Digestive Diseases and Sciences (2020) 65:1125–1133
https://doi.org/10.1007/s10620-019-05821-1

ORIGINAL ARTICLE

Fecal Transplants by Colonoscopy and Capsules Are Cost-Effective Strategies for Treating Recurrent *Clostridioides difficile* Infection

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Received: 13 March 2019 / Accepted: 28 August 2019 / Published online: 6 September 2019

Abstract

Background Recurrent *Clostridioides difficile* infections (CDIs) occur frequently and pose a substantial economic burden on the US healthcare system. The landscape for the treatment of CDI is evolving.

Aim To elucidate the most cost-effective strategy for managing recurrent CDI.

Methods A decision tree analysis was created from a modified third-party payer's perspective to compare the cost-effectiveness of five strategies for patients experiencing their first CDI recurrence: oral vancomycin, fidaxomicin, fecal microbiota transplant (FMT) via colonoscopy, FMT via oral capsules, and a one-time infusion of bezlotoxumab with vancomycin. Effectiveness measures were quality-adjusted life years (QALY). A willingness-to-pay (WTP) threshold of $100,000 per QALY was set. One-way and probabilistic sensitivity analyses were performed.

Results Base-case analysis showed that FMT via colonoscopy was associated with the lowest cost at $5250 and that FMT via capsules was also a cost-effective strategy with an incremental cost–effectiveness ratio (ICER) of $31205/QALY. Sensitivity analyses demonstrated that FMT delivered by oral capsules and colonoscopy was comparable cost-effective modalities. At its current cost and effectiveness, bezlotoxumab was not a cost-effective strategy.

Conclusions FMT via oral capsules and colonoscopy is both cost-effective strategies to treat the first recurrence of CDI. Further real-world economic studies are needed to understand the cost-effectiveness of all available strategies.

Keywords Cost-effectiveness · Recurrent *Clostridioides difficile* infections · Fecal microbiota transplants · Bezlotoxumab

Introduction

Clostridioides difficile infection (CDI) is a leading cause of healthcare-associated infections in the USA. Recurrent CDI, defined as a relapse after initial treatment, remains a treatment challenge as up to a quarter of patients will experience a recurrence after appropriate antibiotics and nearly half after a second recurrence [1]. This poses an incredible economic burden on the US healthcare system, now estimated to be more than $5 billion dollars annually [2].

The landscape for treating CDI has changed dramatically over the past decade. Metronidazole is no longer recommended as first-line treatment for initial or recurrent CDI [3]. Treatment for initial episode of CDI usually comprises a 10-day course of oral vancomycin or fidaxomicin. Guidelines recommend a tapered or pulsed course of vancomycin or a 10-day course of fidaxomicin for recurrent episodes. Fecal microbiota transplants (FMTs) are recommended after two or more recurrent episodes of CDI. FMT has been shown to be the most effective therapy for recurrent CDI with efficacy above 90% when administered by colonoscopy [4]. Notably, a recent randomized trial demonstrated that FMT delivered by oral capsules is non-inferior to FMT delivered by colonoscopy [5]. In addition, bezlotoxumab, a fully human monoclonal antibody directed against toxin B produced by *C. difficile*, was recently approved by the FDA for the prevention of CDI recurrence based on two phase 3 clinical trials [6]. However, no clinical recommendations

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have been established guiding its use and there are few studies examining its cost-effectiveness.

Several economic comparative analyses have been conducted to compare the different CDI treatment strategies to inform clinical decision making. These studies have yielded mixed results, partially because they have compared different modalities. A systematic review of 14 cost-effectiveness studies found that when FMT via colonoscopy was included as a modality, it dominated as the most cost-effective strategy to treat recurrent CDI [7]. A recent study incorporating treatment regimens from the 2018 IDSA guidelines also found that FMT was cost-effective for treating second or subsequent recurrences [8]. None of these studies evaluated FMT capsules or bezlotoxumab in their comparison arms.

