated; stopped 12 hours before FMT</p>	<p>recurrent CDI defined as recurrence of diarrhoea after successful antibiotic therapy typically within 7 days of stopping antibiotics;</p>	<p>Not reported</p>	<p>related donors specifics not given</p>
<p>mean 4.5 courses of antibiotics. Metro, vanc, rifax, 1 IVIG Stopped 36 hours before FMT</p>	<p>recurrent (two or more lab confirmed relapses)</p>	<p>Not reported</p>	<p>61(87%) family members; 9(13%) healthy donors</p>
<p>Stopped (usually vanc) 4 hours before bowel prep. Loperamide 4mg either before or immediately after FMT</p>	<p>recurrent (two or more lab confirmed relapses)</p>	<p>Not reported</p>	<p>"Mostly" family. 14 spouses, 9 children, 5 siblings, 3 parents, 1 niece, 1 friend</p>
<p>Antibiotics stopped 24 hours prior to procedure</p>	<p>Refractory / Recurrent and severe</p>	<p>8 colitis, 1 Cdiff, 1 haemorrhoid, 1 pseudomembranous colitis, 1 diverticulosis</p>	<p>10 family, 2 spouses</p>

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1 2 3 4 5 6 7 8 9 10	Antibiotics stopped 48 hours prior to procedure	16 recurrent; 4 severe/complicated	Not reported	10 family, 8 spouses, 2 healthy donors
11 12 13 14 15 16 17	Antibiotics stopped 1-3 days before FMT	recurrent	Not reported	4 family, 14 partner, 1 housemate
18 19 20 21	Vancomycin and / or metronidazole	Recurrent	Not reported	Healthy household members
22 23 24 25 26 27 28 29	Not reported	Refractory	Not reported	Frozen stool: 2 unrelated donors. Fresh stool: Family members, healthy volunteers, or the same universal donors.
30 31 32 33 34 35 36 37 38 39	Combinations of Vancomycin, Metronidazole, Fidoxamicin, Rifaximin	Both	Not reported	7 were from family members, rest were volunteers
40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Combination of metronidazole, vancomycin, rifaximin, bacitracin, nitazoxanide	Both	9/12 normal colonic mucosa, 3/12 had pseudomembranes	All family members (partner:8; child or grandchild:4)

Failed vancomycin taper and or fidaxomicin.	Refractory or recurrent. Defined 3 episodes of mild to moderate CDI or failure of 6-8 week taper with vancomycin, or atleast two episodes of severe CDI resulting in hospitalisation and associated with significant morbidity. Active CDI defined as more than 3 loose stools per day with a positive stool test.	Not reported	Unrelated adult volunteers
Vancomycin and / or metronidazole	Both	Not reported	12 from family members, 1 from unrelated volunteer
Failed on average of five conventional antimicrobial regimes; including metronidazole (81%), vancomycin (99% standard and pulsed) and/or tapered regime with or without rifaxmin (22%) or probiotics (77%).	Recurrent CDI (unresponsive to standard therapy)	Not reported	60% partners/spouses; 27% were either first degree relatives or otherwise related to the patient. ; one case - unknown person. In all, 56 of 77 donors resided in the same household as patient.
Several but eligibility included starting vancomycin for 7 days before procedure and stopping day before	Both. Relapsing defined as three or more episodes of CDI or refractory disease that is unreponsive to traditional antibiotics.	Not reported	Patient identified donors- spouse, family, friend. My co-inhabit
Not reported	Recurrent disease	Not reported	Healthy volunteers

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<p>Conventional therapy with met, van and/or fidaxomicin had failed in all. Some takinh probiotics. Om average</p>	<p>Recurrent defined as recurrence of diarrhoea after completion of treatment. Severe CDI defined as low</p>	<p>Not reported</p>	<p>Donors usually identified by patient. One healthy volunteer not identified by patient</p>
<p>Most patients received metronidazole and/or vancomycin Other antibiotics included fidaxomicin, rifaximin.</p>	<p>Recurrent (>2 recurrences)</p>	<p>Active colitis seen in 26/27 patients with pseudomembranes in 2</p>	<p>Healthy donors selected via thorough clinical evaluation to exclude any transmissible disease. 10 spouse, 12 son or daughter, 1 parent, 4 friends.</p>
<p>Metronidazole and/or Vancomycin</p>	<p>Relapsing and recurrent</p>	<p>Not reported</p>	<p>Spouse or close relative of good health</p>
<p>At least one course of adequate antibiotic therapy (≥ 10 days of Vancomycin at a dose of ≥ 125mg four times a day or ≥ 10 days of Metronidazole at a dose of 500mg three times per day). In FMT group: patients received an abbreviated regimen of Vancomycin (500mg orally four times per day for 4 or 5 days), followed by bowel lavage with 4 liters of macrogol solution (Klean-Prep) on the last day of antibiotic treatment and the suspension of donor feces through a nasoduodenal tube the next day</p>	<p>Recurrent</p>	<p>Not done</p>	<p>Healthy volunteers <60 years of age (faces from 15 donors were used for 43 infusions in the infusion group and for patients who had a relapse after vancomycin treatment)</p>
<p>Patients had a median of 4 (range, 2-16) relapses prior to study enrollment, with 5 (range, 3-15) antibiotic treatment failures of a 6- to 8-week taper with Vancomycin (95% of patients) with or without an alternative antibiotic, including Fidaxomicin (70% of participants). Patients were required to discontinue all antibiotics at least 48 hours prior to the procedure</p>	<p>Relapsing or recurring (having at least 3 episodes of mild-to-moderate CDI OR at least 2 episodes of severe CDI resulting in hospitalization and associated with significant morbidity)</p>	<p>Not reported</p>	<p>Healthy volunteer donor: nonpregnant adults, 18-50 years of age, on no medications, with a normal body mass index</p>
<p>Not clear from paper, but it appears most patients had vancomycin</p>	<p>Refractory and recurrent</p>	<p>Not reported</p>	<p>Donors were relatives in 22 cases (73.3%) and unrelated volunteers in 8 cases (26.7%).</p>

Characteristics	FMT characteristics		
Screening and abx cessation	Fresh/Frozen, Route administered	Sample preparation Transplant sample sourcing, screening, preparation; , volume, mixing solution, storage and time from collection to transplant	Procedure: Bowel Prep/Drugs used prior to FMT i.e Moviprep 2 sachets/PPI (dose), prokinetic (dose), Loperamide FMT administration Follow up method
<p>Within 30 days before donation (usually 7 days) screened: Blood:HAV (HAV ab (IgM and IgG), HBV (ab to HepB surface antigen and core antigen), HCV (HCV ab RIBA-II), HIV-1 & 2 (EIA), Treponema pallidum (rapid plasma reagin test). Stool: C diff (Toxin A or B (cytotoxin) detection), enteric bacterial pathogens (selective stool culture), ova/parasites (light microscopy) No antimicrobial therapy in previous 6 months</p>	<p>Fresh nasogastric, with tube placement on morning of transplant and tube tip placement confirmed by radiography</p>	<p>Stool obtained 6 or less hours prior to transplant. Approx 30g or 2cm³ preferably soft stool selected and homogenised in 50-70ml 0.9N sterile saline (household blender - slow speed setting initially, rising gradually to maximum and continued then for 2-4 min) until sample smooth. Filtered through coffee paper filter x2 allowing adequate time for slow filtration to end.</p>	<p>20mg omeprazole evening before and morning of transplant. 25ml of stool suspension administered then tube flushed with 25ml sterile 0.9N saline. Tube removal. Normal diet and physical activities allowed immediately. Follow up by telephone or clinic visit and stool specimens examined for c.diff toxin A in most patients.</p>
<p>open Biome Criteria followed</p>	<p>Frozen pills</p>	<p>Not stated</p>	<p>Not described</p>
<p>no antibiotics for 6 months; stool tested for C. diff , enteric pathogens, ova and parasites, MDR gram negatives, MRSA, VRE; Serum tested for Hep A, Hep B, Hep C, HIV 1 and 2, strongyloides, treponema, Entamoeba. High risk lifestyle, FH of GI cancer, IBD, systemic diseases, personal GI disease</p>	<p>fresh via colonoscopy</p>	<p>Mean time from donation to infusion was 3.8 hours; mass of donation not stated but mixed with 500mls saline and blended and strained; delivered to right colon through colonoscope</p>	<p>2 groups FMT group received 4L of macrogol bowel cleansing solution for 1-2 days on the last 2 days of vancomycin followed by FMT. The other group had bowel cleansing and vancomycin standard treatment.</p>

