APPENDIX A. SEARCH STRATEGY

Database: Ovid MEDLINE(R)

Search Strategy:

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1 exp Feces/ or (fecal or faecal or feces or faeces or stool or microbiota).mp.

2 (donor or transplant$).mp. or exp Transplants/

3 1 and 2

4 exp Clostridium Infections/ or exp Clostridium difficile/ or exp Enterocolitis, Pseudomembranous/ or (c difficile or c diff or clostridium difficile).mp.

5 3 and 4

6 limit 5 to (english language and humans and yr="1980 -Current")

APPENDIX B. PEER REVIEW COMMENTS/AUTHOR RESPONSES

REVIEWER COMMENT	RESPONSE
1. Are the objectives, scope, and methods for this review clearly described?	
Yes	No response needed
Yes	No response needed
Yes. This review aims to answer questions regarding the efficacy of fecal microbiota transplantation (FMT) for initial, recurrent or refractory C difficile infection (CDI) compared to standard therapy as well as potential harms and patient acceptability. The Methods (source of data and data abstraction/assessment/analysis) are clearly described.	Thank you
Yes; they were well spelled-out.	Thank you
Yes	No response needed
Yes. The purposes of the review, as indicated by the "Key Questions," are specific and are clearly important.	Thank you
Yes	No response needed
2. Is there any indication of bias in our synthesis of the evidence?	
No	No response needed
No	No response needed
No. In general your synthesis of the evidence was accurate and did not appear overly supportive or opposed to FMT. The overwhelmingly positive results from these numerous series and the clinical experiences of many physicians who've used FMT are admittedly "low quality" evidence. Unfortunately, RCTs of this therapy are difficult to perform and, as the use of FMT has expanded rapidly over the past few years, finding subjects willing to be enrolled in a placebo-controlled study will become increasingly difficult. Meanwhile, the large number of patients with recurrent C. difficile infection who've failed standard therapies should be offered FMT based on the evidence we have so far. Inclusion of some of the data on MECHANISMS of effect would be a valuable addition to this systematic review. Researchers have done sequencing of the fecal microbiome of FMT treated patients before and after FMT. Recurrent C. difficile patients have characteristic low diversity of species and lack normally dominant populations of anaerobes. Post-FMT, this dysbiosis is remedied and this coincides with clinical cure. Papers that I suggest including discussion of: Khoruts A. et al. J Clin Gastroenterol; 2010 & Song Y, et al. PLoS One 2013	We have included a brief discussion on the mechanism of FMT in the introduction, including the suggested references.
No. The reviewers took care to point out limitations/possible sources of bias in the available literature	Thank you.
No. There is no bias, although systematic review is obligatorily affected by publication bias.	No response needed
No. Very cautious.	No response needed

Possibly. I believe that some of the authors have previously submitted a letter of intent for a VA CSP on FMT. This raises some concern that the authors might use the ESP process to try to impact funding decisions for their grant proposal. Therefore, I suggest that the ESP leadership consider whether or not further review or action is needed. Specific lines that suggest bias on the part of the authors include: Page 3, line 2: why do they describe the RCT as "one small high risk of bias RCT"? Later, they study is described as "moderate quality" (page 14, line 6). Page 4, line 36: they call for more RCTs. This may be completely appropriate, but is also self-serving and leads the reader to wonder if they would have made the same recommendation if they weren't trying to get funding for an RCT. Page 10, lines 14-17: they say that the strength of evidence is insufficient or low at best but seem to be ignoring the RCT here. It is not clear why the RCT is not included in this section. Page 33, lines 7-9: again, they call for more RCT's. The description of the RCT here and earlier in the review focus on the low response to antibiotics. The study was stopped early because a review by the data monitoring committee felt that they should (or perhaps I don't fully know the story). If it was scientifically inappropriate to stop the study, then they have a case. But if it was deemed unethical to continue the study due to a dramatic difference, shouldn't the focus be on that fact? Page 34, lines 9-14: it is unlikely that the emergence of more virulent or aggressive strains would lead to lower responses with standard therapy, right? So the argument about historical controls is not bolstered by this statement. Page 34, line 22: The urgent call for RCTs can be self-serving here.	Regarding potential COI. We thank the reviewer for highlighting this point and agree that we should disclose the information noted. We take real or potential COI very seriously as ESP reports must be free of significant conflict to be credible and useful for practice and policy. After discussion with ESP leadership we agree that transparency would be enhanced if we include notation that Drs. Drekonja and Shaukat have submitted a proposal to VA-CSP for a randomized trial assessing FMT: "The Veterans Affairs Fecal Microbiota Therapy Trial for Recurrent Clostridium difficile Infection: A Planning Request for a VA Cooperative Study" The LOI proposes a blinded randomized controlled trial to compare FMT (via enema) to a placebo enema, both administered as an adjunctive treatment after a standard course of oral fidaxomicin (10 days) for recurrent CDI, for efficacy in preventing subsequent episodes of recurrent CDI. We now include this disclosure information in the Preface. Of note, Dr. Drekonja had previously submitted a similar proposal that was not approved for VA planning. Subsequent to our being awarded the contract for, and during the conduct of, the FMT ESP review Drs. Drekonja and Shaukat were informed of an opportunity for additional FMT studies through VA-CSP and encouraged by this reviewer to submit a revised proposal for consideration. Drs. Drekonja and Shaukat did this. and have not yet received reviewer comments or funding decisions. Page 3: The discrepancy was an error. We apologize and have corrected this so that the study is appropriately rated as moderate quality and as moderate risk of bias. Study quality and strength of evidence is assessed solely by our ESP core staff who are methodologically trained in these assessment methods. Our methodology is consistent with that widely used in the ESP and the AHRQ-EPC program. Content collaborators (in this case Drs. Shaukat, Drekonja, Reich and Gezahegn) do not perform these assessments. We make them aware of our findings and discuss our rationale. We routinely employ 2 individuals (Dr. Greer and Mr. MacDonald to independently assess study quality and overall strength of evidence). The ESP director reviews and resolves through discussion any discrepancies. Page 4: Please see our comment above regarding assessment methods for study quality and strength of evidence. We continue to believe that the current evidence is insufficient to fully address the effectiveness and comparative effectiveness of FMT. Randomized controlled trials are the highest quality studies to accurately assess effectiveness and comparative effectiveness. We have further refined our future research needs section to identify specific gaps that might be addressed by RCTs as well as other potential study designs that are needed to close additional gaps in knowledge. Page 10: We have included mention of the 2 RCTs in this sentence but strength of evidence would typically be considered low even taking into account the contributions of the 2 RCTs. Page 33: Information about the early stopping of the RCT has been added. Page 34: We have clarified the statement about historical controls. Page 34: We have deleted the word "urgent" and modified the research needs sections of both the Executive Summary and the full report.

3. Are there any published or unpublished studies that we may have overlooked?	
No	
The review is complete for the time period studied. However, there is a paper published subsequent to the review period, which is a small (n=20), randomized, nonblinded trial of FMT using frozen stool comparing delivery via NG tube to delivery via colonoscopy (Youngster I et al. Clin Infect Dis 2014 Apr 23; epub ahead of print).	Thank you for the suggested reference. We have added this paper.
Yes. Key Question #1 (recurrent CDI by colonoscopy) Rohlke F, Surawicz C, Stollman N. Fecal Flora Reconstitution for Recurrent Clostridium difficile infection: Results and Methodology. J Clin Gastroenterol 2010;44:567-70. Key Question #4 (harms) Our paper was recently accepted and would be an important addition to your safety discussion. In this multicenter series of 80 immunocompromised patients treated with FMT and at least 12 weeks of post FMT follow up, there were no infections transmitted. Kelly C. Ihunnah C. Fischer M, et al. Fecal Microbiota Transplant for Treatment of Clostridium difficile Infection in Immunocompromised Patients. Am J Gastro Accepted 2014. This data was also presented orally at the American College of Gastroenterology 2013 meeting in San Diego	Thank you for the suggestions. KQ#1 We have added the Rohlke data (and deleted the Brandt paper which included some patients from the Rohlke series). KQ#4 We have added the Kelly 2014 paper to the report.
No	No response needed
Yes. Yoon et al. J Clin Gastroenterol 2010; 44; 562-66	We have added the Yoon data (and deleted the Brandt paper which included some patients from the Yoon series).
Not sure. This web site (section on C diff in this author's briefing) may be worth considering: http://haicontroversies.blogspot.com/2014/05/the-year-in-infection-control-2014.html.	Thank you for the suggestion. Our review protocol specifies that we include data from peer-reviewed journal publications.
The authors may wish to include this paper: Kelly et al. "Fecal Microbiota Transplant for Treatment of *Clostridium difficile* Infection in Immunocompromised Patients." *The American Journal of Gastroenterology*. advance online publication 3 June 2014; doi: 10.1038/ajg.2014.133.	Thank you for the suggested reference. We have added this paper.
No	
4. Please write any additional suggestions or comments below. If applicable, please indicate the page and line numbers from the draft report.	
Well done and thorough review and interpretation of peer reviewed published literature on FMT. I would recommend that the authors provide distinguishing definitions for recurrent CDI and refractory CDI.	Thank you for the suggestion. We have added definitions in the Methods section where we describe our Population.
It is unclear to me why the event rate for the VanNood trial is cited at 0.81 since the overall rate of cure was >0.90 when patients who received >1 FMT were included. All of the patients had received multiple courses of antibiotics, so it could be argued that FMT is being held to a higher standard. This may be important because unlike a drug, which is highly standardized, human stool is not, and it may be that a small fraction of donors do not have the flora necessary to cure C. difficile, and subsequent transplant with a different donor may be curative. This phenomenon is seen in clinical practice.	Patients in the control arms of the van Nood trial were considered to have failed after a single course of antimicrobial therapy, and were then offered treatment with donor feces off protocol. Thus, we believe that it is most appropriate to apply the same criteria for FMT (assessment of the primary endpoint after one treatment course). Otherwise, the comparison becomes biased, in that one treatment (FMT) is allowed to have 2 attempts at success, whereas the control treatments are allowed only one. We do separately report the success rates observed after multiple attempts of FMT, which we think conveys more information to our readers.