The aim of our study was to analyze the cost-effectiveness of oral vancomycin, fidaxomicin, vancomycin followed by FMT via colonoscopy, vancomycin followed by FMT via oral capsules, and vancomycin with bezlotoxumab for the management of the first recurrence of CDI.

Materials and Methods

Model Design

We conducted a decision-analytic model from a modified third-party payer's perspective using TreeAge Pro (TreeAge Software Inc., Williamstown, MA) to compare five strategies of interest (Table 1). The first-line therapies for the strategies were a tapered six-week course of vancomycin, a 10-day course of fidaxomicin, a 10-day course of vancomycin followed by FMT via colonoscopy, a 10-day course of vancomycin followed by FMT via capsules, and a one-time infusion of bezlotoxumab during a 10-day course of vancomycin. Our model was based in part on previously published decision tree analytic models for treating recurrent CDI [9–11].

The patient modeled in the study was a 65-year-old community-dwelling adult experiencing a first recurrence of mild-to-moderate CDI. At the outpatient visit for the first recurrence of CDI, one of the five above treatment strategies could be selected. Following treatment, patients could experience a cure or failure, which could progress to fulminant colitis requiring hospitalization and potentially colectomy. Patients who experienced a cure could also experience a subsequent recurrence. We assumed that patients remained healthy between the end of their treatment and their next recurrence and modeled up to two subsequent recurrences. For patients who experienced a third recurrence after being treated with vancomycin, fidaxomicin, or bezlotoxumab, they received FMT via colonoscopy as currently recommended by the ACG and IDSA/SHEA guidelines [3, 12]. Patients who received FMT for their initial therapy were given repeat FMT by the same mode for all subsequent recurrences. Patients were modeled in the state of "persistent recurrent CDI" if they experienced treatment failure following a third recurrence. The time horizon was 6 months based on duration of a recurrence cycle of 8 weeks, reflecting the time frame for when the majority of recurrent CDI episodes occur [13]. Discounting was not applied because the time horizon was less than 1 year. Figure 1 shows a schematic representation of our model.

Model Variables

Inputs used for the base-case analysis for clinical probabilities, costs, and utilities were pooled from literature including clinical studies and systematic reviews and are summarized in Table 2. A range for sensitivity analysis varying between 25% below and above average values was used when data for probabilities, costs, and utilities were limited.

Table 1 Strategies of interest

Treatment	Dose	Frequency	Duration
Vancomycin	125 mg	125 mg four times daily × 14 days	6 weeks
		125 mg twice daily × 7 days	
		125 mg daily × 7 days	
		125 mg every other day × 7 days	
		125 mg every third day × 7 days	
Fidaxomicin	200 mg	Twice daily	10 days
Bezlotoxumab	10 mg/kg	One-time infusion	
+ vancomycin	125 mg	Four times daily	10 days
FMT via capsules	30 pills	Once	Once
+ vancomycin	125 mg	Four times daily	10 days
FMT via colonoscopy	–	Once	Once
+ vancomycin	125 mg	Four times daily	10 days

FMT fecal microbiota transplantation

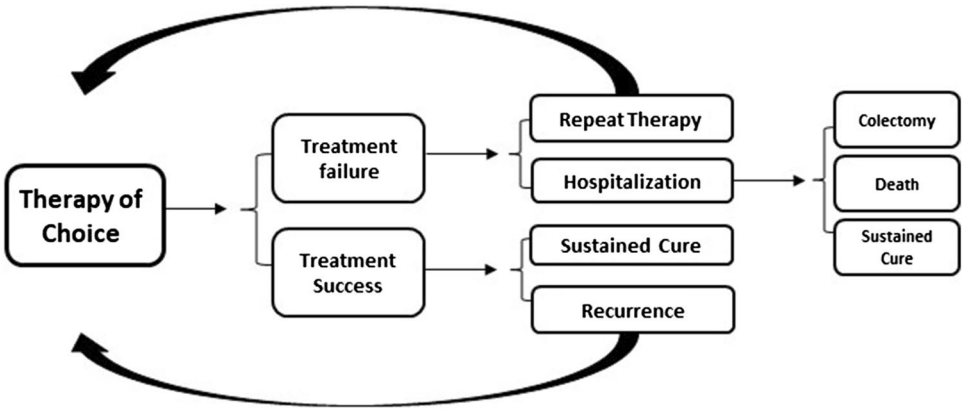


Fig. 1 Schematic of decision tree modeling strategies for treating the first recurrent episode *Clostridioides difficile* infection