<p>Sporicidal disinfection was performed in patient rooms as per institutional protocols; specific instructions with handouts regarding sporicidal home cleaning were provided to patients to prevent reinfection.</p>	<p>Fresh or frozen via Colonoscopy and NG tube</p>	<p>Not reported</p>	<p>Not reported</p>
<p>Some tests are performed for screening: serology for hepatitis A, B and C, human immunodeficiency virus (HIV), fecal parasitology, fecal test for Clostridium difficile, and fecal culture.</p>	<p>Fresh via enteroscope</p>	<p>Mixed in N. Saline. Volume and other variables not stated</p>	<p>Not reported</p>
<p>Donors were screened for hepatitis A, B and C and HIV infection, as well as enteric bacterial pathogens including Salmonella, Shigella, Campylobacter and Yersinia species.</p>	<p>Fresh via Gastroscopy or colonoscopy</p>	<p>A fresh stool sample of 50–100 g was obtained from the donor on the day of the instillation procedure. The stool sample was spread out onto a gauze pad which was then placed in a strainer. The gauze was flushed with 250 ml sterile 0.9% NaCl and the resulting suspension was collected and aspirated into syringes. A flexible videogastroscope was introduced into the distal duodenum. Approximately 200 ml of sample solution was introduced</p>	<p>No bowel prep given to colonic delivered FMT</p>

<p>The donor had to submit their medical records and underwent serologic testing for HIV and Hepatitis B and C, and stool testing that included screening for routine enteric pathogens, <i>C. difficile</i> toxin B, and examination for ova and parasites, and <i>Giardia</i> and <i>Cryptosporidium</i> antigens. Donors were excluded if they had GI co-morbidities or had used antibiotics within 3 months.</p>	<p>Fresh or frozen via Colonoscopy</p>	<p>Approximately 50g of fecal material was placed into a standard commercial blender (Oster, Subeem, Rye, NY) and homogenized in 250 ml of sterile, non-bacteriostatic normal saline. Faecal suspension, if stored, was put in 10% glycerol and stored at -80 for up to 8 weeks. The frozen preparation was diluted in 250ml saline before infusion.</p>	<p>Patients were maintained on full dose of vancomycin (125mg, four times daily by mouth) until 2 days before the FMT procedure. The day before the procedure, the patients were prepped using a split dosage polyethylene glycol purge (GoLYTELY or MoviPrep), which is standard in our endoscopy unit, before colonoscopies to wash out residual antibiotic and fecal material.</p>
<p>Not reported</p>	<p>Oral capsules vs colonoscopy</p>	<p>Not reported</p>	<p>Not reported</p>
<p>Blood was screened for hepatitis B surface antigen, hepatitis C antibody, Helicobacter pylori and syphilis serologic markers, human immunodeficiency virus types 1 and 2, and human T-lymphotropic virus types I and II. Stool was processed for enteric bacterial pathogens, C difficile toxin, and ova and parasites.</p>	<p>Retention enema</p>	<p>Approximately 150 g of fresh stool collected was emulsified in 300 mL of sterile water. The supernatant component was administered rectally by enema.</p>	<p>All CDI therapy was discontinued at least 24 hours prior to FT.</p>
<p>no antibiotics in preceding 90 days; blood for HAV, HBV, HCV, HIV 1&2, Treponema pallidum; stool for culture for bacteria, stain for ova and parasites, C. diff. toxin A and B</p>	<p>Fresh via colonoscopy</p>	<p>stool obtained 6 hours or less prior to transplant; 6-8 tablespoons of donor stool added and shaken in 1litre of sterile water passed through gauze. Aliquoted in 60ml syringes.</p>	<p>polyethelene glycol bowel prep night before transplant; 500-960mls administered via scope mainly to right colon; Avoid defecating for 30-45 mins</p>

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<p>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26</p> <p>Not reported</p>	<p>fresh or frozen not stated; 12 of 16 centres used colonoscopy route</p>	<p>Not reported</p>	<p>prep not stated; questionnaire sent out to 16 centres to retrospectively collect data; method of follow up at each centre not stated but had to have data for at least 12 weeks to be eligible for inclusion</p>
<p>27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60</p> <p>Testing for HIV-1 and HIV-2 was performed within 2 weeks before donation for FMT. Other serologic and stool testing was performed within 1 month before FMT and included testing for hepatitis A, B, and C viruses; testing for <i>Treponema pallidum</i>; polymerase chain reaction (PCR) testing for detection of <i>C difficile</i> toxin; culture for enteric pathogens (<i>Escherichia coli</i>, <i>Salmonella</i>, <i>Shigella</i>, <i>Yersinia</i>, <i>Campylobacter</i>, <i>Listeria monocytogenes</i>, <i>Vibrio parahaemolyticus</i>, and <i>V cholerae</i>); testing for fecal <i>Giardia</i> and <i>Cryptosporidium</i> antigens; acid-fast stain for detection of <i>Cyclospora</i> and <i>Isospora</i>; ova and parasite testing; and enzyme immunoassay for detection of Rotavirus.</p>	<p>Fresh via colonoscopy</p>	<p>The protocol specified a "dose" of 100 g of stool diluted in 500 mL of nonbacteriostatic 0.9% normal saline immediately before the procedure, but the study relied on fresh stool, which has unpredictable weight and volume, and most provided specimens were less than 100 g.</p>	<p>Donors took an osmotic laxative (magnesium hydroxide) the evening before and provided fresh stool the day of FMT. All donor specimens were transported on ice and processed within 6 hours of collection. Patients were given a standard bowel purge (sodium sulfate, potassium sulfate, and magnesium sulfate oral solution) the evening before the procedure. For patient convenience, sodium sulfate, potassium sulfate, and magnesium sulfate oral solution was substituted for the polyethylene glycol (PEG) bowel purge described in the study protocol.</p>

