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**Review**

# A systematic review of economic evaluation in fecal microbiota transplantation

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## Abstract

Background: Fecal microbiota transplantation (FMT) is an effective therapy in recurrent *Clostridium difficile* infection (rCDI). It is only recommended for this indication by European and American guidelines. Other indications of FMT are being studied, such as inflammatory bowel disease (IBD), and they have shown promising results.

Objectives: To identify and review published FMT-related economic evaluations (EEs) to assess their quality and the economic impact of FMT in the treatment of these diseases.

Data sources: The systematic literature research was conducted in both PubMed and Cochrane to identify EEs published before July 1, 2019.

Study eligibility criteria: Articles were included if they concerned FMT (whatever the disease and its line of treatment), if they reported full or partial EEs, and if they were written in English. Articles were excluded if they did not concern FMT; if they did not report an EE; or if they were a systematic review, editorial, comment, letter to the editor, practice point, or poster.

Methods: A measurement tool, AMSTAR, was used to optimize the quality of this systematic review. Based on the CHEERS checklist, data were identified and extracted from articles. The quality of each EE was assessed using the Drummond checklist.

Results: Overall, 9 EEs were included: all EEs were full evaluations and 8 were cost-utility analyses (CUAs). All EEs had a Drummond score $\geq 7$, which indicated high quality. All CUAs related to rCDI and IBD concluded that FMT was cost-effective compared with other reference treatments, at a threshold $\leq$$50,000/QALY. One EE about initial CDI showed that FMT was dominated by metronidazole.

Conclusions: Despite a limited number of EEs, FMT seems to be a promising and cost-effective treatment for rCDI. More EE studies on other diseases like IBD are necessary to address FMT efficiency for new indications. Therefore, our systematic review provides a framework for healthcare decision making.

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In 2015 in the United States, the costs of *Clostridium difficile* infection (CDI) and associated care were US$6.3 billion.[1] In Europe, these costs were estimated at €3 billion per year, ranging from €5,798 ($6,448) to €11,202 ($12,457)per episode.[2] These costs are expected to nearly double over the next 40 years, depending on the increase of patients at risk of developing CDI. This potentially substantial increase may be explained by the number of elderly patients, antibiotic consumption, the development of resistance to conventional antibiotics (eg, metronidazole, vancomycin, and fidaxomicin), and the emergence of hypervirulent strains.[2–4] The major problem with CDI is that despite adequate antibiotic therapy, 10%–30% of patients will experience a recurrence, with the risk approaching 60% after the third episode.[5]

Fecal microbiota transplantation (FMT) is an effective therapy for CDI, leading to a significant reduction of recurrent *Clostridium difficile* infection (rCDI) and reduced incidence of adverse events when compared to conventional antibiotics (eg, vancomycin and fidaxomicin).[4,6–8] FMT is currently recommended by both European and American guidelines for multiple rCDI.[9,10] Other indications of FMT are being studied, such as inflammatory bowel diseases (IBDs; eg, ulcerative colitis and Crohn's disease), obesity, type 2 diabetes, or graft-versus-host disease.[11–23] However, to date, FMT has not yet been recommended for use in daily practice for these diseases.

FMT is an intervention in which a fecal suspension from a healthy donor is transferred into the gut of a patient to replace depleted components of the gut microbiota.[24] No general agreement has been reached on the best approach for delivering fecal

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microbiota nor on the optimal transplantation volume. Thus, various routes of administration have been described either via the upper or via the lower gastrointestinal (GI) tract. FMT via upper GI delivery methods include nasogastric tubes (FMTng) or duodenal infusion (FMTdi), whereas FMT via lower GI delivery methods mainly involve colonoscopy (FMTc) or enema (FMTen).[25] More recently, randomized clinical trials have indicated that the use of oral capsules was not inferior to other modes of administration.[26–29]

The status of FMT is different between countries. The Food and Drug Administration (FDA) and Health Canada consider FMT a biological tissue; the American FDA considers it an investigational new drug; and the European Medicine Agency allows each country the possibility of assigning a qualification. In France, FMT is considered a drug.[30–32]