Page 18 lines 24-28. Note: Patients included in the Brandt series from 2012 (long-term follow up study) INCLUDED overlap of cases reported in Mellow 2011, Kelly 2012, Yoon 2012 AND Rohlke 2010. It would be better to analyze each of these series individually (which have more complete data on these patients) rather than Brandt's long term f/u study (which pools all of these other studies). The question of FMT for severe/complicated CDI comes up very frequently. There is much less literature to support use of FMT in these severe and/or complicated cases. You included some of this in with the "refractory" efficacy discussion (Weingarden 2013), but it should really be a separate discussion and analysis. Weingarden 2012, Neemann K, et al. Transpl Infect Dis 2012 You DM, et al. Ann Intern Med 2008 and Aroniadis O, et al. DDW 2013 (oral presentation and abstract) are other cases/series that specifically were performed for severe disease. In Research gaps/future research (page 34) you could include list of ongoing clinical trials (clinicaltrials.gov), including a double blind-sham controlled RCT of FMT via colonoscopy being conducted at Brown (PI-Kelly) and Montefiore (Brandt).	Page 18 Thank you for the suggestions. We have deleted the Brandt series and now report each of the series individually. We agree that the question of FMT for severe/complicated CDI is common. We did not specifically create such a category for analysis, but note that the reports identified also are described as being "refractory to medical therapy" (You 2008), and "this patient's refractory CDI" (Neeman 2012). Thus, we believe that this is an appropriate place to discuss these cases. The cases presented in You 2008 and Neeman 2012 are briefly discussed, but since they are single case reports they did not meet our inclusion criteria. Similarly, the Aroniadis abstract is not included since we did not include unpublished data. We were unable to locate the citation for Weingarden 2012. We have added a list of ongoing trials from clinicaltrials.gov.
- Is there a specific microbiota population dynamics reference for p6/line 41-end of paragraph (post-CDI treatment microbiome perturbations)? - It may be useful to include references regarding resilience of microbiota post-antibiotic treatment or in setting of C. difficile e.g. a C. difficile/FMT microbiota dynamics study by Song et al (PLOSOne 2013)) - It could also be helpful to specifically invoke the term microbial diversity in discussing alteration of the gut microbiome.	The issue of microbial diversity has been added to the executive summary.
In general, the document is very well-written and provides an exhaustive (perhaps a bit too exhaustive) review of the literature. Specific comments follow: - The review should compare and contrast its findings more clearly with the meta-analysis by Kassam et al. Am J Gastro 2013. In this study, the RCT by van Nood was not included but the systematic review included 273 patients with pooled resolution rate for CDI of 89%, and lower route FMT performing better than upper route FMT (91% vs 80.6%). - Key question 3 probably does not merit equal footing as a "key" question such as FMT for recurrent or refractory CDI. The scarcity of pertinent literature illustrates this, and standard of care is specific antibiotic therapy. - The van Nood RCT, despite its limitations, is still the only RCT available, and is referred variably in the review as low quality, moderate quality, and high risk of bias. The quality description should be consistent, and the RCT provides valuable information despite its limitations and the fact it was stopped early because most patients in the control arms developed CDI recurrence. Furthermore, the RCT used upper route FMT in its active arm, which is probably less effective than lower route FMT based on Kassam meta-analysis results and less desirable by patients. Overall, I think the review needs to state more explicitly that the pooled literature shows that lower route FMT particularly colonoscopy is associated with very high-about 90%- cure rate for recurrent CDI. - Data regarding long-term safety of FMT are lacking, and this should be better highlighted in KQ4, particularly in the summary statements. This is probably a more relevant question than short-term adverse events (which are otherwise well detailed in the document). - A relevant point is to address is effectiveness of FMT based on CDI severity/C difficile strain (specifically the virulent NAP1/027 strain). This is addressed in the study by Mattila et al. - FMT has been used for a variety of indications unrelated to CDI which are probably beyond the scope of this review. It could be worth mentioning this in the preamble.	Since the only trial that directly compared to methods of transplantation demonstrated no significant difference, we are hesitant to endorse one route of administration over another based on overall success rates. We have provided the overall success rates for each route, but again caution that direct comparisons are difficult to make between studies. We have clarified this in the executive summary and in the results section. The Key Questions were developed *a priori* and therefore we present the available evidence on FMT for recurrent or refractory CDI We have corrected the discrepancy on the reporting of the risk of bias of the van Nood RCT. We rated the study as moderate risk of bias. See comment above regarding upper route vs. lower route. We have added a statement regarding the lack of long-term safety data to the relevant section. We have added a statement about *C. Difficile* strain to the results from the Matilla et al. study. We agree that it is beyond the scope of this review, and since CDI is the only indication for FMT for which the FDA does not require an investigational new drug application, we opted to not discuss such investigational uses

Figures 2, 3, and 4 should probably be changed to go from 0 to 1 not from -1 to 1 because the data represent rates, and rates can't be less than zero. If I'm misunderstanding the data please ignore this comment.	Your understanding of the data is correct. We are unable to correct this with the software we have available to generate the plots.
- The authors do a nice job describing the response rates with FMT. However, there is little to no discussion of the expected rate of response with additional courses of antibiotics. There is only a brief mention of this toward the very end of the document, other than some mention that the response rate to antibiotics in the RCT was lower than expected. It seems that some additional data on the response rate with antibiotics would be appropriate to put in context the results with FMT in the case series. For example, if studies of antibiotics show 75% response rates, then the FMT results are not very impressive. But if the response rates are around 30%, then the FMT results seem more impressive. - The authors state that the RCT on FMT was stopped due to a low rate of response to antibiotics in the control group. This statement only tells half the story. The study was not stopped simply due to a low response rate in the control group. The study was stopped because a planned interim analysis showed a significant difference, which required the data safety monitoring board to terminate the study early. The statistical methods used in this study are rigorous and the authors of the ESP should not downplay the dramatically significant results here. The authors need to be careful in how they describe this study so as not to bias the readers, or the conclusions of the ESP analysis. - The section on side-effects doesn't review the potential adverse events that were summarized earlier in the document. I wonder why the authors didn't simply put all of the adverse events in this section, rather than make the reader look through the entire document.	We have included data regarding the expected rate of response to additional antibiotic courses in the introduction. -As described in the online appendix to the article by van Nood et al., the interim analysis was not planned, but rather was requested by the principle investigator when multiple individuals involved with the trial became aware of an "(unexpected) extremely low response rate in the 2 control arms, which seemed much lower than the 60% used in the sample size calculation. The principle investigator subsequently requested the data safety monitoring board (DSMB) for advice." We believe that our characterization of the study is accurate. We have clarified that this discussion is regarding potential side effects beyond those observed and reported in the section on harms. Since much is written about these potential harms, and they also may be relevant with regard to future FDA regulations, we believe that a discussion of these potential harms is appropriate in the discussion section.
One major comment is that the document doesn't review the data on the expected "cure" rates with antibiotic therapy. Given that there is only one RCT of FMT vs. antibiotics and the rest of the data is case-series, it would seem appropriate to include a discussion of the effectiveness of antibiotics for recurrent CDI. This can put the case-series data in perspective (acknowledging the limitations of historical controls). The data on this topic are only briefly mentioned on page 33, lines 11-15. Page 2, line 30-34: why did the initial search miss those 15 articles? That is >50% of the included articles and is concerning. Minor comments:) Page 1, line 22: add "cases" after "500") Page 1, line 23: add "been reported" after "have") Page 11, figure 1: under "Excluded", I would suggest changing the order of the third bullet to state "Not case report with adverse event or case series" since case series don't need adverse events to be included) Page 17, line 19: suggest expanding on the case of possible peritonitis and pneumonia) Page 22, line 31: should it read "with only two OTHER of the six…"?) Page 29, line 24: why not move all discussion of harms into this section so they are all described in one place in the review?) Page 38, line 34: "toward" is misspelled	We have added information on expected "cure" rates with antibiotic therapy. Please see the 2nd paragraph of the introduction in the executive summary (page 1), the introduction to main report (page 7), and the summary and discussion (page 42). Page 2: We, too, were concerned about articles missed during our search. We looked at MeSH terms used to index the missed articles and concluded that the issue was use of different terminology (*eg,* instillation instead of transplantation) over the years. We searched multiple recent systematic reviews and reference lists of all included studies in an attempt to not miss any eligible publications. Minor Comments: Thank you for your careful read of the report.) change has been made) sentence has been modified) change has been made) we have noted that little information was provided by the authors of the series reporting this possible adverse event) we believe this sentence is clear as is) we have moved a summary of harms to KQ4) change has been made
5. Please provide any recommendations on how this report can be revised to more directly address or assist implementation needs.	

No specific recommendations beyond correcting a few typos (eg. C. Diff vs. C. diff used interchangeably in the text).	We have attempted to locate and correct all typographical errors.
None at this time, as the review was not designed to specifically support or not support implementation. However, as acknowledged in the review, there is likely to be ongoing trepidation about the 'unknowns' of manipulating the gut microbiome, particularly as new research is constantly emerging about its varied roles in our physiology. It's definitely helpful to present this as an opportunity for expediting high-quality research (as opposed to a potential source of liability).	Thank you.
None. Best to get a final copy edit, check references, etc. and release, ASAP than to make a lot of minor changes. Timeliness is important.	We agree.

