Washington State Health Care Authority

Fecal Microbiota Transplantation

Final evidence report: Appendices

September 30, 2016

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Fecal Microbiota Transplantation

Provided by:

Spectrum Research, Inc.

Final Report
APPENDICES

September 30, 2016

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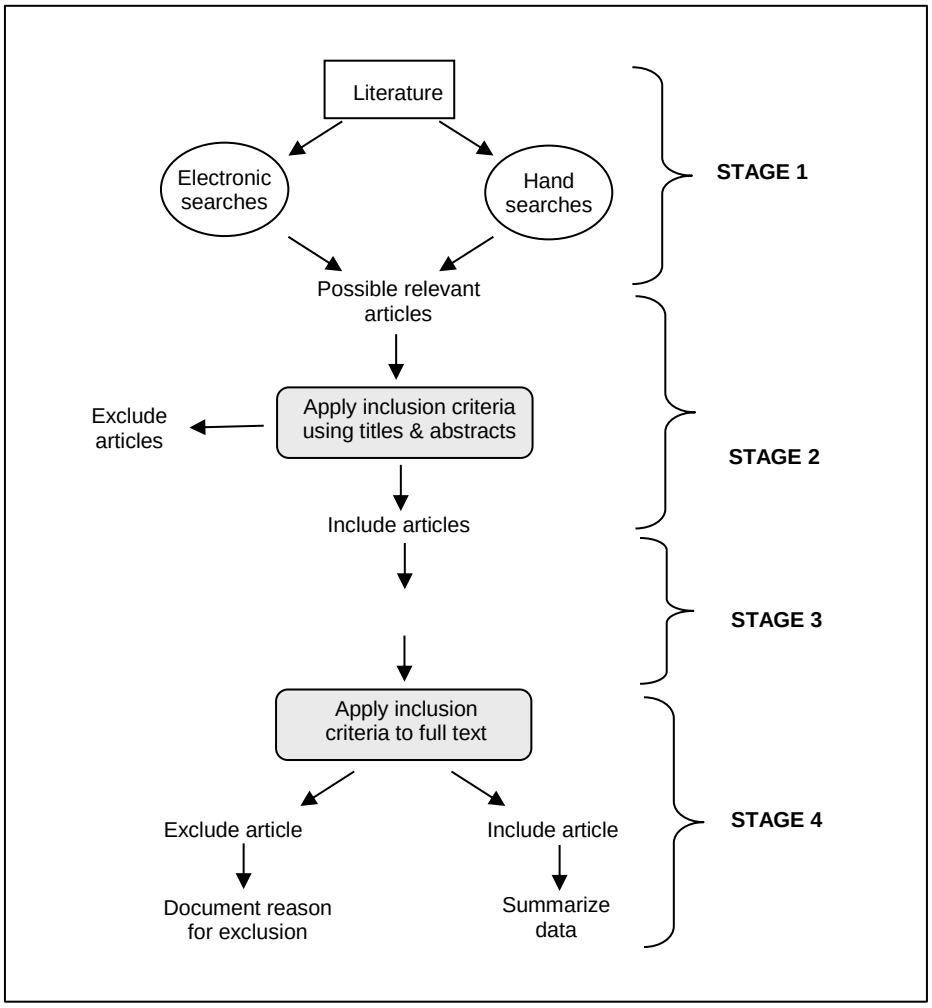
APPENDIX A. Algorithm for Article Selection



APPENDIX B. Search Strategies

Below is the search strategy for PubMed. Parallel strategies were used to search other electronic databases listed below. Keyword searches were conducted in the other listed resources.

Search strategy (PubMed)
Search period: through 4/27/2016, updated 9/2/2016
Filters: Abstract available, English

	Search terms	Articles (4/27/16)	Articles (9/2/16)
1.	Fecal Microbiota Transplantation[MeSH]	43	72
2.	((fecal[TI] OR feces[TI] OR faecal[TI]) AND (transplantation*[TI] OR transplant[TI] OR transplants*[TI] OR infusion*[TI] OR instillation*[TI]))	263	304
3.	("fecal microbiota transplantation" OR "fecal microbiota transplantations" OR "intestinal microbiota transfer" OR "intestinal microbiota transfers" OR "fecal transplantation" OR "fecal transplantations" OR "fecal transplant" OR "fecal transplants" OR "donor feces infusion" OR "donor feces infusions")	563	653
4.	#1 OR #2 OR #3	634	720
5.	#4 NOT (Disease Models, Animal[MeSH] OR mice[TI] OR mouse[TI] OR murine[TI] OR rat[TI] OR animal[TI])	562	638
6.	#5 NOT (Case Reports[Publication Type])	530	603

Parallel strategies were used to search the Cochrane Library, EMBASE, and others listed below. Keyword searches were conducted in the other listed resources.

Electronic Database Searches

The following databases have been searched for relevant information:

Agency for Healthcare Research and Quality (AHRQ)
Cumulative Index to Nursing and Allied Health (CINAHL)
Cochrane Database of Systematic Reviews
Cochrane Registry of Clinical Trials (CENTRAL)
Cochrane Review Methodology Database
Database of Reviews of Effectiveness (Cochrane Library)
EMBASE
PubMed
Informational Network of Agencies for Health Technology Assessment (INAHTA)
NHS Economic Evaluation Database
HSTAT (Health Services/Technology Assessment Text)
EconLIT

Additional Economics, Clinical Guideline and Gray Literature Databases

AHRQ – Healthcare Cost and Utilization Project
Canadian Agency for Drugs and Technologies in Health
Centers for Medicare and Medicaid Services (CMS)
Food and Drug Administration (FDA)
Google
Institute for Clinical Systems Improvement (ICSI)
National Guideline Clearinghouse

APPENDIX C. Excluded Articles

Articles excluded as primary studies after full text review*, with reason for exclusion.

	Citation	Reason for exclusion after full-text review
1.	Bakken JS. Staggered and tapered antibiotic withdrawal with administration of kefir for recurrent Clostridium difficile infection. Clin Infect Dis 2014;59:858-61.	Wrong intervention (kefir administration, FMT not used)
2.	Emanuelsson F, Claesson BE, Ljungstrom L, Tvede M, Ung KA. Faecal microbiota transplantation and bacteriotherapy for recurrent Clostridium difficile infection: a retrospective evaluation of 31 patients. Scand J Infect Dis 2014;46:89-97.	Case series with <30 FMT patients (only 23 patients (which is less than our threshold for inclusion of 30 patients) underwent FMT; the remaining 8 patients underwent infusion of a bacterial culture (not feces))
3.	Furuya-Kanamori L, Doi SA, Paterson DL, et al. Upper Versus Lower Gastrointestinal Delivery for Transplantation of Fecal Microbiota in Recurrent or Refractory Clostridium difficile Infection: A Collaborative Analysis of Individual Patient Data From 14 Studies. J Clin Gastroenterol 2016.	Indirect comparison (compares FMT routes of administration using case series data).
4.	Hamilton MJ, Weingarden AR, Sadowsky MJ, Khoruts A. Standardized frozen preparation for transplantation of fecal microbiota for recurrent Clostridium difficile infection. Am J Gastroenterol 2012;107:761-7.	All patients appear to be included in the Khoruts case series (which is included in this report)
5.	Kao D, Roach B, Beck P, Hotte N, Madsen K, Louie T. A dual center, randomized trial comparing colonoscopy and oral capsule delivered fecal microbiota transplantation in the treatment of recurrent clostridium difficile infection: Preliminary results. American Journal of Gastroenterology 2015;110:S553.	Wrong study type (conference abstract only)
6.	Mergenhagen KA, Wojciechowski AL, Paladino JA. A review of the economics of treating Clostridium difficile infection. Pharmacoeconomics 2014;32:639-50.	Wrong study type (not a full economic evaluation)
7.	Szabolcs V, Zsuzsanna N, Áron V, et al. Experience with fecal microbiota transplantation in the treatment of clostridium difficile infection. Orvosi Hetilap 2014;155:1758-62.	Not in English.
8.	Vermeire S, Joossens M, Verbeke K, et al. Donor Species Richness Determines Faecal Microbiota Transplantation Success in Inflammatory Bowel Disease. J Crohns Colitis 2016;10:387-94.	Wrong study type (included at title-abstract review as a potential cohort study comparing different routes of administration, however the results are not stratified and no comparison can be made (and insufficient patients were studied (N<30) for the study to be included as a case series).
9.	Zellmer C, De Wolfe TJ, Van Hoof S, Blakney R, Safdar N. Patient	Case series with <70% follow-

	Citation	Reason for exclusion after full-text review
	Perspectives on Fecal Microbiota Transplantation for Clostridium Difficile Infection. Infectious diseases and therapy 2016.	up.
(note)	Waye A, Atkins K, Kao D. Cost Averted With Timely Fecal Microbiota Transplantation in the Management of Recurrent Clostridium difficile Infection in Alberta, Canada. J Clin Gastroenterol 2016.	Excluded for KQ5 (econ) as the study does not formally link cost with outcome and is thus not a complete economic evaluation. However the study is included for KQ1 (retrospective comparative database study).

*The following articles were excluded at title-abstract as duplicate publications: the abstracts were identical to those of included studies:

- Bourlioux P. Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent Clostridium difficile infection. Ann Pharm Fr 2015;73:163-8. doi: 10.1016/j.pharma.2015.02.001. Epub Mar 4.
  - Duplicate of included publication (Cammarota G, Masucci L, Ianiro G, et al. Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent Clostridium difficile infection. Aliment Pharmacol Ther 2015;41:835-43.)

- Hirsch BE, Saraiya N, Poeth K, Schwartz RM, Epstein ME, Honig G. Fecal Microbiota Transplantation Induces Remission in Patients With Active Ulcerative Colitis in a Randomized Controlled Trial. BMC Infect Dis 2015;15:191.:10.1186/s12879-015-0930-z.
  - Duplicate of included publication (Moayyedi P, Surette MG, Kim PT, et al. Fecal Microbiota Transplantation Induces Remission in Patients With Active Ulcerative Colitis in a Randomized Controlled Trial. Gastroenterology 2015;149:102-9 e6.)

- Kumar R, Maynard CL, Eipers P, et al. Frozen vs Fresh Fecal Microbiota Transplantation and Clinical Resolution of Diarrhea in Patients With Recurrent Clostridium difficile Infection: A Randomized Clinical Trial. BMC Microbiol 2016;16:5.:10.1186/s12866-015-0622-2. .
  - Duplicate of included publication (Lee CH, Steiner T, Petrof EO, et al. Frozen vs Fresh Fecal Microbiota Transplantation and Clinical Resolution of Diarrhea in Patients With Recurrent Clostridium difficile Infection: A Randomized Clinical Trial. JAMA 2016;315:142-9.)

- Rosenfeld CS. Findings From a Randomized Controlled Trial of Fecal Transplantation for Patients With Ulcerative Colitis. Drug Metab Dispos 2015;43:1557-71. doi: 10.124/dmd.115.063826. Epub 2015 Apr 7.
  - Duplicate of included publication (Rossen NG, Fuentes S, van der Spek MJ, et al. Findings From a Randomized Controlled Trial of Fecal Transplantation for Patients With Ulcerative Colitis. Gastroenterology 2015;149:110-8 e4.)

- Zellmer C, De Wolfe TJ, Van Hoof S, Blakney R, Safdar N. Economic Evaluation of Fecal Microbiota Transplantation for the Treatment of Recurrent Clostridium Difficile Infection in Australia. Infect Dis Ther 2016;5:155-64. doi: 10.1007/s40121-016-0106-1. Epub 2016 Apr 5.
  - Duplicate of included publication (Merlo G, Graves N, Brain D, Connelly L. Economic Evaluation of Fecal Microbiota Transplantation for the Treatment of Recurrent Clostridium Difficile Infection in Australia. J Gastroenterol Hepatol 2016.)

APPENDIX D. Class of Evidence, Strength of Evidence, and QHES Determination

Each study is rated against pre-set criteria that resulted in a Risk of Bias (RoB) assessment and presented in a table. The criteria are listed in the Tables below.

Definition of the risk of bias for studies on therapy*

Risk of Bias	Studies of Therapy*	
	Study design	**Criteria***
Low risk: Study adheres to commonly held tenets of high quality design, execution and avoidance of bias	Good quality RCT	• Random sequence generation • Statement of allocation concealment • Intent-to-treat analysis • Blind or independent assessment for primary outcome(s) • Co-interventions applied equally • F/U rate of 80%+ and <10% difference in F/U between groups • Controlling for possible confounding‡
Moderately low risk: Study has potential for some bias; study does not meet all criteria for class I, but deficiencies not likely to invalidate results or introduce significant bias	Moderate quality RCT	• Violation of one or two of the criteria for good quality RCT
	Good quality cohort	• Blind or independent assessment for primary outcome(s) • Co-interventions applied equally • F/U rate of 80%+ and <10% difference in F/U between groups • Controlling for possible confounding‡
Moderately High risk: Study has significant flaws in design and/or execution that increase potential for bias that may invalidate study results	Poor quality RCT	• Violation of three or more of the criteria for good quality RCT
	Moderate or poor quality cohort	• Violation of any of the criteria for good quality cohort
	Case-control	• Any case-control design
High risk: Study has significant potential for bias; lack of comparison group precludes direct assessment of important outcomes	Case series	• Any case series design

* Additional domains evaluated in studies performing a formal test of interaction for subgroup modification (i.e., HTE) based on recommendations from Oxman and Guyatt[3]:

- Is the subgroup variable a characteristic specified at baseline or after randomization? (subgroup hypotheses should be developed a priori)
- Did the hypothesis precede rather than follow the analysis and include a hypothesized direction that was subsequently confirmed?
- Was the subgroup hypothesis one of a smaller number tested?

† Outcome assessment is independent of healthcare personnel judgment. Reliable data are data such as mortality or re-operation.
‡ Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.

Determination of Overall Quality of Evidence

Following the assessment of the quality of each individual study included in the report, an overall "quality of evidence" for the relevant question or topic is determined. Methods for determining the overall quality of evidence are variable across the literature and are most applicable to evaluation of therapeutic studies.

SRI's method incorporates the primary domains of quality (risk of bias), quantity of studies and consistency of results across studies as described by AHRQ.

The following four possible levels and their definition will be reported:

- **High** – High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate** - Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- **Low** - Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and likely to change the estimate.
- **Insufficient** – Evidence either is unavailable or does not permit a conclusion.

All AHRQ "required" and "additional" domains (risk of bias, consistency, directness, precision, publication bias) are assessed. Bodies of evidence consisting of RCTs were initially considered as High strength of evidence, while those comprised of nonrandomized studies began as Low strength of evidence. The strength of evidence could be downgraded based on the limitations described above. There are also situations where the nonrandomized studies could be upgraded, including the presence of plausible unmeasured confounding and bias that would decrease an observed effect or increase an effect if none was observed, and large magnitude of effect (strength of association).

Example methodology outline for determining overall strength of evidence (SoE):

All AHRQ "required" and "additional" domains* are assessed. Only those that influence the baseline grade are listed in table.

Baseline strength: HIGH = majority of articles RCTs. LOW = majority of articles cohort studies.

DOWNGRADE: Risk of bias for the individual article evaluations (1 or 2); Inconsistency** of results (1 or 2); Indirectness of evidence (1 or 2); Imprecision of effect estimates (1 or 2); Sub-group analyses not stated *a priori* and no test for interaction (2)

UPGRADE: Large magnitude of effect (1 or 2); Dose response gradient (1)

Outcome	Strength of Evidence	Conclusions & Comments	Baseline	DOWNGRADE	UPGRADE
Outcome	**HIGH**	Summary of findings	**HIGH** RCTs	**NO** consistent, direct, and precise estimates	**NO**
Outcome	**MODERATE**	Summary of findings	**LOW** Cohort studies	**NO** consistent, direct, and precise estimates	**YES** Large effect
Outcome	**LOW**	Summary of findings	**HIGH** RCTs	**YES (2)** Inconsistent Indirect	**NO**

*Required domains: risk of bias, consistency, directness, precision. Plausible confounding that would decrease observed effect is accounted for in our baseline risk of bias assessment through individual article evaluation. Additional domains: dose-response, strength of association, publication bias.

**Single study = "consistency unknown", not downgraded

Assessment of Economic Studies

Full formal economic analyses evaluate both costs and clinical outcomes of two or more alternative interventions. The four primary types are cost minimization analysis (CMA), cost-utility analysis (CUA), cost-effectiveness analysis (CEA), and cost-benefit analyses (CBA). Each employs different methodologies, potentially complicating critical appraisal, but some common criteria can be assessed across studies.

No standard, universally accepted method of critical appraisal of economic analyses is currently in use. A number of checklists [Canadian, BMJ, AMA] are available to facilitate critique of such studies. The Quality of Health Economic Studies (QHES) instrument developed by Ofman, et al[2]. QHES embodies the primary components relevant for critical appraisal of economic studies[1,2]. It also incorporates a weighted scoring process and which was used as one factor to assess included economic studies. This tool has not yet undergone extensive evaluation for broader use but provides a valuable starting point for critique.

In addition to assessment of criteria in the QHES, other factors are important in critical appraisal of studies from an epidemiologic perspective to assist in evaluation of generalizability and potential sources of study bias.

Such factors include:

- Are the interventions applied to similar populations (e.g., with respect to age, gender, medical conditions, etc.)? To what extent are the populations for each intervention comparable and are differences considered or accounted for? To what extent are population characteristics consistent with "real world" applications of the comparators?
- Are the sample sizes adequate so as to provide a reasonable representation of individuals to whom the technology would be applied?
- What types of studies form the basis for the data used in the analyses? Data (e.g., complication rates) from randomized controlled trials or well-conducted, methodologically rigorous cohort studies for data collection are generally of highest quality compared with case series or studies with historical cohorts.
- Were the interventions applied in a comparable manner (e.g., similar protocols, follow-up procedures, evaluation of outcomes, etc.)?
- How were the data and/or patients selected or sampled (e.g., a random selection of claims for the intervention from a given year/source or all claims)? What specific inclusion/exclusion criteria or processes were used?
- Were the outcomes and consequences of the interventions being compared comparable for each? (e.g., were all of the relevant consequences/complications for each intervention considered or do they primarily reflect those for one intervention?)

Assessment of the overall strength of evidence for formal economic analyses does not appear to be documented in the literature.

References

1. Chiou CF, Hay JW, Wallace JF, et al. Development and validation of a grading system for the quality of cost-effectiveness studies. Med Care 2003;41:32-44.
2. Ofman JJ, Sullivan SD, Neumann PJ, et al. Examining the value and quality of health economic analyses: implications of utilizing the QHES. J Manag Care Pharm 2003;9:53-61.
3. Oxman AD, Guyatt GH. A consumer's guide to subgroup analyses. Ann Intern Med 1992;116:78-84.

APPENDIX E. Study quality: Risk of bias and QHES evaluation

Appendix Table E1. CDI Risk of Bias Evaluation: FMT vs. antibiotics or placebo studies

Study year	Random sequence generation	Statement of concealment*	Intention to treat*	Blind outcome assessment	Co-interventions applied equally	Complete F/U of ≥80%	<10% difference in F/U between groups	Controlling for confounding	Risk of Bias
RCTs									
Cammarota 2015	Yes	Yes	Yes	No	Yes	Yes (92%)	No (100% vs. 84%)	Yes	Mod Low
van Nood 2013	Yes	Yes	No	Yes†	Yes	Yes (95%)	Yes (94% vs. 92% vs. 100%)	No	Mod Low
Kelly 2016	Yes	Yes	Yes	Yes	Yes	Yes (93%)	Yes (95% vs. 92%)	Yes	Low
Cohort studies									
Lagier 2015	*(n/a)*	*(n/a)*	*(n/a)*	Unclear	Unclear	Yes (96%)	Yes (100% vs. 96%)	No	Mod High

n/a: not applicable

*Domains assessed for RCTs only

†The primary outcome of cure was determined by a blinded adjudication committee based on stool test results for C. difficile toxin and patient-reported diarrhea (as recorded in a stool diary); patients were not blinded to treatment received.