In the context of rational decision making in health care, and as an integral part of health technology assessment (HTA), the economic evaluation (EE) of healthcare products has become a necessity. One of the major challenges in healthcare research is to provide cost-effectiveness data that are relevant to daily practices and that may be required to optimize the consumption of healthcare resources. Decision making for coverage and reimbursement of new drugs is being increasingly supported by EE in many countries including Australia, Canada, and the United Kingdom.[33,34] The quality of EE must be high to instill trust in the accuracy of the results and to support informed decisions. Among several EE methods,[35] the most common and recommended in HTA are cost-effectiveness analyses (CEAs) and cost-utility analyses (CUAs).[36] The choice of method depends on the nature of the expected health effects of the interventions under study. A CEA is required when health-related quality of life (HRQOL) is not identified as a relevant health effect of the studied interventions; health outcome is measured by the length of life in life years (LYs). Otherwise, CUA is the preferred method when HRQOL is identified as an important health effect of interventions; health outcome is measured by the length of life weighted by a valuation of the HRQOL, represented by health-state utility values (HSUVs), to produce quality-adjusted LYs (QALYs). The HSUV is measured on a scale anchored by 1 (best imaginable health state, ie, perfect health) and 0 (worst imaginable health state, ie, death) using patient preference-based measures.[37]

In this context, the aims of the present study were to systematically identify and review published FMT-related EEs and to assess their quality.

## Method

We adopted an optimal method to enhance the quality of our systematic review based on modified AMSTAR, a reliable and valid measurement tool consisting of 11 items.[38]

### Search strategy

A systematic literature search was conducted in PubMed and Cochrane to identify published EEs. An articles was included if it concerned FMT (whatever the disease and its line of treatment), if it reported full or partial economic evaluations, and if it was written in English. An articles was excluded if it did not concern FMT, if it did not report an EE, or if it was a systematic review, an editorial, a comment, a letter to the editor, a practice point, or a poster.

Medical subject headings (MeSH) terms were individually selected using the National Library of Medicine controlled vocabulary thesaurus used for indexing articles for PubMed, (ie, MeSH database) before being combined: (1) cost–benefit analysis or economic evaluation or cost effectiveness or cost analysis or cost savings and (2) fecal microbiota transplantation or fecal transplantation or fecal transplant). The full request in both electronic sources PubMed and Cochrane is presented in Appendix A (online).

### Article selection

The titles and abstracts of all identified articles were screened and analyzed by 1 reviewer (S.D.) and checked by a second reviewer (V.N.) to determine whether each article corresponded to the previously defined topic and whether it was an original EE. Second, after initial screening, the full text of each selected article was independently analyzed by both reviewers. In addition, the reference lists of all selected studies were screened to identify other potentially relevant articles that had not been identified by the 2 electronic means. Consensus was reached in cases of disagreement between the 2 reviewers. The main reason for excluding a given article was recorded.

### Data extraction

Based on the CHEERS checklist, the following data were identified and extracted from each selected article: year of publication; journal; main location of the first author; sponsor; conflict of interest; topic (ie, CDI or IBD); line of treatment (ie, initial or recurrent for CDI); aim(s) of the EE; examination of both the costs and the consequences of alternative interventions; examination and comparison of at least 2 interventions; type of EE (full, including CEA, cost-minimization analysis, CUA, cost–benefit analysis; or partial, including cost description [ie, cost-of-illness], cost analysis and cost–outcome description); number of interventions compared $\geq$ 2; compared interventions; population analyzed (hypothetical cohort of patients, patients included in a clinical trial, patients of a national or a local institution); perspective (ie, the point of view from which the costs and health effects are recorded and assessed: societal, healthcare system); country and continent of origin; time horizon (ie, the period during which patients were followed measuring costs and health effects, long enough to reflect all expected differences between the interventions being compared); main data source of costs (derived from local databases(s), national database(s), the literature, etc); year of reference for costs; main data source of effectiveness (derived from the results of clinical trial(s), literature, original study), and especially health-state utility values if applicable; decision making analysis model (yes or no); Markov model in medical decision-making (yes or no); discounting of costs and effectiveness (ie, the reflection of the present value of future costs and health effects) and discount rate; results in terms of costs; effectiveness (LY, QALY, etc) and cost-effectiveness (ICER) or cost-utility (ICUR); and difference between ICER and ICUR according to the threshold and deterministic and probabilistic sensitivity analyses (ie, the characterization of uncertainty; yes [complete], yes [partial], no, and not assessable).