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16	no antibiotics for 3 months; stool tested for C. diff toxin PCR, enteric pathogens, ova and parasites, Cryptosporidium, Microspora; Serum tested for Hep A, Hep B, Hep C, HIV 1 and 2; H. pylori' Human T lymphotropic virus	fresh via colonoscopy	stool obtained within 30 mins of transplantation; 50g of stool into 200mls of saline and blended; Aspirated into single 60ml syringe for delivery	4 litres polyethelene glycol bowel prep; 60mls administered via scope into right colon; follow up combination of clinic, telephone and questionnaires
17 18 19 20 21 22 23 24 25 26 27 28	no antibiotics for 3 months; stool tested for C. diff , enteric pathogens, ova and parasites; Serum tested for Hep A, Hep B, Hep C, HIV 1 and 2; CMV, EBV, high risk behaviours, systemic antineoplastic drugs, immunosuppressives, history of GI disease. Directed donors to avoid foods which recipient may be allergic to for 5 days prior.	fresh via NGT	time from collection to transplant not stated; 30g stool added to 100mls saline and blended;filtered through gauze; 30-60mls infused	8.5g-17g polyethylene glycol in 8oz of water 3 times a day for 2 days prior to FMT; omeprazole 1mg/kg orally day before and on day of FMT; follow up all patients called 2 days after FMT, further follow up combination of clinic, telephone and repeat C. diff. testing
29 30 31 32 33 34 35 36	no antibiotics for 6 months; stool tested for C. diff , enteric pathogens, ova and parasites, norovirus,enterovirus; Serum tested for Hep A, Hep B, Hep C, HIV 1 and 2, human IT-cell lymphotropic virus 1&2, treponema	retention enema	time from collection to transplant not stated; 150g stool added to 300mls water and homogenised with spatula 100mls infused	no bowel prep stated;100mls infused via enema;follow up methods not stated but retrospective analysis extracted from clinical record
37 38 39 40 41 42 43 44 45	Questionnaire. Pathogens, HIV, HABC, CMV, EBV, syphilis, strongyloides, entamoeba. Screening every 4 months	Fresh and Frozen. Lower GI route	100g of stool homogenised and mixed in 300mls of water. If frozen kept for 30 days at -20C. If fresh administered within 24hrs.	Nil

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<p>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17</p> <p>Within 30 days before donation (usually 7 days) screened: Blood:HAV (HAV ab (IgM and IgG), HBV (ab to HepB surface antigen and core antigen), HCV (HCV ab RIBA-II), HIV-1 & 2 (EIA), Treponema pallidum (rapid plasma reagin test). Stool: C diff (Toxin A or B (cytotoxin) detection), enteric bacterial pathogens (selective stool culture), ova/parasites (light microscopy) No antimicrobial therapy in previous 6 months</p>	<p>Fresh via NGT</p>	<p>time between stool collection and transplant not stated; 30g of stool blended with 150mls saline and filtered; 30mls infused via NGT</p>	<p>no bowel prep stated;30mls infused via NGT;omeprazole given prior to FMT; follow up methods not stated but retrospective analysis extracted from clinical record</p>
<p>18 19 20 21 22 23 24 25 26 27</p> <p>No antibiotics for 6 months. Blood for FBC, CRP, protein,creatinine, LFTs, HBV, HCV, HIV 1 &2, treponema. Stools for Cdiff, pathogens, OCP,</p>	<p>Fresh, within 6 hours colonoscopic</p>	<p>Stool obtained 6 or less hours prior to transplant. Homogenised in 100-200ml water.</p>	<p>Colonic lavage ith 4l PE solution.</p>
<p>28 29 30 31 32 33 34 35 36 37</p> <p>No antibiotics for 3 months. Excluded chronic gastrointestinal condirions, active peptic ulcer disease, GERD, IBS,IBD,polyps, mlaincancy. Blood for HABCV, HIV, Treponema, stool for culture, OCP, cryptosporidium, microsporidia, Cdiff</p>	<p>Fresh, colonoscope</p>	<p>Donors given 30ml MgOh evening before donation. Stools within 6 hours of passage blended with 100ml Nsaline and sieved for delivery.</p>	<p>Bowel prep for colonoscopy (not stated which), 4mg operamide either before or after FMT</p>
<p>38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60</p> <p>High risk behaviours, no antibiotics for 3 months, Blood for HIV, HABC, STDs, stooll for bacterial culture, OCP, Cdiff</p>	<p>Fresh, colonoscope (11); 1 nasoduodenal</p>	<p>Donor given mg citrate before. stool collected within 6 hours of precedure. 6-8 tablespoons to 1l tap water, shaken.</p>	<p>PEG bowel prep, 400-500 ml to TI/Right colon. Patients given 2 tablets of diphenoxylate/atropine. A week later 2 month course of Saccharomyces boulardii</p>

1 2 3 4 5 6 7 8 9 10	3 unselected. High risk behaviours, antibiotics in 3 months, blood for HIV, HABC, terponema, stool for Cdiff, bacterial culture, OCP, Giardia, Cryptosporidium,	Fresh, colonoscopy	Time between donation and colonoscopy not stated	On day of treatment patients given 2 imodium tablets 2 hours prior and 1 after. Bowel prep not recorded.
11 12 13 14 15 16 17	Selective based on discretion. Blood from some for viruses (HABC, HIV), stool from some for Cdiff and enteric pathogens	Fresh colonoscopy	Time between donation and colonoscopy not stated	PEG bowel prep. Some (not clear how many) had 2 imodium immediately after and then again 6 hours after FMT
18 19 20 21	Screened for occult infectious conditions and no abx use in preceeding 3 months	Fresh, Upper GI (NG or PEG)	30 g of donor stool in mixed in saline. 25mls given in an infusion.	Pre-treated with 3 days of vancomycin and proton pump inhibitor prior to procedure
22 23 24 25 26 27 28 29	No significant medical history, no antibiotics for prior six months. Donor feces were screened for enteric pathogens and blood was screened for antibodies to hepatitis A, B, and C; HIV; and Treponema pallidum within 2 weeks of donations	Fresh: 26 patients; Frozen: 23 patients. Administered by colonoscopy	30g of stool in 200mls of saline or glycerol. If frozen stored in -80C for up to 16 weeks.	Polyethylene glycol prior to procedure
30 31 32 33 34 35 36 37 38 39	Not reported	Fresh, both routes	Not reported	Not reported
40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Donor feces were screened for enteric pathogens and blood was screened for antibodies to hepatitis A, B, and C; HIV	Fresh via colonoscopy	Stool collected morning of transplant, filtered and mixed with saline. 250 - 400mls infused into patient.	Abx stopped 3 days prior to FMT

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16	Age range 18-50 years, BMI 18.5 - 25. No significant medical history, not pregnant, no antibiotics for prior six months. Donor feces were screened for enteric pathogens and blood was screened for antibodies to hepatitis A, B, and C; HIV; and Treponema pallidum within 2 weeks of donations. Donors refrain from common allergens for 5 days before donation.	Capsule (oral) frozen for mean of 113 days (range 30-252 days).	Each inoculum was prepared from the feces of a single donor. The final slurry was concentrated by centrifugation and resuspended in saline at one-tenth the volume. Fecal matter solution was pipetted into size 0 capsules (650 µL), which were closed and then secondarily sealed in size 00 capsules. Capsules were stored frozen at -80°C (-112°F) till use. A full treatment of 30 capsules contained sieved, concentrated material derived from a mean of 48 g of fecal matter (mean per capsule, 1.6 g; range, 1.0-2.05 g). Samples stored for 4 weeks without use to allow for retesting for HIV, hep B and C. (full screening and exclusion details given in appendix)	Abx stopped 48 hrs prior to FMT
17 18 19 20 21 22 23	Donor feces were screened for enteric pathogens and blood was screened for antibodies to hepatitis A, B, and C; HIV	Fresh. Upper GI in 13 patients, lower GI in 1 patient	Fresh stool sample (30-50 g) homogenized and mixed with water. About 120-180 ml of the suspension was instilled through NGT; 300-500 ml was administered if IMT was done via colonoscopy.	Abx stopped 24 hrs prior to FMT and given proton pump inhibitor prior to procedure
24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47	Excluded if abx within preceding 3 months. Exclusion criteria also included immunosuppressive agents, including chemotherapeutic agents; had known or recent exposure to HIV, hepatitis B or C; had a current communicable disease; participated in high-risk sexual behaviors; used illicit drugs; had a history of incarceration; traveled within 6 months to areas with endemic diarrheal illnesses; or had history of inflammatory bowel disease, irritable bowel syndrome or chronic diarrhea, gastrointestinal malignancy or polyposis). Blood tested for HIV, Hep A/B/C and stool for OCP and giardia antigen and cryptosporidium	Fresh (within 8 hours), colonoscopy	Suspended in saline, mixed by hand or blender, filtered and infused as 300 to 700 mls	Abx stopped 48 to 72 hrs prior to FMT. Bowel prep given before procedure
48 49 50 51 52 53 54 55	no abs for 3 months. No laxatives, history of constipation, no history of GI disease, travel in 3 months, not on immunosuppressives or chemo. No metabolic syndrome, autoimmune, atopic disease	Fresh (within 6 hours), colonoscopy	Fresh in blender 500ml N.saline, strained. 60ml drawn up in 8-9 syringes per patient.	Abs stopped prior to procedure.
56 57 58 59 60	screening as per FDA guidelines 2011	Frozen stool (> 2 months in 16 patients and <2 months in 4 patients), colonoscopy route in 19, jejunal	30g in 120ml N.saline, divided into 50ml aliquots	Not reported