Table 2 Model probabilities, costs, and utilities

Variable	Mean	Distribution	Range	Reference
Clinical probabilities				
FMT colonoscopy—cure	0.914	Beta	0.881–0.947	[4, 5, 14–16]
FMT colonoscopy—recurrence	0.084	Beta	0.076–0.091	[4, 5, 14–16]
FMT capsules—cure	0.830	Beta	0.70–0.962	[5, 17–19]
FMT capsules—recurrence	0.084	Beta	0.076–0.091	[5, 17–19]
Vancomycin taper—cure	0.776	Beta	0.690–0.863	[20–22]
Vancomycin taper—recurrence	0.363	Beta	0.310–0.417	[20–22]
Fidaxomicin—cure	0.885	Beta	0.841–0.937	[20, 23, 24]
Fidaxomicin—recurrence	0.179	Beta	0.154–0.203	[20, 23, 24]
Bezlotoxumab + vancomycin—cure	0.800	Beta	0.770–0.820	[6]
Bezlotoxumab + vancomycin—recurrence	0.165	Beta	0.134–0.208	[6]
Hospitalization for CDI	0.257	Beta	0.174–0.340	[1, 25]
Receiving colectomy for severe CDI	0.192	Beta	0.103–0.280	[26, 27]
Mortality from colectomy	0.46	Beta	0.350–0.570	[26–28]
Mortality from severe CDI	0.33	Beta	0.110–0.470	[25–27]
Costs, 2019 US$				
FMT via colonoscopy	$2671	Gamma	$2003–3339	[29], CMS
FMT via capsules	$1950	Gamma	$1462–2438	[29]
Vancomycin, 6-week course	$2542	Gamma	$1907–3177	[30]
Fidaxomicin, 10-day course	$4639	Gamma	$3479–5799	[30]
Bezlotoxumab per dose	$4560	Gamma	$3420–5700	[30]
Hospitalization for *C. Difficile*	$22,321	Gamma	$16,741–27,901	[2]
Colectomy	$28,448	Gamma	$24,003–32,892	[31, 32]
Utilities				
Healthy 65-year-old	0.88	Beta	0.84-0.92	[33]
Recurrent CDI	0.77	Beta	0.695–0.845	[32]
Post-colectomy	0.536	Beta	0.504–0.568	[34]
Death	0			

FMT fecal microbiota transplantation, *CMS* Centers for Medicare and Medicaid Services

Clinical probabilities were derived from primary clinical trials, case series, and systematic reviews. Cost inputs were obtained from public sources including the Center for Medicare and Medicaid Services Fee Schedule and databases for average wholesale drug prices. Our perspective was from a modified third-party payer which included costs associated with the therapy of choice including costs of medications, hospitalizations, and any procedures. The cost of FMT via colonoscopy given in Table 2 reflects the reimbursable cost of a colonoscopy in an outpatient facility setting (CPT code 45378) and the cost of frozen, ready-to-use microbiota preparations from OpenBiome which

are screened for multi-drug-resistant organisms (MDROs). We also obtained the cost of FMT capsules from OpenBiome [29]. The cost of a 10-day course of vancomycin was added to both fecal transplant arms in our analysis.

The main efficacy outcome in our study was quality-adjusted life years (QALY), which was obtained by multiplying utility values by the amount of time a patient spent in that disease state. Utilities for patients with recurrent CDI have not been established in the literature so we derived utility values from other validated states associated with other gastrointestinal conditions [34]. The median age was 65 for our cohort and a utility of 0.88 was assigned for a healthy patient [33].