A dominant strategy is both less expensive and more effective than the comparator strategy, whatever the willingness-to-pay threshold. On the contrary, a strategy that is both more expensive and less effective is classified as "dominated." After ICER analysis, if the strategy is most effective but more costly than the comparator

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**Table 1.** Characteristics of the 9 Economic Evaluations Included in the Systematic Review

| Study Characteristic | No. | % |
|---|---|---|
| Selected articles | 9 | 100.0 |
| Year of publication | | |
| 2014 | 2 | 22.2 |
| 2015 | 1 | 11.1 |
| 2016 | 3 | 33.4 |
| 2017 | 2 | 22.2 |
| 2018 | 1 | 11.1 |
| Main location of the first author | | |
| University | 3 | 33.3 |
| Research team | 1 | 11.1 |
| University and hospital | 4 | 44.5 |
| University and research group | 1 | 11.1 |
| Sponsor | | |
| No | 4 | 44.4 |
| Yes | 4 | 44.4 |
| Not reported | 1 | 11.2 |
| No conflict of interest | 9 | 100.0 |
| Topic | | |
| *Clostridium Difficile* infection | 8 | 88.9 |
| Ulcerative colitis and Crohn's disease | 1 | 11.1 |
| Line of treatment for *Clostridium difficile* infection | | |
| Initial | 1 | 12.5 |
| Recurrence | 6 | 75.0 |
| Initial and recurrence | 1 | 12.5 |

strategy, dominance can be extended to specific willingness-to-pay threshold. Extended dominance rules out any strategy with a higher ICER than a more effective strategy.

To allow direct comparisons across countries, all costs were converted to US dollars and then inflated to the reference year of 2019.[39,40]

### *Quality assessment of the economic evaluations*

A critical appraisal of the methodological quality of health economic evaluations is not simple to carry out, and it may depend on the subjective performance of the evaluator. As previously described, using the Drummond checklist as a scoring system has the advantage of allowing a comparison between different EEs and their results; thus, it is more objective and provides a way to measure the transferability of an EE and its results.[39,41,42] However, as with any rating scale, a major limitation of the Drummond checklist is the likelihood of bias, even when the interobserver variability between reviewers is good.[43,44] Thus, the quality assessment of each selected CUA was performed by 2 independent reviewers (S.D. and V.N.). When there was disagreement, a consensus was reached using this checklist based on 10 questions; the checklist provided a framework for assessing methodological quality. For each question, there were 4 possible responses: yes, no, not clear, and not appropriate. One point was assigned for each "yes" response. The lowest and highest possible scores were thus 0 and 10, respectively. A score ≥7 was considered high quality.[41]

## Results

### *Article selection*

The search in both PubMed and Cochrane identified 46 articles, but 1 was a duplicate. In addition, 36 were excluded after screening and analyzing titles and abstracts for exclusion criteria (Fig. 1). In total, 9 articles were analyzed and eligible for the systematic review (Appendix B online).[44–52]

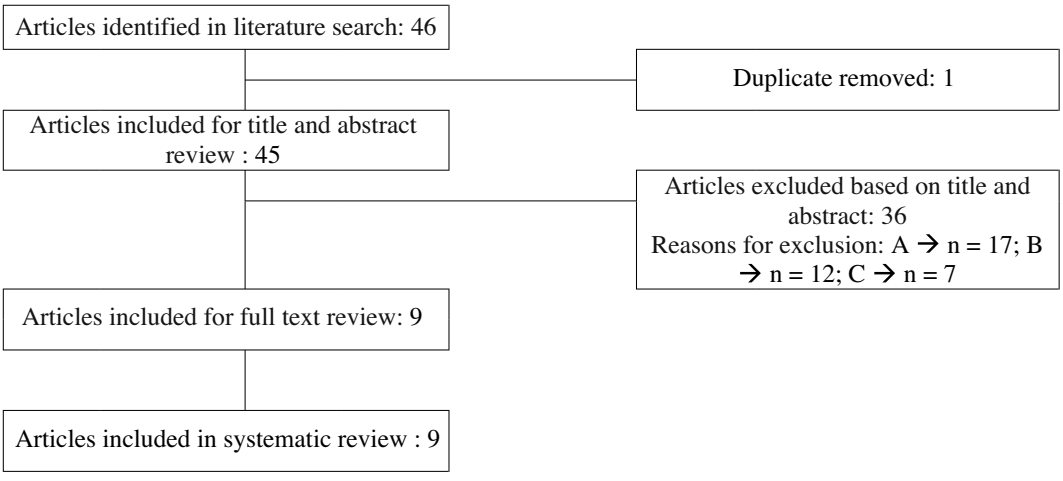


**Fig. 1.** CONSORT flow diagram of literature review. (A) not only FMT. (B) FMT but did not report economic evaluation. (C) Systematic review, editorial, comment, letter to the editor, practice point and poster. Note. EEs, economic evaluations; FMT, fecal microbiota transplantation.