Unclear: no information provided unless otherwise noted below

Reasons for No credit (or unclear credit if for reason other than no info provided):

- Cammarota: Blinding: neither patients nor researchers blinded; Loss to follow-up: authors stated that 3 patients in the control group were lost to follow-up though it wasn't clear when this occurred
- van Nood: Intention to Treat: one patient in FMT group was excluded after deviation from protocol (the patient needed high-dose prednisolone due to a rapid decline in renal-graft function (the graft dysfunction was noted "immediately after randomization", the patient received vancomycin for 45 days and after a relapse was successfully treated with FMT); Controlling for Confounding: no credit given because multiple variables were unbalanced between groups at baseline and were not controlled for (e.g., mean age, sex, Charlson comorbidity index, previous failure of antibiotic treatment)
- Lagier: Controlling for Confounding: no credit given because there was no explicit statement that either (a) factors that could affect outcomes were evaluated as potential confounders or (b) specific factors were controlled for.

Appendix Table E2. IBD Risk of Bias Evaluation: FMT vs. placebo studies

Study year	Random sequence generation	Statement of concealment*	Intention to treat*	Blind outcome assessment	Co-interventions applied equally	Complete F/U of ≥80%	<10% difference in F/U between groups	Controlling for confounding	Risk of Bias
RCTs									
Moayyedi 2015	Yes	Yes	Yes	Yes	Yes	Yes (93%)	Yes (92% vs. 95%)	Yes†	**Low**
Rossen 2015	Unclear	Unclear	No	Yes	Yes	Varies‡ (6 weeks: 76% (37/49); 12 weeks: 80% (39/49))	Yes‡ 6 weeks: (71% (17/24) vs. 80% (20/25); 12 weeks: (75% (18/24) vs. 84% (21/25))	No	**Mod High**

n/a: not applicable

*Domains assessed for RCTs only

† Although there were baseline differences b/w groups that were not controlled for (age, sex, white race, presence of pancolitis, and concomitant use of immunosuppressants), the authors performed logistic regression analysis for all of these factors and found that none were associated with the primary outcome (remission).

‡ Rossen 2015 follow-up details:

- We assumed 49 patients were randomized (FMT-D: n=24; FMT-A: n=25: although 50 were initially randomized 1:1 to the FMT-D and FMT-A groups (so 25 randomized to each group), 1 patient (in the FDT-D group) was excluded post-randomization due to wrong diagnosis. We re-included one (other) FMT-D patient that the authors excluded from all analyses because no treatment was received.
- 6 weeks:
  - FMT-D: 6 FMT-D patients did not attend the 6-week evaluation; 1 FMT-D patient was excluded from all analyses because no treatment was received: total FMT-D follow-up: 17/24
  - FMT-A: 5 FMT-D patients did not attend the 6-week evaluation: total FMT-A follow-up: 20/25
- 12 weeks:
  - FMT-D: 1 FMT-D patient did not attend the 12-week evaluation; 3 FMT-D patients needed rescue therapy and were excluded; 1 FMT-D patient received antibiotic therapy for traveller's diarrhea and was excluded; and 1 FMT-D patient was excluded from all analyses because no treatment was received: total FMT-D follow-up: 18/24
  - FMT-A: 1 FMT-A patient did not attend the 12-week evaluation; 3 FMT-A patients needed rescue therapy and were excluded;: total FMT-A follow-up: 21/25

Unclear: no information provided unless otherwise noted below

Reasons for No credit (or unclear credit if for reason other than no info provided):

- Rossen: Intention to Treat: no credit given, as two patients were excluded from the study after randomization and not included in any analysis; Controlling for Confounding: no credit given because two patients randomized were excluded from baseline characteristics and there were differences between groups in baseline characteristics that were not evaluated or controlled for (% patients with E2/left-sided disease, E3/pancolitis; % patients with concomitant drug treatment; and differences in Mayo score; differences in SCCAI score)

Appendix Table E3. CDI Risk of Bias Evaluation: FMT vs. FMT (comparisons of different routes, forms, timing of administration) studies

Study year	Random sequence generation	Statement of concealment*	Intention to treat*	Blind outcome assessment	Co-interventions applied equally	Complete F/U of ≥80%	<10% difference in F/U between groups	Controlling for confounding	Risk of Bias
RCTs									
Lee 2016	Yes	Yes	No	Yes†	Yes	Yes (91%)	Yes (91% (83/91) vs. 91% (107/118))	No	Mod Low
Youngster 2014	Yes	Yes	Yes	No	Yes	Yes (100%)	Yes (100% vs. 100%)	No	Mod Low
Cohort studies									
Satokari 2015	*(n/a)*	*(n/a)*	*(n/a)*	No	Yes	Yes (12 weeks: 100%; 12 months: 86%)	12 weeks: Yes (100% vs. 100%) 12 months: No (96% vs. 74%)	No	Mod High
Waye 2016	*(n/a)*	*(n/a)*	*(n/a)*	No	Unclear	Yes (94%)	Unclear	No	Mod High

n/a: not applicable

*Domains assessed for RCTs only

†Lee: Credit given for blind outcome assessment as patients (and the investigator) were blinded and the primary outcome was no recurrence of CDI-related diarrhea (patient-reported) in the absence of need for antibiotics; further, a data monitoring board monitored the trial

Unclear: no information provided unless otherwise noted below

Reasons for No credit (or unclear credit if for reason other than no info provided):

- Lee: Intention to Treat: no credit as 6 patients were excluded after randomization ("for safety reasons", prior to treatment) and were omitted from all analyses; Controlling for Confounding: no credit as baseline characteristics were not reported for all patients randomized (and instead were only reported for the patients who received FMT), in addition, there were slight differences between groups that were not controlled for (factors with baseline differences: % of patients: inpatient at time of FMT, mild CDI severity, severe CDI severity, <2 CDI recurrences, ≥2 CDI recurrences).
- Youngster: Blind assessment: no credit as the study was open-label and no information was reported to indicate outcome assessment was blinded; Controlling for Confounding: no credit given because there was a large difference in time since initial CDI b/w groups (7 vs. 12 months) that was not controlled for
- Satokari: Blind assessment: no credit as the study was conducted retrospectively and no information was provided to indicate that blind outcome assessment was performed; Controlling for Confounding: no credit given because there was no explicit statement that either (a) factors that could affect outcomes were evaluated as potential confounders or (b) specific factors were controlled for.
- Waye: Blind assessment: no credit as the study was a retrospective database study; Controlling for Confounding: no credit given because there was no explicit statement that either (a) factors that could affect outcomes were evaluated as potential confounders or (b) specific factors were controlled for.

Appendix Table E4. Quality of Health Economic Studies (QHES) score of included articles

QHES Question (points possible)		Konijeti 2014	Lapointe-Shaw 2016	Merlo 2016	Varier 2015	Varier 2014
1.	Was the study objective presented in a clear, specific, and measurable manner? (7 pts)	7	7	7	7	7
2.	Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated? (4 pts)	4	4	0	4	4
3.	Were variable estimates used in the analysis from the best available source (i.e. randomized controlled trial = best, expert opinion = worst)? (8 pts)	8	8	8	0	0
4.	If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study? (1 pt)	1	1	1	1	1
5.	Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions? (9 pts)	9	9	0	9	9
6.	Was incremental analysis performed between alternatives for resources and costs? (6 pts)	6	6	6	6	6
7.	Was the methodology for data abstraction (including the value of health states and other benefits) stated? (5 pts)	0	0	0	0	0
8.	Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate? (7 pts)	7	0	0	0	0
9.	Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described? (8 pts)	8	8	8	8	8
10.	Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term, long-term and negative outcomes included? (6 pts)	6	6	6	6	6
11.	Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used? (7 pts)	7	7	7	7	7
12.	Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner? (8 pts)	8	8	0	8	8
13.	Were the choice of economic model, main assumptions, and limitations of the study stated and justified? (7 pts)	7	7	0	7	7
14.	Did the author(s) explicitly discuss direction and magnitude of potential biases? (6 pts)	0	6	0	0	0
15.	Were the conclusions/recommendations of the study justified and based	8	8	8	8	8

QHES Question (points possible)		Konijeti 2014	Lapointe-Shaw 2016	Merlo 2016	Varier 2015	Varier 2014
	on the study results? (8 pts)					
16.	Was there a statement disclosing the source of funding for the study? (3 pts)	3	3	3	3	0
	Total score:	**89**	**88**	**54**	**74**	**71**

APPENDIX F. Study Characteristics Data Abstraction Tables

Appendix Table F1. CDI Study and Patient Characteristics Data Abstraction Tables: FMT vs. Antibiotics

Study (Country)	N	Inclusion & Exclusion Criteria	Interventions	Donor feces	Route	Repeat Treatment	Length, % f/u	Co-interventions	Patient Characteristics	Funding
RCTs										
Cammarota 2015 (Italy) NOTE: The trial was stopped early (at 1-year interim analysis) b/c "FMT showed a significantly higher efficacy than vancomycin" after consulting an independent committee (inc. 2 internists and 1 gastroenter-ologist)	N=39	Inclusion: Age ≥18 years, life expectancy ≥3 mos., recurrence of *C. difficile* (diarrhea (see below) plus stool positive for *C. difficile* toxin ≤10 days of end of last course of antibiotics)) after ≥1 course of adequate antibiotic therapy (see below); able to undergo colonoscopy Diarrhea: ≥3 loose or watery stools per day for ≥2 consecutive days, or ≥8 loose stools w/in 48 hours Adequate antibiotic therapy: Vancomycin ≥125 mg 4x/day X ≥10 days, or metronidazole 500 mg 3x/day X ≥10 days Exclusion: **P**rolonged immunodeficiency due to recent	FMT + bowel lavage (n=20): Short-course of vancomycin (125 mg orally 4x/day X 3 days), on last 1 or 2 days of antibiotics a bowel lavage was performed (4L macrogol solution (SELG ESSE (not defined))), and FMT performed on the following day using fresh donor feces and administration via colonoscopy Vancomycin (n=19): Standard-course of vancomycin (125 mg orally 4x/day X 10 days) and then a pulse regimen for ≥3 weeks (125-500 mg every 2-3 days)	Fresh donor feces collected on day of use (time from collection to infusion ≤6 (mean 3.8 ± 0.8) hours), diluted with 500 ml sterile saline, mixed, strained, and infused Donor: age <50 years, preferably patient's relatives or friends, no antibiotic use in prior 6 mos. or had evidence of other intestinal disease; not meeting additional exclusion	Colono-scopy (~10 min. procedure, patient re-cumbent for ≥1 hr. post-FMT, patient monitored for 2 hours)	Upon infection recurrence: FMT: Repeat FMT every 3 days until resolution; if >1 repeat FMT needed patients were restricted to light diet and underwent bowel lavage with 2L solution prior to colon-oscopy. (NOTE: this was amended from original protocol after two patients underwent FMT; the original protocol was a single repeat FMT procedure	10 weeks from end of last received treatment (i.e., 10 weeks from last FMT procedure, 10 weeks from end of vancomycin treatment) % f/u NR FMT vs. vancomycin: NR vs. 84% (16/19)	None reported	FMT+ bowel lavage vs. Vancomycin (p>0.05 for all as reported by study) Age (mean (range)): 71 (29-89) vs. 75 (49-93) % Female: 60% (12/20) vs. 58% (11/19) Recurrences of CDI (median (range)): 3 (2-5) vs. 3 (1-4) Stool frequency/24 hours (median (range)): 6 (2-15) vs. 6 (2-12) Prior tapered vancomycin therapy: 95% (19/20) vs. 84% (16/19) Days of antibiotic use for CDI since initial diagnosis: NR Antibiotic use prior to CDI: 100% (20/20) vs. 100% (19/19)	Partially funded by the Catholic University of Rome. Statement of no personal conflicts of interest.

Study (Country)	N	Inclusion & Exclusion Criteria	Interventions	Donor feces	Route	Repeat Treatment	Length, % f/u	Co-interventions	Patient Characteristics	Funding
		chemotherapy, HIV infection, or prolonged steroid use; pregnancy; antibiotic use other than metronidazole, vancomycin, or fidaxomicin at baseline; admission to intensive care unit; requirement for vasoactive drugs; other infectious causes of diarrhea		criteria*; pre-screened for multiple pathogens (viruses, bacteria, parasites).		within 1 week; this was done after the first 2 patients died from sepsis after recurrence) Antibiotic group: FMT not offered			Hospital-acquired CDI: 50% (10/20) vs. 74% (14/19) Karnofsky performance status: NR Charlson comorbidity index (0-100 (best))‡ (median (range)): 2 (0-5) vs. 2 (1-5) Admitted to hospital at inclusion:75% (15/20) vs. 84% (16/19) Use of proton-pump inhibitor: 55% (11/20) vs. 68% (13/19) Admitted to ICU within previous month: NR Feeding tube present: NR Stool positive for *C. difficile* toxin at inclusion: 59% (23/39) (NR by treatment group)	
van Nood 2013 (The Netherlands) NOTE: The trial was stopped early (at interim analysis	N=43	Inclusion: Age ≥18 years, life expectancy ≥3 mos., recurrence of *C. difficile* (diarrhea (see below) plus stool positive for *C. difficile* toxin using the Meridian A/B	FMT + bowel lavage (n=17): Short-course of vancomycin (500 mg orally 4x/day X 4-5 days), on last day of antibiotics a bowel lavage was performed (4L macrogol solution	Fresh donor feces collected on day of use (time from collection to infusion ≤6 (mean 3.1 ± 1.9)	Nasoduo-denal tube (2-3 minutes per 50 ml); tube removed 30 minutes after infusion;	Upon infection recurrence: FMT: repeat FMT procedure using feces from a	6 mos. 95% (41/43) FMT: 94% (16/17) Vancomycin: 92% (12/13) Vancomycin + bowel lavage:	None reported	FMT vs. Vancomycin vs. Vancomycin + bowel lavage (p>0.05 for all as reported by study): Age (mean ± SD):	Grant-supported (The Netherlands Organization for Health Research and Development, Spinoza Award to one

Study (Country)	N	Inclusion & Exclusion Criteria	Interventions	Donor feces	Route	Repeat Treatment	Length, % f/u	Co-interventions	Patient Characteristics	Funding
conducted ad-hoc) b/c "most patients in both control groups had a relapse" as advised by the data and safety monitoring board		toxin premier test)) after ≥1 course of adequate antibiotic therapy (see below) Diarrhea: ≥3 loose or watery stools per day for ≥2 consecutive days, or ≥8 loose stools w/in 48 hours Adequate antibiotic therapy: Vancomycin ≥125 mg 4x/day X ≥10 days, or metronidazole 500 mg 3x/day X ≥10 days Exclusion: Prolonged compromised immunity due to recent chemotherapy, HIV infection with CD4 count <240, or prolonged prednisolone use at dose of ≥60 mg/day; antibiotic use at baseline other than for *C. difficile* infection; admission to intensive care unit; use of vasopressor medication	(Klean-Prep)), and FMT performed on the following day using fresh donor feces and nasoduodenal administration Vancomycin alone (n=13): Standard-course of vancomycin (500 mg orally 4x/day X 14 days) Vancomycin + bowel lavage (n=13): Standard-course of vancomycin + bowel lavage on day 4 or 5.	hours), diluted with 500 ml sterile saline, mixed, strained, and infused Donor: age <60 years, pre-screened for multiple pathogens (viruses, bacteria, parasites).	patients monitored for 2 hours	different donor Antibiotic groups: FMT offered off-protocol	100% (13/13) Note: In FMT group, 1 patient excluded (required high-dose prednisolone for rapid decline in renal graft function noticed immediately following randomization but prior to FMT) In vancomycin group, 1 patient received treatment, then discontinued all medication b/c of severe heart failure and chronic obstructive pulmonary disease; patient died 13 days post-randomization (no data reported,		73 ± 13 vs. 66 ± 14 vs. 69 ± 16 % Female: 50% (8/16) vs. 54% (7/13) vs. 23% (3/13) Recurrences of CDI (median (range)): 3 (1-5) vs. 3 (1-4) vs. 2 (1-9) Stool frequency/24 hours (median (range)): 5 (3-20) vs. 5 (3-12) vs. 5 (3-10) Prior failure of tapered vancomycin therapy: 62% (10/16) vs. 62% (8/13) vs. 46% (6/13) Days of antibiotic use for CDI since initial diagnosis, (mean ± SD): 63 ± 41 vs. 51 ± 27 vs. 49 ± 38 Reported antibiotic use prior to CDI: 100% (16/16) vs. 92% (12/13) vs. 100% (13/13) Hospital-acquired CDI: 62% (10/16) vs. 46% (6/13) vs.	investigator from the Organization Organiztion for Scientific Research); primary investigator received lecture fees from Astellas, 3 investigators served on advisory board and received consulting fees from Astellas; 2 investigators served on advisory board and received consulting fees from Microbex.

Study (Country)	N	Inclusion & Exclusion Criteria	Interventions	Donor feces	Route	Repeat Treatment	Length, % f/u	Co-interventions	Patient Characteristics	Funding
							patient considered to have failed treatment in analysis)		77% (10/13) Karnofsky performance status (0-100 (higher function)), (mean ± SD†): 50 ± 18 vs. 50 ± 17 vs. 56 ± 21 Charlson comorbidity index (median (range)): 3 (0-4) vs. 1 (0-8) vs. 1 (0-6) Admitted to hospital at inclusion: 31% (5/16) vs. 31% (4/13) vs. 31% (4/13) Use of proton-pump inhibitor: 81% (13/16) vs. 77% (10/13) vs. 85% (11/13) Admitted to ICU within previous month: 6% (1/16) vs. 0% (0/13) vs. 8% (1/13) Feeding tube present: 19% (3/16) vs. 15% (2/13) vs. 15% (2/13)	
Cohort studies										
Lagier 2015 Retrospective	N=61	Inclusion: Patients hospitalized for *C. difficile*	FMT + bowel lavage (n=16): Treated starting	Fresh donor feces (≥30 g) produced	Naso-duodenal tube;	In case of relapse or treatment	Unclear; outcomes reported up to	None reported	FMT vs. control Age (mean (range)): 84 (65-	IHU Méditerranée Infection

Study (Country)	N	Inclusion & Exclusion Criteria	Interventions	Donor feces	Route	Repeat Treatment	Length, % f/u	Co-interventions	Patient Characteristics	Funding
with historical controls (France)		ribotype 027 (CD027)-associated diarrhea Exclusion: prolonged compromised immunity and patients treated by antibiotics for infections other than *C. difficile* on the day of fecal microbiota transplant	12/2013. Conventional antibiotic treatment (see below, no further details provided); bowel lavage (4L Klean Prep or two glasses of Fast Prep); FMT was performed on the following day using fresh donor feces and nasoduodenal administration Control group (n=45): Treated between 3/2013 and 11/2013. *Antibiotic regimen only (n=42/45)* •For mild cases: metronidazole (500 mg 3x daily for 14 days) •For severe cases†: metronidazole (500 mg 3x daily for 14 days) and vancomycin (125 mg 4x daily for 14 days) *FMT after at least 3*	≤6 hours prior to use; diluted in 400 ml of 0.9% NaCl and mixed using a blender for ≥10 mins (filtered to eliminate debris if needed); kept at room temperature in a syringe until infusion Donor: healthy family members or volunteers; pre-screened for multiple pathogens (viruses, bacteria, parasites); Excluded: BMI >30, active cancer, diarrhea, or under-going treatment	positioning was performed and checked by a chest X-ray, then 200 ml of 1.4 % bicarbonates was instilled 15 min before transplantation	failure: FMT + bowel lavage: second fecal trans-plantation Control group: Antibiotic regimen only •For mild cases: vancomycin (125 mg 4x daily for 14 days), then fidaxomicin (200 mg 2x daily for 10 days) as third step •For severe cases†: fidaxomicin (200 mg 2x daily for 10 days) FMT after at least 2 relapses: NA	166 days (%NR) For primary outcome of mortality at 31 days, 95.1% (58/61) FMT: 100% (16/16) Control: 95.6% (43/45)		94) years vs. 84 (48-101) years % Female: 87.5% (2/16) vs. 57.5% (19/45) Recurrences of CDI (mean, range): 0.0 vs. NR (1 to ≥3) Simplified Acute Physiology Score (mean (range)): 27 (13-71) vs. 28 (13-87) Malignancy: 25.0% (4/16) vs. 24.4% (11/45) Diabetes: 18.8% (3/16) vs. 22.2% (10/45) AIDS: 0% vs. 2.2% (1/45)	The authors declare that they have no conflict of interest

Study (Country)	N	Inclusion & Exclusion Criteria	Interventions	Donor feces	Route	Repeat Treatment	Length, % f/u	Co-interventions	Patient Characteristics	Funding
			relapses/ recurrences (n=3/45) Upon recurrence after at least three courses of antibiotics, patients were offered FMT.	with immuno-suppressive drugs or antibiotics in previous 3 mos.						