Table 3 Base-case analysis of competing strategies for management of first recurrence of *Clostridioides difficile* infection

Treatment	Cost	QALY	ICER
FMT via colonoscopy	5250	0.435	
FMT via capsules	5436	0.429	31,205
Vancomycin	7006	0.421	(Dominated)
Fidaxomicin	7557	0.429	(Dominated)
Bezlotoxumab	9612	0.426	(Dominated)

Costs values are reported as 2019 US dollars

FMT fecal microbiota transplantation, *ICER* incremental cost–effectiveness ratios, *QALY* quality-adjusted life year

Base-Case and Sensitivity Analysis

The primary outcome from base-case analysis was the incremental cost–effectiveness ratio (ICER) between the five different therapies, calculated by dividing the incremental costs by the number of QALYs gained. This was compared to our willingness-to-pay (WTP) threshold, which was set at $100,000 for this study. Costs were assessed from a modified third-party perspective as detailed above. To evaluate for uncertainties in our model, we conducted one-way and two-way sensitivity analyses by varying inputs within stated parameters. Probabilistic sensitivity analysis (PSA) was conducted using 10,000 second-order Monte Carlo simulations to assess uncertainty in all parameters. Probabilities and utilities were modeled using a beta distribution, and costs were modeled using a gamma distribution.

Results

Base-Case Analysis

The results of base-case analysis demonstrating the cost and relative effectiveness of each strategy are given in Table 3. Initial treatment of the first episode of recurrent CDI with FMT via colonoscopy was associated with the lowest cost, $5250, with a QALY of 0.435. Our analysis also demonstrated FMT via capsules was a cost-effective treatment strategy based on our model, with an expected cost of $5436 in our base-case scenario and ICER of $31205/QALY. Bezlotoxumab and vancomycin were associated with a cost higher than that of a vancomycin taper or a course of fidaxomicin. Based on our WTP threshold, the strategies of vancomycin taper, fidaxomicin, and vancomycin with bezlotoxumab were dominated.

Sensitivity Analysis

One-way and two-way sensitivity analysis identified threshold values of several important input parameters for which FMT delivered by colonoscopy was no longer the dominant strategy. We performed threshold analysis to identify threshold values at which FMT via capsules would become the dominant strategy. At an effectiveness of greater than 84.5% or cost less than $3035 (including the cost of a 10-day course of vancomycin), FMT via capsules became the dominant strategy (Fig. 2a). FMT via capsules also dominated when the cost of a colonoscopy approach and a 10-day course of vancomycin exceeded $4075. We also considered a scenario where bezlotoxumab would be the most cost-effective measure by conducting two-way sensitivity analysis to assess the impact of varying the cost of bezlotoxumab along with its effectiveness. At its current effectiveness, one dose of bezlotoxumab along with a 10-day course of vancomycin would have to cost less than $2390 to be a more cost-effective measure compared to FMT via colonoscopy. Even if the clinical effectiveness of vancomycin with bezlotoxumab was greater than 95%, this strategy remains dominated at its current cost (Fig. 2b).

We then performed a multivariate probability sensitivity analysis varying all parameters simultaneously in 10,000 Monte Carlo simulations to account for inherent uncertainty in the model. We generated a cost-effectiveness acceptability curve that provides a quantitative value of certainty that a specified intervention is cost-effective at different WTP thresholds. Figure 3 demonstrates that

FMT via colonoscopy was the most beneficial strategy in 49.5% of trials and FMT via capsules was favored in 42.3% of trials at a WTP threshold of $100,00/QALY. At a WTP threshold of $50,000/QALY, FMT via colonoscopy was the most beneficial strategy in 46.6% of trials and FMT via capsules was favored in 44.3%. FMT via capsules dominated as the most beneficial strategy at all WTP thresholds less than $28,500/QALY.