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**Table 2.** Synthesis of Basic Elements of the 9 Economic Evaluations Included in the Systematic Review

| Article Element | No. | % |
|---|---|---|
| Selected articles | 9 | 100.0 |
| Examination of both the costs and effectiveness of alternative interventions | 8 | 88.9 |
| Examination of at least 2 interventions | 8 | 88.9 |
| Full or partial economic evaluation | | |
| Full | 8 | 88.9 |
| Partial | 1 | 11.1 |
| Type of economic evaluation | | |
| Cost-utility analysis | 7 | 77.8 |
| Cost-effectiveness analysis and cost-utility analysis | 1 | 11.1 |
| Cost analysis | 1 | 11.1 |
| ≥ 2 compared interventions | 9 | 100.00 |
| Analyzed population, hypothetical cohort of patients | 5 | 55.6 |
| Patient included in a clinical trial or from a national or a local institution | 4 | 44.4 |
| Perspective | | |
| Healthcare system | 6 | 66.7 |
| Societal | 2 | 22.2 |
| Societal and medical | 1 | 11.1 |
| Continent of origin | | |
| North America | 5 | 55.6 |
| Europe | 1 | 11.1 |
| Asia | 2 | 22.2 |
| Oceania | 1 | 11.1 |
| Time horizon | | |
| Episode | 1 | 11.1 |
| ≤1 year | 7 | 77.8 |
| Not reported | 1 | 11.1 |
| Main data source of costs | | |
| Derived from local or national database(s) | 3 | 33.3 |
| Derived from local or national database(s) and assumptions | 1 | 11.1 |
| Derived from local and/or national database(s) and the literature | 5 | 55.6 |
| Main data source of effectiveness | | |
| Derived from local database and the literature | 1 | 11.1 |
| Derived from the literature | 3 | 33.4 |
| Derived from the literature and from the results of clinical trials | 1 | 11.1 |
| Derived from the literature and assumptions | 2 | 22.2 |
| Derived from the results of clinical trial(s) | 1 | 11.1 |
| Not applicable (because partial economic evaluation) | 1 | 11.1 |
| Main data source of health-state utility values if cost-utility analysis | | |
| Derived from the results of clinical trials and local database | 1 | 11.1 |
| Derived from the results of clinical trials and the literature | 2 | 22.2 |
| Derived from the literature | 2 | 22.2 |
| Derived from the literature and assumptions | 3 | 33.4 |
| Not applicable (partial economic evaluation) | 1 | 11.1 |
| Model | | |
| Yes | 7 | 77.8 |
| *Markov model* | 2 | 22.2 |
| Discounting of costs and effectiveness | | |
| Yes | 2 | 22.2 |
| No | 6 | 66.7 |
| Not reported | 1 | 11.1 |
| Sensitivity analysis | | |
| Yes, complete | 4 | 44.4 |
| Yes, partial | 5 | 55.6 |
| Deterministic sensitivity analysis | | |
| Yes, complete | 4 | 44.5 |
| Yes, partial | 3 | 33.3 |
| No | 2 | 22.2 |
| Probabilistic sensitivity analysis | | |
| Yes, complete | 6 | 66.7 |
| Yes, partial | 2 | 22.2 |
| No | 1 | 11.1 |

### *Synthesis of basic elements of economic evaluations*

The characteristics of the 9 EEs are summarized in Table 1. All EEs were published in a clinical journal after 2013. Only 1 article evaluated initial CDI (iCDI), but 7 evaluated rCDI. Only 1 article assessed FMT EE in IBD (both ulcerative colitis and Crohn's disease) and 8 EEs were full EEs. At least 2 interventions were assessed by all authors. Authors usually conducted their analyses from the perspective of the healthcare system (n = 6). The main continent of origin was North America (n = 5), and the time horizon ranged from 1 episode (n = 1) to 1 year (n = 7).