*Donor exclusion criteria: antibiotic use ≤6 mos., evidence of possible intestinal disease, "lifestyle associated with increased risk for contracting infections," travel to tropical area in prior 3 mos., new sexual relation in prior 6 mos., recent needle stick accident, prior receipt of blood products, tattoos, inflammatory bowel disease or gastrointestinal cancer history in family, systemic disease, use of drugs that could be found in feces that posed risk to patient.
†van Nood: the study indicated that these scores were medians, however medians were otherwise reported with ranges and the table containing the data is footnoted to indicate that scores were reported as mean ± SD.

Appendix Table F2. CDI Study and Patient Characteristics Data Abstraction Tables: FMT vs. Placebo

Study (Country)	N	Inclusion & Exclusion Criteria	Interventions	Donor feces	Route	Repeat Treatment	Length, % f/u	Co-interventions	Patient Characteristics	Funding
RCTs										
Kelly 2016 (USA)	N= 46	Inclusion: Adult outpatients with ≥3 CDI recurrences (≥3 unformed stools over 24 hours for 2 consecutive days; documented by a positive stool test for *C. difficile* or by evidence of pseudomembranes on colonoscopy) despite a course of tapered or pulsed vancomycin (or other antibiotic used for CDI) (or were not able to taper or discontinue vancomycin or other antibiotic used for CDI). The most recent occurrence of CDI was treated with ≥10 days vancomycin, with continued therapy up to 2-3 days prior to FMT infusion. Exclusion: Age ≥75, inflammatory bowel disease, irritable bowel syndrome, chronic diarrheal	Donor FMT + bowel lavage (n=22): ≥10 day course vancomycin, with continued therapy up to 2-3 days prior to FMT infusion (dose NR), bowel lavage performed day before FMT, and FMT performed on the following day using fresh donor feces and administration via colonoscopy Autologous FMT + bowel lavage (n=24): Same as Donor FMT except autologous stool infused	Fresh donor or autologous feces collected on day of use (time from collection to infusion ≤6 hours), diluted proportionately with sterile saline, mixed, and infused. Mean stool dose infused was 64 ± 25 g (range, 25-100g). Donor: healthy volunteer or patient-identified donor, pre-screened for multiple pathogens (viruses, bacteria,	Colono-scopy (~10 min. procedure, patient re-cumbent for ≥1 hr. post-FMT, patient monitored for 2 hours)	Upon infection recurrence within 8 weeks: Donor FMT: repeat FMT procedure using feces from a different donor Autologous FMT: repeat FMT procedure using donor feces	2 mos. (8 weeks) 93% (43/46) Donor FMT: 95% (21/22) Autologous FMT: 92% (22/24)	None reported	Donor FMT (n=22) vs. Autologous FMT (n=24): Age (mean ± SD): 48 ± 16 vs. 55 ± 14 (p=0.12) % Female: 82% (18/22) vs. 79% (19/24) BMI (mean ± SD): 28 ± 8 vs. 27 ± 7 Charlson comorbidity index (median (range)): 1 (0-4) vs. 0 (0-3) Duration of CDI since initial diagnosis (mean ± SD (range)): 9 ± 9 (3-36) vs. 12 ± 12 (3-48) months Recurrences of CDI (mean ± SD (range)): 4 ± 2 (3-9) vs. 5 ± 2 (2-10) Duration of oral vancomycin therapy (mean ± SD (range)): 28 ± 36 (6-140) vs. 23 ± 30 (8-148) weeks % Prior fidaxomicin use: 27% (6/22) vs.	National Institute of Diabetes and Digestive and Kidney Diseases

Study (Country)	N	Inclusion & Exclusion Criteria	Interventions	Donor feces	Route	Repeat Treatment	Length, % f/u	Co-interventions	Patient Characteristics	Funding
		disorder, immunocomprised condition, anaphylactic food allergy, history of FMT, untreated in situ colorectal cancer, inability to undergo colonoscopy.		parasites). Autoogous feces: all patients underwent a bowel purge prior to FMT; the first stool passed was collected and used for the autologous FMT treatment (if that was the treatment allocated)					33% (8/24) % Prior rifaximin use: 13% (3/22) vs. 4% (1/24) % Proton pump inhibitor use: 9% (2/22) vs. 8% (2/24)	
Cohort studies										
(None)										

*Donor exclusion criteria: antibiotic use ≤6 mos., evidence of possible intestinal disease, "lifestyle associated with increased risk for contracting infections," travel to tropical area in prior 3 mos., new sexual relation in prior 6 mos., recent needle stick accident, prior receipt of blood products, tattoos, inflammatory bowel disease or gastrointestinal cancer history in family, systemic disease, use of drugs that could be found in feces that posed risk to patient.
†van Nood: the study indicated that these scores were medians, however medians were otherwise reported with ranges and the table containing the data is footnoted to indicate that scores were reported as mean ± SD.

Appendix Table F3. IBD Study and Patient Characteristics Data Abstraction Tables: FMT vs. Alternative Treatment

Study (Country)	N	Inclusion & Exclusion Criteria	Interventions	Donor feces	Route	Repeat Treatment	Length, % f/u	Co-interventions	Patient Characteristics	Funding
RCTs										
Moayyedi 2015 (Canada) Note: The trial was stopped early at the approximate 50% recruitment point "for futility because the primary endpoint was unlikely to be achieved as specified in the protocol".	N = 75	Inclusion: ≥18 years or older with active UC defined as a Mayo Clinic score ≥4 with an endoscopic Mayo Clinic score ≥1. Concomitant treatments for ulcerative colitis (UC), such as mesalamine, glucocorticoids, immunosuppressive therapy (e.g., azathioprine), or tumor necrosis factor antagonists were permitted, provided these had been used at a stable dose for at least 12 weeks (4 weeks for glucocorticoids) and disease remained active. Exclusion: Antibiotics or probiotics in the last 30 days, had concomitant *C. difficile* infection or another enteric pathogen, had a disease severity that required	FMT (n = 38): No prior bowel lavage or antibiotics given. 50 mL FMT administered as a retention enema with patient in left lateral position with instructions to retain for at least 20 minutes. Repeated once a week for six weeks. Placebo (n = 37): 50 mL water given as a retention enema with patient in left lateral position with instructions to retain for at least 20 minutes. Repeated once a week for six weeks.	50 g of donor feces was collected and mixed with 300 mL of commercial bottled drinking water. Mixture was emulsified for 3-5 minutes then allowed to settle for 5 minutes. Supernatant was either adminstered immediately or stored at -20°C. Donor: Aged 18-60, screened for enteric pathogens such as *Salmonella, Shigella,*	Retention enema with instructions to retain for at least 20 minutes.	FMT and Placebo: Once a week for six weeks per protocol.	7 weeks for both groups; 12 months for FMT patients only % f/u: 93.3% (70/75) % f/u, FMT vs. placebo: 94.7% (36/38) vs. 91.8% (344/37)	None (Note: concomitant treatments for UC (see patient characteristics column) were permitted, provided these had been used at a stable dose for at least 12 weeks (4 weeks for glucocorticoids) and disease remained active)	FMT vs. Placebo ($p < 0.05$ unless otherwise noted) Age (mean ± SD): 42.2 ± 15.0 vs. 35.8 ± 12.1, p = 0.045 % male: 47% (18/38) vs. 70% (26/37), p = 0.044 % white: 95% (36/38) vs. 78% (29/37) % nonsmoker: 50% (19/38) vs. 57% (21/37) % UC < 1 year: 11% (4/38) vs. 11% (4/37) % Pancolitis: (62.5% (20/36) vs. 37.5% (12/37) Concomitant medications: *% Mesalamine therapy:* 55% (21/38) vs. 54% (20/37) *% glucocorticoids:* 39% (15/38) vs. 35% (13/37) *% immunosuppressants:* 29% (11/38) vs. 16% (6/37) *% anti-TNF*	Funded by Hamilton Academic Health Sciences Organization (HAHSO) and Crohn's and Colitis Canada (CCC). COIs: Dr. Moayyedi's chair partly funded by an unrestricted donation given to McMaster University by AstraZeneca; received honoraria for speaking and/or serving on the advisory board for AstraZeneca, Actavis, and Shire Pharmaceuticals. Dr Marshall served as a speaker and/or served on the advisory board for Abbott/Abbvie, Actavis, Aptalis, Ferring,

Study (Country)	N	Inclusion & Exclusion Criteria	Interventions	Donor feces	Route	Repeat Treatment	Length, % f/u	Co-interventions	Patient Characteristics	Funding
		hospitalization, were pregnant, or were unable to give informed consent.		*Campylobacter, E. Coli 0157 H7, Yersinia*, as well as ova, cysts, and parasites and *C. difficile* toxin. Had negative serology for HIV ½, hepatitis A IgM, hepatitis B surface antigen, hepatitis C antibody, syphilis, human T-lymphotrophic virus 1/II and be screened negative for vancomycin-resistant *Enterococcus* or methicillin-resistant *Staphylococcus aureus.*					*therapy:* 13% (5/38) vs. 5% (2/37) Years had UC (mean ± SD): 7.9 ± 5.6 vs. 7.0 ± 6.8 Full Mayo Clinical score, 0-12 (worst) (mean ± SD) (: 8.24 ± 2.61 vs. 7.86 ± 2.28 IBDQ score, 0-224 (best) (mean ± SD): 130.3 ± 36.3 vs. 134.4 ± 32.3 EQ-5D score, 0-100 (best) (mean ± SD): 75.7 ± 20.4 vs. 78.2 ± 15.4	Janssen, Proctor & Gamble, Shire, and Takeda. Dr Reinisch served as a speaker and/or served on the advisory board for Abbott Laboratories, Abbvie, Aesca, Amgen, AM Pharma, Aptalis, Astellas, Astra Zeneca, Avaxia, Bioclinica, Biogen IDEC, Bristol-Myers Squibb, Cellerix, Chemocentryx, Celgene, Centocor, Celltrion, Danone Austria, Elan, Falk Pharma GmbH, Ferring, Galapagos, Genentech, Grünenthal, Inova, Janssen, Johnson & Johnson, Kyowa Hakko Kirin Pharma, Lipid

Study (Country)	N	Inclusion & Exclusion Criteria	Interventions	Donor feces	Route	Repeat Treatment	Length, % f/u	Co-interventions	Patient Characteristics	Funding
										Therapeutics, MedImmune, Millenium, Mitsubishi Tanabe Pharma Corporation, MSD, Novartis, Ocera, Otsuka, PDL, Pharmacosmos, Pfizer, Procter & Gamble, Prometheus, Robarts Clinical Trial, Schering-Plough, Setpointmedical, Shire, Takeda, Therakos, Tigenix, UCB, Vifor, Yakult, Zyngenia, and 4SC. Dr Armstrong has received speakers' fees, consulting fees, research funding, or unrestricted support for educational events from Abbott, Abbvie, Actavis, Aptalis, AstraZeneca, Cook, Cubist, Ferring, Forest, Janssen, Merck, Olympus,

Study (Country)	N	Inclusion & Exclusion Criteria	Interventions	Donor feces	Route	Repeat Treatment	Length, % f/u	Co-interventions	Patient Characteristics	Funding
										Pendopharm, Pentax, Shire, Takeda. and Warner-Chilcott. Dr Kassam was Chief Medical Officer for OpenBiome (after trial was completed). Dr Lee served as a speaker and/or served on the advisory board for Cubist, Merck, and Rebiotix. The remaining authors disclose no conflicts.
Rossen 2015 (Amsterdam) Note: Trial stopped recruiting early because based on observed treatment effect of less than expected, PIs were advised to stop trial due to futility.	N = 48	Inclusion: Established UC according to the Lennard-Jones criteria, a patient-reported Simple Clinical Colitis Activity Index (SCCAI) of ≥4 and ≤11 and stable medication, which was continued during the study period. Endoscopic Mayo score of ≥1 at baseline sigmoidoscopy.	FMT + bowel lavage (n=23): Bowel lavage consisting of 2 L macrogol solution (Moviprep) and 2L clear liquids were administered the evening prior to treatment. A nasoduodenal tube was placed using the Cortrak method or endoscopy. 500 mL of donor feces + NaCl mixture was administered to patient was administered to	Median 120 g (IQR, 85-208 g) feces collected from donor. Fecal samples collected and divided in stored in a -20°C freezer within 24 hours after production	Nasoduodenal; tube was placed using the Cortrak method or endoscopy.	FMT and autologous microbiota transplant: Two treatments, administered 3 weeks apart per protocol.	12 weeks, 96% f/u.	None (Note: subjects were allowed to continue concomitant medication (see patient characteristic column) provided they were on stable doses for the 8 weeks before inclusion)	FMT + bowel lavage vs. Donor microbiota transplant + bowel lavage ($p < 0.05$ unless otherwise noted) Age (median [IQR]): 40.0 (33.0-56.0) vs. 41.0 (30.0-48.0) % male: 47.8% (11/23) vs. 44.0% (11/25) Median disease duration (years (range)): 7 (0.27) vs. 9 (0.27)	MLDS grant 2011 (WO 11-17) to Noortje G. Rossen and NWO-Spinoza grant 2008 to Willem M. de Vos. Authors disclose no COIs.

Study (Country)	N	Inclusion & Exclusion Criteria	Interventions	Donor feces	Route	Repeat Treatment	Length, % f/u	Co-interventions	Patient Characteristics	Funding
		Exclusion: Use of anti-tumor necrosis factor or methotrexate treatment within 8 weeks before inclusion, or cyclosporine within 4 weeks before inclusion; infectious cause of a UC disease flare, history of colectomy, a current stoma, a life expectancy of <12 months, pregnancy, and hospital admission; no antibiotics or probiotics within 6 weeks before inclusion	patient within 6 hours after fecal harvesting. Autologous fecal microbiota + bowel lavage (n=25): Bowel lavage consisting of 2 L macrogol solution (Moviprep) and 2L clear liquids were administered the evening prior to treatment. A nasoduodenal tube was placed using the Cortrak method or endoscopy. 500 mL of autologous feces + sodium chloride mixture was administered to patient was administered to patient within 6 hours after fecal harvesting.	and subsequentially transferred to -80°C. Donor: Donors were ≥18 years of age and screened for fecal donation using the Dutch Red Cross Questionnaire addressing risk factors for potential transmissible diseases used for screening of blood donors in The Netherlands. Stool and serology screening was performed for bacterial, parasitic,					Extent of disease: *E1, proctitis:* 4.4% (1/23) vs. 0% (0/25) *E2, left-sided:* 65.2% (15/23) vs. 44% (11/25) *E3, pancolitis:* 30.4% (74/23) vs. 56% (14/25) Concomitant drug treatment: 91.3% (21/23) vs. 72% (18/25) *Mesalamine oral:* 65.2% (15/23) vs. 60% (15/25) *Mesalamine/corticosteroid rectal:* 21.7% (5/23) vs. 28% (7/25) *Immunosuppresants:* 30.4% (7/23) vs. 32% (8/25) Systemic corticosteroids (<10 mg): 21.7% (5/23) vs. 20% (5/25) Loperamide: 8.7% (2/23) vs. 0% (0/25) Prior anti-TNF therapy: 30.4% (7/23) vs. 28% (7/25) Median SCCAI score at inclusion (range): 10 (5-11) vs. 8 (4-11), p =	

Study (Country)	N	Inclusion & Exclusion Criteria	Interventions	Donor feces	Route	Repeat Treatment	Length, % f/u	Co-interventions	Patient Characteristics	Funding
				and viral pathogens. Donors were not allowed to have used antibiotics within 8 weeks before screening.					0.01 <u>Mayo endoscopic score at inclusion:</u> *Mayo 1:* 17.4% (4/23) vs. 8% (2/25) *Mayo 2:* 47.8% (11/23) vs. 64% (16/25) *Mayo 3:* 34.8% (8/23) vs. 28% (7/25) <u>Site of disease at inclusion:</u> *Rectum only:* 17.4% (4/23) vs. 8% (2/25) *Left side of colon:* 60.9% (14/23) vs. 68% (17/25) *Proximal to the splenic flexure:* 21.7% (5/23) vs. 24% (6/25)	
Cohort studies										
(None)										

CDI: *Clostridium difficile* infection; EQ-5D: EuroQol 5D; F/U: Follow-up; FMT: Fecal microbiota transplant; IBDQ: Irritable bowel disease questionnaire; ICU: Intensive care unit; NR: Not reported; RCT: Randomized controlled trial; SCCAI: Simple clinical colitis activity index; SD: Standard deviation; TNF: tumor necrosis factor; UC: Ulcerative colitis

*Donor exclusion criteria: antibiotic use ≤6 mos., evidence of possible intestinal disease, "lifestyle associated with increased risk for contracting infections," travel to tropical area in prior 3 mos., new sexual relation in prior 6 mos., recent needle stick accident, prior receipt of blood products, tattoos, inflammatory bowel disease or gastrointestinal cancer history in family, systemic disease, use of drugs that could be found in feces that posed risk to patient.

Appendix Table F4. CDI Study and Patient Characteristics Data Abstraction Tables: Comparisons of different routes of FMT administration

Study (Country)	N	Inclusion & Exclusion Criteria	Interventions	Donor feces	Route	Repeat Treatment	Length, % f/u	Co-interventions	Patient Characteristics	Funding
RCTs										
Youngster 2014 (United States)	N = 20	Inclusion: Refractory or recurrent CDI, as defined by a relapse of CDI after having at least 3 episodes of mild-to-moderate CDI and failure of a 6- to 8-week taper with vancomycin with or without an alternative antibiotic, OR at least 2 episodes of severe CDI resulting in hospitalization and associated with significant morbidity. Active CDI was defined as diarrhea (>3 loose stools per day) with a positive stool test for *C. difficile* toxin. Exclusion: Presence of anatomic contraindication to NGT or colonoscopy, delayed gastric emptying syndrome, recurrent aspirations, pregnancy, significantly	FMT via Colonoscopy (n=10): Patients underwent a standard bowel preparation with 4 liters of polyethylene glycol electrolyte solution, followed by endoscopic administration to the right colon of 90 cc thawed inoculum. Fecal material was further diluted to 250 cc for adults and 160 cc for pediatric patients. Patients were asked to retain the material as long as possible after the procedure and were given a single oral dose of loperamide at the time of the procedure. FMT via Nasogastric Tube (n=10): Patients were prescribed 2 mg/kg/day, up to 20 mg, of omeprazole orally	Each inoculum was derived from approximately 41 g of fecal matter. Inocula used in this study were stored frozen for up to 156 days (range 29-156 days). Donors were asked to take a dose of milk of magnesia the day before fecal collection to facilitate manipulation of the sample. A suspension was generated in normal saline without	Colonoscopy (n = 10) or nasogastric tube (n = 10)	Patients in both study arms who showed no improvement in diarrheal symptoms were offered a second FMT by their preferred route of administration. To minimize potential infectious exposures, inoculum from the same donor was used for the repeat administration.	8 weeks, 100% (20/20) f/u	Patients were required to discontinue all antibiotics at least 48 hours prior to the procedure. Stable oral prednisone treatment up to 40 mg daily was allowed.	Colonoscopy vs. Nasogastric Tube FMT, p > 0.05 for all Age (mean ± SD): 50.4 ± 28.8 vs. 58.6 ± 19.6 % male: 40% (4/10) vs. 50% (5/10) Time since initial CDI (median [range], mos.): 7 [3-34) vs. 12 [3-66] % patients with hospital-acquired CDI: 20% (2/10) vs. 30% (3/10) Number of CDI recurrences prior to FMT (median [range]): 4 [2-7] vs. 5 [3-16] % patients with previous vancomycin taper: 90% (9/10) vs. 100% (10/10) % patients with previous use of fidaxomicin: 50% (5/10) vs. 70% (7/10) % patients with hospital admissions in the past due to CDI:	Federal funds from the National Institute of Allergy and Infectious Diseases, NIH, Department of Health and Human Services (contract number HHSN272200900018C); Harvard Catalyst, The Harvard Clinical and Translational Science Center, funded by the National Center for Research Resources and the National Center for Advancing Translational Sciences, NIH (award 8UL1TR000170-05), and financial contributions from Harvard University and its affiliated

Study (Country)	N	Inclusion & Exclusion Criteria	Interventions	Donor feces	Route	Repeat Treatment	Length, % f/u	Co-interventions	Patient Characteristics	Funding
		compromised immunity (immunosuppressive medications, recent chemotherapy, decompensated liver cirrhosis, advanced human immunodeficiency virus [HIV]/AIDS [CD4 count <250 cells/µL], neutropenia with absolute neutrophil count <1000/µL, recent bone marrow transplant, or other cause of severe immunodeficiency), and having a history of significant allergy to foods not excluded from the donor diet.	for 48 hours prior to the procedure. An age- and size-appropriate NGT was inserted, proper positioning in the stomach was documented by radiography, and 90 cc of inoculum was administered. In these patients the inoculum was not further diluted, to minimize risk of vomiting and aspiration. The NGT was removed promptly after administration and subjects were asked to drink a glass of water to facilitate dilution of stomach contents and transit into the small intestine.	preservatives and materials were passed through 4 sieves to remove particulate material. The final slurry was concentrated 3-fold by centrifucation and then resuspended in sterile saline with 10% glycerol added as a bacterial cryoprotectant. Inocula were then frozen at -80°C pending use. Donors: Healthy, nonpregnant adults 18-50 years of					60% (6/10) vs. 70% (7/10) % patients as inpatients at time of FMT: 20% (2/10) vs. 30% (3/10) No. of bowel movements 1 d prior to FMT (median [range]): 6 [4-13] vs. 7 [5-13] Self-reported health status 1 d prior to FMT (median [range], scale 1-10 (best)): 5 (2-7) vs. 4 [1-10]	academic healthcare centers. M. B. S. is on the board of directors of OpenBiome, a 501(c)3 nonprofit aimed at expanding access to fecal microbiota preparations by providing screened, ready-to-use fecal material for clinical use. E. L. H. is the recipient of a sponsored research award from Seres Health, Cambridge, Massachusetts, to Massachusetts General Hospital for a clinical trial related to treatment of C. difficile colitis.