Discussion

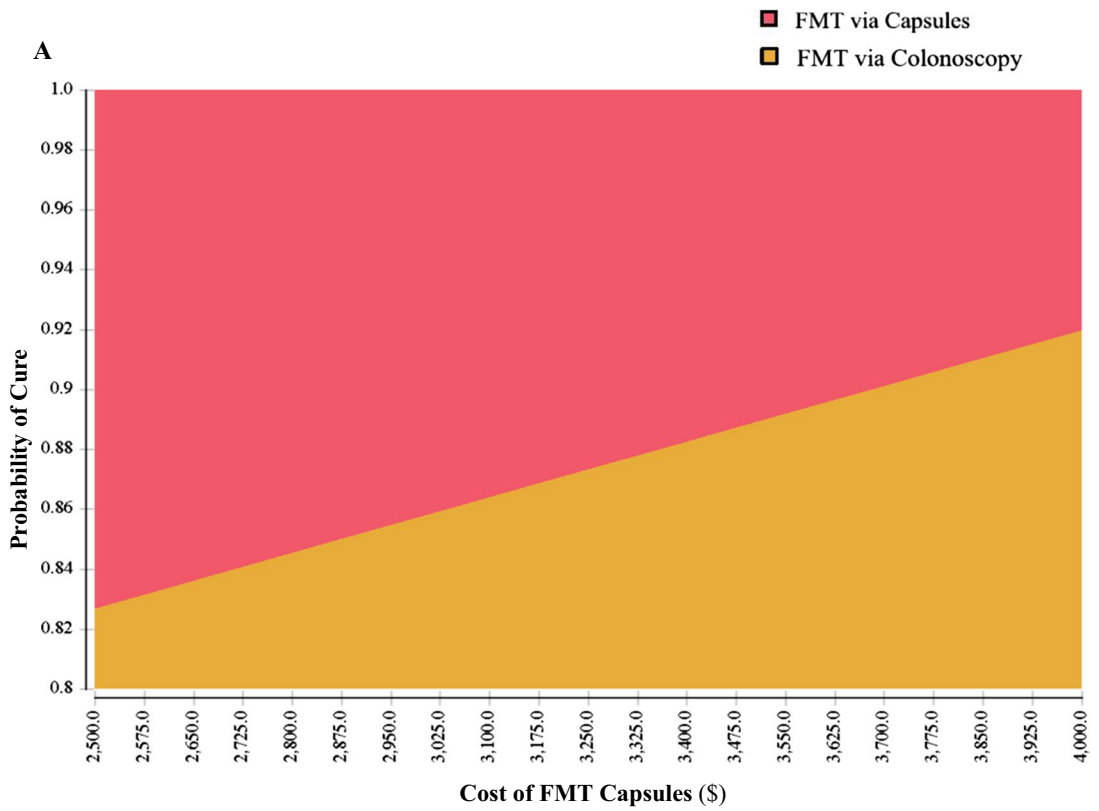
Recurrent CDI poses a significant economic burden to our healthcare system. Our analysis is the first study to evaluate the cost-effectiveness of FMT and bezlotoxumab in conjunction with the most promising strategies in our armamentarium in treating recurrent CDI.

Consistent with several previous cost-effectiveness analyses that have compared competing strategies for recurrent CDI, FMT via colonoscopy was associated with the lowest cost in our base-case scenario. However, when accounting for uncertainties in our model in sensitivity analysis, we found that FMT via colonoscopy and FMT via capsules are comparable cost-effective strategies for treating the first recurrence of CDI and dominate other available strategies.