APPENDIX C. EVIDENCE TABLES

Appendix C, Table 1. Study Characteristics

Author, year Country Design Funding Source Risk of Bias (RCTs)	Inclusion/Exclusion Criteria	Intervention Treatment Location Definition of Response Follow-up Duration	Patient Characteristics (means unless otherwise noted)	Donor Characteristics (means unless otherwise noted)
RECURRENT CDI – UPPER GASTROINTESTINAL TRACT VS. COLONOSCOPY				
Youngster, 2014[29] Country: USA Design: RCT Funding Source: National Institute of Allergy and Infectious Diseases Risk of Bias Assessment: *Allocation concealment:* adequate *Blinding:* open label *Intention to treat analysis*: yes (last outcome carried forward) *Withdrawals/ dropouts adequately described*: no *Overall:* Moderate risk of bias	Inclusion: Age 7 to 90 years; refractory or recurrent CDI (relapse after at least 3 episodes of mild/moderate CDI and failure of 6-8 week taper of vancomycin OR at least 2 episodes of severe CDI resulting in hospitalization Exclusion: presence of anatomic contraindications to nasogastric tube or colonoscopy; delayed gastric emptying syndrome, recurrent aspirations, pregnancy, significantly compromised immunity, history of significant allergy to foods not excluded from donor diet Method of diagnosis: (+) toxin	Intervention: Group 1) Bowel preparation (4 L polyethylene glycol electrolyte solution); colonoscopic administration of 90 cc thawed inoculum to the right colon; further diluted to 250 cc for adults and 160 cc for pediatric patients; instructed to retain material as long as possible; oral loperamide given at time of procedure Group 2) 2 mg/kg/day (up to 20 mg) oral omeprazole for 48 hrs prior to procedure; nasogastric tube placement documented by radiography; administration of 90 cc inoculum; tube removed; patients drank glass of water Treatment Location: 25% inpatient; 75% outpatient Definition of Response: clinical resolution of diarrhea off antibiotics for *C. difficile,* without relapse within 8 weeks Follow-up duration: 6 months	N=20 Age (yr): 55 Gender (Male%): 45% Race/Ethnicity (%): NR BMI: NR *Immune Status*: NR *Time from first CDI diagnosis to FMT (days*): 289 *Number of CDI Recurrences:* 4.5 (median); range = 2 to 16 *Prior Treatment*: 95% had vancomycin taper, 60% had previous use of fidaxomicin *Current Treatment with Antimicrobials*: Antimicrobials discontinued at least 48 hours prior to procedure	N=5 *Relationship to Patients*: Not related *Inclusion*: volunteers, healthy, non-pregnant, 19-50 years old, on no medications, normal BMI (18.5-25 kg/m^2), no significant past medical history, no use of antibiotics in past 6 months Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* exposure to infectious agents, blood count, liver function, lipid profile, antinuclear antigen, FOBT HIV: Yes Hepatitis: A, B, C Auto-Immune Disease: NR but excluded significant medical history Cancer: FOBT *Other:* enteric bacterial pathogens, *Treponema pallidum* NOTE: donors were asked to refrain from eating common allergens (tree nuts, eggs, peanuts, shellfish) within 5 days of stool donation; donations were escrowed for 5 weeks to allow retesting of donors for HIV, Hep B, and Hep C

Author, year Country Design Funding Source Risk of Bias (RCTs)	Inclusion/Exclusion Criteria	Intervention Treatment Location Definition of Response Follow-up Duration	Patient Characteristics (means unless otherwise noted)	Donor Characteristics (means unless otherwise noted)
RECURRENT CDI – UPPER GASTROINTESTINAL TRACT				
van Nood, 2013[20] Country: Netherlands, Finland Design: RCT Funding Source: Netherlands Organiza-tion for Health Research and Devel-opment; Organization for Scientific Research Risk of Bias Assessment: *Allocation concealment:* Adequate *Blinding:* Open label; outcome assessed by adjudication committee *Intention to treat analysis*: Modified (excluded 1 patient with no treatment) *Withdrawals/ dropouts adequately described*: Yes *Overall:* Moderate Risk of Bias	Inclusion: Age >18 yrs, >3 month life expectancy, diarrhea with + *C. difficile*, at least one course of vancomycin at 125mg QID x 10+ days or metronidazole 500mg TID x 10+ days Exclusion: prolonged compromised immunity d/t recent chemo, HIV+ with CD4 < 240, prolonged prednisolone at least 60mg daily, pregnancy, current antibiotics for something other than *C. difficile*, ICU admission, need for vasopressors Method of diagnosis: + toxin by PCR and diarrhea	Intervention: Bowel lavage followed the next day with nasoduodenal infusion of donor feces (FMT, n=16) Comparators: 1) vancomycin x 14 days (V, n=13); 2) vancomycin + bowel lavage (VB, n=13) Feces collected day of, diluted w/500cc NS, stirred, supernatant strained and poured into sterile bottle; 141+/-71g of donor stool at 50mL/min over 2-3 min Treatment Location: Hospital: FMT: 5/16 (31%), V 4/13 (31%), VB 4/13 (31%) Definition of Response: Cure without relapse within 10 weeks after initiation of therapy; blinded committee decided which patients were cured Duration of Follow-up: 10 weeks, another 10 weeks if 2nd transplant Withdrawals (%): 0 Lost to Follow-up (%): 0	N=43 (Patient characteristics for N=42 with one patient excluded) Age (yr): 70 FMT: 73 +/-13 Vanc: 66+/-14 VB: 69+/-16 Gender (Male%): 58% FMT: 8 (50%) V: 6(46%) VB: 10 (77%) Race/Ethnicity (%): NR BMI: 23 FMT: 22+/-3 V: 22+/-4 VB: 24+/-4 *Immune Status*: excluded immunocompromised *Time from first diagnosis to FMT:* NR *Number of Recurrences of CDI*: FMT 3 (1-5), V 3 (1-4), VB 2 (1-9) (mean = 2.7) *Prior Treatment*: vancomycin and/ or metronidazole *Current Antibiotic Treatment*: Abbreviated vancomycin 500mg QID x 4-5 days with until day before transplant.	N=15 *Relationship to Patients*: NR *Inclusion:* See below Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: yes Hepatitis:A-C Auto-Immune Disease:n Cancer: no *Other: Questionnaire re: transmissible diseases* Stool for enteric pathogens, parasites (*Blastocystis hominis* and Dientamoeba fragilis), *C. difficile* Serum HTLV 1&2, cytomegalovirus, Epstein-Barr virus, *Treponema, Strongyloides, Entamoeba*

Author, year Country Design Funding Source Risk of Bias (RCTs)	**Inclusion/Exclusion Criteria**	**Intervention Treatment Location Definition of Response Follow-up Duration**	**Patient Characteristics (means unless otherwise noted)**	**Donor Characteristics (means unless otherwise noted)**
Rubin, 2013[30] Country: USA Design: RCS Funding Source: Duluth Clinic Foundation	Inclusion: All patients undergoing FMT for lab confirmed toxin + CDI with ≥2 recurrences, had FMT via protocol, follow up ≥60 days after procedure Exclusion: Non-CDI FMT, surgically shortened GI tract, data had already been reported Method of diagnosis: + toxin (EIA) with diarrhea	Intervention: Proton pump inhibitor the evening before and morning of FMT; FMT via nasogastric tube, gastroscope (7) or already present PEG (4); approx. 30 g stool mixed in 50-70 ml saline, transplant ~ 25mL of stool/ saline mix Treatment Location: NR Definition of Response: Resolution of diarrhea without recurrence within 60 days of FMT Duration of Follow-up: 60 days	N=74 (72 adults, 2 children) Age (yr): 63 (median) Gender (Male%): 35% Race/Ethnicity (%): NR BMI:NR *Immune Status:* malignant illness (8), active corticosteroid (7) *Time from first diagnosis to FMT:* 206 days (51-1282) *Number of Recurrences of CDI:* NR *Prior Treatment:* at least 2 courses metronidazole and/or vancomycin and/or fidaxomicin *Current Antibiotic Treatment:* Vancomycin 125mg QID ≥3 days pre-FMT stopped day prior	N=NR *Relationship to Patients:* "healthy close household member" *Inclusion:* No antibiotics within 3 months Age (yr):NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: yes Hepatitis: yes Auto-Immune Disease: no Cancer: no *Other: C. difficile, Treponema pallidum,* ova and parasites, "enteric pathogens
Garborg, 2010[31] Country: Norway Design: RCS Funding Source: None stated	Inclusion: First or second recurrence of CDAD Exclusion: NR Method of Diagnosis: (+) *C. difficile* toxin (37), clinical (2), pseudomembranous colitis (1)	Intervention: Gastroscope or colonoscopic installation of 200mL of donor stool solution collected day of procedure Treatment Location: Inpatient and ambulatory Definition of Response: No further hospital contact due to CDAD symptoms within 80 days of FMT Duration of Follow-up: 80 days	N=40, one patient had 2 courses in 2 years; treated as a separate case Age (yr): 75 (53-94) Gender (Male%): 47% Race/Ethnicity (%):NR BMI: NR *Immune Status:* NR (one with acute myelogenous leukemia) *Time from first diagnosis to FMT:* NR *Number of Recurrences of CDI*: NR *Prior Treatment:* metronidazole and/or vancomycin *Current Antibiotic Treatment*: metronidazole or vancomycin until symptoms resolved; stopped evening prior to intervention	N=NR Relationship to Patients: Close relatives or other household members. Inclusion: No symptoms of GI disease or a history of chronic infectious disease Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: yes Hepatitis: A-C Auto-Immune Disease: no Cancer: no *Other:* enteric bacterial pathogens