Study (Country)	N	Inclusion & Exclusion Criteria	Interventions	Donor feces	Route	Repeat Treatment	Length, % f/u	Co-interventions	Patient Characteristics	Funding
				age, on no medication, with a normal BMI (18.5-25 g/m^2). Donors were screened for using the American Associatoion of Blood Banks donor questionnaire for exposure to infectious agents, and underwent physical examination and general laboratory screening tests within 30 days of donations. All results had to be within normal range for age and						

Study (Country)	N	Inclusion & Exclusion Criteria	Interventions	Donor feces	Route	Repeat Treatment	Length, % f/u	Co-interventions	Patient Characteristics	Funding
				sex. Donor feces were screened for enteric bacterial pathogens; antibodies to hepatitis A, B, and C; HIV, and *Treponema pallidium.* Donations were escrowed for an additional 4 weeks to allow retesting of donors for HIB and hepatitis B and C prior to clinical use of the inoculum.						
Cohort studies										
(None)										

CDI: *Clostridium difficile* infection; F/U: Follow-up; FMT: Fecal microbiota transplant; NR: Not reported; RCT: Randomized controlled trial; SD: Standard deviation

Appendix Table F5. CDI Study and Patient Characteristics Data Abstraction Tables: Comparisons of different timing of FMT administration

Study (Country)	N	Inclusion & Exclusion Criteria	Interventions	Donor feces	Route	Repeat Treatment	Length, % f/u	Co-interventions	Patient Characteristics	Funding
RCTs										
(None)										
Cohort studies										
Waye 2016 Retrospective cohort (Canada)	N= 75	Inclusion: Adults; FMT for recurrent CDI (at least 2 recurrences of mild-to-moderate CDI, or at least 1 recurrence of severe CDI); FMT delivered by colonoscopy, gastroscopy, or a nasogastric tube; and post-FMT follow-up for at least 3 months. Exclusion: Life expectancy <90 days after FMT; refractory CDI or evidence of toxic megacolon; active cancer at the time of FMT; only 1 CDI recurrence; and non-Alberta resident.	Timely FMT (n=30) after 2 recurrences of CDI Delayed FMT (n=45) after ≥3 recurrences of CDI All patients were treated with a standard course of vancomycin prior to FMT; no further details provided	Both fresh (29%, 22/75) and frozen (71%, 53/75) stool used (based on availability); Timely vs. Delayed FMT: fresh, 33% (10/30) vs. 27% (12/45) and frozen (67%, 20/30) vs. 73% (33/45); no detail provided regarding prepara-tion Donor: Universal 81% (61/75) and family 19% (14/75); Timely vs. Delayed	Colono-scopy (majority), gastro-scopy and nasto-gastric tube; 4 L of golytely the night before FMT regardless of route of delivery; vancomycin discontinue d 24 hours before FMT	If CDI recurred of during follow-up, a second FMT following a course of vancomyci n was offered.	Overall: mean 12.2 months (93.8%; 75/80) Timely FMT: mean 11.7 months (%NR) Delayed FMT: 12.6 months (%NR)	None reported	Timely vs. Delayed FMT Age (mean): 62.1 vs. 68.1 years % female: 53% (16/30) vs. 51% (23/45) Charlson index 0-2: 44% (13/30) vs. 20% (9/45); 3+: 56% (17/30) vs. 80% (36/45); p=0.006 No. CDI episodes, mean (95% CI): 3 (NA) vs. 4.8 (4.4-5.1); p=0.0001 No. hospital admissions due to CDI, mean (95% CI): 0.9 (0.3-1.4) vs. 2.3 (1.7-2.8); p=0.001 No. days in hospital due to CDI, mean (95% CI): 8.0 (2.2-13.8) vs. 21.8 (14.0-29.5); p=0.009 No. ER visits due to CDI, mean (95% CI): 1.3 (0.9-1.8) vs. 2.6 (1.9-3.3)	University of Alberta Hospital Foundation; authors declare no conflicts of interest

Study (Country)	N	Inclusion & Exclusion Criteria	Interventions	Donor feces	Route	Repeat Treatment	Length, % f/u	Co-interventions	Patient Characteristics	Funding
				FMT: universal, 77% (23/30) vs. 84% (38/45) and family 23%, (7/30) vs. 16% (7/45); all pre-screened for multiple pathogens (viruses, bacteria, parasites)						

CDI: *Clostridium difficile* infection; F/U: Follow-up; FMT: Fecal microbiota transplant; NR: Not reported; RCT: Randomized controlled trial; SD: Standard deviation

Appendix Table F6. CDI Study and Patient Characteristics Data Abstraction Tables: Comparisons of types of fecal preparation

Study (Country)	N	Inclusion & Exclusion Criteria	Interventions	Donor feces	Route	Repeat Treatment	Length, % f/u	Co-interventions	Patient Characteristics	Funding
RCTs										
Lee 2016 (Canada)	N = 232	Inclusion: Age 18 years or older; able to provide informed consent; history of CDI (positive toxin test plus diarrhea (≤3 loose stools/24 hours for 48 hours)) that had either recurred (recurrence of symptoms for ≥48 hours within 8 weeks of appropriate therapy) or was refractory (persistent or worsening diarrhea plus either: abnominal pain, fever, or white blood counts >15.0 X 10^9/L) to oral vancomycin (500mg 4X/day for ≥5 days) Exclusion: Planned or actively taking an investigational product for another study; patients with neutropenia with absolute neutrophil count <0.5 x 109/L; evidence of toxic megacolon or gastrointestinal	Frozen FMT (n = 114): Approximately 100 g of stool sample was diluted with 300 mL of commercially bottled water and emulsified using a sterile wooden spatula. Gauze was placed on top of an empty container to strain the solids, and 50 ml of the suspension in the container was aspirated into 60-mL syringes, which were also used to administer the enemas. Fresh FMT (n = 118): Approximately 100 g of stool sample was diluted with 300 mL of commercially bottled water and emulsified using a sterile wooden spatula. Gauze was placed on top of an empty container to strain the solids, and 50 ml of the suspension in the	Fresh stool samples from healthy donors were transported to the processing laboratories within 5 hours of collection and stored at 5°C until frozen or used for FMT. Patients randomized to receive fresh FMT received the suspension within 24 hours of collection. Those randomized to receive the frozen FMT received the suspension within 24	Retention enema	Frozen and Fresh FMT: Patients received FMT enema on day 1, and treatment could be repeated on days 5-8 following randomization if no improvement was observed. Patients not responding to 2 FMTs were offered repeat FMT or antibiotic therapy.	13 weeks % f/u modified intention to treat population: 94.4% % f/u per-protocol population: 76.7%	All patients received suppressive antibiotics for their most recent episode of CDI, which was discontinued 24 to 48 hours prior to FMT.	mITT population only Frozen vs. Fresh FMT Age (mean ± SD): 73 ± 16.4 vs. 72.5 ± 16.2 % <65 y: 25% (27/108) vs. 24.3% (27/111) % ≥65 y: 75% (81/108) vs. 75.7% (84/111) % male: 33.3% (36/108) vs. 33.3% (37/111) % inpatient at time of FMT: 47.7% (51/107) vs. 54.1% (60/111) Severity of CDI at baseline: *Mild CDI:* 38% (41/108) vs. 29.7% (33/111) *Moderate CDI:* 45.4% (49/108) vs. 46% (51/111) *Severe CDI:* 16.7% (18/108) vs. 24.3% (27/111) % presence of abdominal pain: 58.3% (63/108) vs. 63.3% (69/109)	Funded by Physicians Services Incorporated, Natural Sciences and Engineering Council, National Science Foundation, and Gastrointestinal Diseases Research Unit, Kingston General Hospital, Ontario. Dr. Lee reports participating in clinical trials for ViroPharma, Actelion, Cubist, and Merck and serving as a member of the advisory boards for Rebiotix and Merck. Dr. Steiner reports receiving consulting fees

Study (Country)	N	Inclusion & Exclusion Criteria	Interventions	Donor feces	Route	Repeat Treatment	Length, % f/u	Co-interventions	Patient Characteristics	Funding
		perforation on abdominal x-ray; peripheral white blood cell count > 30.0 x 109/L AND temperature >38.0° C; active gastroenteritis due to *Salmonella, Shigella, E. coli* 0157H7, *Yersinia* or Campylobacter; presence of colostomy; unable to tolerate FMT or enema for any reason; anticipated requirement for systemic antibiotic therapy for more than 7 days; actively taking *Saccharomyces boulardii*; severe underlying disease such that the patient is not expected to survive for at least 30 days; any condition that, in the opinion of the investigator, that the treatment may pose a health risk to the patient.	container was aspirated into 60-mL syringes, which were also used to administer the enemas.	hours of thawing. Frozen suspensions were kept at −20°C for a maximum of 30 days and thawed overnight at 25°C; anaerobic bacteria counts have been found to remain stable for at least 30 days when stored at −20°C.					CDI Characteristics: *Health care-associated:* 47.7% (51/107) vs. 54.1% (60/111) *Community-associated:* 52.3% (56/107) vs. 45.9% (51/111) *Refractory:* 5.6% (6/108) vs. 8.1% (9/111) *Patients with recurrent:* 94.4% (102/108) vs. 92% (102/111) No. of CDI recurrences per patient (mean ± SD): 2.7 ± 1.7 vs. 2.5 ± 1.5 % patients with <2 recurrences of CDI: 92.6% (100/108) vs. 84.7% (94/111) % patients with ≥2 recurrences of CDI: 7.4% (8/108) vs. 15.3% (17/111) Duration of CDI, days (median [range]): *From initial diagnosis to first FMT:* 91 [18-842)	and an unrestricted grant from Cubist, consulting fees and a phase 3 trial contract from Merck Canada, and a phase 3 trial contract from Sanofi Pasteur; additionally, his institution was recently approved as a site for a phase 2b randomized clinical trial of frozen stool product with Rebiotix. Dr Petrof reports holding a patent for synthetic stool formation. Dr Crowther reports receiving grants from the Heart and Stroke Foundation of Ontario, Leo Pharma, and Bayer, as well as funding for educational materials from Alexion, Ortho

Study (Country)	N	Inclusion & Exclusion Criteria	Interventions	Donor feces	Route	Repeat Treatment	Length, % f/u	Co-interventions	Patient Characteristics	Funding
									vs. 82 [6-1351) *Antibiotic use prior to FMT:* 58 [13-645) vs. 43.5 [6-811] % positive C. diff toxin test at time of FMT: 40.1% (43/105) vs. 41.5% (44/106) % patients treated with combination of metronidazole and vancomycin, pre-FMT: 34.3% (37/108) vs. 32.7% (35/107) % patients treated with ≥1 vancomycin taper regimen, pre-FMT: 94.3% (100/106) vs. 90% (97/109) Per-protocol population only Age (mean ± SD): 72.2 ± 15.9 vs. 72.9 ± 15.4 % <65 y: 26.4% (24/91) vs. 24.1% (21/87) % ≥65 y: 73.6% (67/91) vs. 75.9% (66/87) % male: 36.3% (33/91) vs. 37.9% (33/87)	Clinical Diagnostics, BMS-Pfizer Alliance, Leo Pharma, Bayer, Celgene, Shire, and CSL Behring. Dr Kim reports serving as a member of the advisory board for Rebiotix. No other authors reported disclosures.

Study (Country)	N	Inclusion & Exclusion Criteria	Interventions	Donor feces	Route	Repeat Treatment	Length, % f/u	Co-interventions	Patient Characteristics	Funding
									% inpatient at time of FMT: 45.6% (41/90) vs. 52.9% (46/87) Severity of CDI at baseline: *Mild CDI:* 40.7% (37/91) vs. 35.6% (31.87) *Moderate CDI:* 45.1% (41/91) vs. 40.2% (35/87) *Severe CDI:* 14.3% (13/91) vs. 24.1% (21/87) % presence of abdominal pain: 57.8% (52/90) vs. 61.2% (52/85) CDI Characteristics: *Health care-associated:* 45.6% (41/90) vs. 52.9% (46/87) *Community-associated:* 54.4% (49/90) vs. 47.1% (41/87) *Refractory:* 4.4% (4/91) vs. 7.9% (6/87) *Patients with recurrent:* 95.6% (87/91) vs. 93.1% (81/87) No. of CDI recurrences per patient (mean ± SD): 2.8 ± 1.7 vs.	

Study (Country)	N	Inclusion & Exclusion Criteria	Interventions	Donor feces	Route	Repeat Treatment	Length, % f/u	Co-interventions	Patient Characteristics	Funding
									2.5 ± 1.4 % patients with <2 recurrences of CDI: 92.3% (84/91) vs. 83.9% (73/87) % patients with ≥2 recurrences of CDI: 7.7% (7/91) vs. 16.1% (14/87) Duration of CDI, days (median [range]): *From initial diagnosis to first FMT:* 103.5 [18-842) vs. 84.5 [14-870] *Antibiotic use prior to FMT:* 60 [13-645] vs. 45 [11-811] % positive C. diff toxin test at time of FMT: 40.9% (36/88) vs. 41% (34/83) % patients treated with combination of metronidazole and vancomycin, pre-FMT: 30% (27/91) vs. 30.1% (25/83) % patients treated with ≥1 vancomycin taper regimen, pre-FMT: 93.3%	

Study (Country)	N	Inclusion & Exclusion Criteria	Interventions	Donor feces	Route	Repeat Treatment	Length, % f/u	Co-interventions	Patient Characteristics	Funding
									(83/89) vs. 88.2% (75/85)	
Cohort studies										
Satokari 2015 Retrospective cohort (Finland)	N= 49	Inclusion: treated in Helsinki University Central Hospital, from December 2007 through February 2014; laboratory-confirmed recurrent CDI; refractive to standard therapy Exclusion: contraindication for performing colonic lavage or colonoscopy; need for continuous antibiotic treatment for other indication than CDI; and inability to understand the treatment nature e.g. due to dementia	Fresh stool for FMT (n=26) from individual donor‡ (n=15) or universal donor‡ (n=11) Frozen stool for FMT (n=23) from universal donor‡; All patients received vancomycin treatment, which was discontinued at an average of 36 hrs. before FMT	Fresh stool: produced ≤6 hours prior to use; 30 g suspended in 150 ml of tap water by using a spatula and adminstered within 15 mins Frozen stool: from 2 universal donors; frozen within 1.5 hours of defecation; 30 g weighted into 250 mL plastic container (Sarstedt) and sterile saline (0.9% NaCl) added to 150 ml;	Colon-oscopy, 2 100 ml syringes; colonic lavage via oral administration of PEG the day before procedure; routine biopsy specimens taken from ileum, colon transversum, colon descendens, sigmoid colon, and rectrum	Various treatment given for relapse on an individual basis including repeat FMT, antibiotics and immuno-globulins	12 wks. (100%) 12 mos. Overall: 85.7% (42/49) Frozen FMT: 73.9% (17/23) Fresh FMT: 96.2% (25/26)	None reported	Fresh vs. frozen FMT Age (mean (range)): 52 (22-81) years vs. 61 (20-88) years % Female: 76.9% (20/26) vs. 60.9% (14/23) No. relapses before FMT (mean (range)): 4.6 (2-12) vs. 4.0 (1-6) Days from first CDI to FMT: (mean (range)): 147 (60-360) vs. 148 (42-312)	Academy of Finland (grants 138902 and 258439), Mary and Georg Ehrnrooth Foundation, and the Finnish Foundation for Gastroenterological Research; the work was independent of the funding

Study (Country)	N	Inclusion & Exclusion Criteria	Interventions	Donor feces	Route	Repeat Treatment	Length, % f/u	Co-interventions	Patient Characteristics	Funding
				feces suspended using a spatula; then 20 ml of 85% glycerol added to the final concentration of 10%, followed by quick manual mixing and freezing at -80^{o} C; thawing done over 4-5 hrs. at room temperature or at 37^{o} C in a water bath; before use suspension was again mixed and pulled into 2 100 mL syringes (when necessary, passed through a pre-sterilized, stainless						

Study (Country)	N	Inclusion & Exclusion Criteria	Interventions	Donor feces	Route	Repeat Treatment	Length, % f/u	Co-interventions	Patient Characteristics	Funding
				steel tea strainer to remove particles) Donor: healthy family members (individual) or volunteers (universal); pre-screened for multiple pathogens (viruses, bacteria, parasites); with no antimicrobial therapy is past 6 months, and no intestinal symptoms						

CDI: *Clostridium difficile* infection; EQ-5D: EuroQol 5D; F/U: Follow-up; FMT: Fecal microbiota transplant; IBDQ: Irritable bowel disease questionnaire; ICU: Intensive care unit; NR: Not reported; RCT: Randomized controlled trial; SCCAI: Simple clinical colitis activity index; SD: Standard deviation; TNF: tumor necrosis factor; UC: Ulcerative colitis