Excluded if "history of antibiotic use" (time not specified), high risk behaviour, prisoners, GI disease.	Fresh. Initial FMT in 118(81%) colonoscopy, 13(9%) OGD, 3(2%)	Milk of magnesia to donors. 60-100g stool suspended in 300-500ml nsaline, mixed, sieved. 75-200ml for upper route (OGD, enteroscopy), 250-400ml colonoscopically,	Bowel prep given. Loperamide after FMT
Blood and stool screened for transmissible diseases	Fresh, given via a combination of jejunal and colonic route	25-30g of stool given as 180mls via enteroscopy and 270mls via colonoscopy	Not mentioned
Potential donors were accepted only if serum antibodies against HIV 1 and 2, hepatitis C virus, and hepatitis B surface antigen were negative, as were stool cultures for Salmonella, Shigella, Campylobacter, enterohemolytic Escherichia coli, and Clostridium	Fresh, given as enema (lower GI)	50g of fresh faeces prepared in an anaerobic cabinet by adding and stirring small portions of pre-reduced and pre-warmed (37 °C) sterile isotonic saline, to a total of 500 ml.	Not mentioned
Questionnaire addressing risk factors for potentially transmissible diseases. Donor feces were screened for parasites, including Blastocystis hominis and Dientamoeba fragilis; C.difficile, and enteropathogenic bacteria. Blood was screened for HIV; human T-cell lymphotropic virus types 1 and 2; hepatitis A,B, and C; cytomegalovirus; Epstein-Barr virus; Treponema pallidum; Strongyloides stercoralis; and Entamoeba histolytica. A donor pool was created, and screening was repeated every 4 months. Before donation, another questionnaire was used to screen for recent illnesses.	Fresh via nasoduodenal tube	Feces were collected by the donor on the day of infusion and immediately transported to the hospital. Feces were diluted with 500mls of sterile saline 0.9%. This solution was stirred, and the supernatant strained and poured in a sterile bottle. A mean (+SD) of 141+-71g of feces was infused. The mean time from defecation to infusion was 3.1+-1.9 hours	Bowel lavage with 4 liters of macrogol solution (Klean-Prep) on the last day of antibiotic treatment. Within 6 hours after collection of feces by the donor, the solution was infused through a nasoduodenal tube (2 to 3 minutes per 50mls). The tube was removed 30 minutes after the infusion, and patients were monitored for 2 hours. Patients kept a stool diary and were questioned about stool frequency and consistency, medication use, and adverse effects. Stool tests for C.difficile toxin were performed on days 14,21,35, and 70 and whenever diarrhoea occurred.
Volunteers were excluded for any significant past medical history or any use of antibiotics in the preceding 6 months. Initial screening using the American Association of Blood Banks donor questionnaire for exposure to infectious agents. Physical examination and general laboratory screening tests (within 30 days of donations). All results had to be within normal range for age and sex. Donor feces were screened for enteric bacterial	Frozen via colonoscopy or NGT	Donors were asked to take a dose of milk of magnesia the day before fecal collections to facilitate manipulation of the sample. A fecal suspension was generated in normal saline without preservatives, using commercial blender. Materials were passed through 4 sieves to remove particulate material. The final slurry was concentrated 3-fold by centrifugation and then resuspended in sterile saline with 10% glycerol added as a bacterial cryoprotectant. Inocula were then frozen at -80 C pending use. Each sieved inoculum was calculated to have been derived from approximately 41g of fecal material. Inocula were stored frozen for up to 156 days, range, 29-156 days; frozen material was thawed in a 37 C water bath, and then kept on ice until delivery.	Subjects assigned to colonoscopic administration underwent a standard bowel preparation with 4 liters of PEG solution, followed by endoscopic administration to the right colon of 90 cc thawed inoculum:further diluted to 250cc for adults and 160 cc for paediatric patients. Patients were given a single oral dose of loperamide at the time of procedure. Subjects assigned to NGT delivery of FMT were
Pre-medical examination was carried out with a questionnaire in order to rule out high-risk individuals (such as drug use, promiscuity, known illness, taking antibiotics or trips abroad in the past six months). Stool samples	Fresh stool delivered via nasogastric route in 15 patients and nasoduodenal route in 15 patients	60 grams, it was placed in 200 mL of mortar physiological saline (0.9%) and harvested. then the homogenate of 4 x 4 cm was filtered sterile gauze pads transferred to another vessel and finally were taken from the filtrate up to 100 ml syringe and given to patient within 6 hours.	Antibiotics were stopped prior to transplant and patients were given laxatives. Patients received both metoclopramide and high dose proton pump inhibitor on the day of the transplant.

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Total no of infusions	Define primary outcome
not explicitly stated. Data implies a single infusion on a single occasion for each patient	Not explicitly stated, but authors report outcome based on symptom resolution and / or CDI toxin negativity
NA	Clinical resolution of diarrhoea at 8 weeks
13/20 had 1 FMT; 6/20 had co-existent PMC and received infusions every 3 days until symptom resolution (4 had 2 infusions, 1 had 3 infusions and 1 had 4 infusions	Resolution of diarrhoea 10 weeks after the end of the treatments

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Not reported	Early Failure rate defined as non-response or recurrence of diarrhoea with either toxin or PCR positive CDI within 1 month of FMT
1 infusion via enteroscopy	not defined in paper but implied symptom free to end of follow up
1 infusion via gastroscopy or colonoscopy	successful treatment defined as no further contact with the clinic due to CDI symptoms within 80 days of FMT

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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17	4 of 43 had repeat infusion	Not specified
18 19 20 21 22	1 infusion via colonoscopy or 1 course of capsules.	Defined as cure but no time period given
23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41	Five patients underwent a second FT because of ongoing diarrhea; 3 had symptom resolution and 2 continued to experience diarrhea despite 2 FTs.	resolution of symptoms- no time period defined
42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	not explicitly stated but implies single infusion for all patients	Prevention of further CDI relapse and/or significant diarrhoea requiring vancomycin; time frame for outcome not stated

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 78 patients had single infusion; 12 patients had 2 infusions	response defined as absence of diarrhoea or marked reduction in stool frequency and without need for further antibiotics within 12 weeks after 1 or more FMTs
27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 1 infusion via colonoscopy	Resolution of diarrhoea without need for anti CDI therapy during 8 week follow up

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16	18 had single infusion; 2 had 2 infusions	Resolution of diarrhoea without recurrence of symptoms within 3 months of FMT
17 18 19 20 21 22 23 24 25 26 27 28	9 patients had single infusion, 1 patient had 2 infusions	Not defined in paper but implied symptom free to end of follow up
29 30 31 32 33 34 35 36 37	if no resolution of diarrhoea after 7 days post FMT then further enema give. Range given 1-10(46/94 had 1 FMT, 20/94 had 2 FMT, 17/94 had 3 FMT, 11/94 had 4 or more)	Cured following FMT if no recurrence of diarrhoea at 6 months follow up
38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	1, if no response at day 4, then further FMT and if no response then FMT or abx. Primary outcome based on up to 2 FMTs.	Clinical resolution of diarrhea without relapse at 13 weeks

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17	14/15 had 1 FMT;1/15 had 2 FMT	Not explicitly stated but implied that "cure" was no symptoms at follow up after 1 FMT
18 19 20 21 22 23 24 25 26 27	67 had 1; 3 had 2	Resolution diarrhea without a positive C difficile toxin stool test at 12 weeks
28 29 30 31 32 33 34 35 36 37	28 had 1; 3 had 2	Not defined.
38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	1 infusion in all but 1 patient who had repeat via ND route	No strict definition. Authors state : 'A successful treatment was determined by the resolution of diarrhea, a fall in white cell count, or absence of fever and an improvement in vital signs'.