A synthesis of the basic elements of the 9 EEs is summarized in Table 2. Cost was derived from local or national database(s), the literature, or assumptions. Effectiveness was essentially derived from the literature. A model had been developed in 7 EEs. A discounting of costs and effectiveness was carried out in 25% of the cases. A complete sensitivity analysis had been conducted in 3 EEs.

### *Synthesis of results of economic evaluation*

In the treatment of iCDI, FMTc, FMTen and FMTng were dominant versus vancomycin (V) but were dominated versus metronidazole (M) (Table 3).[51] In the treatment of rCDI, FMTc, FMTen, FMTdi and FMTng were dominant versus vancomycin, metronidazole, and fidaxomicin in 6 EEs[44,46–49,52] and were cost-effective at a threshold of ≤$50,000/QALY for Merlo et al[48] and Baro et al.[46] In the treatment of IBD, FMT was cost-effective at the willingness-to-pay threshold of $20,158. Among different modes of administration (ie, FMTc, FMTen, FMTdi, and FMTng), FMTc was dominant.[44,46]

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**TABLE 3.** Synthesis of Characteristics and Results of the 9 Economic Evaluations Included in the Systematic Review

| Reference | Aim(s) of economic analysis | Type of economic evaluation | Compared interventions | Population analyzed | Perspective | Country | Time-horizon | Year reference | Discounting of costs and effectiveness | Discount rate (%) | Cost of compared interventions | Effectiveness of compared interventions | Incremental cost-utility *ratio* (ICUR) | Incremental cost-effectiveness *ratio* (ICER) | Difference between ICUR and ICER according to threshold | Results of economic evaluation if no CUA and/or CEA | Sensitivity analysis | Deterministic sensitivity analysis | Probabilistic sensitivity analysis |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CDI initial | | | | | | | | | | | | | | | | | | | |
| Varier et al. Clin Microbiol Infect 2014 | To estimate the CE of FMT versus either V or M as therapeutic options for initial CDI | CUA | FMTc *versus* V *versus* M | Hypothetical cohort of patients with on diagnosis of CDI from a multicenter long-term follow-up study | Health care system (assumption) | US | 90 days | 2011 | No | / | M: $1,259<br>FMTc: $1,801<br>V: $2,040 | M: 0.238 QALY<br>FMTc: 0.242 QALY<br>V: 0.241 QALY | FMTc *versus* M: $134,850/ QALY V *versus* FMTc: dominated | Not applicable | No | No applicable | Yes, partial | Yes, partial | Yes, partial |
| CDI Initial and ≥1st recurrence | | | | | | | | | | | | | | | | | | | |
| Jiang et al. PLoS One 2018 | To examine the potential cost-effectiveness of ribotype-guided FMT in Chinese patients with severe CDI from the perspective of healthcare provider | CUA | Treatment ribotype-guided FMT *versus* V | Hypothetical cohort of adult patients with severe CDI in the hospital setting | Health care system | China | 30 days | 2018 | No | / | Ribotype-guided FMT: $9 111<br>V : $10 128 | Ribotype-guided FMT: 0.998 QALY loss<br>V: 1.470 QALY loss | Ribotype-guided FMT versus V: dominant | Not applicable | / | Not applicable | Yes, complete | Yes, complete | Yes, complete |
| CDI ≥1st recurrence | | | | | | | | | | | | | | | | | | | |
| Konijeti et al. Clin Infect Dis 2014 | To analyze the CE of 4 competing strategies for the management of rCDI where the first-line treatments were M, V, F, or FMT. | CUA | FMTc *versus* V *versus* M *versus* F | Hypothetical cohort of adult patients with a median age of 65 years. | Societal | US | 1 year | 2012 | No | / | V: $3,142<br>FMTc: $3,398<br>M: $4,252<br>F: $4,597 | V: 0.8580 QALY<br>FMTc: 0.8719 QALY<br>M: 0.8292 QALY<br>F: 0.8653 QALY | FMTc *versus* V: $18,362/ QALY*<br>M *versus* FMTc: dominated | Not applicable | No | No applicable | Yes, complete | Yes, complete | Yes, complete |