Appendix Table F7. CDI Case Series Data Abstraction Tables: FMT

Study	Condition	N	Demographics:	FMT details	% F/U (n/N)	Cure Definition	Primary Effectiveness Outcomes	Adverse Events
Prospective								
Khoruts 2016 (prospective)	Recurrent CDI (≥2 recurrences) ± IBD CDI alone: n=229 CDI + IBD: n=43	N=272	**Age:** CDI alone: 60.8 ± 17.3 CDI + IBD: 38.8 ± 17.9 Overall: 57.2 ± 19.2 **Female:** CDI alone: 72.9% (167/229) CDI + IBD: 51.2 (22/43) Overall: 69.5% (189/272) **Recurrences:** CDI alone: CDI + IBD: Overall: ≥2 (~5 relapses/patient)	**Route**: Colonoscopic **Prep**: Fresh or frozen **Donor**: NR	100%† (272/272)	Cure ("success rate in clearing infection"): not clearly defined, but is assumed to be the absence of a relapse (diarrhea (>3 loose bowel movements over a 24 hour period) and laboratory confirmation of *C difficile* in stool within the 2 month period))	**Results at 2 mos.** **Cure after 1 FMT:** CDI alone: 92.1% (211/229)* CDI + IBD: 74.4% (32/43)* Overall: 89.3% (243/272) **Cure after ≥2 FMT:** CDI alone: 98.7% (NR/NR) CDI + IBD: 82.9% (NR/NR) Overall: NC **No. Additional FMTs:** NR **CDI-related mortality:** NR **All-cause mortality:** NR	NR
Orenstein 2015 (prospective)	Recurrent CDI (≥2 recurrences)	N=34 ‡	**Age**: 66.8 (range 26.7 to 89.6) **Female**: 67.6% (23/34) **Recurrences**: ≥2 (mean NR)	**Route**: Enema **Prep**: Frozen **Donor**: RBX2660 (microbiota suspension product) from 4 donors	91% (31/34)	Absence of CDI-associated diarrhea (≥3 unformed stools/day for ≥2 days) through 8 weeks after FMT	**Cure after 1 FMT:** 52% (16/31) at 8 weeks **Cure after ≥1 FMT:** 87% (27/31) at 8 weeks **No. Additional FMTs:** 1 additional: 45% (15/31) patients	**FMT-related mortality**: 0% (0/34) through 6 mos. **Serious FMT-related adverse events:** 0% (0/34) § through 6 mos. **Other adverse events**: 82%

Study	Condition	N	Demographics:	FMT details	% F/U (n/N)	Cure Definition	Primary Effectiveness Outcomes	Adverse Events
							through 6 mos. **CDI-related mortality:** 0% (0/32) at 6 mos. **All-cause mortality:** 3% (1/32) at 6 mos. (respiratory failure)	(28/34) through 6 mos. (total of 188 adverse events occurred, of which 59% (110/188) were considered to be related to CDI. The authors did not state which were attributed to FMT.)
Retrospective								
Agrawal 2015 (retrospective)	Recurrent (≥1 relapse) (n=89), severe (n=45), or complicated (n=12) CDI	N=166**	**Age** (range): 78.6 (65 to 97) **Female**: 68.5% (100/146) **Recurrences**: 1 to 5- 76.3% (106/139) >5 - 23.7% (33/139)	**Route:** Various: Colonoscopy alone- 78.1% (114/146), Colonoscopy AND enema- 2.7% (4/146), EGD- 8.9% (13/146), push enteroscopy- 2.1% (3/146), flexible sigmoidoscopy- 6.2% (9/146), fecal enema 2.1% (3/146) **Prep**: Fresh **Donor**: usually identified by patient, if not available, anonymous, standardized	88% (146/166)††	Resolution of CDI symptoms after initial FMT with no recurrence in the subsequent 12 weeks.	**Cure after 1 FMT:** Overall- 82.9% (121/146) at 12 weeks RCDI- 82% (73/89)* at 12 weeks SCDI- 91% (41/45)* at 12 weeks CCDI- 66% (8/12) at 12 weeks **Cure after ≥1 FMT:** Overall-93.8% (137/146) at >12 weeks **No. Additional FMTs:** 1 additional FMT: 12 patients at <12 weeks 3 patients at >12 weeks 2 additional FMT: 1 patient at >12 weeks	**FMT-related mortality:** 0% (0/146) at 1 year **AEs after FMT procedure (timing NR):** CDI-negative diarrhea- 4.8% (7/146) CDI-negative constipation- 2.7% (4/146) **Serious AEs attributed to CDI and/or FMT**: Hospitalizations for recurrent diarrhea: 4.1% (6/146) at 12 weeks

Study	Condition	N	Demographics:	FMT details	% F/U (n/N)	Cure Definition	Primary Effectiveness Outcomes	Adverse Events
				donors provided by physician			**CDI-related mortality**: 1.4% (2/146) through 1 year **All-cause mortality**: 8.2% (12/146) through 7 months CDI related (n=2, same patients included above) (cause: decompensated heart failure, cancer, Alzheimer disease, stroke, pneumonia)	
Lee 2014 (retrospective)	Recurrent or refractory CDI	N=94	**Age**: 71.8 ± 15.7 **Female**: 56.4% (53/94) **Recurrences**: NR	**Route**: Retention enema **Prep**: Fresh **Donor**: Volunteer	100% (94/94)	No recurrence of diarrhea at 6 mos. follow up	**Cure after 1 FMT:** 47.9% (45/94) at 24 mos. **Cure after ≥1 FMT:** 86.2% (81/94) at 24 mos. **Cure after ≥1 FMT ± antibiotic between FMT treatments:** 91.5% (86/94) at 24 mos. **No. Additional Treatments:** 1 additional FMT: 20 2 additional FMT: 14 3+ additional FMT: 5 2 additional FMT + antibiotics between	**FMT-related mortality:** 0% (0/94) through 24 mos. **Significant adverse events**: 0% (0/94) through 24 mos. **Adverse events**: Transient constipation and excess flatulence-10% (9/94) (timing NR)

Study	Condition	N	Demographics:	FMT details	% F/U (n/N)	Cure Definition	Primary Effectiveness Outcomes	Adverse Events
							FMTs: 3 3+ additional FMT + antibiotics between FMTs: 6 (all at 6 mos. f/u) **CDI-related mortality:** 0% (0/94) at 24 mos. **All-cause mortality:** 6.4% (6/94) at 24 mos. (all elderly, had multiple underlying significant comorbidities, death due to critical illness)	
Rubin 2013 (retrospective)	Recurrent (≥2 recurrences) CDI	N=75	**Age**: 63 (median) (range 6-94) **Female**: 65.3% (49/75) **Recurrences**: ≥2 laboratory-confirmed recurrences of CDI	**Route**: Stomach via nasogastric tube (n=64), gastroscope (n=7), or previously placed percutaneous endoscopic gastroscopy tube (n=4) **Prep**: Fresh **Donor**: Close household member	97% (74/75)	Primary cure: resolution of diarrhea without recurrence within 60 days of FMT.	**Cure after 1 FMT:** 78.7% (59/75) at 60 days **Cure after ≥1 FMT:** NR **No. additional FMTs**: 1 in 1 patient (1/75) **CDI related mortality:** 0% (0/75) at 60 days **All-cause mortality:** 0% (0/75) at 60 days	**FMT related mortality:** 0% (0/75) through 60 days **Other adverse events:** No adverse events or intolerance to FMT through 60 days

Study	Condition	N	Demographics:	FMT details	% F/U (n/N)	Cure Definition	Primary Effectiveness Outcomes	Adverse Events
Kelly 2014 (retrospective)	Immuno-compromised patients with: Recurrent CDI- 55% (44/80) Refractory CDI - 11% (9/80) Complicated CDI- 34% (27/80)	N=82	**Age**: 50.4 ‡‡ (range 6.5 to 88) **Female**: 48% (38/80) **Recurrences**: NR	**Route**: endoscopic lower gastrointestinal **Prep**: NR **Donor**: NR	98% (80/82)	Absence of diarrhea or marked reduction in stool frequency without the need for further anti-CDI therapy.	**Cure after 1 FMT**: 78% (62/80) at 12 weeks **Cure after ≥1 FMT:** 89% (70/80) at 12 weeks **No. Additional FMTs:** 1 additional- 12 at 12 weeks **CDI related mortality:** 0% (0/80) at 12 weeks **All-cause mortality:** 2.5% (2/80) at 12 weeks (death from pneumonia, FMT procedure) 6.3% (5/80) at 6 mos. (3 deaths occurred after 6 months and all attributed to chronic progressive illnesses)	**FMT-related mortality**: 1.3% (1/80) through 12 weeks (patient had advanced esophageal cancer and cachexia, aspirated during sedation during colonoscopy, and died of respiratory failure the next day) **Hospitalizations (through 12 weeks):** Self-limited abdominal pain, 1.3% (1/80) IBD flares, 5% (3/80) Unrelated to FMT§§: 7.5% (6/80) **Other AEs:** Self-limited diarrheal illness: 3.8% (3/80) at 12 weeks Fever: 1.3% (1/80) at 1 day Bloating and abdominal discomfort immediately post-FMT: 3.8% (3/80) at 1-2 days

Study	Condition	N	Demographics:	FMT details	% F/U (n/N)	Cure Definition	Primary Effectiveness Outcomes	Adverse Events
								Hip pain: 1.3% (1/80) at 12 weeks Crohn's flare: 1.3% (1/80) at 12 weeks Pertussis: 1.3% (1/80) at 30 days Nausea: 1.3% (1/80) at 30 days Minor mucosal tear during colonoscopy for FMT: 1.3% (1/80) periprocedurally
Brandt 2012 (retrospective)	Recurrent CDI	N=94	**Age**: 65 ± 17 **Female**: 73% (56/77) **Recurrences**: All patients were recurrent, number of recurrences NR	**Route**: Colonoscopy **Prep**: Fresh **Donor**: Spouse or partner (60%), First degree relative or otherwise related (27%), Unknown to patient (1.3%)	82% (77/94)	Primary cure rate: diarrhea without recurrence within 90 days of FMT Secondary Cure rate: patients with resolution of *C. difficile*-associated diarrhea after 1 further course of vancomycin with or without repeat FMT.	**Cure after 1 FMT:** 91% (70/77) at 90 days **Cure after ≥1 FMT**: 94% (72/77) **No. Additional FMTs:** 1 additional FMT: 2 patients at 90 days **CDI-related mortality**: 0% (0/77) **All-cause mortality:** 9.1% (7/77) at NR days (cause of death: Unknown (hospice care) (n=1), metastatic colon cancer present before FMT (n=1), metastatic ovarian cancer (n=1),	**FMT-related mortality**: 0% (0/77) through 90 days **Other adverse events**: NR

Study	Condition	N	Demographics:	FMT details	% F/U (n/N)	Cure Definition	Primary Effectiveness Outcomes	Adverse Events
							pneumonia (n=1), myocardial infarction (n=1), cerebral vascular accident (n=1), sepsis (n=1))	
Mattila 2012 (retrospective)	Recurrent CDI (≥1 recurrence)	N=70	**Age:** 73 (range 22-90) **Female**: 60% (42/70) **Recurrences**: 3.5 (range 1-12)	**Route**: Ileocolonoscopy **Prep**: Fresh **Donor**: Close relatives or household donors (61/70), Healthy volunteer donor (9/70)	100% (70/70)	Treatment failure was defined as persisting diarrhea with a positive *C difficile* toxin stool test.	**Cure after 1 FMT:** 94% (66/70) at 12 weeks **Cure after ≥1 FMT:** 94% (66/70) at 12 weeks, 94% (66/70) at 1 year **No. Addtitional FMTs:** 1 additional FMT: 1 patient at 3 mos, 3 patients at 1 year **CDI-related mortality:** 5.7% (4/70) at 3 mos., 5.7% (4/70) at 1 year **All-cause mortality:** 7.1% (5/70) at 3 mos. 21.4% (15/70) at 1 year (details NR)	**FMT related mortality:** 0% (0/70) through 3 mos., 0% (0/70) through 1 year No severe adverse events related to FMT
Garborg 2010 (retrospective)	Recurrent CDI (≥1-2 recurrences)	N=40	**Age**: 75 (range 53-94) **Female**: 53% (21/40) **Recurrences**: NR	**Route**: Gastroscope (n = 38) or colonoscope in the sigmoid or transverse colon (n=2)	98% (39/40)***	Successful treatment was defined as no further contact with our clinic due to CDAD symptoms	**Follow-up at 80 days:** **Cure after 1 FMT:** Duodenal- 74% (28/38) Colonic- 50% (1/2)	**FMT related mortality:** NR **Other adverse events:** No procedure-related complications or

Study	Condition	N	Demographics:	FMT details	% F/U (n/N)	Cure Definition	Primary Effectiveness Outcomes	Adverse Events
				Prep: Fresh **Donor**: Close relatives or other household members		within 80 days after FDIT.	Combined- 73% (29/40) at 80 days **Cure after ≥1 FMT:** Duodenal- 82% (31/38) Colonic- 50% (2/4) Combined- 83% (33/40) **No. Additional FMTs:** 1 additional FMT at 6 weeks Duodenal- 4 patients Colonic- 2 patients Combined- 6 patients **CDI-related mortality:** 5% (2/40) **All-cause mortality:** 15% (6/40)	adverse events.
Jorup-Ronstrom 2012 (retrospective)	Recurrent CDI (≥3 relapses)	N=32	**Age, median (range)**: 75 (27-94) **Female**: 63% (20/32) **Recurrences**: ≥3 (mean NR)	**Route**: Enema or colonoscopic **Prep**: Frozen, harvested and re-cultivated for years prior **Donor**: single healthy donor	100% (32/32)	Cure: no relapse occurred after having received a fecal transplant, a single or repeated treatments.	**Cure after 1 FMT**: 69% (22/32) at median 26 mos. **Cure after ≥1 FMT:** 91% (29/32) at median 26 mos. **No. Additional FMTs:** 1 additional FMT: 5 patients at median 26 mos.	**FMT-related mortality:** NR **Other adverse events:** No adverse events caused by transplantation

Study	Condition	N	Demographics:	FMT details	% F/U (n/N)	Cure Definition	Primary Effectiveness Outcomes	Adverse Events
							CDI-related mortality: NR **All-cause mortality:** NR	
Patel 2013 (retrospective)	Recurrent CDI (≥1 recurrence)	N=31	**Age**: 61.3 ± 19 **Female**: 55% (16/31) **Recurrences**: 4 ± 1.4	**Route**: Colonoscopic **Prep**: fresh **Donor**: spouse (n=14), child (n=9), sibling (n=5), parent (n=3), niece (n=1), friend (n=2)	97% (30/31) at 1 month	Bowel pattern††† improved or returned to baseline before the index infection	**Cure after 1 FMT:** 87% (26/30) at 1 month, 91% (21/23) at 3 months, 100% (6/6) at 1 year **Cure after ≥1 FMT:** NR **No. Additional FMTs:** 1 additional FMT: 3 at 1 year **CDI-related mortality:** NR **All-cause mortality:** 3% (1/30) at 3 mos. (cancer)	**FMT-related mortality:** 0% (0/31) through 1 year **Other Adverse Events:** Microperforation during the FMT procedure‡‡‡: 2.9% (1/34)
Pediatric patients								
Kronman 2015 (retrospective)	Recurrent CDI (≥3 recurrences)	N=10	**Age, median (IQR):** 5.4 (2.7-10.6) (pediatric) **Female:** 60% (6/10) **Recurrences:** ≥3	**Route**: NG tube (n=7) or nasoduodenal (n=1) or nasojejunal tube (n=2) placed pro patients with high risk of emesis	100% (10/10)	Complete resolution of symptoms (i.e. asymptomatic)	**Cure after 1 FMT:** 90% (9/10) at median 44 days **Cure after ≥1 FMT:** 90% (9/10) at median 44 days	**FMT-related mortality:** NR **Other adverse events:** Vomiting: 10% (1/10) immediately post-

Study	Condition	N	Demographics:	FMT details	% F/U (n/N)	Cure Definition	Primary Effectiveness Outcomes	Adverse Events
			(mean NR)	**Prep**: NR (discussion implies fresh) **Donor**: parents (n=9) sibling (n=1)			**No. additional FMTs:** 1 additional FMT: 1 at 5 mos. **CDI-related mortality:** NR **All-cause mortality:** NR	op Mucoid stools: 10% (1/10) for 2 days post-op "no additional adverse events were noted"
Russell 2014 (retrospective)	Recurrent CDI alone (n=7) or + IBD (n=3)	N=10	**Age**: 7.8 ± 6.1 §§§ (pediatric) **Female**: 40% (4/10) **Recurrences**: 4.1 ± 1.6§§§	**Route**: Stomach via nasogastric tube (n=2) or cecum via colonoscope (n=8) **Prep**: Fresh **Donor**: Parents (n=10)	100% (10/10) at 3 mos. 90% (9/10) at 4+ mos.	Resolution of symptoms	**Cure after 1 FMT:** 2 mos.- 70% (7/10) 3 mos.- 70% (7/10) 4 mos.- 70% (7/10) 6 mos.- 60% (6/10) 9 mos.- 60% (6/10) 12 mos.- 50% (5/10) **Cure after ≥1 FMT:** NR **No. Additional FMTs:** None **CDI-related mortality:** NR **All-cause mortality:** NR	**FMT-related mortality:** NR **Other adverse events:** Short term gastrointestinal distress (timing NR)****: 60% (6/10) Long term self-limited mucoid stools at 2 weeks: 10% (1/10)

AE: Adverse event; CDAD: *Clostridium difficile* associated diarrhea; CDI: *Clostridium difficile* infection; EGD: esophagogastroduodenoscopy; FDIT: faecal donor instillation therapy; FMT: fecal microbial transfer; F/U: follow-up; IQR: interquartile range; NG: nasogastric; NR: not reported; RBT: rectal bacteriotherapy; SD: standard deviation

*Calculated by Spectrum Research, Inc using two out of these three: numerator, denominator, and percent.

†Khoruts 2016: Assumed 100% follow-up for the entire cohort of patients: IBD patients clearly had 100% follow-up (as stated in text and Supplemental Table 2); CDI patients were assumed to have 100% follow-up based on the inclusion of consecutive patients that were followed prospectively for two months.

‡Orenstein 2015/Ray 2016: 40 patients were enrolled, then 6 were excluded who failed the toxin screen test prior to FMT

§Orenstein 2015/Ray 2016: 7/34 patients experienced serious adverse events that were judged by an independent safety monitor to not be related to FMT (severe abdominal pain, pelvic fracture, respiratory failure (after hip fracture), UTI, COPD exacerbation, pulmonary edema due to dialysis, pneumonia, 4 further episodes of CDI, gram negative bacteria, hyoxemia, recurrent CDI, adenocarcinoma lung, pneumothorax after procedure, chest pain after biopsy, chemotherapy, knife stab wound)

**Agrawal 2015: 168 eligible, but 2 patients refused to participate

††Agrawal 2015: Although 10/146 patients died of unrelated causes between 19 days and 7 mos. post-FMT, these patients were included in the primary outcome of cure through 12 weeks (121/146 cured) and since cure status was not reported for these 10 patients, they were not counted as lost to F/U

‡‡Kelly 2014: Weighted mean calculated from pediatric and adult mean ages and n's.

§§Kelly 2014: AEs unrelated to FMT: Catheter line infection (n=1), influenza after the f/u period (n=1), fall and hip fracture (n=1), colectomy (n=1), cerebrovascular accident (n=1), fever, diarrhea, pancytopenia (n=1)

***Garborg 2010: How the authors arrived at N=39 versus N=40 is not clear: the study states that a retrospective review of the medical records of 40 patients w/ verified or suspected recurrent CDI treated b/w 1994-2008, and that only pts w/ recurrent CDI undergoing FMT were included (no other inclusion/exclusion criteria were specified). However, the results indicate that only 39 patients met the inclusion criteria. Since it is not clear why 1 patient did not meet the inclusion criteria (all 40 should have met the inclusion criteria by their definitions) we made the conservative assumption that all 40 patients were included and that 1 patient was lost to F/U.

†††Patel 2013: Diarrhea outcome used for "cure", as overall cure was not defined in the paper (other outcomes included abdominal pain and fatigue)

‡‡‡Patel 2013: Microperforation caused by a biopsy of an area of presumed ischemic small-bowel injury during the FMT procedure; this patient had previously undergone a subtotal colectomy for chronic colonic megacolon and had recurrent anastomotic obstruction and a chronically dilated small bowel in addition to the recurrent CDI.

§§§Russell 2014: Mean (age, recurrences) calculated by Spectrum using individual statistics of each patient given in study table.