1 2 3 4 5 6 7 8 9 10	1	Resolution defined as positive stools after FMT.
11 12 13 14 15 16 17	1	not defined in paper but implied symptom free to end of follow up
18 19 20 21	1	Resolution of diarrhea without recurrence within 60 days of FMT
22 23 24 25 26 27 28 29	1	Resolution of diarrhoea with a negative C. difficile toxin stool test at 3 months
30 31 32 33 34 35 36 37 38 39	1 infusion in 27 patients, multiple infusions in 4 patients	Resolution was defined as the absence of significant diarrhea (diarrhea as defined by at least three episodes per day) or a marked reduction in diarrhea not requiring antibiotic therapy.
40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	1	Clinical response was defined as absence of diarrhea, cramps, and fever within 3 to 5 days of transplant

N/A	Response defined as less than 3 bowel movements in 24 hrs
1 in 10 patients, 2 in 2 patients, and 3 in 2 patients received three FMTs	Defined as less than 3 loose bowel movements a day for 2 consecutive days after FMT and no need for further CDI therapy on day 7.
1 infusion in 75 patients, 2 infusions in 2 patients	Resolution without recurrence within 90 days including those that needed a second infusion or antibiotics
1 infusion	Primary outcome not defined
1 infusion in 17 patients, 2 infusions in 3 patients	Resolution of diarrhoea and/or absence of CDI toxin in stool as measured by PCR after at least 3 months follow up

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146 had one infusion, 12 out of 25 early recurrences had another	Initial Resolution of CDI symptoms with no recurrence after 12
1	Resolution of diarrhoea and disappearance of stool Cdiff toxin
1 in 22 patients and 2 in 1 patient	Resolution of diarrhoea in 3 days with no recurrence in 3 months
16 patients had 1 infusion; 3 who did not respond in this group had 2nd infusion.	Cure without relapse within 10 weeks after the initiation of therapy. For patients in the infusion group who required a second infusion of donor feces, follow up was extended to 10 weeks after the second infusion. Cure was defined as an absence of diarrhoea or persistent diarrhoea that could be explained by other causes with three consecutive negative stool tests for C.difficile toxin. Relapse was defined as diarrhoea with a positive stool test for C.difficile toxin.
20 patients in both study arms had one infusion (14 was cured after the first infusion (70%)). One patient in the NGT arm refused subsequent retreatment. The remaining 5 patients were given a second infusion (4 patients obtained cure after second infusion, resulting in an overall cure rate of 90%).	Clinical resolution of diarrhoea off antibiotics for C.difficile, without relapse within 8 weeks. For patients who required a second treatment dose, a follow-up was calculated starting at the time of the second administration.
1 infusion in 27 patients and 2 infusions in 3 patients.	Primary cure rate was defined as resolution of symptoms without recurrence within 6 weeks after a single FMT, while secondary cure rate was calculated

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Results	
Flow/loss of patients Response definition Data on each response definition (and definition of demoninator) % Notes	Outcome 1 infusion
<p>Overall response rate: 15/16 (94%). Pretreatment vm eliminated or reduced diarrhoea in most patients. 1/19 patients had missing documentation 2/18 patients died 14/16 patients submitted post transplant stool samples (20 samples total). The two non-submitted appeared to be diarrhoea free (upto 90 days). Response definition: c diff toxin negative. 13/14 had negative stool test for c.diff toxin 1/14 had relapse and positive c.diff toxin stoll test 17 days post transplant. Therefore response rates are: 92.9% (13/14) for those submitting a stool sample 81.2% (13/16) for those followed up who were still alive; with those not submitting a stool sample assumed worse case (ie. c diff. toxin positive) 81.2% (13/16) for those who provided a sample or died (assumed worse case- ie. c diff toxin positive) 72.2% (13/18) assuming those who died or did not submit a stool sample were worse case (ie. c diff. toxin positive). 68.4% (13/19) assuming those who died or did not submit a stool sample or had missing documentation were worse case (ie. c diff. toxin positive) As pateints were pre-treated with vm study authors state "<i>It was not possible to differentiate between patients whose colitis resolved as a result of their pretransplantation course of vancomycin and those with colitis improved as a result of stool transplantation itself</i>" although patients had previously had multiple ab treatments without overal success. There were no episodes of post-transplantation diarrhoea among the the 15 patients (c diff negative or non samply supplying) who survived the 90 day follow-up period. (unclear statement: not sure what total follow up period was after 90 days or whether this means during the 90 days).</p>	15/16 (94%)
<p>7/9 (77%) high dose and 7/10 (70%) low dose diarrhoea free at 8 weeks. Of the 5 non-responders 4/5 (80%) cured with high dose re-challenge. -94% secondary cure rate</p>	NA
<p>Primary end point defined as resolution of diarrhoea associated with C. diff infection 10 weeks after the end of treatment; in FMT group 18/20 (90%) achieved primary end point; In vanc group 5/19 (26%)patients achieved primary end point</p>	13/20(65%)

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<p>Breakdown cure rates from both derivation and validation cohorts: recurrent CDI - 357/403 (89%), severe CDI 10/40 (25%), severe-complicated CDI 8/19 (42%). Total cure rate 375/462 (81.2%)</p>	<p>not reported</p>
<p>12 patients treated but 6 month follow up only available for 11. Response rate 10/11 (91%) in patients with full follow up. Response rate 10/12 (83%) in all patients treated. In only one of 11 cases did the bacterial infection relapse, after a new cycle of antibiotic therapy to treat an urinary tract infection, without diarrhea.</p>	<p>10/12 (83%)</p>
<p>A total of 33 of 40 treatment episodes (83%) were successfully treated with FMT. In 29 of 40 treatments (73%) the first treatment was successful, with no documented recurrence of diarrhoeal disease within 80 days. Of the 11 patients failing to respond to the first instillation treatment, 6 patients received a second instillation, 4 of which were successful. Initially 38 patients given FMT via gastroscop (response to single infusion 28/38 (74%)) and 2 patients given FMT via colonoscopy (response 1/2 (50%)). 11 non-responders 6 were given 2nd FMT responses 3/4 (75%) via gastroscop and 1/2 (50%) via colonoscopy</p>	<p>29/40 (73%)</p>