Author, year Country Design Funding Source Risk of Bias (RCTs)	Inclusion/Exclusion Criteria	Intervention Treatment Location Definition of Response Follow-up Duration	Patient Characteristics (means unless otherwise noted)	Donor Characteristics (means unless otherwise noted)
MacConnachie, 2009[32] Country: UK Design: RCS Funding Source: None reported	Inclusion: At least one 10-day course each of vancomycin and metronidazole and recurrence of loose stool following successful antibiotics treatment in a patient recently treated for toxin positive CDAD Exclusion: NR Method of diagnosis: + toxin	Intervention: Proton pump inhibitor prior to FMT; 30g donor stool obtained, blended w/150mL of normal saline; 30mL of solution administered via nasogastric tube Treatment Location: Hospital Definition of Response: Not stated Duration of Follow-up: 16 weeks (median) (range 4-24 weeks)	N=15 Age (yr): 82 (68-95) Gender (Male%): 7% Race/Ethnicity (%): NR BMI: NR *Immune Status*: NR *Time from first diagnosis to FMT*: NR *Number of Recurrences of CDI:* 4 (3-7) *Prior Treatment*: metronidazole, vancomycin, IV immunoglobulin *Current Antibiotic Treatment*: Vancomycin 125mg QID until 12 hrs before procedure	N= NR *Relationship to Patients:* "related" *Inclusion:* "healthy" and negative screen as below Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* blood borne viruses, syphilis, enteropathogens
Aas, 2003[33] Country: USA Design: RCS Funding Source: St. Mary's Duluth Clinic	Inclusion: *C. difficile* with ≥2 lab confirmed relapses, adequate clinical and lab documentation of post-transplant course Exclusion: NR Method of Diagnosis: (+) *C. difficile* toxin	Intervention: 20mg omeprazole the evening before and morning of FMT; nasogastric administration of donor stool (25mL) Treatment Location: Hospital (5/18, 28%) and GI clinic (13/18, 72%) Definition of Response: No laboratory documentation of *C.* difficile colitis during 90 days after FMT; clinical response to FMT; no treatment for *C. difficile* colitis during 90 days after FMT; no record of repeated hospitalization for diagnosis and treatment of diarrhea Duration of Follow-up: 90 days	N=18 Age (yr): 73 (51-88) Gender (Male%): 28% Race/Ethnicity (%): NR BMI: NR *Immune Status*: Crohn's colitis (1), leukemia (1) *Time from first diagnosis to FMT:* 102 +/- 24 days (25-497) *Number of Recurrences of CDI:* 3.6 antibiotic courses (2-7) *Prior Treatment*: metronidazole, vancomycin *Current Antibiotic Treatment:* ≥4 day pretreatment with vancomycin 250mg every 8 hours to reduce *C. difficile* load; stopped evening prior	N=16 Relationship to Patients: Spouse, partner, household family member (15) or healthy donor (1) Inclusion: No antimicrobials within 6 months Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: y Hepatitis: y Auto-Immune Disease: no Cancer: no *Other: C. difficile, Treponema pallidum,* ova and parasites, "enteric pathogens
RECURRENT CDI – COLONOSCOPY				

Author, year Country Design Funding Source Risk of Bias (RCTs)	Inclusion/Exclusion Criteria	Intervention Treatment Location Definition of Response Follow-up Duration	Patient Characteristics (means unless otherwise noted)	Donor Characteristics (means unless otherwise noted)
Cammarota, 2014[34] Country: Italy Design: RCS Funding Source: NR	Inclusion: Recurrent or relapsing CDI or moderate CDI not responding to standard therapy; severe colitis with no response to standard therapy after 48 hours Exclusion: NR Method of diagnosis: + toxin (reported for 2 cases)	Intervention: Large volume bowel preparation; colonoscopy, fresh stool (within 6 hours) mixed with saline, 250 to 500 mL administered Treatment Location: Inpatient (33%), outpatient (33%), unclear (33%) Definition of Response: Resolution of symptoms and absence of relapse within 8 weeks Duration of Follow-up: 4 to 5 months NOTE: unclear if protocol for intervention, definition of response, and protocol for donor screening were developed before or after this series of patients	N=3 Age (yr): 67 Gender (Male%): 66% Race/Ethnicity (%): NR BMI: NR *Immune Status:* NR *Time from first diagnosis to FMT:* NR *Number of Recurrences of CDI:* 1-5 *Prior Treatment:* metronidazole, vancomycin *Current Antibiotic Treatment:* NR	N=NR *Relationship to Patients*: Child (1), sibling (1), NR (1) *Inclusion*: Excluded - risk of infectious agent, high risk sexual behaviors, use of illicit drugs, GI co- morbidities, recent antibiotic therapy, immunosuppressive medications, major surgery, metabolic syndrome, multiple sclerosis, atopic diseases Age (yr): NR Gender (Male%): both reported donors were male Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: yes Hepatitis: A-C Auto-Immune Disease: NR Cancer: no *Other: CD toxin, enteric pathogens, giardia, cryptosporidium, ova and parasites, syphilis*
Pathak, 2014[35] Country: USA Design: RCS Funding Source: NR	Inclusion: Recurrent CDI not responding to standard therapy Exclusion: GI tract could not be used for FMT (*ie,* malignancy, obstruction, perforation) Method of diagnosis: NR	Intervention: Colonoscopy (n=11) or nasoduodenal tube (n=1); standard bowel preparation the night before procedure; fresh feces (within 6 hours of procedure); 6 to 8 tablespoons in 1 liter tap water; colonoscope advanced to cecum or terminal ileum when possible; 400-500 cc instilled at farthest point then 50-60 cc every 10 cm during withdrawal of colonoscope; 2 tablets of diphenoxylate/atropine to slow excretion Treatment Location: Community hospital Definition of Response: Resolution of diarrhea, fall in white cell count, absence of fever, improvement in vital signs Duration of Follow-up: 2 to 29 months	N=12 Age (yr): 72 Gender (Male%): 33% Race/Ethnicity (%): NR BMI: NR *Immune Status:* NR *Time from first diagnosis to FMT:* 4 months to 2 years *Number of Recurrences of CDI:* NR *Prior Treatment:* metronidazole (4), vancomycin (12), fidaxomicin (8) *Current Antibiotic Treatment:* Stopped 24 hours prior to procedure	N=12 *Relationship to Patients*: Spouse (2), child (8), sibling, niece *Inclusion*: Preferred family members or first-degree relatives; excluded for HIV, STDs, Hepatitis B and C, high-risk sexual behaviors, drug use, tattoos or body piercing, imprisonment, known current communicable disease, GI comorbidities, antibiotic use in past 90 days Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: yes Hepatitis: A-C Auto-Immune Disease: no Cancer: excluded for GI malignancy *Other: STDs, enteric pathogens, ova and parasites, C. difficile toxins A, B*

Author, year Country Design Funding Source Risk of Bias (RCTs)	Inclusion/Exclusion Criteria	Intervention Treatment Location Definition of Response Follow-up Duration	Patient Characteristics (means unless otherwise noted)	Donor Characteristics (means unless otherwise noted)
Patel, 2013[36] Country: USA Design: RCS Funding Source: NR	Inclusion: ≥2 prior episodes of CDI and ongoing diarrhea in the absence of antimicrobial therapy Exclusion: NR Method of diagnosis: + toxin by PCR or EIA	Intervention: Standard split-dose bowel preparation; colonoscopy, fresh stool mixed with saline within 6 hours, into TI or cecum. 360mL (180-600). 4mg loperamide peri-procedure Treatment Location: Outpatient (n=30), inpatient Definition of Response: Improvement (>75%) or resolution of diarrhea and other symptoms (weight loss, abdominal pain, fatigue) Duration of Follow-up: 1 week to 1 year (n=6)	N=31[a] Age (yr): 61.3 +/- 19.3 Gender (Male%): 45% Race/Ethnicity (%): NR BMI: NR *Immune Status:* Immunosupressed, (prednisone use (n=3), hypogamma-globulinemia (n=2), liver transplant (n=1), renal transplant (n=1), methotrexate use (n=1)) Also UC (n=3), Crohn (n=2) *Time from first diagnosis to FMT:* 340 days (18-2205) *Number of Recurrences of CDI:* 4 (2-7) *Prior Treatment:* metronidazole (31), vancomycin (31), fidaxomicin (6), rifaximin (10), probiotic (23) *Current Antibiotic Treatment:* discontinued 4 hrs prior to bowel prep	N=33 *Relationship to Patients*: Spouse (n=14), child (n=9), sibling (n=5), parent (n=3), niece, friend *Inclusion*: No chronic GI disorder, IBD or IBS, history of colon cancer or polyps, antibiotics or hospitalization within 3 months Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: yes Hepatitis: A-C Auto-Immune Disease: no Cancer: no *Other: HTLV I/II, rapid plasma regain or syphilis EIA, stool bacterial culture, ova and parasites, cryptosporidium antigen, microsporidia smear, C. difficile toxin (PCR or EIA)*
Hamilton, 2012[37] Country: USA Design: RCS Funding Source: Minnesota Medical Foundation, NIH, MinnCRest Postdoctoral Fellowship	Inclusion: History of symptomatic toxin positive *C. difficile* with 2+ subsequent recurrences; minimum of 6wks tapered or pulsed vancomycin or 1 month vancomycin followed by a minimum of 2 week rifaximin “chaser” Exclusion: Age <18, medical fragility from non *C. difficile* problems resulting in life expectancy <1 year Method of Diagnosis: (+) toxin	Intervention: Standard split-dose bowel preparation; colonoscopy with 220-240 ml to terminal ileum and cecum; some also received 50 ml to areas of maximal diverticulosis Stool sample collected 1-2 hrs before procedure 50g stool 250mL normal saline in blender Alternate: 2 volunteers, with frozen stool thawed 2-4 hrs before procedure (used immediately or stored 1-8 wks before transplant) Treatment Location: Colonoscopy suite Definition of Response: Resolution of diarrhea and negative stool testing for *C. difficile* at 2 months following FMT Duration of Follow-up: 2 months	N=43 Age (yr): 59 +/- 21 Gender (Male%): 28% Race/Ethnicity (%): NR BMI: NR *Immune Status*: IBD in 14/43 *Time from first diagnosis to FMT*: 12.2 +/- 10.3 months *Number of Recurrences of CDI*: 5.9 +/- 3.3 *Prior Treatment*: vancomycin, metronidazole, fidaxomicin (n=1), nitazoxanide (n=3) *Current Antibiotic Treatment*: Vancomycin until 2 days before.	N=12 *Relationship to Patients*: Mother (n=2), daughter (n=1), son (n=3), wife (n=1), husband (n=1), friend (n=2), volunteer (n=2) I*nclusion*: No risk factors for HIV, hepatitis, current communicable disease, travel to endemic diarrhea area, antibiotics within 3 months, other GI disease, metabolic syndrome, autoimmunity, allergic diseases (last 2 relative). Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: yes Hepatitis: B & C Auto-Immune Disease: yes via questionnaire Cancer: yes *Other:* enteric pathogens, *C. difficile* toxin B, O&P, Giardia, cryptosporidium antigens