| Lapointe-Shaw et al. PLoS One 2016 | To evaluate the CE of multiple treatment options for rCDI, in order to inform Canadian policymakers, hospital managers and clinicians | CUA | FMTc *versus* FMTen *versus* FMTng *versus* V *versus* M *versus* F | Hypothetical cohort of 1000 patients. The typical patient modelled in the study a 70 years-old community-dwelling person experiencing their first recurrence of CDI. | Health care system | Canada | 18 weeks | 2014 | Yes | 5% | FMTc:$4,227<br>M: $4,340<br>FMTen: $4,565<br>V: $4,776<br>FMTng: $4,782<br>F: $5,898 | M: 9.090 QALY<br>FMTen: 9.260 QALY<br>V: 9.030 QALY<br>FMTng: 9.150 QALY<br>F:9.160 QALY | FMTc *versus* FMTen: dominant<br>FMTc *versus* V: dominant<br>FMTc *versus* FMTng: dominant<br>FMTc *versus* F: dominant | Not applicable | / | Not applicable | Yes, complete | Yes, complete | Yes, complete |
| Merlo et al. J Gastroenterol Hepatol 2016 | To determine the value of using FMT rather than standard V therapy, for the treatment of rCDI. | CEA and CUA | FMTc *versus* FMTdi *versus* V | Hypothetical cohort of 1000 patients aged 65 years with recurrent CDI, after at least one course of antibiotic therapy | Health care system | Australia | Not reported | 2015 | Yes | 5% | FMTdi versus V : + $3,277<br>FMTc versus V: + $3,318 | FMTdi *versus* V: 1.400 Lys<br>FMTc *versus* V:1.400 LYs<br>FMTdi *versus* V: 1.200 QALY<br>FMTc *versus* V:1.200 QALY | FMTdi *versus* V: dominant<br>FMTc *versus* V: dominant | FMTdi *versus* V: dominant<br>FMTc *versus* V: dominant | Not applicable | Not applicable | Yes, partial | No | Yes, complete |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CDI ≥2nd recurrence | | | | | | | | | | | | | | | | | | |
| Waye et al. J Clin Gastroenterol 2016 | To estimate the direct medical cost impact of 2 groups of patients to the Alberta health-care system: patients who received timely FMT, defined as after 2 recurrences, compared with those receiving delayed FMT, defined as > 3 recurrences of CDI. | CA | The timely FMT group (FMT=2 recurrences) *versus* The delayed FMT group (FMT ≥ 3 recurrences) | 75 patients who received FMTc, FMTgs or FMTng for rCDI between October 2012 and September 2014 in Edmonton and had undergone post-FMT follow-up for at least 3months | Health care system | Canada | Episode | 2013 | Not reported | / | The timely FMT group: $20,743 The delayed FMT group $44,789 | Not applicable | Not applicable | Not applicable | No | Not applicable | Yes, partial | Yes, partial | No |
| Baro et al. PLoS One 2017 | To analyze the CE of 5 strategies constructed from the European Society of Clinical Microbiology and Infectious diseases (ESCMID) guideline for the management of multiple recurrence of CDI in adults, where the first-line treatments were pulsed-tapered V, F, FMTc, FMTdi, and FTMen | CUA | FMTc *versus* FMTen *versus* FMTdi *versus* V versus F | Adult experiencing a second recurrence of the mild-to-moderate CDI at an outpatient visit diagnosed | Societal | France | 78 days | 2016 | No | / | V: $1,154 FMTen: $1,505 FMTc: $1,697 FMTdi: $1,714 F: $2,303 | V: 0.1812 QALY FMTen: 0.2019 QALY FMTc: 0.2047 QALY FMTdi: 0.2013 QALY F:0.1988 QALY | F *versus* V : dominated, FMTdi *versus* *V* : dominated, FMTc versusFMTen: $68,837/QALY , FMTen versus V : $16,909/QALY | Not applicable | / | Not applicable | Yes, complete | Yes, complete | Yes, complete |
| CDI ≥3rd recurrence | | | | | | | | | | | | | | | | | | |
| Varier et al. Infect Control Hosp Epidemiol 2015 | To estimate the CE of FMTc compared with V for the treatment of rCDI in adults, specifically following guidelines proposed by the ACG and AGA | CUA | FMTc *versus* V | Patients after the third recurrence of CDI, following guidelines published in April 2013 | Health care system | US | 90 days | 2011 | No | / | FMTc: $1,781 V: $4,041 | FMTc: 0.242 QALY V: 0.235 QALY | FMTc *versus* V: dominant | Not applicable | / | No | Yes, partial | Yes, partial | Yes, complete |
| IBD | | | | | | | | | | | | | | | | | | |
| Zhang et al. Oncotarget 2017 | To evaluate the CE and economic value of FMT for treatment of IBD in China | CUA | Treatment pre-FMT *versus* treatment post-FMT | 104 patients with IBD: 33 patients with ulcerative colitis and 71 patients with Crohn's disease | Medical and societal | China | 1 year | 2014 | No | / | Medical: Post FMT: $366,709 Pre FMT: $550,934 Societal: Post FMT: $423,845 Pré FMT: $639,100 | Pre FMT: 0.634 QALY Post FMT: 0.773 QALY | Post-FMT *versus* pre-FMT: dominant | Not applicable | / | Not applicable | Yes, partial | No | Yes, partial |