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17	The overall rate of infection clearance was 41/43 (95%), as evidenced by symptom resolution and negative PCR testing for <i>C. difficile</i> toxin B after 2 months of follow-up. Response rate from fresh FMT was 11/12 vs 19/21 from frozen FMT	37/43 (86%)
18 19 20 21 22	Overall response rate: 41/43 (95%). Cure rate colonoscopy group 21/21 (100%) and 20/22 (91%) in capsule group.	41/43 (95%)
23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41	After FMT, 25 of 27 (93%) experienced clinical resolution. Of these, 22 resolved within 24 hours of transplant. Five patients underwent a second FMT because of ongoing diarrhea; 3 had symptom resolution and 2 continued to experience diarrhea despite 2 FMTs.	22/27 (81%)
42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	26 sequential patients follow up and analysis available for all. 24/26 (92.3%) achieved primary outcome;	24/26 (92.3%)

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<p>82 patients met inclusion criteria but analysis based on results of 80 patients as 2 lost to follow up (2 deaths so no 12 week follow up data fro these patients and excluded from final analysis); 80 patients in 16 centres had FMT for CDI with co-existing immunocompromise (36 IBD and on immunosuppression, 19 solid organ transplants, 3 HIV/AIDS, 7 cancer and treatment with chemo, 15 chronic illness); response defined as absence of diarrhoea or marked reduction in stool frequency and without need for further antibiotics within 12 weeks after 1 or more FMTs; cure after 1 infusion 62/80 (77.5%); cure after 2 infusions 70/80 (87.5%); if 82 patients included in analysis cure after 1 infusion is 62/82 (75.6%) or 2 infusions is 70/82 (85.3%)</p>	<p>62/80 (77.5%)</p>
<p>In the intention-to-treat analysis, 20 of 22 patients (90.9%) in the donor FMT group achieved clinical cure compared with 15 of 24 (62.5%) in the autologous FMT group (P = 0.042). Resolution after autologous FMT differed by site (9 of 10 vs. 6 of 14 [P = 0.033]). All 9 patients who developed recurrent CDI after autologous FMT were free of further CDI after subsequent donor FMT. Direct clinic follow up at 2 and 8 weeks</p>	<p>20 / 22 (90.9%)</p>

<p>20 patients analysed; Response defined as primary cure rate- no recurrence of symptoms of diarrhoea within 3 months of single FMT infusion; secondary cure rate was defined as no recurrence of symptoms within 3 months after 2 infusions of FMT; 9/9 community acquired CDI had single infusion with cure rate of 100%; 9/11 Hospital acquired CDI had single infusion with cure rate of 82%; 2 patients in the hospital acquired group had second infusion and cured so secondary rate in this group was 100%</p>	<p>18/20 (90%)</p>
<p>10 patients; response not explicitly defined but appears to be resolution of infection (how this determined is not stated); 9/10 had resolution, 1/10 had further FMT after relapse at 2 months following course of antibiotics.</p>	<p>9/10 (90%)</p>
<p>94 patients in total given FMT; response defined as no diarrhoea for 6 months post FMT; overall response to FMT alone was); 5/94 patients received responded to FMT and vancomycin combination giving a further increment in cure of 5.3%, giving an overall cure rate of 91.5%; 8 patients did not respond to FMT of which 6 died and included as FMT failures; 11 patients received 4 or more FMTs NB the authors state this cohort is an expansion of previously published series by Lee et al 2011 which included the same first 27 patients (are we double counting this?)</p>	<p>45/94 (47.9%)</p>
<p>Overall response as per primary outcome - up to two infusions (ITT) - 159/219 (73%).</p>	<p>113/219 (52%)</p>

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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16	11/15 were diarrhoea free during follow up of median 16 weeks (range 4 to 24 weeks). Follow up period not used to define response; Response rate 73.3% calculated on being diarrhoea free at follow up after single infusion	11/15 (73%)
17 18 19 20 21 22 23 24 25 26 27	Resolution of symptms during 12 weeks follow up in 66/70 (94%). 34/34 (100%) in non-027 CDI; 32/36 (89%) in 027-CDI. Of the 4 027-CDI all died 1.5-3 months after. One who refused colectomy, two of CDI, one with myelome reated uraemia. This patient was retreated with antibiotics for pneumococcal septicaemis and meningitis after 1st FMT	63/70 (90%)
28 29 30 31 32 33 34 35 36 37	Of the 30 patients who had diarrhoea 29/30 (97%) had improvement or resolution of diarrhoea. Median time to improvement 3 days. At 3 months 91% (21/23) had maintained improvement or resolution. Of those who had 2 had subtotal colectomies and second FMT via upper OGD. All three improved in 5 days; one had a recurrence.	26/30 (87%)
38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Overall cure rate: 12/12 (100%).	11/12 (92%)

20/20 (100%)	20/20 (100%)
19/20 (95%) responded to first treatment remaining symptom free for follow up of 6 months to 5 years. The one patient who did not respond was retreated after 5 months with same donor-immediately successful -so secondary cure rate 100%. 3 patients represented at 4months-6 years after but these were re infections following repeat treatment with antibiotics	19/20 (95%)
Overall response rate: 59/75 (79%). Response rate if patients only included if primary outcome and negative CDI toxin post FMT: 57/75 (76%). Secondary cure rate (patients failed FMT, but subsequently resolved diarrhea after a course of oral vancomycin): 68/75 (91%).	59/75 (79%)
Overall response rate: 47/49 (96%). Other response rates: FMT with fresh faeces, individual donor: 14/15 (93%). FMT with fresh faeces, universal donor: 11/11 (100%). FMT with frozen faeces, universal donor: 22/23 (96%).	47/49 (96%)
Overall response rate 27/31 (87%). If given via upper GI route 3/9 (33%). If given via lower GI route (including those that didn't respond to upper GI route) 24/28 (85%).	24/31 (77%)
Overall response rate 12/12 (100%). If exclude pre-transplant CDI toxin negative patients: 9/9 (100%)	12/12 (100%)

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8	Overall response rate 18/20 (90% (95%CI 68-98%)) at 8 weeks. Initial response rate 14/20 (70%), those who	
9	failed retreated after average of 7 days.	NA
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18	Overall response rate 11/14 (79%). 8 remained cured at 100 day follow up (3 deaths from underlying	
19	cancer).	8/14 (57%)
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35	70/77 (91) met primary outcome at 90 days.	70/77 (91%)
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50	20/22 (91%%) responded at 3 months. 2 that relapsed had a further infusion (one by upper GI route) with	
51	both responding	19/22 (86%)
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57	20/20 (100%) overall response rate	17/20 (85%)
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1 2 3 4 5 6 7 8 9 10	Initial Resolution of CDI symptoms with no recurrence after 12 weeks-121/146. 25 developed recurrence within 12 weeks. 12 had more than 1 FMT but with antibiotics therefore not included in the analysis	121/146 (82.9%)
11 12 13 14 15 16 17	27/27 (100%) at 1-3 month after FMT.	27/27 (100%)
18 19 20 21 22 23 24 25	Overall response rate: 16/23 (70%)	15/23 (65%)
26 27 28 29 30 31 32 33 34 35 36 37 38 39 40	The primary end point was cure without relapse within 10 weeks after the initiation of therapy. For patients in the infusion group who required a second infusion of donor feces, follow up was extended to 10 weeks after the second infusion. The secondary end point was cure without relapse after 5 weeks. Cure was defined as an absence of diarrhoea or persistent diarrhoea that could be explained by other causes with three consecutive negative stool tests for <i>C.difficile</i> toxin. <i>Relapse was defined as diarrhoea with a positive stool test for C.difficile toxin.</i> An adjudication committee whose members were unaware of study-group assignments decided which patients were cured.	13/16 (81%)
41 42 43 44 45 46 47 48 49 50 51 52 53	The primary endpoint was clinical resolution of diarrhoea off antibiotics for <i>C.difficile</i> , without relapse within 8 weeks. For patients who required a second treatment dose, follow-up was calculated starting at the time of the second administration. Resolution of diarrhoea was defined as <3 bowel movements per 24 hours. Secondary endpoints included improvement in subjective well-being per standardized questionnaire and presence of adverse events.	14/20 (70%)
54 55 56 57 58 59 60	With the use of the nasogastric tube, the primary and secondary cure rate was 80% and 93.3%, respectively. When given via nasoduodenal route, the primary cure rate was 100%. This results in an overall primary cure of 90.0% and a secondary cure rate of 96.7%.	27/30 (90%)