****Russell 2014: Gastrointestinal distress included 1 or more of the following: bloating, cramping, loose stools, abdominal pain, gassiness, diarrhea, blood in stool

Appendix Table F8. IBD Case Series Data Abstraction Tables: FMT

Study	Condition	N	Demographics:	FMT details	% F/U (n/N)	Cure Definition	Primary Effectiveness Outcomes	Adverse Events
Prospective								
Cui 2015 (prospective)	Crohn's disease (moderate to severe)	N=41	**Age**: 38.0 ± 13.8 **Female**: 37% (11/30) **Disease duration**: 7.4 ± 5.3 years **Disease Activity** (HBI (0- no upper limit (higher is worse))): 11.7 ± 4.5	**Route**: Gastroscope into patients' mid-gut **Prep**: Fresh **Donor**: chosen by patient (n=23, with feces from 2 donors used in ≥2 patients) or fecal microbiota from bacteria bank (number of patients receiving this NR but estimated to be minority based on above info)	73% (30/41)	**Clinical Remission**: HBI score ≤4 **Clinical improvement**: decrease of HBI >3	**Clinical Remission**: 1 week: 60% (18/30) 1 mo.: 77% (23/30) 3 mos.: 70% (21/30) 6 mos.: 60% (18/30) 9 mos.: 52 % (11/21) 12 mos.: 53% (8/15) 15 mos.: 57 (4/7) **Clinical Improvement**: 1 week: 83% (25/30) 1 mo.: 87% (26/30) 3 mos.: 80% (24/30) 6 mos.: 67% (20/30) 9 mos.: 57% (12/21) 12 mos.: 60% (9/15) 15 mos.: 86% (6/7) **No. Additional FMTs**: NR **IBD-related mortality***: 0% (0/30) at 6 mos. **All-cause mortality***: 0% (0/30) at 6 mos.	**FMT-related mortality***: 0% (0/30)* at 6 mos. **Serious Adverse events:** "No severe or obvious adverse events during, after, or during long-term f/u" **Other adverse events:** Fever (1-6 h post FMT; authors attributed to anesthesia): 7% (2/30) Increased diarrhea (1-6 h post FMT): 23% (7/30) Pain: 0% (0/30) Fecal ileus: 0% (0/30)
Pediatric patients								
Kunde 2013 (prospective)	Ulcerative colitis (mild to moderate) in pediatric population	N=10	**Age**: 18 (median)(range, 7-20) (pediatric population) **Female**: 40% (4/10)	**Route**: Retention enema, 5 consecutive days **Prep**: Fresh	90% (9/10)†	**Remission:** Decrease in PUCAI to <10 **Improvement**: Decrease in PUCAI by >15 points after FMT	**Remission‡**: 1 week: 33% (3/9) 2 weeks: 33% (3/9) 3 weeks: 33% (3/9) 4 weeks: 33% (3/9) **Improvement‡**:	**FMT-related mortality:** 0% (0/10) at 4 weeks **Serious Adverse Events:** 0% (0/10) at 4 weeks **Other adverse events (f/u**

Study	Condition	N	Demographics:	FMT details	% F/U (n/N)	Cure Definition	Primary Effectiveness Outcomes	Adverse Events
			Duration: 3.5 ± 2.6 years **Disease activity** (PUCAI (0-85) (worse)): 39.5 ± 11.4 (range 15-65)	**Donor**: first degree relatives (n=9), family friend (n=1)			1 week: 78% (7/9) 2 weeks: 89% (8/9) 3 weeks: 78% (7/9) 4 weeks: 67% (6/9) **No. Additional FMTs**: NR **IBD-related mortality**: 0% (0/10) at 4 weeks **All-cause mortality**: 0% (0/10) at 4 weeks	**was 4 weeks duration):** Could not retain enema: 10% (1/10) Bloating/flatulence During FMT: 70% (7/10) During follow-up: 40% (4/10) Overall: 90% (9/10) Abdominal pain/cramping During FMT: 50% (5/10) During follow-up: 60% (6/10) Overall: 60% (6/10) Diarrhea During FMT: 40% (4/10) During follow-up: 50% (5/10) Overall: 60% (6/10) Blood in stool During FMT: 20% (2/10) During follow-up: 30% (3/10) Overall: 30% (3/10) Fatigue During FMT: 10% (1/10) During follow-up: 20% (2/10) Overall: 20% (2/10) Fever During FMT: 20% (2/10) During follow-up: 0% (0/10) Overall: 20% (2/10) Lower Back Pain (due to positioning while performing FMT) During FMT: 10% (1/10) During follow-up: 0% (0/10) Overall: 10% (1/10)

Study	Condition	N	Demographics:	FMT details	% F/U (n/N)	Cure Definition	Primary Effectiveness Outcomes	Adverse Events
								Disabling hematochezia (temporally unrelated to FMT): During FMT: 0% (0/10) During follow-up: 10% (1/10) Overall: 10% (1/10) Other AEs unrelated to FMT**
Retrospective								
(None)								

FMT: fecal microbial transfer; F/U: follow-up; HBI: Harvey-Bradshaw Index; IBD: Irritable Bowel Disease; IQR: interquartile range; NG: nasogastric; PUCAI: Pediatric Ulcerative Colitis Activity Index; SD: standard deviation

*Cui 2015: Author stated no severe or obvious adverse events during endoscopic infusion after FMT and long-term follow up, authors used Common Terminology Criteria for Adverse Events (version 3.0) which includes death

† Kunde 2013: 1 patient was lost to follow-up as the intervention failed (patient could not retain enema as necessary for intervention)

‡Kunde 2013: Calculated from extracting data presented in Figure 2, interpreting based on remission and improvement definitions provided.

§Kunde 2013: Note that patients received 1 treatment daily for 5 days, per protocol; through they received many enemas, it was part of 1 whole treatment.

**Kunde 2013: Included cervical lymphadenopathy, headache/nausea/vomiting from concurrent medication use

APPENDIX G. Case Series Results Tables

Appendix Table G1. CDI Case Series Effectiveness Results Table: Cure following Single FMT

Outcome	Cure % (n/N)	F/U	FMT (number received)	Case Series	Population
Cure: Absence of CDI-related diarrhea plus negative stool test*	92.1% (211/229)	2 mos.	Colonoscopic (1 FMT)	Khoruts 2016 (prospective)	Recurrent CDI
	74% (32/43)	2 mos.	Colonoscopic (1 FMT)	Khoruts 2016 (prospective)	Recurrent CDI + IBD
	94% (66/70)	3 mos.	Colonoscopic (1 FMT)	Mattila 2012 (retrospective)	Recurrent CDI
Cure: Absence of CDI-related diarrhea	87% (26/30)	1 mos.	Colonoscopic (1 FMT)	Patel 2013 (retrospective)	Recurrent CDI
	90% (9/10)	1.5 mos. (median)	Nasal route (various) (1 FMT)	Kronman 2015 (retrospective)	Recurrent CDI; Pediatric patients
	52% (16/31)	2 mos.	Enema (1 FMT)	Orenstein 2015 (prospective)	Recurrent CDI
	79% (59/75)	2 mos.	Nasogastric (or other gastric route) (1 FMT)	Rubin 2013 (retrospective)	Recurrent CDI
	73% (29/40)	2.7 mos.	Gastroscopic or colonoscopic (1 FMT)	Garborg 2010 (retrospective)	Recurrent CDI
	82% (73/89)	3 mos.	Various (1 FMT)	Agrawal 2015 (retrospective)	Recurrent CDI
	78% (62/80)	3 mos.	Endoscopic (lower GI)	Kelly 2014 (retrospective)	Recurrent, refractory, or complicated CDI and immuno-compromised
	91% (70/77)	3 mos.	Colonoscopic (1 FMT)	Brandt 2012 (retrospective)	Recurrent CDI
	86% (73/57)	3 mos.	Various (1 FMT)	Agrawal 2015 (retrospective)	Severe or Complicated CDI
	48% (45/94)	6 & 24 mos.†	Enema (1 FMT)	Lee 2014 (retrospective)	Recurrent or refractory CDI
	69% (22/32)	26 mos. (median)	Enema or colonoscopic (1 FMT)	Jorup-Ronstrom 2012 (retrospective)	Recurrent CDI
	90% (9/10)	Range 1-48 mos.	Nasogastric or colonoscopic	Russel 2014 (retrospective)	Recurrent CDI alone (n=7) or +

Outcome	Cure % (n/N)	F/U	FMT (number received)	Case Series	Population
			(1 FMT)		IBD (n=3); Pediatric patients

CI: confidence interval; FMT: fecal microbiota transfer; F/U: follow-up
*See Appendix Table X for detailed definitions used in each study
†The authors stated that all patients who responded to FMT remained CDI-free between 6 and 24 months.

Appendix Table G2. CDI Case Series Effectiveness Results Table: Additional Procedures following First FMT

# Additional Procedures	Additional FMT(s) % (n/N)	Subsequent Cure % (n/N)	F/U	Case Series	Population
1 additional FMT	15% (6/40)	67% (4/6)	1.5 mos.	Garborg 2010 (retrospective)	Recurrent CDI
1 additional FMT	1% (1/75)	NR	2 mos.	Rubin 2013 (retrospective)	Recurrent CDI
1 additional FMT	15% (12/80)	67% (8/12)	3 mos.	Kelly 2014 (retrospective)	Recurrent, refractory, or complicated CDI and immuno-compromised
1 additional FMT	3% (2/77)	100% (2/2)	3 mos.	Brandt 2012 (retrospective)	Recurrent CDI
1 additional FMT	10% (1/10)	0% (0/1)	5 mos.	Kronman 2015 (retrospective)	Recurrent CDI; Pediatric patients
1 additional FMT	48% (15/31)	77% (11/14)	6 mos.	Orenstein 2015 (prospective)	Recurrent CDI
1 additional FMT	6% (4/70)	67% (2/3)	12 mos.	Mattila 2012 (retrospective)	Recurrent CDI
1 additional FMT	9.6% (14/146)	100% (14/14)	12 mos.	Agrawal 2015 (retrospective)	Recurrent, severe, or complicated CDI
1 additional FMT	10% (3/30)	67% (2/3)	12 mos.	Patel 2013 (retrospective)	Recurrent CDI
2 additional FMTs	0.7% (1/146)	100% (1/1)	12 mos.	Agrawal 2015 (retrospective)	Recurrent, severe, or complicated CDI
1 additional FMT	21% (20/94)	95% (19/20)	24 mos.	Lee 2014 (retrospective)	Recurrent or refractory CDI
2 additional FMTs	15% (14/94)	86% (12/14)	24 mos.	Lee 2014 (retrospective)	Recurrent or refractory CDI
≥3 additional FMTs	5% (5/94)	100% (5/5)	24 mos.	Lee 2014 (retrospective)	Recurrent or refractory CDI
1 additional FMT	16% (5/32)	80% (4/5)	26 mos. (median)	Jorup-Ronstrom 2012 (retrospective)	Recurrent CDI
Nasogastric or colonoscopic (1 FMT)	0% (0/10)	NA	Range 1-48 mos.	Russel 2014 (retrospective)	Recurrent CDI alone (n=7) or + IBD (n=3); Pediatric patients

CI: confidence interval; FMT: fecal microbiota transfer; F/U: follow-up

Appendix Table G3. CDI Case Series Effectiveness Results Table: Mortality

Outcome	% (n/N)	F/U	Case Series	Population
Mortality attributed to CDI	5% (2/40)	2 mos.	Garborg 2010 (retrospective)	Recurrent CDI
	0% (0/75)	2 mos.	Rubin 2013 (retrospective)	Recurrent CDI
	0% (0/80)	3 mos.	Kelly 2014 (retrospective)	Recurrent, refractory, or complicated CDI and immuno-compromised
	6% (4/70)	3 & 12 mos.	Mattila 2012 (retrospective)	Recurrent CDI
	0% (0/32)	6 mos.	Orenstein 2015 (prospective)	Recurrent CDI
	1.4% (2/146)	12 mos.	Agrawal 2015 (retrospective)	Recurrent, severe, or complicated CDI
	0% (0/94)	24 mos.	Lee 2014 (retrospective)	Recurrent or refractory CDI
All-cause mortality	0% (0/75)	2 mos.	Rubin 2013 (retrospective)	Recurrent CDI
	15% (6/40)	2 mos.	Garborg 2010 (retrospective)	Recurrent CDI
	9% (7/77)	3 mos.	Brandt 2012 (retrospective)	Recurrent CDI
	7% (5/70)	3 mos.	Mattila 2012 (retrospective)	Recurrent CDI
	3% (1/30)	3 mos.	Patel 2013 (retrospective)	Recurrent CDI
	6% (5/80)	6 mos.	Kelly 2014 (retrospective)	Recurrent, refractory, or complicated CDI and immuno-compromised
	3% (1/32)	6 mos.	Orenstein 2015 (prospective)	Recurrent CDI
	8.2% (12/146)	7 mos.	Agrawal 2015 (retrospective)	Recurrent, severe, or complicated CDI
	21% (15/70)	12 mos.	Mattila 2012 (retrospective)	Recurrent CDI
	6% (6/94)	24 mos.	Lee 2014 (retrospective)	Recurrent or refractory CDI

FMT: fecal microbiota transfer; F/U: follow-up

Appendix Table G4. CDI Case Series Safety Results Summary Table: FMT

Adverse event	% (n/N)	F/U	Population	Case Series
Serious Adverse Events				
FMT-related mortality	0% (0/75)	2 mos.	Recurrent CDI	Rubin 2013 (retrospective)
	1% (1/80)*	3 mos.	Immunocompromised + Recurrent, Refractory, or Complicated CDI	Kelly 2014 (retrospective)
	0% (0/77)	3 mos.	Recurrent CDI	Brandt 2012 (retrospective)
	0% (0/70)	3 mos.	Recurrent CDI	Mattila 2012 (retrospective)
	0% (0/34)	6 mos.	Recurrent CDI	Orenstein 2015/Ray 2016 (prospective)
	0% (0/146)	12 mos.	Recurrent or complicated CDI	Agrawal 2015 (retrospective)
	0% (0/31)	12 mos.	Recurrent CDI	Patel 2013 (retrospective)
	0% (0/94)	24 mos.	Recurrent or refractory CDI	Lee 2014 (retrospective)
Serious/Significant AEs§	0% (0/94)	24 mos.	Recurrent or refractory CDI	Lee 2014 (retrospective)
Serious/Significant FMT-related AEs§	0% (0/34)	6 mos.	Recurrent CDI	Orenstein 2015/Ray 2016 (prospective)
Serious/Significant AEs related to FMT§	0% (0/70)	12 mos.	Recurrent CDI	Mattila 2012 (retrospective)
Hospitalization for FMT-related abdominal pain, (self-limited)	1% (1/80)	3 mos.	Immunocompromised + Recurrent, Refractory, or Complicated CDI	Kelly 2014 (retrospective)
Hospitalization for FMT or CDI-related diarrhea	4.1% (6/146)	3 mos.	Recurrent or complicated CDI	Agrawal 2015 (retrospective)
Non-serious Adverse Events				
Bloating and abdominal discomfort	4% (3/80)	Immediately postop	Immunocompromised + Recurrent, Refractory, or Complicated CDI	Kelly 2014 (retrospective)
Constipation (CDI-negative)	2.7% (4/146)	NR	Recurrent or complicated CDI	Agrawal 2015 (retrospective)
Constipation and excess flatulence (transient)	10% (9/94)	NR	Recurrent or refractory CDI	Lee 2014 (retrospective)
Crohn's flare	1% (1/80)	3 mos.	Immunocompromised + Recurrent, Refractory, or Complicated CDI	Kelly 2014 (retrospective)
Diarrhea (CDI-negative)	4.8% (7/146)	NR	Recurrent or complicated CDI	Agrawal 2015 (retrospective)

Adverse event	% (n/N)	F/U	Population	Case Series
Diarrheal illness, self-limited	4% (3/80)	3 mos.	Immunocompromised + Recurrent, Refractory, or Complicated CDI	Kelly 2014 (retrospective)
Fever	1% (1/80)	1 day	Immunocompromised + Recurrent, Refractory, or Complicated CDI	Kelly 2014 (retrospective)
Gastrointestinal distress (short term)	60% (6/10)	NR	Recurrent CDI ± IBD, Pediatric	Russell 2014 (retrospective)
Hip pain	1% (1/80)	3 mos.	Immunocompromised + Recurrent, Refractory, or Complicated CDI	Kelly 2014 (retrospective)
Hospitalization unrelated to FMT	8% (6/80)	3 mos.	Immunocompromised + Recurrent, Refractory, or Complicated CDI	Kelly 2014 (retrospective)
IBD flare (hospitalized)†	5% (3/80)	3 mos.	Immunocompromised + Recurrent, Refractory, or Complicated CDI	Kelly 2014 (retrospective)
Microperforation (caused by biopsy of area presumed ischemic small-bowel injury during FMT)	3% (1/34)	Periprocedural	Recurrent CDI	Patel 2013 (retrospective)
Minor mucosal tear during colonoscopy for FMT	1% (1/80)	Postop	Immunocompromised + Recurrent, Refractory, or Complicated CDI	Kelly 2014 (retrospective)
Mucoid stools	10% (1/10)	2 days postop	Recurrent CDI, Pediatric	Kronman 2015 (retrospective)
Mucoid stools (long-term, self-limited)	10% (1/10)	0.5 mos.	Recurrent CDI ± IBD, Pediatric	Russell 2014 (retrospective)
Nausea	1% (1/80)	1 mo.	Immunocompromised + Recurrent, Refractory, or Complicated CDI	Kelly 2014 (retrospective)
Pertussis	1% (1/80)	1 mo.	Immunocompromised + Recurrent, Refractory, or Complicated CDI	Kelly 2014 (retrospective)
Vomiting	10% (1/10)	Immediately Postop	Recurrent CDI, Pediatric	Kronman 2015 (retrospective)
AEs§	0% (0/75)	2 mos.	Recurrent CDI	Rubin 2013 (retrospective)
AEs‡	82% (28/34)‡	6 mos.	Recurrent CDI	Orenstein 2015/Ray 2016 (prospective)

Adverse event	% (n/N)	F/U	Population	Case Series
FMT-related AEs§	0% (0/32)	NR	Recurrent CDI	Jorup-Ronstrum 2012 (retrospective)
FMT-related AEs§	0% (0/40)	2.5 mos.	Recurrent CDI	Garborg 2010 (retrospective)

AE: Adverse event; CDI: *Clostridium difficile* infection; FMT: fecal microbiota transplant; F/U: follow-up; IBD: irritable bowel disease; NR: not reported

*Kelly 2014: Patient had advanced esophageal cancer and cachexia, aspirated during sedation during colonoscopy, died of respiratory failure next day

†Kelly 2014: IBD was present before FMT treatment

‡Orenstein 2015/Ray 2016: A total of 188 adverse events occurred, of which 59% (110/188) were related to CDI, authors did not state which were attributed to FMT. AEs included gastrointestinal disorders, infections, general disorders (chills, fever, etc.), respiratory disorders, musculoskeletal disorders, nervous system disorders, and others.