Our sensitivity analyses demonstrate that if FMT delivered by capsules can achieve a consistent cure rate of greater than 84.5%, it becomes the dominant strategy. Promising data have emerged from a recent randomized trial that suggests FMT delivery by capsules may be non-inferior to FMT via colonoscopy with primary cure rates exceeding 90% [5]. Previous studies (some of which used commercially prepared capsules) showed primary clinical cure rates in the 70–80% range, though they were able to achieve 90% clinical cure rate with multiple doses [17–19]. Large-scale clinical trials are underway to assess the clinical efficacy of commercially available FMT products [35–38]. The cost for FMT via colonoscopy may be underestimated in our study; as in previous cost-effectiveness analyses, the costs for a colonoscopy reflect only what is reimbursable to the facility and physician and does not account for indirect costs such as anesthesia and post-procedural monitoring. However, this is tempered by the fact that our study was from a modified third-party perspective and included the non-reimbursable cost of microbiota preparations from OpenBiome. Our reasoning for including this cost in our analysis was twofold. First, incorporation of the cost of the fecal product allowed us to conduct a commensurate cost-effectiveness comparison with commercial FMT capsules. Secondly, inclusion of the cost of the fecal product reflects the likely future reimbursement scheme of microbiome-based products given the efficacy of FMT in treating recurrent CDI. As colonoscopies are more resource intensive and not appropriate or available for all candidates, FMT via capsules may be the most cost-effective regimen in treating recurrent CDI in many scenarios.

Given the relative novelty of bezlotoxumab as a modality for treating recurrent CDI, there is a paucity of data on outcomes compared to other strategies. In the MODIFY I/II trials, bezlotoxumab was studied in conjunction with metronidazole, vancomycin, or fidaxomicin [6]. Two cost-effectiveness studies involving bezlotoxumab were recently published with different conclusions [39, 40]. The first study compared bezlotoxumab with standard of care and found that bezlotoxumab was more cost-effective [39]. The second study compared vancomycin, fidaxomicin, and vancomycin with bezlotoxumab, finding that vancomycin alone was the most cost-effective regimen for the treatment of a first recurrent episode of CDI [39]. Our analysis found that vancomycin with bezlotoxumab at its current cost and efficacy is not a cost-effective strategy in treating recurrent CDI.

This study has several important limitations. First, we extrapolated data from multiple studies to inform our inputs for costs, effectiveness, and utilities. The parameters for costs fluctuate across diverse care settings. Treating *C. difficile* in an inpatient setting is associated with a different set of costs such as drug pricing which can vary depending on the healthcare system. Costs of fecal preparations are also in flux as OpenBiome is currently the sole commercial source; this is exemplified by the doubling of the cost of fecal products in March 2019. In our modified third-party perspective, we did not account for the indirect costs from a patient or societal perspective. Future studies on how the patient-based experience varies with FMT via capsules in comparison with colonoscopy will also inform cost–utility analysis [41]. There are also wide-ranging data for the clinical effectiveness and recurrence for all five of the strategies evaluated in our analysis, reflecting the heterogeneous characteristics of the studies in the primary literature. No prospective data on recurrence have been published for FMT oral capsules, so we based our estimates on available data from studies which documented lack of clinical resolution as a surrogate. Modified uses of current therapies may also lead to changes to our treatment paradigms such as a recent trial which demonstrated that extended-pulsed fidaxomicin was superior to