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1 or more infusions	Total follow up period	Adverse events - mild	Adverse events - serious	1. Were selection/eligibility criteria adequately reported?
15/16(94%)	90 days post transplantation, assessed by examination of medical records.	no mention	2 patients died between transplant and follow up stool testing for c.diff toxin. One had end stage renal disease and was receiving peritoneal dialysis. Developed peritonitis 3 days post transplant and died shortly after. The second patient died 14 days post transplant of pneumonia complicating COPD and atherosclerosis (study authors state: " <i>the possibility that the use of the nasogastric tube contributed to the peritonitis cannot be excluded</i> ")	yes
19/20 (95%)	Not reported	None reported	none reported	yes
18/20(90%)	primary end point 10 weeks after end of treatment	none in vanc group; FMT group 19/20 had transient diarrhoea, 12/20 had abdominal pain and bloating	2 deaths in FMT arm	yes

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18 19 20 21 22 23 24 25 26 27 28 29	10/12 (83%)	6 months	Not reported	None	yes
30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	33/40 (82.5%)	80 days	Not reported	5 deaths; The remaining 5 patients had serious co-morbid conditions and died 3 weeks–2 months after the FDIT procedure. Two of these 5 patients were seriously weakened after long lasting diarrhoeal disease, 1 being the oldest patient in the series (94 y). Additionally, 1 patient had advanced stage Wegener's granulomatosis with complications, 1 patient had acute myelogenous leukaemia requiring repeated antibiotic treatment for other infections, and 1 patient with advanced cardiovascular disease developed fulminant colitis and underwent subtotal colectomy, and subsequently died of complications.	yes

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9	41/43 (95%)	12 months	Not reported	Not reported	yes
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18	41/43 (95%)	Not specified	Transient nausea and vomiting	None	yes
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32	25/27 (93%)	mean follow-up at 427.3 days after transplant.	Not reported	Not reported	yes
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46	24/26 (92.3%)	follow up mean 10.7 months ranged from 2-30 months	mild diarrhoea post FMT in 3 patients	no serious adverse events	yes
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70/80 (87.5%)	minimum of 12 weeks required; mean follow up 11m (range 3-46m)	self limited diarrhoea in 3, fever in 1, bloating and abdo discomfort in 3, hip pain in 1, Crohn's flare in 1, Pertussis in 1, nausea in 1, minor mucosal tear at colonoscopy in 1	deaths- 1 due to pneumonia, 1 due to aspiration at time of colonoscopy; hospitalisations- 1 due to fever and encephalopathy, 1 due to abdo pain after FMT, 3 due to IBD flare, 1 colectomy, 1 hip fracture, 1 influenza, catheter infection	yes
21 / 22 (90.9%)	8 weeks for efficacy, 6 months for safety	Chills were reported more frequently after autologous than donor FMT (P = 0.053). Rates of other solicited AEs (fever, abdominal pain, bloating, nausea, vomiting, diarrhea, flatulence, anorexia, and constipation) did not differ significantly between groups.	There were no SAEs related to FMT.	yes

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20/20 (100%)	minimum of 6 months (range not stated)	self limited diarrhoea in 4; abdominal pain in 3; nausea in 2; fatigue 13	none stated	yes
10/10 (100%)	median duration of follow up 44 days (range 13-700 days)	vomiting post FMT in 1; mucoid stools for 2 days after FMT	none stated	yes
81/94 (86.2%)	6-24 months	10% had transient constipation and flatulence post FMT	6 deaths due to critical illness, not felt to be due to FMT or CDI directly but these 6 are included in the 8 who failed to respond overall	Yes
193/219 (88.1%)	13 weeks	Transient diarrhoea (70%), abdominal cramps (10%), nausea (5%) in 24 hours post FMT; constipation (20%) and flatulence (25%) in follow up period	19 deaths in total 13 week study period (unrelated). 12 patients required hospitalization because of illnesses unrelated to FMT	Yes

12/15(80%)	median 16 weeks (4 weeks to 24 weeks) not predefined	none	none stated	Yes
66/70 (94%)	1 year. 4 with initial favourable response had relapse after receiving antibiotics. 2 of these were successfully treated with FMT; 2 with recurrent antibiotics for CDI	None reported	None related to FMT	Yes
29/30 (97%)	1 year 6 out of 6 maintained improvement	Not reported	Micro-perforation but not related to FMT. One death at 3 months after due to metastatic pancreatic cancer.	Yes
12/12 (100%)	No recurrences within 90 days of FMT. Total follow up from 2 to 29 months	None reported	None related to FMT	Yes

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20/20 (100%)	Follow up mean 3 months (range 0-10)	1 pain/nausea after colonoscopy, 1 continued diarrhoea (CDIFF neg) ? Bile salt malabsorption after cholecystectomy, 2 transient bloat/ cramps	1 perforation related to colonoscopy sealed with clip	Yes
20/20 (100%)	6 months to 5 years	None reported	none reported	Yes
59/75 (79%)	60 days	None	None	Yes
47/49 (96%)	All followed up for 12 weeks and 42 patients followed up for 1 year	Mild transient fever in 2 (frozen FMT)	3 deaths (unrelated)	Yes
27/31 (87%)	Mean 9 months (range 2-24)	Worsening arthritis, constipation, diarrhoea, urinary tract infection.	5 deaths; not attributed to FMT. Stroke, myocardial infarction, aspiration pneumonia, hospitalisation for CDI not as a consequence of FMT.	Yes
12/12 (100%)	3 weeks to 8 years	Not reported	None	Yes

18/20 (90%)	Primary outcome based on 8 weeks however patients followed up for 6 months	Transient abdominal cramping and bloating in 6 patients (30%) that resolved in 72 hours	1 hospitalised with a documented relapse of severe CDI after taking 15 capsules but had successful treatment after receiving the remaining 15 capsules after discharge. No other severe adverse events (grade 2 or above).	Yes
11/14 (79%)	100 days	Not reported	4 deaths within 30 days of FMT unrelated to FMT.	Yes
70/77 (91%)	Minimum 90 days, but median 17 months	None reported	4 patients reported a new medical condition after FMT (peripheral neuropathy, Sjogrens, ITP and rheumatoid arthritis)	No
21/22 (95%)	Range 2 weeks to 17 months with ave length 3 months	pain in one patient	none	No
20/20 (100%)	Minimum 3 months (but up to 14 months)	None	None	No

121/146 (82.9%)	mean follow up 12.3 (range 1-48) months	CDI-negative diarrhoea in 7(4.8%) and constipation in 4(2.7%)	within 12 weeks-6 hospitalizations due to CDI and/or FMT. One debilitated	No
27/27 (100%)	Ranged from 9.7 -34 months (mean 20.6 months)	Low grade fever (18.5%) and bloating (11.1%)	None	Yes
16/23 (70%)	Median follow up of 18 months (range 0-201 months)	Nil	Nil	Yes
15/16(94%)	After first infusion at 10 weeks; follow up was extended to 10 weeks after the second infusion	94% immediate diarrhoea, 31% abdominal pain with cramping, 19% belching - resolved within 3 hours. During follow up 3 patients had constipation (19%). 2 patient had infections: one patient with recurrent UTI had UTI	1 hospitalisation for symptomatic choledocholithiasis (unrelated)	Yes
18/20 (90%)	8 weeks follow up for primary response	Mild abdominal discomfort and bloating in 4 patients (20%). One child treated colonoscopically had a transient fever of 38.8 C on day 2 that resolved spontaneously	2 deaths (unrelated), 1 new diagnosis of malignancy (unrelated), 1 hospitalisation for Fournier gangrene (unrelated)	Yes
29/30 (97%)	6 weeks	Nausea in one patient. Nil else	Nil	Yes

