RESEARCH ARTICLE

Cost-Effectiveness Analysis of Six Strategies to Treat Recurrent Clostridium difficile Infection

Lauren Lapointe-Shaw1,2*, Kim L. Tran2, Peter C. Coyte3, Rebecca L. Hancock-Howard3, Jeff Powis1,4, Susan M. Poutanen1,2,5, Susy Hota1,2

1 Department of Medicine, University of Toronto, Toronto, Canada, 2 Department of Medicine, University Health Network, Toronto, Canada, 3 Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Canada, 4 Department of Medicine, Toronto East General Hospital, Toronto, Canada, 5 Department of Medicine and Medical Microbiology, Mount Sinai Hospital, Toronto, Canada

* lauren.lapointe.shaw@mail.utoronto.ca

Abstract

Objective

To assess the cost-effectiveness of six treatment strategies for patients diagnosed with recurrent Clostridium difficile infection (CDI) in Canada: 1. oral metronidazole; 2. oral vancomycin; 3. oral fidaxomicin; 4. fecal transplantation by enema; 5. fecal transplantation by nasogastric tube; and 6. fecal transplantation by colonoscopy.

Perspective

Public insurer for all hospital and physician services.

Setting

Ontario, Canada.

Methods

A decision analytic model was used to model costs and lifetime health effects of each strategy for a typical patient experiencing up to three recurrences, over 18 weeks. Recurrence data and utilities were obtained from published sources. Cost data was obtained from published sources and hospitals in Toronto, Canada. The willingness-to-pay threshold was $50,000/QALY gained.

Results

Fecal transplantation by colonoscopy dominated all other strategies in the base case, as it was less costly and more effective than all alternatives. After accounting for uncertainty in all model parameters, there was an 87% probability that fecal transplantation by colonoscopy was the most beneficial strategy. If colonoscopy was not available, fecal transplantation by enema was cost-effective at $1,708 per QALY gained, compared to metronidazole.
In addition, fecal transplantation by enema was the preferred strategy if the probability of recurrence following this strategy was below 8.7%. If fecal transplantation by any means was unavailable, fidaxomicin was cost-effective at an additional cost of $25,968 per QALY gained, compared to metronidazole.

Conclusion

Fecal transplantation by colonoscopy (or enema, if colonoscopy is unavailable) is cost-effective for treating recurrent CDI in Canada. Where fecal transplantation is not available, fidaxomicin is also cost-effective.

Background

Clostridium difficile infection (CDI), a common healthcare-associated infection, is associated with significant morbidity and mortality. [1, 2] CDI results from exposure to C. difficile in the setting of disrupted intestinal microbiota, most commonly resulting from antibiotic use. [3] The standard treatment for a first episode of CDI is antibiotic therapy with either metronidazole or oral vancomycin. [4] Nonetheless, 15–28% of cases recur after discontinuation of antibiotics. [5–7] Patients who experience one recurrence are at a significantly higher risk of having additional recurrences. [8, 9]

The current standard of care for recurrent CDI is antibiotic therapy, with first recurrences treated with either metronidazole or oral vancomycin. [4] A prolonged taper-pulse course of oral vancomycin is recommended for all subsequent recurrences. [4] Recurrence rates with vancomycin vary widely in the literature, between 31% and 75%, with varying dose, duration of administration, as well as length of follow-up. [7, 9–12]

Fidaxomicin and fecal transplantation by various routes are alternatives that potentially offer lower rates of recurrence. [13, 14] However, both of these newer treatments have significant barriers to adoption. In the case of fidaxomicin, the high cost of the drug has been cited as a major disadvantage, one which has limited its coverage under provincial drug plans to one 10-day course. [15] The results of cost-effectiveness analyses of fidaxomicin for first episode and first recurrence have yielded conflicting results. [16, 17] A Canadian Cost-Benefit Analysis comparing fidaxomicin to vancomycin found that fidaxomicin cost an incremental $18,190 per second recurrence avoided. [18]

Similarly, fecal transplantation is a promising treatment for recurrent CDI, with cure rates reported between 80 and 94%. [9, 14] Despite low reported rates of adverse events with fecal transplantation, concerns about unknown health risks persist, including the risk of infectious disease transmission. [14] Consequently, Health Canada has restricted its use to clinical trials until recently. [19, 20] In addition to regulatory limitations, the cost of supporting processes, infrastructure and personnel are perceived as barriers to the adoption of fecal transplantation by clinicians and institutions. [21]

A cost-effectiveness analysis of treatments for recurrent CDI conducted using Medicare payment information from the United States found fecal transplantation by colonoscopy to be cost-effective compared to oral vancomycin alone for the treatment of recurrent CDI. [22] Conclusions from this study may not apply to other jurisdictions where systems and costs of care are different. In Canada, national and provincial policymakers (such as each province’s Ministry of Health) determine which treatment options are available to patients, and which will be publicly funded. The purpose of this study was to evaluate the cost-effectiveness of multiple treatment options for recurrent CDI, in order to inform Canadian policymakers, hospital managers and clinicians.
Methods

We conducted a cost-effectiveness analysis of six treatment strategies for the first and subsequent recurrences of CDI.