A
FMT via Capsules
FMT via Colonoscopy
Probability of Cure
1.0
0.98
0.96
0.94
0.92
0.9
0.88
0.86
0.84
0.82
0.8
2,500.0
2,575.0
2,650.0
2,725.0
2,800.0
2,875.0
2,950.0
3,025.0
3,100.0
3,175.0
3,250.0
3,325.0
3,400.0
3,475.0
3,550.0
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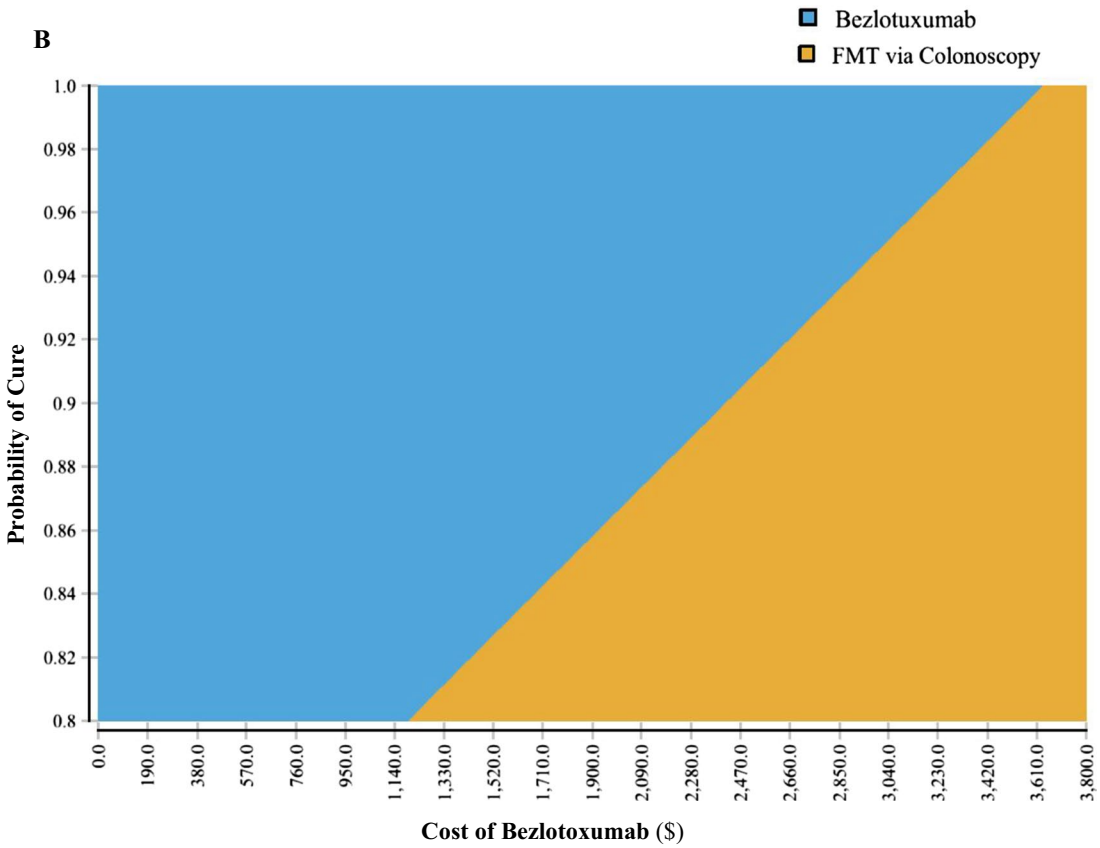
3,700.0
3,775.0
3,850.0
3,925.0
4,000.0
Cost of FMT Capsules ($)


B
Bezlotuxumab
FMT via Colonoscopy
Probability of Cure
1.0
0.98
0.96
0.94
0.92
0.9
0.88
0.86
0.84
0.82
0.8
0.0
190.0
380.0
570.0
760.0
950.0
1,140.0
1,330.0
1,520.0
1,710.0
1,900.0
2,090.0
2,280.0
2,470.0
2,660.0
2,850.0
3,040.0
3,230.0
3,420.0
3,610.0
3,800.0
Cost of Bezlotoxumab ($)

◂**Fig. 2** Two-way sensitivity analysis on cost and probability of clinical cure of recurrent *Clostridioides difficile* infection with FMT capsules (**a**) and bezlotoxumab (**b**). The smaller shaded area represents the most cost-effective strategy at any given cost and efficacy of FMT capsules (**a**) and bezlotoxumab (**b**). Cost values are reported as 2019 dollars. *FMT* fecal microbiota transplant

standard dose vancomycin for sustained cure of CDI [42]. We did not evaluate how treatment effectiveness would be impacted by different strains of *C. difficile* (e.g. BI/NAP1/O27) and special populations such as immunocompromised patients or patients with inflammatory bowel disease [43]. We also assumed probabilities of cure, recurrence, and hospitalization rates would be similar for all recurrences of CDI given lack of validated data for all strategies included in this study. In addition, there remains a need for validated quality of life utility weights for CDI-related health states [44].