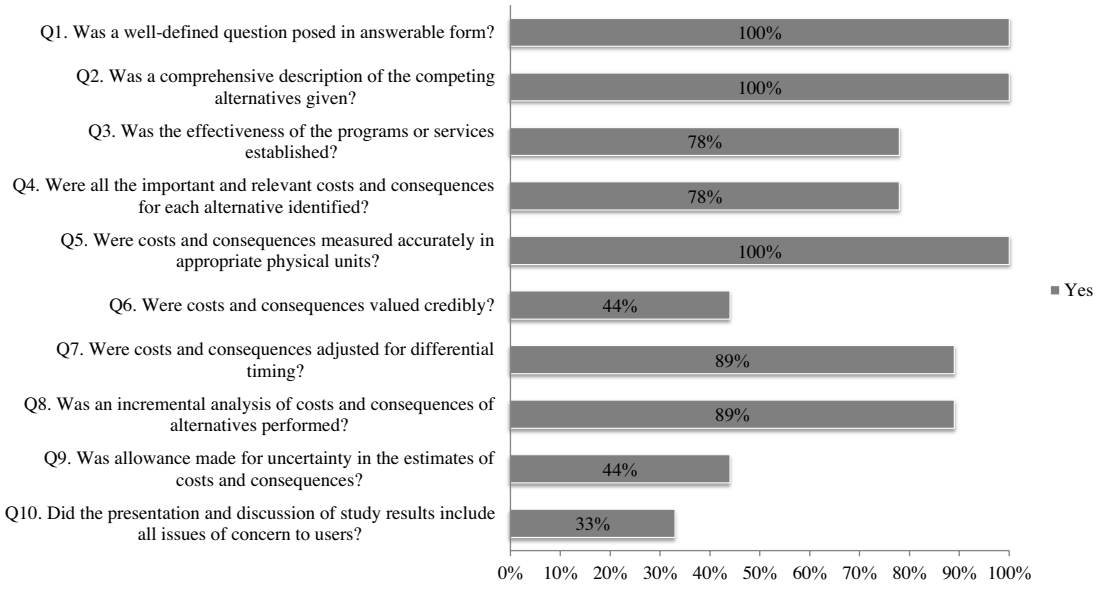


**Fig. 2.** Percentage of "Yes" for each question of Drummond 10-point checklist for assessing economic evaluations.

### *Quality assessment of the economic evaluations*

The median Drummond score of the 9 selected EEs was 7 (range, 6–10; first quartile, 6; third quartile, 9). The result of the quality assessment is provided in Fig. 2 and Appendix C (online). Of these 9 EEs, 6 had a Drummond score ≥ 7. Each was a full EE.

## Discussion

In this systematic review, we aimed to assess the economic impact of FMT as a new therapy. A trustworthy and valid measurement tool, AMSTAR, was used first to search for and select articles and then to extract data to optimize the quality of this systematic review.[38] In addition, 9 FMT-related EEs were identified and were deemed cost-effective for rCDI but not for iCDI. A single EE found FMT to be cost-effective for IBD. According to the only EE about IBD, the treatment was cost-effective, but more EEs are necessary to confirm this finding. To date, American and European guidelines only recommend FMT for multiple rCDI.[6,8,11] An EE showed that the strategy of American guidelines recommending the use of FMT in multiple rCDI was a cost-effective one, thus validating its usefulness.[53] Although FMT seems to be a cost-effective and promising therapy for rCDI and other diseases like IBD, it will be necessary to provide decision makers of healthcare policies with additional EEs to adequately inform the adoption of appropriate guidelines.