Treatments compared

1. 2-week course of oral metronidazole followed by a 6-week taper-pulse course of oral vancomycin for subsequent recurrences (this strategy will be referred to as “metronidazole”)

2. 2-week course of oral vancomycin followed by a 6-week taper-pulse course of oral vancomycin for subsequent recurrences (this strategy will be referred to as “vancomycin”)

3. 10-day course of oral fidaxomicin followed by a 6 week taper-pulse course of oral vancomycin for subsequent recurrences (this strategy will be referred to as “fidaxomicin”)

4. 2-week course of oral vancomycin with fecal transplantation via enema followed by the same (vancomycin and fecal transplantation by enema) using a different donor at each subsequent recurrence (this strategy will be referred to as “fecal transplantation by enema”)

5. 2-week course of oral vancomycin with fecal transplantation via nasogastric tube (NG) followed by the same (vancomycin and fecal transplantation by NG) using a different donor at each subsequent recurrence (this strategy will be referred to as “fecal transplantation by NG”)

6. 2-week course of oral vancomycin with fecal transplantation via colonoscopy followed by the same (vancomycin and fecal transplantation by colonoscopy) using a different donor at each subsequent recurrence (this strategy will be referred to as “fecal transplantation by colonoscopy”)

Perspective

In Canada, the provincial Ministries of Health assume the cost of hospital care, physician services, and a varying proportion of outpatient drug costs. We adopted the perspective of the Ontario Ministry of Health and Long-Term Care for this study.

Model Structure and Assumptions

A decision-analytic model incorporating Markov processes was developed using TreeAge Pro 2013 (S1 File, TreeAge Software Inc., Williamstown, MA). The typical patient modelled in the study was a 70-year old community-dwelling person experiencing their first recurrence of CDI (the first episode of CDI was not included in the model). This represents the mean age of a patient with recurrent CDI in published studies.[9, 23] We assumed that recurrence and treatment could only occur once every six week cycle, reflecting the duration of the oral vancomycin taper-pulse, as well as the timing of recurrence, occurring within two weeks of antibiotic discontinuation in 81% of patients.[8] Thus, the modeled cycle length was six weeks. In the first cycle, all patients experienced a recurrence of CDI. In subsequent cycles, patients could be well (no recurrence), dead, or experience another recurrence, according to the events that occurred in the previous cycle (see Fig 1). As the mean number of CDI recurrences is just below three, we modelled up to three recurrences (three cycles) totaling an 18 week period.[8, 9] We did not model recurrences following 18 weeks because of the uncertain nature of the probability of recurrence over time.
Patients experiencing persistent diarrhea while being treated with oral metronidazole were deemed non-responders and were switched to oral vancomycin after six days of therapy, consistent with previous definitions of metronidazole non-response.[24] Patients with further recurrences after receiving metronidazole, fidaxomicin or vancomycin received a 6-week taper-pulse course of oral vancomycin.[4] Although current guidelines recommend considering fecal transplantation for a third recurrence following treatment with vancomycin, this option is not yet widely available in Canada, and patients are typically treated with repeat taper-pulse vancomycin. Dose and duration of all included antibiotics are detailed in Table 1 and are consistent with published guidelines.[4] Fidaxomicin dose and duration was consistent with that used in clinical trials.[13, 25]

Treatment with fecal transplantation by enema or nasogastric tube included a 14-day course of oral vancomycin to reflect practice in our centres, where donors are screened in real time. Donors are typically close friends or family identified by the patient; patients are treated with vancomycin while results of donor screening tests are pending. For fecal transplantation strategies, each treatment consisted of a single transplantation procedure.