Our study is a simulation model and simplifies real-world scenarios with a limited time horizon. Long-term feasibility studies are needed to capture a more realistic cost perspective. Our model also did not encompass all possible *C. difficile*-related interventions and outcomes including adverse effects of the modalities of interest. The FDA recently issued a safety alert regarding two FMT recipients who developed invasive infections caused by MDROs transmitted from one FMT donor [45]. These two cases underscore the need for additional safety data with FMT, and the FDA has mandated that all FMT products, under investigational use, be screened for MDROs. The long-term safety profile of fecal transplants is uncertain and will be elucidated in the coming years as data accrue from an ongoing national FMT registry [46, 47]. We assumed all patients who experienced a third recurrence would be able to obtain FMT delivered by colonoscopy, but there are many circumstances where this option is inappropriate, contraindicated, or unavailable [48].

Our study is the first to demonstrate that FMT via colonoscopy and FMT via oral capsules are both cost-effective modalities to treat the first recurrence of CDI. Vancomycin plus bezlotoxumab does not appear to be a cost-effective measure in treating recurrent CDI compared to the other strategies evaluated in our study. While FMT is currently recommended after three CDI recurrences, studies have shown that FMT may result in lower healthcare utilization if positioned earlier in the treatment algorithm [49, 50]. There are even data to suggest FMT may be effective for an initial *C. difficile* infection [51]. Our study provides additional impetus for clinicians to consider FMT, whether administered through colonoscopy or oral capsules, as an early strategy in the management of recurrent CDI whenever possible. Further real-world economic studies are needed to understand the cost-effectiveness of all available strategies.

Author's contribution AMG serves as the guarantor of the article. All authors contributed to the inception, design, and research of the study. All authors approved the final version of the manuscript.

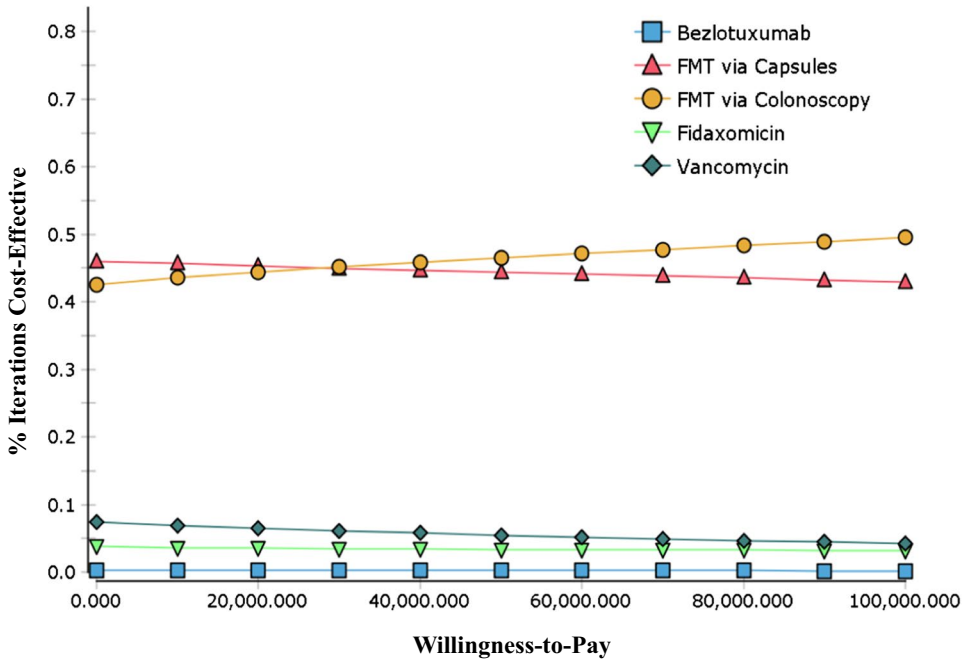


Fig. 3 Acceptability curve of treatments of first recurrence of *Clostridioides difficile* infection. This figure illustrates the proportion of the time each treatment was cost-effective at different willingness-to-pay thresholds. *FMT* fecal microbiota transplantation

Compliance with Ethical Standards

Conflicts of interest Ari M. Grinspan has received lecture fees and honorarium from Merck.

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