Author, year Country Design Funding Source Risk of Bias (RCTs)	Inclusion/Exclusion Criteria	Intervention Treatment Location Definition of Response Follow-up Duration	Patient Characteristics (means unless otherwise noted)	Donor Characteristics (means unless otherwise noted)
Kelly, 2012[38] Country: USA Design: RCS Funding Source: None	Inclusion: At least 3 recurrences of CDI Exclusion: NR Method of diagnosis: NR	Intervention: Standard bowel preparation; colonoscopy to TI or cecum, 500-960mL most to R colon; avoid defecating 30-45 mins; fresh specimen within 6 hours mixed in sterile water; Treatment Location: Outpatient Definition of Response: Did not suffer documented *C. difficile* relapse and/ or free of significant diarrhea requiring vancomycin Duration of Follow-up: 10.7 months (range 2-30 months)	N=26 Age (yr): 59 (19-86) Gender (Male%): 8% Race/Ethnicity (%): White 100% BMI: NR *Immune Status*: NR *Time from first diagnosis to FMT*: 12.6 mo (4-84) *Number of Recurrences of CDI*: "at least 3" *Prior Treatment:* Metronidazole (n=25), saccharomyces (n=23), tapering vancomycin (n=25). rifaximin (n=19), lactobacillus (n=4), IVIG (n=2) *Current Antibiotic Treatment*: vancomycin or metronidazole discontinued 2-3 days prior	N=26 *Relationship to Patients*: Partner (n=2), sibling (n=3), spouse (n=10), child (n=9), cousin (n=1), friend (n=1) *Inclusion*: No antibiotics within 90 days Age (yr): NR Gender (Male%): 54% Race/Ethnicity (%): NR BMI: NR *Screen for: See questionnaire*[b] HIV: yes Hepatitis: A-C Auto-Immune Disease: no Cancer: no *Other: Syphilis, Stool culture for enteric pathogens, ova and parasites, giardia antigen, C. difficile A and B*
Mattila, 2012[39] Country: Finland Design: RCS Funding Source: Finnish Foundation for Gastroenterological Research	Inclusion: Lab confirmed recurrent CDI despite antimicrobial treatment Exclusion: FMT not meeting above criteria and not done via colonoscopy per protocol Method of diagnosis: + culture and toxin	Intervention: Standard bowel preparation; 100mL infused via colonoscopy into the cecum; donor stool obtained within 6 hrs; 20-30mL homogenized in 100-200mL of saline Treatment Location: 60 (86%) outpatient Definition of Response: No persistent diarrhea with positive toxin stool test Duration of Follow-up: 12 mo	N=70 Age (yr): 73 (22-90) Gender (Male%): 40% Race/Ethnicity (%): NR BMI: NR *Immune Status*: NR *Time from first diagnosis to FMT*: 133 days (46-360) *Number of Recurrences of CDI:* 3.5 (1-12) *Prior Treatment:* 4.5 (2-12) Vancomycin, metronidazole, fidaxomicin, IVIG (n=1) *Current Antibiotic Treatment*: 4+ days of pretreatment with vancomycin or metronidazole until a reduction of symptoms occurred; discontinued at least 36 hrs prior	N=62 *Relationship to Patients*: Close relative or household contact (n=61), volunteer (n=1) *Inclusion:* No antibiotics last 6 months and no intestinal symptoms Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: yes Hepatitis: B,C Auto-Immune Disease: no Cancer: no *Other: Ova and parasites, C. difficile, enteric pathogens, Treponema pallidum, total blood count, C-reactive protein, creatinine, liver enzymes*

Author, year Country Design Funding Source Risk of Bias (RCTs)	Inclusion/Exclusion Criteria	Intervention Treatment Location Definition of Response Follow-up Duration	Patient Characteristics (means unless otherwise noted)	Donor Characteristics (means unless otherwise noted)
Mellow, 2011[40] Country: USA Design: RCS Funding Source: NR	Inclusion: Recurrent (at least 3 recurrences, n=12) or refractory (n=1) CDI; active CDI or on treatment Exclusion: Terminally ill Method of diagnosis: *C. difficile* toxin by EIA & diarrhea	Intervention: Standard bowel preparation; colonoscopy; 300-600mL stool infused - 100mL to TI, remaining 50% cecum, last bit throughout colon Treatment Location: Outpatient endoscopy suite; 8/13 in hospital or homebound at time of procedure Definition of Response: Not stated Duration of Follow-up: 5 months (range 1-10 months)	N=13 Age (yr): 67 (32-87) Gender (Male%): 54% Race/Ethnicity (%): NR BMI: NR *Immune Status*: NR. Colon cancer, lymphoma, radiation proctitis, Crohn's (n=1 each), insulin dependent diabetes (n=2) *Time from first diagnosis to FMT:* 10.7 (1-24) *Number of Recurrences of CDI*: 4 (3-7) *Prior Treatment*: metronidazole, vancomycin *Current Antibiotic Treatment*: NR, discontinued 48 hrs before FMT if taking antibiotics	N=NR *Relationship to Patients*: Person chosen by patient *Inclusion:* No antibiotics last 8 wks, acute or chronic diarrhea, immunosuppressant use or known immune disorder, current or prior chemotherapy Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: yes Hepatitis: A-C Auto-Immune Disease: screening questions Cancer: no *Other: C. difficile EIA, Treponema pallidum, enteric pathogens, ova and parasites*
Rohlke, 2010[41] Country: USA Design: RCS Funding Source: No funding support	Inclusion: *C. difficile* toxin positivity, consistently recurring symptoms over at least 6 months despite at least 3 courses of traditional treatments (including pulsed and tapered vancomycin) Exclusion: None reported Method of diagnosis: Toxin (+)	Intervention: 4.0L polyethelyne glycol purge evening before procedure; max of 350cc mixed with saline (generally 200-300cc) via colonoscopy under moderate sedation (intent was ileal intubation); stool infused during withdrawal initially; later all material instilled at proximal most extent of exam; patients at one site took 2 tablets diphenoxylate and atropine immediately after procedure and 5 hours later; bed rest at least several hours after procedure Treatment Location: 2 "medical centers"; treated as outpatients Definition of Response: Not stated Follow-up duration: 27.2 months (range 6 months to 5 years)	N=19 Age (yr): 49 (29-82) Gender (Male%): 11% Race/Ethnicity (%): NR BMI: NR *Immune Status*: NR *Time from first CDI diagnosis to FMT (day*s): NR *Number of CDI Recurrences: NR* *Prior Treatment*: "generally vancomycin" *Current Treatment with Antimicrobials*: NR; stopped 1 to 3 days before FMT	N=19 *Relationship to Patients*: 74% partners, 21% family members, 5% housemates *Inclusion*: no recent antibiotic use, no current or recent diarrheal illness, no hospital or health care workers, no at-risk sexual behaviors Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* Screening was selective based on recipient's discretion and desires HIV: NR Hepatitis: NR Auto-Immune Disease: NR Cancer: NR *Other:* NR

Author, year Country Design Funding Source Risk of Bias (RCTs)	Inclusion/Exclusion Criteria	Intervention Treatment Location Definition of Response Follow-up Duration	Patient Characteristics (means unless otherwise noted)	Donor Characteristics (means unless otherwise noted)
Yoon, 2010[42] Country: USA Design: RCS (5 patients excluded) Funding Source: No funding support	Inclusion: *C. difficile* + toxin diarrhea and recurrence despite standard therapies Exclusion: colitis (tests suggestive of IBD, n=1); cloaco-genic rectal carcino-ma (n=1); colon-oscopy (aphthous ulcers and biopsy specimens showing lymphoid aggregates and focal cryptitis , n=1); Crohn's (n=1); unable to contact for follow-up data (n=1) Method of diagnosis: (+) toxin	Intervention: Colonoscopy with 250-400cc injected in 10-20 cc increments every 5 to 10 cm of withdrawal distance; encouraged patients with retain infused stool for at least 4 hours Treatment Location: NR Definition of Response: Absence of diarrhea, cramps, and fever within 3 to 5 days of FMT Follow-up duration: 3 weeks to 8 years	N=12 Age (yr): 66 (30-86) Gender (Male%): 25% Race/Ethnicity (%): NR BMI: NR *Immune Status*: None immune suppressed based on comorbid conditions listed *Time from first CDI diagnosis to FMT (days):* 79 to 1532 days (mean 351 days, median 209 days) *Number of CDI Recurrences: NR* *Prior Treatment:* metronidazole (oral n=12, IV n=3); vancomycin (n=12); nitazoxanide (n=3), rifaximin (n=4), cholestyramine (n=4), *lactobacilil (n=4), Saccharomyes boulardii (n=7)* *Current Treatment with Antimicrobials*: advised patients to discontinue 3 days before procedure but not controlled	N=12 *Relationship to Patients*: spouse/ partner 67%; son/daughter/grand-daughter 33% *Inclusion*: No GI symptoms; "healthy" Age (yr): NR Gender (Male%): 50% Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: at discretion of treating physician; 3/12 screened Hepatitis: at discretion of treating physician; 3/12 screened Auto-Immune Disease: NR Cancer: NR *Other: C. difficile* toxin assay (8/12), stool culture and ova and parasites study (3/12) at discretion of treating physician
RECURRENT CDI –ENEMA				
Emanuelsson, 2013[43] Country: Sweden Design: RCS Funding Source: R&D Council at Skaraborgs Hospital Skovde	Inclusion: "all patients treated with FMT or RBT d/t severe relapsing and therapy-resistant CDI" between 1994-2011 Exclusion: NR Method of diagnosis: + culture and/or toxin by EIA	Intervention: At least 50g fresh feces mixed with saline to 500mL then flushed into rectal catheter (enema); patients lie on left side for 20 min, stomach another 20 min Treatment Location: GI clinic Definition of Response: Sustained resolution of symptoms (loss of perception of illness and discontinuation of diarrhea within 3 days and no signs of recurrence within 3 months) Duration of Follow-up: 18 months (range 0-21 months)	N=23* Age (yr): 67 (25-93) Gender (Male%): 38% Race/Ethnicity (%): NR BMI: NR *Immune Status*: uterine cancer, TB (2), PMR (2), DLBCL (2, one BMT), prostate ca, *Time from first diagnosis to FMT*: 5 months (1-16) *Number of Recurrences of CDI*: 3 antibiotics courses (1-5) *Prior Treatment*: Metronidazole and/or vancomycin (some tapered dosing) *Current Antibiotic Treatment*: NR; stopped morning of FMT	N=NR *Relationship to Patients*: Spouse or close relative *Inclusion*: "good health, no GI disease, no recent antibiotics use" Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: yes Hepatitis: B and C Auto-Immune Disease: no Cancer: no *Other: Salmonella, Shigella, Campylobacter, enterohemolytic Escherichia coli, C. difficile*