Table 1. Medication doses and durations used in our analysis.

| Agent                        | Dose                      | Frequency       | Duration                  |
|------------------------------|---------------------------|-----------------|---------------------------|
| Metronidazole                | 500 mg orally             | Three times daily | 14 days (6 days if no response) |
| Vancomycin*                  | 125 mg orally             | Four times daily | 14 days                   |
| Vancomycin Taper-Pulse (6 weeks total) | 125 mg orally four times daily for 14 days, followed by 125 mg orally twice daily for 7 days, followed by 125 mg orally once daily for 7 days, followed by 125 mg orally every other day for 7 days 125mg orally every third day for 7 days | | |
| Fidaxomicin                  | 200 mg orally             | Twice daily     | 10 days                   |

* 14-day course of vancomycin also used in fecal transplantation strategies.
Model Outcomes

The primary outcomes were quality-adjusted life years (QALY) and costs in each treatment strategy. These were then used to compare strategies using the incremental cost-effectiveness ratio (ICER). QALYs are obtained by multiplying the time in a health state by the QALY weight of that health state, a measure of quality of life. A half-cycle correction was used for all QALYs in order to prevent systematic over- or under-estimation of payoffs with each cycle.[26] Treatment costs were assigned at the start of each cycle as this reflects when a diagnosis of recurrence and a treatment decision was made. Cost of hospitalization was modelled as a transitional cost in the middle of the cycle, for the proportion of recurrences requiring hospitalisation. We estimated the health effects of recurrences over the patient’s remaining lifetime, as is recommended by the Society of Medical Decision-Making.[27] This approach accounts for the years of life lost as a result of a CDI-related death and therefore could be expected to result in a lower ICER for treatments that reduce mortality relative to standard care. This was done by adding the QALY-weighted remaining life expectancy to the QALYs accrued in the final cycle of the model. The QALY weight used was that of an otherwise well community-dwelling person. Thus, the final cycle effectiveness for all non-death states was: 0.5*utility-weighted cycle length + discounted life expectancy*QALY weight.

Model Parameters

Our source data were obtained from the published literature and hospital administrators; no unpublished patient-level information was used in this study.

Probabilities. Model transition probabilities were taken from published sources (see Table 2). Information on the proportion of outpatient cases of CDI admitted to hospital was obtained by multiplying the probability of hospitalization among CDI patients, 62% [28], by the probability that the primary reason for hospitalization was CDI, 28%.[29] This estimate for the probability of hospitalization was similar to the proportion of patients experiencing a non-recurrence complication of CDI from the Canadian Nosocomial Infection Surveillance Program (CNISP).[23] These complications included dehydration and gastrointestinal bleeding, conditions which would be expected to lead to hospital admission. Because criteria to define severe CDI are contradictory and have not been validated, and because our costing data and mortality estimates were for all hospitalized patients with CDI, we did not model severe CDI separately from CDI requiring hospitalization.[4, 30]

Our model did not distinguish between lack of clinical resolution and recurrence. We obtained the probability of recurrence after fecal transplantation from a systematic review.[54] We re-extracted source data from included studies to obtain estimates for upper gastrointestinal, enema and colonoscopy-delivered fecal transplantation. For fecal transplantation by NG, we updated the results of the systematic review to include a randomized controlled trial.[9] There is no published prospective data on recurrence rates after a 6-week vancomycin taper-pulse regimen. We obtained our estimate from a secondary analysis of a randomized controlled trial of patients with recurrent CDI; our estimate pooled together 19 patients receiving a tapering dose of vancomycin with 10 patients receiving a “taper-pulse” regimen.[10]

If confidence intervals and/or standard errors were not reported in source publications, exact binomial confidence intervals were calculated for individual studies. Where more than one study contributed to the point estimate, probabilities were pooled using a random effects model of pooled binomial proportions. These analyses were executed using the “binom” and “metaprop” packages available in R (R Foundation for Statistical Computing, Vienna, Austria, 2013).
Table 2. Point estimates, range and distribution for all model variables.