The 9 selected FMT-related EEs are full and 8 of them are CUAs. In infectious diseases, a CUA should be preferred to a CEA, especially for the EE of FMT, because of its special impact on the quality of life. To improve the quality of future EEs, it is important to provide a thorough evaluation, which has not been done thus far.[9] Thus, using disease-related health-state utility values is necessary to precisely measure the length of life weighted by a valuation of the HRQOL. To date, no CDI- or IBD-related health-state utility values are available for FMT. Therefore, the estimation of quality of life and cost-utility may be biased.

Methods used by authors and topics addressed by EEs varied among the 9 EEs. In fact, the lines of treatment could be different: initial, greater than or equal to first recurrence, greater than or equal to second recurrence, or greater than or equal to third recurrence for CDI. Dosages and comparative reference treatments (eg, vancomycin, fidaxomicin, and metronidazole) were also disparate among the EEs.[44,47,49] The various routes of FMT administration were compared: FMTc, FMTen, FMTdi, and FMTng. Analyzed population, perspective, time horizon, source of costs, and source of effectiveness were also different among the 9 EEs. In addition, 8 EEs were based on a model such as the Markov model.

Overall, FMT interventions generate many costs. All of the expenses must be considered to estimate the exact cost of this therapy: donor selection, preparation of fecal material with antibiotics, fecal delivery, and both short-term and long-term monitoring of patients for efficacy outcomes and adverse events.[20,54] There are differences among countries, especially regarding donor selection. Moreover, FMT has some risks such as the transmission of multidrug-resistant organisms. The authors of various studies did not calculate the overall cost of FMT in the same way, which influenced the results of their EEs. For example, Merlo et al[48] considered that the overall cost included blood and stool screening, human, material and technical time, pretreatment, obtaining, storing, preparing and administering the fecal infusion, whereas Varier et al[47] considered that it included only screening donors and recipients, and the cost of antibiotics and adverse events.

In the treatment of rCDI, FMT was cost-effective at a threshold of ≤$50,000/QALY for Merlo et al[48] and Baro et al.[46] However, FMT was also cost-effective because it was dominant in 4 EEs compared with vancomycin and was dominant in 2 EEs compared with fidaxomicin.[44,46–49,52] In the treatment of iCDI, FMT was dominated by metronidazole but was dominant versus vancomycin.[51] Nevertheless, metronidazole is no longer recommended as a first-line therapy in this indication. Only 1 EE regarding IBD included and demonstrated its efficiency at the willingness-to-pay threshold of $20,158. The use of drugs was significantly reduced after FMT in this study.[44]

All CUAs related to rCDI and IBD in this systematic review concluded that FMT was cost-effective in comparison with other

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reference treatments at a threshold of ≤$50,000/QALY.[44–52] Another review that included only 4 studies about FMT in rCDI also concluded that FMT was cost-effective.[55] FMT was considered cost-effective if it was less expensive and more effective than other treatments (FMT was dominant).[44,47,48,52] Otherwise, FMT was more expensive but more effective compared with other treatments.[46,48] Moreover, in these 4 studies, different routes of fecal delivery were reported, and FMTc achieved higher resolution rates. Indeed, FMTen, FMTdi, and FMTng had a QALY lower than FMTc. FMTc was dominant compared with other modes of administration.[44,46]

Our analysis has several limitations other than those previously identified. First, it included only EEs written in English. Secondly, unpublished EEs (grey literature) and EEs of other electronic sources were not included, which may also have introduced some bias. Thirdly, we may have overestimated or underestimated the methodological quality of these EEs. Indeed, assessing methodological quality was often difficult and could have involved some subjectivity on the part of the reviewers.

In conclusion, after examining 9 EEs, FMT seems to be a promising and cost-effective treatment for rCDI but not for iCDI. American and European guidelines recommend the use of FMT for the treatment of rCDI, but additional EEs are needed to accurately identify its place within the therapeutic armamentarium of this disease. In addition, more EE studies on other diseases like IBD are necessary to assess FMT efficiency for new indications. Despite the limited number of EEs in the present study, our review suggests that FMT may be a cost-saving intervention in managing rCDI. It also provides decision makers of healthcare policies with additional information about the cost-effectiveness of FMT.

**Supplementary material.** To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2019.371

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