Author, year Country Design Funding Source Risk of Bias (RCTs)	Inclusion/Exclusion Criteria	Intervention Treatment Location Definition of Response Follow-up Duration	Patient Characteristics (means unless otherwise noted)	Donor Characteristics (means unless otherwise noted)
Silverman, 2010[44] Country: Canada Design: RCS Funding Source: NR	Inclusion: Recurrent CDI, living at home Exclusion: NR Method of diagnosis: *C. difficile* toxin	Intervention: 50mL of stool with 200mL saline, family to administer via enema, patient to lay on left side as long as possible; may repeat procedure if diarrhea recurs within 1 hour Treatment Location: Home Definition of Response: Clinical success Duration of Follow-up: Clinic visit at 2 weeks; follow-up 8.6 months (range 4-14 months)	N=7 Age (yr): 72 (30-88) Gender (Male%): 57% Race/Ethnicity (%): NR BMI: NR *Immune Status*: NR *Time from first diagnosis to FMT*: 13 months (6-23) *Number of Recurrences of CDI*: NR *Prior Treatment*: vancomycin, metronidazole, saccharomyces and *S. boulardii* prior to FMT to ensure patients were asymptomatic until 24-48 hours before FMT *Current Antibiotic Treatment*: metronidazole 500mg TID or vancomycin 125mg QID with saccharomyces 500mg BID stopped 24-48 hrs before transplant	N=7 *Relationship to Patients*: child (n=4), sibling (n=1), spouse (n=1), grandchild (n=1) *Inclusion*: No history of GI illness, malignancy, antibiotic use or hospitalization within 3 months Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: yes Hepatitis: A-C Auto-Immune Disease: no Cancer: no *Other: HTLV I/II, syphilis EIA, H pylori antibody, C. difficile, culture, ova and parasites, cryptosporidia, microspora*
Gustafson, 1999[45] Country: Sweden Design: Prospective case series Funding Source: Swedish Medical Research Council & Karolinska Institute funds	Inclusion: Hospitalized patients with antibiotic associated diarrhea; 6 had + C diff toxin Exclusion: NR Method of diagnosis: toxin	Intervention: Coloscope with 20mL enema of homogenized donor stool and pasteurized cow milk into the rectum Treatment Location: Hospital Definition of Response: “Clinically well” defined as <3 stools per day and normal consistency Duration of Follow-up: 18 months	N=6 (with CDI +) Age (yr): 60.8 (30-83) Gender (Male%): 83% Race/Ethnicity (%): NR BMI: NR *Immune Status*: NR *Time from first diagnosis to FMT:* NR *Number of Recurrences of CDI*: NR *Prior Treatment:* Metronidazole (n=2) *Current Antibiotic Treatment:* none (last antibiotic dose was 7 to 60 days before FMT)	N=1 *Relationship to Patients*: Healthy donor *Inclusion*: NR Age (yr): NR Gender (Male%): 0% Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: yes Hepatitis: A-C Auto-Immune Disease: no Cancer: no *Other: cytomegalovirus, Epstein-Barr virus, C difficile, “bacterial pathogens”*

Author, year Country Design Funding Source Risk of Bias (RCTs)	**Inclusion/Exclusion Criteria**	**Intervention Treatment Location Definition of Response Follow-up Duration**	**Patient Characteristics (means unless otherwise noted)**	**Donor Characteristics (means unless otherwise noted)**
Paterson, 1994[46] Country: Australia Design: RCS Funding Source: NR	Inclusion: Relapsing toxin + *C. difficile* Exclusion: NR Method of diagnosis: +toxin	Intervention: Rectal tube infusion of 400mL of mixed feces and saline daily for 3 days[c] Treatment Location: NR Definition of Response: Not stated Duration of Follow-up: NR	N=7 Age (yr): 56 (30-80) Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Immune Status*: NR, multiple myeloma (n=1) *Time from first diagnosis to FMT*: NR *Number of Recurrences of CDI:* 3 (1-4) *Prior Treatment*: Vancomycin, metronidazole, bacitracin or cholestyramine *Current Antibiotic Treatment*: NR	N=NR *Relationship to Patients*: "relative" I*nclusion*: NR Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: yes Hepatitis: B+C Auto-Immune Disease: no Cancer: no *Other: C. difficile, enteric pathogens*
Tvede, 1989[47] Country: Denmark Design: RCS Funding Source: NR	Inclusion: Relapsed CDI Exclusion: NR Method of diagnosis: Culture and toxin	Intervention: Enema, 50g stool with 500mL saline Treatment Location: NR Definition of Response: Not stated Duration of Follow-up: 12 months	N=2 Age (yr): 60 (59-60) Gender (Male%): 50% Race/Ethnicity (%): NR BMI: NR *Immune Status*: NR *Time from first diagnosis to FMT:* 17 (15-18) months *Number of Recurrences of CDI:* 3 (2-4) *Prior Treatment*: Vancomycin, cholestyramine, metronidazole, fusidic acid *Current Antibiotic Treatment*: NR	N=2 *Relationship to Patients*: Husband (n=1), daughter (n=1) *Inclusion*: NR Age (yr): NR Gender (Male%): 50% Race/Ethnicity (%): NR BMI: NR *Screen for: NR*

Author, year Country Design Funding Source Risk of Bias (RCTs)	Inclusion/Exclusion Criteria	Intervention Treatment Location Definition of Response Follow-up Duration	Patient Characteristics (means unless otherwise noted)	Donor Characteristics (means unless otherwise noted)
RECURRENT CDI –UPPER GASTROINTESTINAL TRACT AND COLONOSCOPY				
Dutta, 2014[48] Country: USA Design: Prospective case series Funding Source: Gastroenterology Research Fund, Sinai Hospital Baltimore. Institute for Genome Sciences, University of Maryland	Inclusion: ≥3 recurrences of CDI ages 18-90 Exclusion: Critically ill, cancer and immunocompromised patients Method of diagnosis: Toxin by ELISA with diarrhea ≥ 3 stools/day	Intervention: 180cc into JEJUNUM via enteroscopy and 270cc via colonoscopy Treatment Location: NR Definition of Response: Resolution of diarrhea and disappearance of stool *C. difficile* toxin Duration of Follow-up: 21 months (range 10-34)	N=27 Age (yr): 65 (18-89) Gender (Male%): 19% Race/Ethnicity (%): Caucasian (74), African American (22), Asian (4) BMI: NR *Immune Status*: NR *Time from first diagnosis to FMT*: 12.9 months (2.5-27) *Number of Recurrences of CDI*: 4.6 (3-5) *Prior Treatment*: metronidazole (n=24), vancomycin (n=26), fidaxo-micin (n=13), rifaxomycin (n=6), ni-tazoxanide, cholestyramine (n=1) *Current Antibiotic Treatment*: NR	N=27 *Relationship to Patients*: Spouse (n=10), Child (n=13), parent (n=4) *Inclusion*: NR Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Other: Screen for "history, physical and blood testing to exclude any transmissible diseases"*
REFRACTORY CDI – COLONOSCOPY				
Weingarden, 2013[49] Country: USA Design: RCS Funding Source: NIH	Inclusion: Severe CDI refractory to antibiotics[d] Exclusion: NR Method of diagnosis: NR	Intervention: Colonoscopy admin of stool; 50g stool with 250mL saline either thawed (n=3) or fresh (n=1); 220-240 ml to terminal ileum and cecum; 50 ml to colonic areas with maximum diverticulosis Treatment Location: Hospital Definition of Response: Not stated Duration of Follow-up: Up to one year	N=4 Age (yr): 72.8 (66-83) Gender (Male%): 25% Race/Ethnicity (%): NR BMI: NR *Immune Status*: ovarian cancer on chemo (n=1) *Time from first diagnosis to FMT*: NA *Number of Recurrences of CDI*: NA *Prior Treatment*: metronidazole (oral & IV), vancomycin (oral) *Current Antibiotic Treatment*: metronidazole held 48hrs prior, vancomycin 12-24 hrs prior	N=1 *Relationship to Patients*: Volunteer *Inclusion:* No risk factors for HIV, hepatitis, communicable disease, travel to endemic diarrhea area, antibiotics (3 months), GI disease, metabolic syndrome, autoimmunity, allergy (last 2 relative) Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: yes Hepatitis: yes Auto-Immune Disease: yes via questionnaire Cancer: yes *Other: enteric pathogens, C. difficile toxin B, ova and parasites, Giardia, cryptosporidium antigens*

Author, year Country Design Funding Source Risk of Bias (RCTs)	Inclusion/Exclusion Criteria	Intervention Treatment Location Definition of Response Follow-up Duration	Patient Characteristics (means unless otherwise noted)	Donor Characteristics (means unless otherwise noted)
REFRACTORY CDI –ENEMA				
Lee, 2014[50] Country: Canada Design: RCS Funding Source: Natural Sciences and Engineering Research Council of Canada and National Science Foundation through Statistical and Applied Mathematical Sciences Institute	Inclusion: Recurrent (symptom resolution for at least 2 days after discontinuation of treatment with recurrence of diarrhea) or refractory (ongoing diarrhea despite treatment with at least 5 days oral vancomycin) CDI Exclusion: NR Method of diagnosis: + toxin by EIA or PCR	Intervention: 150g of stool emulsified in 300mL of sterile water; 100 mL of supernatant administered rectally by enema Treatment Location: 70/94 (74.5%) were hospitalized Definition of Response: Clinical resolution of CDI Duration of Follow-up: 6 to 24 months	N=94 Age (yr): 72 (range 24-95) Gender (Male%): 44% Race/Ethnicity (%): NR BMI: NR *Immune Status*: NR *Time from first diagnosis to FMT:* NR *Number of Recurrences of CDI*: NR *Prior Treatment*: Mean of 2.1 courses of antibiotics (metronidazole (79%), vancomycin (75%), vancomycin taper (15%), combination (17%) *Current Antibiotic Treatment*: NR	N=NR *Relationship to Patients*: Unknown volunteers *Inclusion*: No antibiotics in the preceding 6 months Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: yes Hepatitis: B,C Auto-Immune Disease: no Cancer: no *Other: H. pylori serology, HTLV-1&2, C. difficile, ova and parasites,, syphilis serology, "enteric bacterial pathogens"*
Bowden, 1981[51] Country: USA Design: RCS Funding Source: NR	Inclusion: Pseudo-membranous colitis Exclusion: NR Method of diagnosis: Pseudomembranes on direct visualization and diarrhea	Intervention: BID fecal enemas (n=13) or jejunal infusion with cantor tube (n=1), "enteric infusion" (n=1) until symptoms improved; stool prepared in saline and given as retention enema Treatment Location: Hospital Definition of Response: Resolution of symptoms (decrease in number of stools, temperature, white blood cell count); in some cases resolution of pseudomembrane; improvement in well being Duration of Follow-up: NR	N=15 Age (yr): 59 (43-85) Gender (Male%): 40% Race/Ethnicity (%): NR BMI: NR *Immune Status*: NR *Time from first diagnosis to FMT:* NR *Number of Recurrences of CDI*: NR *Prior Treatment*: Kanamycin, tetracycline, neomycin, sulfasuxidine, sulfathalidine, keflin, chloramphenicol, gentamicin, clindamycin, lactobacillus, albumin *Current Antibiotic Treatment*: NR	N=NR *Relationship to Patients*: In-house family, medical students and residents *Inclusion*: NR Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: no Hepatitis: yes Auto-Immune Disease: no Cancer: no *Other: amoebiasis, "other enteric diseases"*