CRD criteria			
2. Were patients recruited consecutively?	3. Were patients recruited prospectively?	4. Was loss to follow-up reported or explained?	5. Were at least 90% of those included at baseline followed up? Record all possibilities
yes	Yes	Yes	Y and N 18/19 (95%); one of 19 receiving stool excluded due to missing documentation. 16/19 (84%); a further two did not submit stool sample for primary outcome of c diff toxin testing (determined to be diarrhoea free at 90 days)
yes	yes	no-abtstract	yes
yes	yes	yes	yes

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yes	No	No	Not known
yes	No	No	Yes
yes	NO	NO	No FU varied significantly

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yes	No	No	Yes
yes	yes	no	yes
yes	No	No	Yes
yes	yes	no loss of follow up	yes 100%

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yes	no	yes	yes. 2 patients excluded from final analysis as lost to follow up did not have 12 week follow up data.
yes	Yes	Yes	Yes

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9	yes	no	no loss of follow up	yes
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22	yes	no	no loss of follow up	yes
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yes	no	no loss of follow up	yes
No;retrospective review	No	No loss to follow up	Retrospective review
Yes	no	No loss to follow up	No. Although stated in results that none developed recurrence at 90 days from table patient 12 only followed for 2 months
yes	no	yes	yes

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13	Yes	No	No follow up very variable	yes
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19	Yes	No	Yes	Yes
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25	Yes	No	Yes	Yes for 12 weeks
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34	Yes	No	No	No FU varied significantly
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42	Yes	No	No	No FU varied significantly
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Yes	Yes	Yes	Yes (100%)
Yes	No	No	Yes
Yes	No	Yes	Retrospective data series based on questionnaires filled by patient or relative
yes	No	No	Doesn't state
Yes	Yes	No	Yes

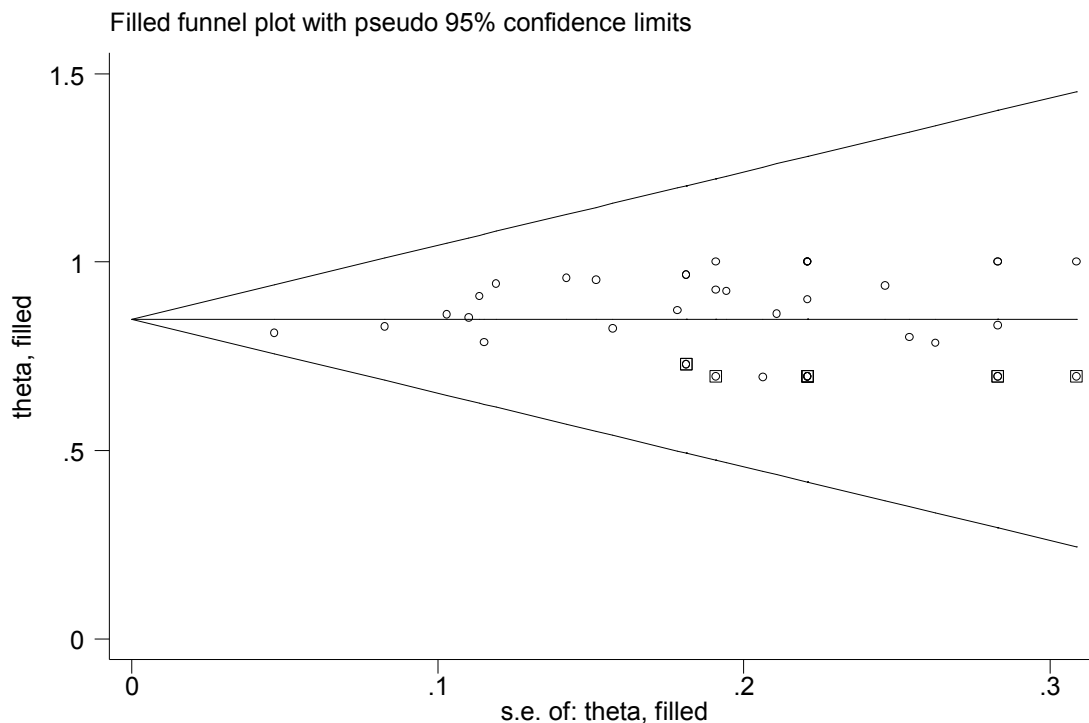
view

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3	yes	No	NO	No
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7	Yes	Yes	No	Yes
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12	No	No	No	No
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29	Yes	Yes	Yes, (reported)	Yes
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47	Yes	Yes	None lost to follow up (reported)	Yes
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56	Yes	No	None lost to follow up (reported)	Yes
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Supplement 2. Funnel plot of the estimated proportion responding to treatment (ovals) in each included study (y-axis) versus it's standard error (x-axis). Plot includes 'studies' added (crosses) by the Duval and Tweedie nonparametric "trim and fill" method of accounting for small study effects in a random effect meta-analysis model

Case series – multiple infusions



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For Peer Review

EMBASE - Search strategy

1. exp Clostridium difficile infection/ or exp Clostridium difficile toxin B/ or exp Clostridium difficile toxin A/
2. clostridium difficile.ti,ab.
3. c diff*.ti,ab.
4. (CDAD or RCDI or CDI).ti,ab.
5. pseudomembranous.ti,ab.
6. exp pseudomembranous colitis/
7. (antibiotic* adj2 (diarrhea or diarrhoea or colitis)).ti,ab.
8. (FMT or HPI).ti,ab.
9. ((fecal or faecal or feces or faeces or stool or microbiota) adj2 (transplant* or infus* or transfus* or implant* or instil* or donat* or donor* or reconstitut* or therap* or bacteriotherapy)).ti,ab.
10. (fecal or faecal or feces or faeces or stool or microbiota).ti,ab.
11. transplant*.ti,ab.
12. exp transplantation/
13. 8 or 9
14. 10 and (11 or 12)
15. 13 or 14
16. or/1-7
17. 15 and 16

MEDLINE - Search strategy

1. Clostridium difficile/
2. clostridium difficile.ti,ab.
3. c diff\$.ti,ab.
4. Enterocolitis, Pseudomembranous/
5. (antibiotic\$ adj2 (diarrhoea or colitis)).ti,ab.
6. (antibiotic\$ adj2 (diarrhea or colitis)).ti,ab.
7. pseudomembranous.ti,ab.
8. (CDAD or CDI).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
9. RCDI.ti,ab.
10. Clostridium Infections/
11. FMT.mp. or HPI.ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
12. ((fecal or faecal or feces or faeces or stool or microbiota) adj2 (transplant\$ or infus\$ or transfus\$ or implant\$ or instil\$ or donat\$ or donor or reconstitut\$ or therap\$ or bacteriotherapy)).ti,ab.
13. (fecal or faecal or feces or faeces or stool or microbiota).ti,ab.
14. (transplant\$ or infus\$ or transfus\$ or implant\$ or instil\$ or donat\$ or donor or reconstitut\$ or therap\$ or bacteriotherapy).ti,ab.
15. Transplantation/
16. Transplants/
17. 11 or 12
18. 14 or 15 or 16
19. 13 and 18
20. 17 or 19
21. or/1-10
22. 20 and 21