§Authors state that there were no adverse events

Appendix Table G5. IBD Case Series Safety Results Summary Table: FMT

Adverse event	% (n/N)	F/U	Population	Case Series
Serious adverse events				
Serious AEs*	00% (0/10)	1 mo.	UC Pediatric	Kunde 2013 (prospective)
Serious AEs*	0% (0/30)	6 mos.	CD	Cui 2015 (prospective)
Disabling hematochezia (unrelated to FMT)	10% (1/10)	1 mo.	UC Pediatric	Kunde 2013 (prospective)
Non-serious adverse events				
Abdominal Pain/Flatulence	50% (5/10)	Periprocedural	UC Pediatric	Kunde 2013 (prospective)
Abdominal Pain/Flatulence	60% (6/10)	1 mo.	UC Pediatric	Kunde 2013 (prospective)
Bloating/flatulence	70% (7/10)	Periprocedural	UC Pediatric	Kunde 2013 (prospective)
Bloating/flatulence	40% (4/10)	1 mo.	UC Pediatric	Kunde 2013 (prospective)
Blood in stool	20% (2/10)	Periprocedural	UC Pediatric	Kunde 2013 (prospective)
Blood in stool	30% (3/10)	1 mo.	UC Pediatric	Kunde 2013 (prospective)
Could not retain enema	10% (1/10)	Periprocedural	UC Pediatric	Kunde 2013 (prospective)
Diarrhea	23% (7/30)	1-6 h. postop	CD	Cui 2015 (prospective)
Diarrhea	40% (4/10)	Periprocedural	UC Pediatric	Kunde 2013 (prospective)
Diarrhea	50% (5/10)	1 mo.	UC Pediatric	Kunde 2013 (prospective)
Disabling hematochezia (temporally unrelated to FMT)	10% (1/10)	1 mo.	UC Pediatric	Kunde 2013 (prospective)
Fatigue	10% (1/10)	Periprocedural	UC Pediatric	Kunde 2013 (prospective)
Fatigue	20% (2/10)	1 mo.	UC Pediatric	Kunde 2013 (prospective)
Fever	20% (2/10)	Periprocedural	UC Pediatric	Kunde 2013 (prospective)
Fever	0% (0/10)	1 mo.	UC Pediatric	Kunde 2013 (prospective)
Fever (authors attributed to anesthesia)	7% (2/30)	1-6 h. postop	CD	Cui 2015 (prospective)
FMT-related mortality	0% (0/30)	6 mos.	CD	Cui 2015 (prospective)
FMT-related mortality	0% (0/10)	1 mo.	UC Pediatric	Kunde 2013 (prospective)
Lower Back Pain (due to positioning during FMT)	10% (1/10)	Periprocedural	UC Pediatric	Kunde 2013 (prospective)
Pain or fecal ileus	0% (0/30)	NR	CD	Cui 2015 (prospective)

AE: Adverse event; CD: Crohn's Disease; FMT: fecal microbiota transplant; F/U: follow-up; UC: ulcerative colitis
*Author noted that there were no serious adverse events

APPENDIX H. Economic Studies: Data Abstraction Tables

Appendix Table H1. CDI Economic Studies Data Abstraction Tables

Author (year) Country Funding QHES	Population Interventions	Design Perspective Time horizon Model	Assumptions	Economic Model specifications	Year, Currency Cost Sources Discounting	Clinical Data Source	Primary Findings	Limitations, risk of bias
Konijeti 2014 United States **Funding**: National Institute of Diabetes and Digestive and Kidney Diseases of the NIH (award number T32DK007191)	Hypothetical cohorts of adult patients with a median age of 65 years undergoing first-line treatment for recurrent CDI **Interventions:** ▪ 3 antibiotic only groups (all oral, 10 day courses): ○ Metronidazole 500 mg 3x/day ○ Vancomycin 125 mg 4x/day ○ Fidaxomicin 200 mg 2x/day ▪ 3 FMT groups (all with 4 days oral vancomycin 500 mg every 6 hrs. prior to procedure, regardless of delivery mode) ○ FMT via colonoscopy ○ FMT via duodenal infusion ○ FMT via enema	CUA Societal perspective 1 year time horizon Decision analytic model	▪ Patients with a first recurrence of CDI were assumed to have mild-moderate disease diagnosed at an outpatient visit ▪ Two additional occurrences following the initial recurrence: ○ Those treated initially by metronidazole received oral vancomycin for a second recurrence and outpatient oral vancomycin pulse/taper for the third recurrence ○ Those treated initially with outpatient oral vancomycin or fidaxomicin were given	▪ Patients enter the model once a diagnosis of CDI is made. ▪ 5 different treatment strategies examined: ○ 3 drug arms vs. FMT via colonoscopy (base case, scenario 1), via duodenal infusion (scenario 2), or via enema (scenario 3) ○ 3 drug strategies compared simultaneously with all three modes of FMT delivery (scenario 4) ○ 3 drug arms alone (assuming FMT may not be available to all patients/in all settings, scenario 5) ▪ Patients contributed	**Year/Currency:** ▪ All costs other than FMT: 2012 $US ▪ FMT: 2013 $US **Cost sources**: ▪ All costs other than FMT: Consumer Price Index ▪ FMT: 2012 Clinical Diagnostic Laboratory Fee Schedule from CMS; CPT code G0455 (stool preparation and instillation) **Costs used for analysis**: ▪ Pharmacological therapies (inpatient and outpatient) ▪ For FMT specifically: ○ donor and recipient laboratory testing ○ 4-day pretreatment	**Clinical Data:** ▪ Cure ▪ Recurrence ▪ Severe CDI if treatment failure ▪ Colectomy for severe CDI ▪ Mortality (from severe CDI, postcolectomy or medical treatment) **Clinical Source:** Published literature and guidelines **Utility Data:** ▪ Healthy patient, age 65 years ▪ Mild-moderate CAD ▪ Severe CDI ▪ Colectomy ▪ Postcolectomy **Utility Source:** Published literature	*Vancomycin vs. Metronidazole vs. Fidaxomicin vs. FMT (delivery mode varies below)* **Scenario 1 - FMT via colonoscopy (base case)** ▪ Cost ($): 2912 vs. 3941 vs. 4261 vs. 3149 ▪ QALY: 0.8580 vs. 0.8292 vs. 0.8653 vs. 0.8719 ▪ ICER for FMT colonoscopy: $17,016; dominated all other treatments **Scenario 2 - FMT via duodenal infusion** ▪ Cost ($): 3531 vs. 3941 vs. 4628 vs. 4208 ▪ QALY: 0.8484 vs. 0.8292 vs. 0.8596 vs. 0.8553 ▪ ICER: NR [referent] vs.	▪ Did not account for potential differences in treatment efficacy or epidemiologic distribution of the more virulent North American pulsed-field gel electrophoresis type 1/restriction endonuclease analysistype B1/ PCR ribotype 027 *C. difficile* strain ▪ Did not model higher recurrence rates because of variations in risk factors for recurrence, specific antibiotic usage, and limited long-term data on recurrences following FMT (studies have shown higher recurrence rates after second or third line antibiotic treatment) ▪ Utilities for mild-

Author (year) Country Funding QHES	Population Interventions	Design Perspective Time horizon Model	Assumptions	Economic Model specifications	Year, Currency Cost Sources Discounting	Clinical Data Source	Primary Findings	Limitations, risk of bias
			outpatient oral vancomycin pulse/taper for a second recurrence, and FMT via colonoscopy (in model comparing different FMT modalities) or treatment with fidaxomicin (in model where FMT was not available) for a third recurrence ○ Those treated initially with FMT were given repeat FMT by the same mode of delivery for a second recurrence, and outpatient oral vancomycin pulse/taper for a third recurrence ▪ Patients cured by	person-time in 1 of 6 health conditions: healthy, mild-moderate CDI, severe CDI, persistent recurrent disease, postcolectomy, and death (death occurred due to severe CDI or following colectomy). ▪ The probabilities of initial cure rates and nonresponse sum to 1; rates of recurrence were modeled as a fraction of the population who achieved clinical cure following the initial CDI recurrence. ▪ QALYs calculated as the product of time in a particular health condition and the utility of that particular condition ▪ Willingness-to-pay threshold set at $50,000 per QALY ▪ Various sensitivity	with vancomycin ○ FMT preparation and instillation ○ Method of delivery (colonoscopy, esophago-gastro-duodeno-scopy; enema) ▪ Hospitalization for CDI ▪ Initial outpatient visit ▪ Follow-up outpatient visits ▪ *Clostridium difficile* nucleic acid amplification testing **Discounting**: NR		Dominated vs. $98,862 vs. $97, 352; oral vancomycin is preferred in this setting **Scenario 3 - FMT via enema** ▪ Cost ($): 3488 vs. 3941 vs. 4602 vs. 4090 ▪ QALY: 0.8485 vs. 0.8292 vs. 0.8597 vs. 0.8543 ▪ ICER: NR [referent] vs. Dominated vs. $99,862 vs. $105,003; oral vancomycin is preferred in this setting **Scenario 4 - FMT via either of the 3 delivery routes** ▪ Cost ($): 2912 vs. 3941 vs. 4261 vs. 3149 (FMT colonoscopy) vs. 4090 (FMT enema) vs. 4208 (FMT duodenal) ▪ QALY: 0.8580 vs. 0.8292 vs. 0.8653 vs. 0.8719 (FMT	moderate and severe CDI had to be extrapolated from other comparable causes of diarrhea, as there are no published estimates of health utility with CDI ▪ Costs attributed to FMT did not include the infrastructure and personnel costs required in establishing an FMT program. ▪ One of the authors (A. N. A.) has served on scientific advisory boards for Prometheus, Inc, Janssen Pharmaceuticals, and Cubist Pharmaceuticals

Author (year) Country Funding QHES	Population Interventions	Design Perspective Time horizon Model	Assumptions	Economic Model specifications	Year, Currency Cost Sources Discounting	Clinical Data Source	Primary Findings	Limitations, risk of bias
			a given treatment strategy were assumed to spend half the duration of treatment in a state of mild-to-moderate or severe disease, and the subsequent half in the healthy state. ▪ Non-responders remained in the initial disease state through the course of treatment, and were then transitioned to mild-moderate CDI with next-line treatment, or severe CDI requiring hospitalization (treated with IV vancomycin plus IV metronidazole) until they were either cured, underwent colectomy, or died.	analyses performed: ○ Model sensitivity analyses (using alternate method of FMT delivery or scenarios where FMT not available); ○ univariate sensitivity analyses (impact of changes in probabilities, costs, and utilities); and ○ probabilistic sensitivity analysis (to account for uncertainty in the model specifications)			colonoscopy) vs. 0.8543 (FMT enema) vs. 0.8553 (FMT duodenal) ▪ ICER for FMT colonoscopy: $17,016; dominated all other treatments **Probabilistic sensitivity analysis**: ICER of $20,285 for FMT colonoscopy vs. vancomycin; supported findings from base cases analysis **Sensitivity analyses of individual variables:** ▪ Cure rate: ○ ≥88.4%: FMT colonoscopy remained most cost-effective (oral vancomycin required a cure rate >95.5% to make in more cost effective	

Author (year) Country Funding QHES	Population Interventions	Design Perspective Time horizon Model	Assumptions	Economic Model specifications	Year, Currency Cost Sources Discounting	Clinical Data Source	Primary Findings	Limitations, risk of bias
			▪ Assumed a median hospitalization duration of 2 weeks ▪ Cost of an enema assumed to be equivalent to an outpatient office visit				than FMT) ○ <88.4%: vancomycin more cost effective; ICER of FMT colonoscopy relative to vancomycin exceeded the willingness-to-pay threshold of $50,000 ○ For FMT via duodenal infusion or enema, if cure rate >85.2% they are more cost-effective than vancomycin ▪ <u>Recurrence rate</u> ○ <14.9%: FMT colonoscopy more cost-effective (oral vancomycin required a recurrence rate <27.2% to make it more cost-effective than FMT) ▪ <u>Cost up to $2724:</u>	

Author (year) Country Funding QHES	Population Interventions	Design Perspective Time horizon Model	Assumptions	Economic Model specifications	Year, Currency Cost Sources Discounting	Clinical Data Source	Primary Findings	Limitations, risk of bias
							○ FMT more cost-effective ▪ Willingness-to-pay threshold of $100,000/QALY ○ FMT colonoscopy most cost effective strategy at cure rates >84.4%	
Varier 2014 United States **Funding**: NR (authors declared no conflicts of interest)	Simulated adult patients undergoing outpatient treatment for initial CDI **Interventions:** ▪ Metronidazole (assumed 500 mg 3x/day) or Vancomycin (assumed 125 mg 4x/day); both oral, 10-14 day course ▪ FMT (assumed via colonoscopy)	CUA Third party payer perspective 90-day time horizon Decision analytic model	▪ Assumed patients entering the model were adults receiving outpatient treatment ▪ Assumed FMT would be as effective for initial CDI as it is for recurrent CDI ▪ Assumed metronidazole was given as 500 mg by mouth three times daily and vancomycin was given as 125 mg by mouth four times daily ▪ Assumed FMT donor stool was administered via colonoscopy ▪ Assumed	▪ Patients enter the model once a diagnosis of CDI is made. ▪ The follow-up period started either at the beginning of antibiotic therapy or after FMT treatment ▪ Patients who had not developed recurrent CDI were considered to be improved, or 'cured'; if patients did not improve, they could either have severe/fulminant colitis or recurrent CDI; these patients remained with that condition of health	2011 $US **Cost Sources** ▪ CMS ▪ Previously published studies ▪ Consumer Price Index ▪ US Bureau of Labor Statistics **Costs used for analysis**: ▪ 10-14 day course of metronidazole ▪ 10-14 day course of vancomycin ▪ Recurrent CDI, which included cost of repeat testing and treatment with another course using vancomycin taper	**Clinical and utilities data:** ▪ Cure ▪ Recurrent CDI ▪ Fulminant colitis ▪ Death ▪ Adverse events related to FMT **Clinical and utility data source:** ▪ Published literature including: clinical studies, systematic reviews, and other cost-effectiveness analyses No published utility values exist for CDI,	**Base case** Cost ($) ▪ Metronidazole: 1167 ▪ Vancomycin: 1890 ▪ FMT: 1669 QALY ▪ Metronidazole: 0.238 ▪ Vancomycin: 0.241 ▪ FMT: 0.242 ICER ▪ Metronidazole: NR (referent) ▪ Vancomycin: Dominated ▪ FMT: 124,964 ▪ FMT was more costly and more effective than metronidazole, and less costly and more	▪ Utilized a simulation model and may not reflect all real-world considerations. ▪ Incorporated data from reports evaluating adult subjects without other serious comorbid conditions such as end-stage renal disease or inflammatory bowel disease (IBD); risks of the strategies may differ in patients with comorbid conditions ▪ Not considered in model: ○ alternative

Author (year) Country Funding QHES	Population Interventions	Design Perspective Time horizon Model	Assumptions	Economic Model specifications	Year, Currency Cost Sources Discounting	Clinical Data Source	Primary Findings	Limitations, risk of bias
			adverse events of FMT were equivalent to aggregate adverse effects of a diagnostic colonoscopy procedure ▪ Assumed that the probability of death from FMT was equivalent to that from colonoscopy, and not related to CDI after procedure ▪ Assumed adverse effects of metronidazole and vancomycin were negligible and thus were not included in the model	for the remainder of the 90-day follow-up. ▪ Sensitivity analyses included: one-way sensitivity analyses varying probabilities of cure and costs of treatments; probabilistic sensitivity analysis using 10,000 second order Monte Carlo simulations.	▪ FMT, which included testing, procedure (CPT 45378) and facility costs ▪ Colitis, considered as an aggregate of severe/fulminant colitis, which includes hospitalization and medical therapy with IV metronidazole and vancomycin, as well as probability and costs of surgery and death ▪ Adverse effects of FMT, estimated to be equivalent to the cost of perforation following colonoscopy **Discounting**: NR	therefore, estimates of the utility of non-infectious diarrhea were used as the values for the utility of colitis- and RCDI-associated diarrhea; utility weights for colitis and recurrent CDI were applied for a duration of 90-days minus the time treated with antimicrobial therapy.	effective (i.e., dominated) than vancomycin **One-way sensitivity analysis** ▪ FMT dominated if its costs were <$584, if the cost of metronidazole was >$559, or of the probability of cure of metronidazole was <71% ▪ Metronidazole dominated both strategies if its probability of cure was >90% **Probabilistic sensitivity analysis (i.e., varying all parameters simultaneously)** ▪ Metronidazole was favored in approximately 55% of model iterations and FMT was	administration routes for FMT ○ inpatient population (assumed all patients were treated on an outpatient basis) ○ CDI severity ▪ Data used for parameters in the model came from studies of varying quality given the paucity of existing studies examining FMT from which to gather inputs ▪ Chose to underestimate some of the parameters associated with metronidazole and vancomycin and to overestimate the respective cure rates of these medications in order to maintain the conservative design of the model (to temper the assumption that FMT for

Author (year) Country Funding QHES	Population Interventions	Design Perspective Time horizon Model	Assumptions	Economic Model specifications	Year, Currency Cost Sources Discounting	Clinical Data Source	Primary Findings	Limitations, risk of bias
							favored in 38% at a willingness-to-pay threshold of $100 000/QALY	initial CDI would be as effective as when used for recurrent CDI). ▪ Due to lack of published utility values for CDI, estimates of the utility of non-infectious diarrhea were used as the values for the utility of colitis- and RCDI-associated diarrhea
Varier 2015 United States **Funding**: Department of Veterans Affairs, Health Services Research & Development grant	Simulated adult patients undergoing outpatient treatment for recurrent CDI **Interventions:** ▪ tapered Vancomycin (assumed 250 mg 4x/day followed by 6-week oral taper) ▪ FMT (assumed via colonoscopy)	CUA Third party payer perspective 90-day time horizon Decision analytic model	▪ Assumed patients entering the model were adults receiving outpatient treatment ▪ Assumed vancomycin was given as 250 mg every 6 hours for 2 weeks followed by a 6-week oral vancomycin taper ▪ Assumed FMT donor stool was administered via colonoscopy ▪ Assumed adverse events	▪ Patients entered the model after the third recurrence (fourth occurrence) of CDI ▪ Patients could be treated with another course of tapered vancomycin or FMT ▪ Patients were followed for 90-days after which point those who had not developed recurrent CDI were considered to be improved, or 'cured'; if patients did not improve,	2011 $US **Cost Sources** ▪ CMS ▪ Previously published cost studies ▪ Consumer Price Index ▪ US Bureau of Labor Statistics **Costs used for analysis**: ▪ Tapered vancomycin course (based on assumption of a prolonged 6-week taper following initial therapy)	**Clinical and utilities data:** ▪ Cure/improved ▪ Recurrent CDI ▪ Fulminant colitis ▪ Death ▪ Adverse events related to FMT **Clinical and utility data source:** ▪ Published literature including: clinical studies, systematic reviews, and other cost-effectiveness analyses	**Base case** Cost ($) ▪ Vancomycin: 3788 ▪ FMT: 1669 QALY ▪ Vancomycin: 0.235 ▪ FMT: 0.242 ICER ▪ Vancomycin: NR ▪ FMT: Dominant **One-way sensitivity analysis** ▪ FMT was more effective than vancomycin if cure rate ≥70% ▪ FMT was less	▪ Utilized a simulation model and may not reflect all real-world considerations. ▪ Incorporated data from reports evaluating adult subjects without other serious comorbid conditions such as end-stage renal disease or inflammatory bowel disease (IBD); risks of the strategies may differ in patients with comorbid

Author (year) Country Funding QHES	Population Interventions	Design Perspective Time horizon Model	Assumptions	Economic Model specifications	Year, Currency Cost Sources Discounting	Clinical Data Source	Primary Findings	Limitations, risk of bias
			of FMT were equivalent to aggregate adverse effects of a diagnostic colonoscopy procedure (including anesthesia) ▪ Assumed that the probability of death from FMT was equivalent to that from colonoscopy ▪ Assumed adverse effects of vancomycin were negligible and thus were not included in the model	they could either have severe/fulminant colitis or recurrent CDI (recurrence could occur at any time after completing therapy); the latter patients remained with that condition of health for the remainder of the 90-day follow-up. ▪ Patients with fulminant colitis were not considered appropriate candidates for FMT administered via colonoscope ▪ Sensitivity analyses included: one-way sensitivity analyses varying probabilities of cure and costs of treatments; probabilistic sensitivity analysis using 10,000 second order Monte Carlo simulations.	▪ FMT, which included donor and recipient screening, procedure, and facility costs ▪ Recurrent CDI, which included cost of repeat testing and treatment with another course using vancomycin taper ▪ Colitis, considered as an aggregate of severe/fulminant colitis, which includes hospitalization and medical therapy, as well as probability and costs of surgery and death ▪ Adverse effects of FMT, estimated to be equivalent to the cost of colonoscopy adverse effects **Discounting**: Not discounted	No published utility values exist for CDI, therefore, previously defined utilities of similar disease states were used as estimates of colitis and recurrent CDI-associated QALYs	costly than vancomycin if cure rate ≥53% ▪ The FMT strategy was less costly than the vancomycin strategy across the entire range of values for the cure rate for vancomycin and was more effective than the vancomycin strategy across the entire range of values for the cost of FMT ▪ FMT strategy was no longer dominant when the cure rate for vancomycin was >90% and when the cost of FMT exceeded $3,205 ▪ With all other values held at their basecase level, the FMT strategy dominated the vancomycin strategy regardless of	conditions ▪ Not considered in model: ○ alternative administration routes for FMT ○ inpatient population (assumed all patients were treated on an outpatient basis) ○ CDI severity ▪ Data used for parameters in the model came from studies of varying quality given the paucity of existing studies examining FMT from which to gather inputs ▪ Chose to underestimate some of the parameters associated with vancomycin (e.g., decided not to incorporate adverse effects of vancomycin and its respective costs) ▪ Due to lack of published utility