Author, year Country Design Funding Source Risk of Bias (RCTs)	Inclusion/Exclusion Criteria	Intervention Treatment Location Definition of Response Follow-up Duration	Patient Characteristics (means unless otherwise noted)	Donor Characteristics (means unless otherwise noted)
Eiseman, 1958[18] Country: USA Design: Case Series Funding Source: NR	Inclusion: Pseudo-membranous enterocolitis Exclusion: NR NOTE: report of 4 cases – 3 refractory CDI, 1 initial therapy (see below)	Intervention: Retention fecal enema using donor feces from a "normal" subject Treatment Location: Hospital Definition of Response: Not stated Follow-up duration: 2 to 10 days (until hospital discharge)	N=3 Age (yr): 52 Gender (Male%): 67% Race/Ethnicity (%): white 33%, Hispanic 33%, NR 33% BMI: NR *Immune Status*: NR *Time from first CDI diagnosis to FMT (days):* 8 (range 1 to 20) *Number of CDI Recurrences:* NR *Prior Treatment*: albamycin, erythromycin, chloromycetin *Current Treatment with Antimicrobials*: NR	N=NR *Relationship to Patients*: NR *Inclusion*: "Normal" subject, no antimicrobials during previous several months Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: NR Hepatitis: NR Auto-Immune Disease: NR Cancer: NR *Other:* NR
INITIAL THERAPY FOR CDI - ENEMA				
Eiseman, 1958[18] Country: USA Design: Case Series Funding Source: NR	Inclusion: See above (1 case in series was FMT as initial therapy) Exclusion: NR	Intervention: Retention fecal enema using donor feces from a "normal" subject Treatment Location: Hospital Definition of Response: Not stated Follow-up duration: 5 days	N=1 Age (yr): 68 Gender (Male%): 100% Race/Ethnicity (%): white 100% BMI: NR *Immune Status*: NR *Time from first CDI diagnosis to FMT (days):* 7 *Number of CDI Recurrences:* NR *Prior Treatment*: albamycin, erythromycin, chloromycetin *Current Treatment with Antimicrobials*: NR	N=NR *Relationship to Patients*: NR *Inclusion*: "Normal" subject, no antimicrobials during previous several months Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: NR Hepatitis: NR Auto-Immune Disease: NR Cancer: NR *Other:* NR

USA = United States of America; UK = United Kingdom; RCS = retrospective case series; RCT = randomized controlled trial; NR = not reported; N = number of subjects; BID = two times a day; BMI = body mass index; CDAD = *Clostridium difficile* associated diarrhea; DI = *Clostridum difficile* infection; EIA = enzyme immunoassay; FMT = fecal microbiota transplantation; FOBT = fecal occult blood test; GI = gastrointestinal; HTLV = human T-cell lymphotropic virus; IV = intravenous; O&P = ova and parasites; PCR = polymerase chain reaction; PEG = percutaneous endoscopic gastroscopy; QID = four times a day; TID = three times a day

[a]Only 30 patients of 31 had diarrhea, which was the primary outcome

[b]Donor Screening Questionnaire

Exclusion Criteria: Risk of infectious agent; Known exposure to HIV or viral hepatitis (within the previous 12 mo); High-risk sexual behaviors (examples: sexual contact with anyone with HIV/AIDS or hepatitis, men who have sex with men, sex for drugs or money); Use of illicit drugs; Tattoo or body piercing within 6mo; Incarceration within previous 12mo; Known current communicable disease; Risk factors for variant Creutzfeldt-Jakob disease; GII comorbidities; History of inflammatory bowel disease; History of irritable bowel syndrome, idiopathic chronic constipation, or chronic diarrhea; History of GI malignancy

Other: Antibiotic use within the preceding 90 d; Recent ingestion of a potential allergen (*eg*, nuts) where recipient has a known allergy to this agent; Systemic autoimmunity, for example, multiple sclerosis, connective tissue disease; Chronic pain syndromes, for example, chronic fatigue syndrome, fibromyalgia

[c]Protocol reported for one of the patients, unclear if others followed same protocol

[d]WBC >20, albumin <2.5, fever, abdominal pain, distension, colonic thickening on CT, ascites

Appendix C, Table 2. Outcomes after Initial Transplant and Adverse Events

Study, yesear Country Design N=	Reported Resolution of Symptoms after Initial FMT - n/N (%)		Time to Resolution of Symptoms, days	Recurrence n/N (%)	All-Cause Mortality n/N (%)	Adverse Events n/N (%)
	3 months or less	Greater than 3 months				
RECURRENT CDI – UPPER GASTROINTESTINAL TRACT VS. COLONOSCOPY						
Youngster 2014[29] USA RCT N=20 (3 pediatric)	Colonoscopy; 8/10 (80) Nasogastric: 6/10 (60) P=.63	NR	NR	0/20 (in 8 week follow-up)	2/20 (10) (at 12 and 21 weeks after FMT)	Mild abdominal discomfort and bloating 4/20 (20) Transient fever: 1/20 (5) (pediatric patient) Adenocarcinoma of esophagus: 1/20 (5) Fournier's gangrene: 1/20 (5)
RECURRENT CDI – UPPER GASTROINTESTINAL TRACT						
Van Nood, 2013[20] Netherlands RCT N=43 (17 FMT, 13 Vancomycin, 13 Vancomycin+BL) NOTE: 1 patient in FMT group was excluded from analysis because of a clinically-driven protocol violation	FMT: 13/16 (81) Vancomycin: 4/13 (31) Vancomycin+BL: 3/13 (23) P<.01	NR	NR	FMT: 3/16 (19) Vancomycin: 8/13 (62) Vancomycin+BL: 7/13 (54)	FMT: 0/16 Vancomycin: 1/13 (8) Vancomycin+BL: 0/13	FMT - day of infusion[a] Diarrhea: 15/16 (94) Cramps: 5/16 (31) Belching: 3/16 (19) Nausea: 1/16 (6) FMT – follow-up Constipation: 3/16 (19) Other (considered un-related to FMT) Infection: 2/16 (13) Hospitalization: 1/16 (6) Vancomycin, Vancomycin+BL: few and mild adverse events only
Rubin, 2012[30] USA RCS N=74 (72 adults)[b]	58/72 (81)	NR	NR	NR	0/72	0/72
Garborg, 2010[31] Norway RCS N=40	29/40 (73)	NR	Usually within 24 hrs	NR	5/40 (13)	NR
MacConnachie, 2009[32] UK RCS N=15	11/15 (73)	NR	NR	4/15 (27)	0/15	Upper GI bleeding: 1/15 (7)
Aas, 2003[33] USA RCS N=18	15/18 (83)	NR	Most reported resolution within 12-24 hrs	1/18 (6)	2/18 (11)	Possible peritonitis day 3 s/p FMT: 1/18 (6) Pneumonia: 1/18 (6)
TOTAL[c]	**132/171 (77)**			**8/59 (14) (4 studies)**	**7/161 (4)[d] (5 studies)**	

Study, yesear Country Design N=	Reported Resolution of Symptoms after Initial FMT - n/N (%)		Time to Resolution of Symptoms, days	Recurrence n/N (%)	All-Cause Mortality n/N (%)	Adverse Events n/N (%)
	3 months or less	Greater than 3 months				
RECURRENT CDI – COLONOSCOPY						
Cammarota 2014[34] Italy RCS N=3	3/3 (100)	NR	2 days after procedure for 1 patient; NR for 2 patients	NR	0/3	0/3
Pathak 2014[35] USA RCS N=12	11/12 (92)	10/12 (83%)	Within 48 hours	0/12	1/12 (8)	0/12
Patel, 2013[36] USA RCS N=31	Diarrhea symptoms 22/30 (73)[e]	Diarrhea symptoms 6/6 (100) who followed up at 1 year	Median: 3 days (1-18)	3/30 (10)	1/31 (3)	Microperforation during procedure 1/31 (3)
Hamilton, 2012[37] USA RCS N=43	37/43 (86) Individual donor: 7/10 (70) Standard donor: Fresh 11/12 (92) Frozen 19/21 (90) P=.127	NR	NR	6/43 (14)	0/43	No serious events Short lived bowel movement irregularity and excessive flatulence in approximately 1/3 of patients
Kelly, 2012[38] USA RCS N=26	25/26 (96)	24/26(92)	Hours to few days	2/26 (8)	NR	NR
Mattila, 2012[39] Finland RCS N=70	66/70 (94)	62/70 (89)	NR	8/70 (11)	3 months: 4/70 (6) 12 months: 14/70 (20)	0/70
Mellow, 2011[40] USA RCS N=12[f]	11/12 (92)	7/9 (78) who were followed for over 3 months or who relapsed prior	Almost all within 7 days	1/12 (8)	3/12 (25)	NR

Study, yesear Country Design N=	Reported Resolution of Symptoms after Initial FMT - n/N (%)		Time to Resolution of Symptoms, days	Recurrence n/N (%)	All-Cause Mortality n/N (%)	Adverse Events n/N (%)
	3 months or less	Greater than 3 months				
Rohlke, 2010[41] USA RCS N=19	18/19 (95)	18/19 (95)	NR	1/19 (5)	NR	NR
Yoon, 2010[42] USA RCS N=12	12/12 (100%)	NR (available follow-up ranged from 3 weeks to 8 years)	NR (by definition, symptoms resolved in 3 to 5 days)	NR	NR	0/12
TOTAL[g]	**213/237 (90)**			**21/222 (10) (8 studies)**	**19/171 (11)[d] (6 studies)**	
RECURRENT CDI –ENEMA						
Emanuelsson, 2013[43] Sweden RCS N=23	15/23 (65)	12/15 (80) (3 had only <3 months follow-up)	NR (success defined as discontinuation of diarrhea within 3 days)	1/23 (4) recurrence a few weeks after initial treatment (treatment was rated as failure)	NR	0/23
Silverman, 2010[44] RCS N=7	7/7 (100)	7/7 (100)	NR	0/7	NR	0/7
Gustafsson, 1999[45] Sweden PCS N=6 CDI	5/6 (83)	5/5 (100)	Most within 4 days (range 2 to 6)	0/6	NR	NR
Paterson, 1994[46] Australia RCS N=7	7/7 (100)[h]	NR	NR	NR	NR	NR
Tvede, 1989[47] Denmark RCS N=2	1/2 (50)	NR	NR	0/2	0	NR
TOTAL	**35/45 (78)**			**1/38 (3) (4 studies)**	**0/2 (1 study)**	

Study, yesear Country Design N=	Reported Resolution of Symptoms after Initial FMT - n/N (%)		Time to Resolution of Symptoms, days	Recurrence n/N (%)	All-Cause Mortality n/N (%)	Adverse Events n/N (%)
	3 months or less	Greater than 3 months				
RECURRENT CDI –UPPER GASTROINTESTINAL TRACT AND COLONOSCOPY						
Dutta, 2014[48] USA PCS N=27	27/27 (100)	27/27 (100)	3 days (range 1-15)	0/27	NR	Low-grade fever: 5/27 (19) Bloating: 3/27 (11)
REFRACTORY CDI – COLONOSCOPY						
Weingarden, 2013[49] USA RCS N=4	0/4 All patients had improvement in symptoms but then recurrence	NA	Improvements noted in 1 to "several" days	4/4 (100) All patients were considered for 2nd procedure; 3/4 were on antibiotics	1/4 (25)	NR
Mellow, 2011[40] USA RCS N=1 (see Recurrent CDI – Colonoscopy)	1/1 (100)	1/1 (100)	NR	0/1	0/1	NR
Total	**1/5 (20)**			**4/5 (80)**	**1/5 (20)**	
REFRACTORY CDI – ENEMA						
Lee, 2014[50] Canada RCS N=94	45/94 (48)	45/94 (48)	NR	0/45	6/94 (6) None attributable to FMT or CDI	Transient constipation and excess flatulence: 10%
Bowden, 1981[51] USA RCS N=16[b] (15 adults)	13/15 (87)[i]	Duration of response not reported	1-12 days	NR	2/15 (13)[j]	"No ill effects from the fecal enemas"
Eiseman, 1958[18] USA RCS N=4 (3 with refractory CDI)	3/3 (100)[j]	NR	1-2 days	Unclear[k]	0/3	NR
TOTAL	**61/112 (54)**			**0/45 (1 study)**	**8/112 (7)**	

Study, yesear Country Design N=	Reported Resolution of Symptoms after Initial FMT - n/N (%)		Time to Resolution of Symptoms, days	Recurrence n/N (%)	All-Cause Mortality n/N (%)	Adverse Events n/N (%)
	3 months or less	Greater than 3 months				
INITIAL THERAPY FOR CDI - ENEMA						
Eisemen, 1958[18] USA RCS N=4 (1 as initial therapy)	1/1 (100)	NR	Within 48 hours	0/1	0/1	NR

BL = bowel lavage; CDI = *C. difficile* infection; FMT = fecal microbiota transplant; GI = gastrointestinal; NR = not reported; PCS = prospective case series; RCS = retrospective case series; s/p = status post

- [a]All lasted less than 3 hrs after infusion
- [b]Children were excluded; 2 patients for Rubin 2012[30] and 1 patient for Bowden 1981[51]
- [c]Includes 10 patients from nasogastric group reported by Youngster 2014[29]
- [d]Does not include 2 deaths reported by Youngster 2014[29] because treatment group was not reported
- [e]One patient lost to follow-up after FMT
- [f]One additional patient had refractory CDI that was successfully treated >3 months (See Refractory CDI – Colonoscopy section); additional 7 patients reported in Addendum with success after initial FMT in 6 of 7(86%) with the remaining patient achieving resolution after repeat FMT with feces from a different donor
- [g]ncludes 10 patients from colonoscopy group reported by Youngster 2014[29]
- [h]All had daily FMT for unspecified amount of time, likely 3 days
- [i]Most patients received fecal enema twice daily for up to 12 days
- [j]One additional patient died of cerebrovascular accident 1 month after treatment
- [k]One patient received 2nd transplant on same day; all 3 patients received another transplant the day after the first but unclear whether the repeat procedures were related to treatment failure

Appendix C, Table 3. Outcomes after Repeat Transplant

Study, year Country Design N=	Repeat Transplant after Initial FMT Failure n/N (%)	Reported Resolution of Symptoms after Repeat Transplant n/N (%)	
		≤ 3 months	> 3 months
RECURRENT CDI – UPPER GASTROINTESTINAL TRACT VS. COLONOSCOPY			
Youngster 2014[25] USA RCT N=20	5/6 (83) (2/2 from colonoscopy group, 3/4 from nasogastric group; all requested nasogastric administration)	4/5 (80%) (2/2 from original colonoscopy group, 2/3 from original nasogastric group	NR
RECURRENT CDI – UPPER GASTROINTESTINAL TRACT			
Van Nood, 2013[16] Netherlands RCT N=43 (16 FMT)	3/3 (100)	2/3 (66.7)	NR
Rubin, 2012[26] USA RCS N=74 (72 adults)	0/14	NA	NA
Garborg, 2010[27] Norway RCS N=40	6/11 (55)	4/6 (67)	NR
MacConnachie, 2009[28] UK RCS N=15	1/4 (25)	1/1 (100)	NR
Aas, 2003[29] USA RCS N=18	0/3	NA	NA
RECURRENT CDI – COLONOSCOPY			
Cammarota 2014[30] Italy RCS N=3	NA	NA	NA
Pathak 2014[31] USA RCS N=12	1/1 (100) (Nasoduodenal approach)	1/1 (100)	NR

Study, year Country Design N=	Repeat Transplant after Initial FMT Failure n/N (%)	Reported Resolution of Symptoms after Repeat Transplant n/N (%)	
		≤ 3 months	> 3 months
Patel, 2013[32] USA RCS N=31	3/8 (38)[a] 2 via upper endoscopy due to subtotal colectomy	3/3 (100)	NR
Hamilton, 2012[33] USA RCS N=43	4/6 (67)	4/4 (100) One had push enteroscopy into jejunum because of colostomy	NR
Kelly, 2012[34] USA RCS N=26	0/1	NA	NA
Mattila, 2012[35] Finland RCS N=70	0/4	NA	NA
Mellow, 2011[36] USA RCS N=12	0/1	NA	NA
Rohlke, 2010[37] USA RCS N=19	1/1 (100)	1/1 (100)	1/1 (100)
Yoon, 2010[38] USA RCS N=12	NA	NA	NA
RECURRENT CDI –ENEMA			
Emanuelsson, 2013[39] Sweden RCS N=23	2/8 (25)	1/2 (50)	1/2 (50)
Silverman, 2010[40] RCS N=7	NA	NA	NA

Study, year Country Design N=	Repeat Transplant after Initial FMT Failure n/N (%)	Reported Resolution of Symptoms after Repeat Transplant n/N (%)	
		≤ 3 months	> 3 months
Gustafsson, 1999[41] Sweden PCS N=6 CDI	1/1 (100)	1/1 (100%)	1/1 (100%)
Paterson, 1994[42] Australia RCS N=7	NA	NA	NA
Tvede, 1989[43] Denmark RCS N=2	1/1 (100)	0/1	NA
RECURRENT CDI –UPPER GASTROINTESTINAL TRACT AND COLONOSCOPY			
Dutta, 2014[44] USA PCS N=27	NA	NA	NA
REFRACTORY CDI – COLONOSCOPY			
Weingarden, 2013[45] USA RCS N=4	2/4 (50%)	2/2 (100%)	2/2 (100%)
Mellow, 2011[36] USA RCS N=1 (see Recurrent CDI - Colonoscopy)	NA	NA	NA
REFRACTORY CDI – ENEMA			
Lee, 2014[46] Canada RCS N=94	48/49 (98)[b,c]	41/48 (85)[b]	41/48 (85)[b]
Bowden, 1981[47] USA RCS N=16 (15 adults)	0/2	NA	NA

Study, year Country Design N=	Repeat Transplant after Initial FMT Failure n/N (%)	Reported Resolution of Symptoms after Repeat Transplant n/N (%)	
		≤ 3 months	> 3 months
Eiseman, 1958[14] USA RCS N=4 (3 with refractory CDI)	NA	NA	NA
INITIAL THERAPY FOR CDI - ENEMA			
Eisemen, 1958[14] USA RCS N=4 (1 as initial therapy)	NA	NA	NA

CDI = *C. difficile* infection; FMT = fecal microbiota transplantation; NA = not applicable; NR = not reported; PCS = prospective case series; RCS = retrospective case series

[a]One patient lost to follow-up after FMT

[b]includes 9 patients treated with antibiotics for ongoing diarrhea between repeat FMTs

[c]20 patients received 2 FMTs, 17 patients received 3 FMTs, and 11 patients received 4 or more FMTs