Author (year) Country Funding QHES	Population Interventions	Design Perspective Time horizon Model	Assumptions	Economic Model specifications	Year, Currency Cost Sources Discounting	Clinical Data Source	Primary Findings	Limitations, risk of bias
							the cost of vancomycin. **Probabilistic sensitivity analysis (i.e., varying all parameters simultaneously)** FMT was more effective and less costly (dominant) that vancomycin in all 10,000 second-order Monte Carlo simulations.	values for CDI, estimates of the utility of similar disease states were used as the values for the utility of colitis- and RCDI-associated diarrhea
Lapoint-Shaw 2016 Canada **Funding**: This project did not utilize any specific project-related financial support; Dr. Lapointe-Shaw is supported by the Clinician Scientist Training Program at the University of Toronto	Adults (mean age 70 years) experiencing their first recurrence of CDI **Interventions:** ▪3 antibiotic only groups (all oral, followed by 6-week taper-pulse course of oral vancomycin for subsequent recurrences): ○ Metronidazole 500 mg 3x/day for 2 weeks ○ Vancomycin 125 mg 4x/day	CUA Public insurer for all hospital and physician services (Ontario Ministry of Health and Long-Term Care) 18 week time horizon Decision analytic model (Markov)	▪Community dwelling persons with a mean age of 70 years ▪Assumed recurrence and treatment could only occur once every 6 week cycle ▪Assumed the probability of recurrence remained fixed over time	▪Model cycle length of 6 weeks and up to 3 recurrences (i.e., total 18-wk period) ▪In the first cycle, all patients experienced recurrence of CDI (first episode of CDI not modeled) ▪In subsequent cycles, patients could be in one of three states: no recurrence, another recurrence, or dead ▪Patients	2014 $Canadian **Cost Sources** ▪Published literature ▪Consumer Price Index for Health and Personal Care ▪University Health Network outpatient pharmacy, for a patient with Ontario Drug Benefit coverage ▪Statistics Canada (for personnel data), with 13% added to account for benefits	**Clinical and Utilities Data:** ▪Hospitalization for CDI ▪Response to oral metronidazole ▪Recurrence following any treatment ▪Death from: ○ all causes, age 70 ○ all causes, age 80 ○ colonoscopy ○ NG tube ○ CDI ○ Relative risk of death	**Health outcomes, per 1,000 patient cohort** <u>Count of recurrences after the first</u>: ▪Vancomycin: 636 ▪Metronidazole: 583 ▪FMT via NG tube: 426 ▪Fidaxomicin: 458 ▪FMT via enema: 340 ▪FMT via colonoscopy: 144 <u>Count of</u>	▪Parameter estimates obtained mostly from observational studies of intermediate or low quality (little to no RCT data available) and limited by short-follow-up periods, possibly underestimating recurrence rates ▪Per procedure cost for FMT via colonoscope obtained from cost study using

Author (year) Country Funding QHES	Population Interventions	Design Perspective Time horizon Model	Assumptions	Economic Model specifications	Year, Currency Cost Sources Discounting	Clinical Data Source	Primary Findings	Limitations, risk of bias
	for 2 weeks ○ Fidaxomicin 200 mg 2x/day for 10 days ▪ 3 FMT groups (all with 2 week course of oral vancomycin 125 mg 4x/day, followed by the same [antibiotic + FMT via specified route] using a different donor at each subsequent recurrence) ○ FMT via enema ○ FMT via NG tube ○ FMT via colonoscopy			experiencing persistent diarrhea while being treated with oral metronidazole were deemed non-responders and were switched to oral vancomycin after 6 days of therapy ▪ Patients with further recurrences after receiving metronidazole, fidaxomicin or vancomycin received a 6-week taper-pulse course of oral vancomycin ▪ A half-cycle correction was used for all QALYs in order to prevent systematic over- or under-estimation of payoffs with each cycle ▪ QALYs accrued by each strategy were obtained by multiplying the QALY weight of a state by the time spent in that state; a discounting rate	▪ Ontario Schedule of Benefits (physician data) ▪ Toronto East General Hospital administrators/ accounting offices ▪ Ontario Case Costing Initiative **Costs used for analysis**: ▪ Medications ▪ FMT by enema, by NG tube, and by colonoscopy ○ for all modes of delivery, costs included: day of procedure; personnel fees (physician; nurse, radiologist, etc.); outpatient visits; laboratory testing (donor and recipient); capital cost (equipment) ▪ Hospitalization (including in-hospital medications) ▪ Outpatient visits	from CDI for additional ten years of age **Source:** ▪ Published literature ▪ Health Utilities Index survey of community dwelling Canadians over age 70	<u>hospitalizations</u>: ▪ Vancomycin: 284 ▪ Metronidazole: 275 ▪ FMT via NG tube: 247 ▪ Fidaxomicin: 253 ▪ FMT via enema: 233 ▪ FMT via colonoscopy: 199 <u>Count of CDI-related deaths (including treatment related)</u>: ▪ Vancomycin: 119 ▪ Metronidazole: 115 ▪ FMT via NG tube: 108 ▪ Fidaxomicin: 106 ▪ FMT via enema: 98 ▪ FMT via colonoscopy: 84 <u>Average life years</u> ▪ Vancomycin: 14.46 ▪ Metronidazole: 14.78	estimates from a high-volume setting (>4000 colonoscopies/ year); in a lower-volume setting it is possible that FMT via colonoscopy could become cost prohibitive ▪ Assumed that probability of recurrence remained fixed over time; however, risk of recurrence is likely confounded by the number of previous recurrences which was not controlled for in this study ▪ Complications such as colectomy or adverse drug events were not modeled ▪ Model did not include any variable for risk of exposure to fecal transplant material itself ▪ Some authors

Author (year) Country Funding QHES	Population Interventions	Design Perspective Time horizon Model	Assumptions	Economic Model specifications	Year, Currency Cost Sources Discounting	Clinical Data Source	Primary Findings	Limitations, risk of bias
				of 5% was applied to QALYs over the patient's remaining lifetime ▪ Willingness-to-pay threshold set at $50,000/QALY ▪ Sensitivity analyses included: ○ One- and two-way sensitivity analyses ○ 0% discount rate for lifetime QALYs ○ Probabilistic analysis using 10,000 Monte Carlo cohort-base simulations ○ Scenario analyses altered by patient age, fidaxomicin patent status (generic expected to be 25% of the per-unit cost of brand name), access to fecal transplant procedures, and number or recurrences	for patients treated with medications only ▪ The cost of two outpatient visits was included in each treatment strategy; in addition, the FMT strategies included an outpatient visit for the stool donor. **Discounting**: Capital costs were annuitized using a 5% discount rate over five years. The annual cost was then distributed over the number of CDI cases seen annually at UHN to derive the typical cost of use per treatment		▪ FMT via NG tube: 14.87 ▪ Fidaxomicin: 14.90 ▪ FMT via enema: 15.04 ▪ FMT via colonoscopy: 15.26 **Base case** <u>Cost ($)</u>: ▪ FMT via colonoscopy: 5246 ▪ Vancomycin: 5929 ▪ Metronidazole: 5386 ▪ FMT via NG tube: 5935 ▪ Fidaxomicin: 7319 ▪ FMT via enema: 5667 <u>QALY</u> ▪ FMT via colonoscopy: 9.40 ▪ Vancomycin: 9.03 ▪ Metronidazole: 9.09 ▪ FMT via NG tube: 9.15 ▪ Fidaxomicin: 9.16	declared conflicts of interest regarding industry

Author (year) Country Funding QHES	Population Interventions	Design Perspective Time horizon Model	Assumptions	Economic Model specifications	Year, Currency Cost Sources Discounting	Clinical Data Source	Primary Findings	Limitations, risk of bias
							▪FMT via enema: 9.26 ICER ▪FMT via colonoscopy dominated over all other strategies **Scenario in which patient is 10 years older** Cost ($): ▪FMT via colonoscopy: 5310 ▪Vancomycin: 6174 ▪Metronidazole: 5598 ▪FMT via NG tube: 6116 ▪Fidaxomicin: 7494 ▪FMT via enema: 5815 QALY ▪FMT via colonoscopy: 6.02 ▪Vancomycin: 5.63 ▪Metronidazole: 5.69 ▪FMT via NG tube: 5.77 ▪Fidaxomicin:	

Author (year) Country Funding QHES	Population Interventions	Design Perspective Time horizon Model	Assumptions	Economic Model specifications	Year, Currency Cost Sources Discounting	Clinical Data Source	Primary Findings	Limitations, risk of bias
							5.77 ▪FMT via enema: 5.87 ICER ▪FMT via colonoscopy dominated over all other strategies **Scenario in which fidaxomicin is off patent** Cost ($): ▪FMT via colonoscopy: 5246 ▪Vancomycin: 5929 ▪Metronidazole: 5386 ▪FMT via NG tube: 5935 ▪Fidaxomicin: 5521 ▪FMT via enema: 5667 QALY ▪FMT via colonoscopy: 9.40 ▪Vancomycin: 9.03 ▪Metronidazole: 9.09 ▪FMT via NG tube: 59.15	

Author (year) Country Funding QHES	Population Interventions	Design Perspective Time horizon Model	Assumptions	Economic Model specifications	Year, Currency Cost Sources Discounting	Clinical Data Source	Primary Findings	Limitations, risk of bias
							▪Fidaxomicin: 9.16 ▪FMT via enema: 9.26 ICER ▪FMT via colonoscopy dominated over all other strategies **Scenario in which no FMT option available** Cost ($): ▪Metronidazole: 5386 ▪Fidaxomicin: 7319 ▪Vancomycin: 5929 QALY ▪Metronidazole: 9.09 ▪Fidaxomicin: 9.16 ▪Vancomycin: 9.03 ICER ▪Metronidazole: NR (referent) ▪Fidaxomicin: $25,968 ▪Vancomycin: Dominated **Scenario in which**	

Author (year) Country Funding QHES	Population Interventions	Design Perspective Time horizon Model	Assumptions	Economic Model specifications	Year, Currency Cost Sources Discounting	Clinical Data Source	Primary Findings	Limitations, risk of bias
							FMT via colonoscopy unavailable Cost ($): ▪Metronidazole: 5386 ▪FMT via enema: 5667 ▪Vancomycin: 5929 ▪FMT via NG tube: 5935 ▪Fidaxomicin: 7319 QALY ▪Metronidazole: 9.09 ▪FMT via enema: 9.26 ▪Vancomycin: 9.03 ▪FMT via NG tube: 9.15 ▪Fidaxomicin: 9.16 ICER ▪Metronidazole: NR (referent) ▪FMT via enema: $1708 ▪Vancomycin, FMT via NG tube, and Fidaxomicin: all Dominated **Scenario of two**	

Author (year) Country Funding QHES	Population Interventions	Design Perspective Time horizon Model	Assumptions	Economic Model specifications	Year, Currency Cost Sources Discounting	Clinical Data Source	Primary Findings	Limitations, risk of bias
							cycles only (single recurrence after the first) Cost ($): ▪Metronidazole: 4793 ▪FMT via colonoscopy: 4918 ▪Vancomycin: 5341 ▪Fidaxomicin: 6722 ▪FMT via NG tube: 5058 ▪FMT via enema: 4954 QALY ▪Metronidazole: 9.14 ▪FMT via colonoscopy: 9.38 ▪Vancomycin: 9.07 ▪Fidaxomicin: 9.21 ▪FMT via NG tube: 9.24 ▪FMT via enema: 9.31 ICER ▪Metronidazole: NR (referent) ▪FMT via colonoscopy: $514	

Author (year) Country Funding QHES	Population Interventions	Design Perspective Time horizon Model	Assumptions	Economic Model specifications	Year, Currency Cost Sources Discounting	Clinical Data Source	Primary Findings	Limitations, risk of bias
							▪Vancomycin, Fidaxomicin, FMT via NG tube, and FMT via enema: all Dominated **Sensitivity analysis varying all parameters within their stated ranges** ▪FMT via enema became preferred strategy when probability of recurrence following this strategy was <8.7%; otherwise, no change **Sensitivity analysis varying costs within their stated ranges** ▪No change to preferred strategy (i.e., FMT colonoscopy); even after removing the discount rate for future QALY	

Author (year) Country Funding QHES	Population Interventions	Design Perspective Time horizon Model	Assumptions	Economic Model specifications	Year, Currency Cost Sources Discounting	Clinical Data Source	Primary Findings	Limitations, risk of bias
							▪Total costs for FMT by colonoscopy would have to exceed $8062 per treatment before FMT via enema became preferred strategy ▪As long as total per-treatment costs were <$1446, FMT colonoscopy was cost-saving compared to all other strategies	
Merlo 2016 Australia **Funding**: The authors did not receive funding for this research	Simulated cohort of patients beginning at the recurrent CDI health state (i.e., relapse of CDI after ≥1 course of antibiotics) N=1000 Age: 65 years % female: NR **Interventions:** ▪Vancomycin: 125 mg 4x daily for 14 days and the same dose for 10 days in subsequent	CUA Hospital perspective Time horizon NR Markov Model with a cycle length of 10 days	▪Patients with ileostomy and those with reversed ileostomy are cured of CDI but are still subject to death from other causes. ▪Patients with subsequent CDI recurrences (after treatment for 1st recurrence) for either the vancomycin or FMT treatment arms were	▪Successfully treated patients moved into the "cure without relapse" health state. ▪Patients who do not respond to therapy can receive another round of treatment, require colectomy, die from fulminant colitis, or die from other causes. ▪After one cycle in the "colectomy" state the patient is	2015 AU$ **Cost Sources** ▪National databases and market prices (unit costs) ▪Pharmaceutical Benefits Schedule (PBS) (pharmaceuticals) ▪National Hospital Cost Data Collection (hospital stay, colectomy, ileostomy) ▪Queensland Health wage rates	**Clinical and utilities data:** ▪Baseline probability of cure without relapse ▪Treatment effect of FMT ▪Transition probabilities (cure without relapse, mortality from CDI, colectomy given CDI, post-colectomy mortality, ileostomy closure,	**Cost, $ (95% CI)** ▪Vancomycin vs. Nasoduodenal FMT**:** increased cost of 4094 (26 to 8161) ▪Vancomycin vs. Colorectal FMT**:** increased cost of 4045 (-33 to 8124) (Cost reduction due to FMT largely a result of faster recovery time reducing length of stay) ▪Colorectal vs. Nasoduodenal	▪Time horizon not specified ▪The model did not incorporate the risks of nasogastric FMT over colorectal FMT such as aspiration and vomiting ▪The costs of hospitalization and adverse events in the model were based on public hospital costs; cost will likely increase when considering

Author (year) Country Funding QHES	Population Interventions	Design Perspective Time horizon Model	Assumptions	Economic Model specifications	Year, Currency Cost Sources Discounting	Clinical Data Source	Primary Findings	Limitations, risk of bias
	rounds of treatment ▪ FMT via nasoduodenal or colorectal route: abbreviated vancomycin course (125 mg 4x daily for 4 to 5 days), followed by bowl lavage with macrogol solution prior to delivery via specific route		assumed to be treated with vancomycin ▪ Each recurrence was assumed to result in an average increase of hospital stay of 3.6 days, after which the patients receiving vancomycin continue their treatment regime after discharge. ▪ Patients who have been cured of CDI are assumed to have the same baseline risk of developing CDI again as the general population ▪ The effectiveness of FMT is assumed to be the same regardless of mode of delivery ▪ FMT Preparation was assumed to require 2 hours of lab	moved to either the "dead" or "ileostomy" states; a proportion of the patients with ileostomy are eligible for ileostomy reversal. ▪ If recurrent CDI developed after the first FMT treatment than patients received a second FMT treatment. ▪ Patients in the model who are cured of recurrent cm but then become reinfected re-entered the model and received 400 mg metronidazole three times daily for 10 days. ▪ Reinfected CDI patients who progress to recurrent CDI received either FMT or vancomycin treatment according to their assigned treatment arm.	(hourly wages) ▪ Medicare Benefits Schedule codes (tube insertion) ▪ Correspondence ▪ Cost of FMT includes: screening of donor; pre-treatment (30-min. consultation with a gastro-enterologist and pre-treatment with abbreviated vancomycin regimen); obtaining, storing and preparing the fecal sample (supplies, personnel); administration of the fecal infusion (supplies, personnel); pretreatment for colonscopy requires loperamide and bowl lavage **Discounting:** 5% annually	reinfection with CDI) ▪ Utility weights/QALY (healthly person age 65 years, CDI, colectomy, ileostomy) **Clinical and utilities data source:** ▪ Clinical trials ▪ Economic models for CDI ▪ Epidemiological literature	FMT: no difference in cost, 48 (-1177 to 1273) **ICER** ▪ Either FMT delivery vs. vancomycin: ○ 1.2 (95% CI, 0.1 to 2.3) QALYs ○ 1.4 (95% CI, 0.4 to 2.4) life years saved (Both FMT strategies resulted in improved QoL and reduced costs compared with vancomycin) ▪ Assuming an annual CDI incidence of 5,000 cases and a recurrence rate of 6.8%, the expected national cost savings of substituting FMT for vancomycin for the treatment of recurrent CDI	private hospitals

Author (year) Country Funding QHES	Population Interventions	Design Perspective Time horizon Model	Assumptions	Economic Model specifications	Year, Currency Cost Sources Discounting	Clinical Data Source	Primary Findings	Limitations, risk of bias
			technologist time per treatment ▪ Three hours of nursing supervision is assumed to be required after FMT procedure.	▪ Probabilistic sensitivity analysis using the Monte Carlo method with 1000 simulations.			would be over AU$I,370,000 per year.	

CDI: *Clostridium difficile* infection; FMT: fecal microbiota transplant; NG: nasogastric

Appendix Table H2. CDI Economic Studies Data Abstraction Tables

	Assumptions from economic analyses		Results from studies included in this HTA		
	Cure	**Recurrence**	**Cure rates from included RCTs**	**Cure rates from included cohort studies**	**Cure rates from included case series**
FMT (colonoscopy)	94.5% (Knoijeti) 91% (83%-100%) (Varier 2014, 2015)* 81.3% (Merlo)†	7.8% (95% CI, 5%-12%) (Lapointe-Shaw)	65% (10 wks, Cammarota) 80% (8 weeks, Youngster)	96% (3 mos., Satokari) 93% (3 mos., Waye; colonoscopy, NG tube or gastroscopy)	52-94% (9 case series, N=808)
FMT (duodenal infusion)	81.3% (Konijeti, Merlo)†	NR	76% (10 wks, Van Nood)	NR	
FMT (NG infusion)	NR	23.3% (95% CI, 15.5%-33.4%) (Lapointe-Shaw)	60% (8 weeks, Youngster)	63%‡ (30d, Lagier‡)	
FMT (enema)	81.5% (Knoijeti)	18.5% (95% CI, 6.3%-38.1%) (Lapointe-Shaw)	51.5% (3.25 mos., Lee)	NR	
Vancomycin	**Oral** 91.6% (Konijeti) 90% (88%-92%) (Varier 2014) 30.8% (Merlo)† **Oral pulse/taper** 69% (Konijeti) 69% (59.1%-75%) (Varier 2015)	**Oral** 51.7% (95% CI, 6.3%-38.1%) (Lapointe-Shaw) **Oral pulse/taper** 17.8% (95% CI, 5.9%-43.1%) (Lapointe-Shaw)	26% - 27% (10 wks, Van Nood, Cammarota)	NR	NA
Metronidazole	71.0% (Konijeti) 80% (65%-85%) (Varier 2014)	40.0% (95% CI, 5.3%-85.3%) (Lapointe-Shaw)	NR	NR	NA
Fidaxomicin	93.7% (Konijeti)	RR compared to vanco: 0.62 (95% CI, 0.36-1.07) (Lapointe-Shaw)	NR	NR	NA

NA: not applicable; NR: not reported

*Varier 2014, Varier 2015: Cure defined as no recurrence within the first 90 days after FMT treatment; assumed that FMT would be as effective for initial CDI as it is for RCDI.

†Merlo: Probability of cure without relapse (considered the same regardless of mode of FMT delivery).

‡First occurrence of CDI.

APPENDIX I. Clinical Experts

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