| Variable                                                                 | Base Case | Range            | Range type           | Distribution Type | Standard Error |
|-------------------------------------------------------------------------|-----------|------------------|----------------------|-------------------|----------------|
| **Transition probabilities and relative risks**                         |           |                  |                      |                   |                |
| Probability of hospitalization for CDI [28, 29]                         | 0.174     | 0.140–0.212      | 95% CI               | Beta              | 0.018          |
| Probability of response to oral metronidazole[31]                       | 0.776     | 0.751–0.800      | 95% CI               | Beta              | 0.012          |
| Probability of recurrence after 2-week course of oral metronidazole [10]| 0.4       | 0.053–0.853      | 95% CI               | Beta              | 0.208          |
| Probability of recurrence after 2-week course of oral vancomycin[9, 10, 25]| 0.517     | 0.389–0.642      | 95% CI               | Beta              | 0.066          |
| Probability of recurrence after 6-week oral vancomycin taper-pulse [10]  | 0.178     | 0.059–0.431      | 95% CI               | Beta              | 0.147          |
| Relative risk of recurrence after 10-day course of fidaxomicin, compared to vancomycin[25] | 0.620     | 0.360–1.07       | 95% CI               | Log-normal        | 0.278          |
| Probability of recurrence after fecal transplantation by enema[32]      | 0.185     | 0.063–0.381      | 95% CI               | Beta              | 0.083          |
| Probability of recurrence after fecal transplantation by nasogastric tube[9, 33–35] | 0.233     | 0.155–0.334      | 95% CI               | Beta              | 0.047          |
| Probability of recurrence after fecal transplantation by colonoscopy [36–43] | 0.078     | 0.050–0.119      | 95% CI               | Beta              | 0.017          |
| Relative risk of recurrence for additional 10 years of age[44]          | 1.16      | 1.07–1.26        | 95% CI               | Log-normal        | 0.05           |
| Probability of death from all causes, age 70[45, 46]                    | 0.002     | 0.0015–0.0023    | Range (men, women)   | Beta              | 0.007          |
| Probability of death from all causes, age 80[45, 46]                    | 0.005     | 0.0043–0.0064    | Range (men, women)   | Beta              | 0.0005         |
| Probability of death from colonoscopy[47]                             | 0.0006    | 0.0003–0.0011    | 95% CI exact         | Beta              | 0.0002         |
| Probability of death from nasogastric tube insertion[48]               | 0.003     | 0.0003–0.0097    | 95% CI               | Beta              | 0.002          |
| Probability of death from CDI [23]                                      | 0.073     | 0.058–0.091      | 95% CI               | Beta              | 0.008          |
| Relative risk of death from CDI for additional ten years of age[49]     | 1.41      | 1.36–1.47        | 95% CI               | Log-normal        | 0.03           |
| **Medication Costs ($)**                                                |           |                  |                      |                   |                |
| Metronidazole, 6 days                                                   | 20        | 10–31            | +/- 50%              | Gamma             | 5              |
| Metronidazole, 2-week course                                            | 39        | 19–58            | +/- 50%              | Gamma             | 10             |
| Vancomycin, 2-week course                                               | 347       | 174–521          | +/- 50%              | Gamma             | 87             |
| Vancomycin, 6-week taper-pulse                                           | 505       | 253–758          | +/- 50%              | Gamma             | 126            |
| Fidaxomicin, 10-day course                                              | 2,405     | 1202–3607        | +/- 50%              | Gamma             | 601            |
| **Costs of fecal transplantation by enema ($)**                         |           |                  |                      |                   |                |
| Day of procedure                                                        | 174       | 87–261           | +/- 50%              | Gamma             | 44             |
| Outpatient visits                                                       | 347       | 176–528          | +/- 50%*             | Gamma             | 90             |
| Laboratory testing                                                      | 425       | 213–638          | +/- 50%              | Gamma             | 108            |
| Capital cost(equipment)                                                 | 6844      | 47–6844          | Range                | Gamma             | 1,723          |
| **Costs of fecal transplantation by nasogastric tube ($)**              |           |                  |                      |                   |                |
| Day of procedure                                                        | 226       | 113–339          | +/- 50%              | Gamma             | 58             |
| Outpatient visits                                                       | 358       | 176–528          | +/- 50%*             | Gamma             | 90             |
| Laboratory testing                                                      | 322       | 161–484          | +/- 50%              | Gamma             | 82             |
| Capital cost(equipment)                                                 | 47        | 47–6844          | **                   | Gamma             | 1,723          |
| **Costs of fecal transplantation by colonoscopy ($)**                   |           |                  |                      |                   |                |
| Day of procedure[50]                                                    | 588       | 294–882          | +/- 50%              | Gamma             | 150            |
| Outpatient visits                                                       | 352       | 176–528          | +/- 50%              | Gamma             | 90             |
| Laboratory testing                                                      | 374       | 187–561          | +/- 50%              | Gamma             | 95             |
| Capital cost(equipment)                                                 | 3446      | 47–6844          | **                   | Gamma             | 1,723          |
| **Other costs**                                                         |           |                  |                      |                   |                |

(Continued)
Costs. All costs were reported in 2014 Canadian dollars. Costs obtained from previous years were inflated to 2014 value using the Consumer Price Index for Health and Personal Care.[55] In 2014, $1.00 in Canadian dollars was equivalent to $0.91 in United States dollars.[56]

Medication costs were obtained from a University Health Network (UHN) outpatient pharmacy (located at Toronto General Hospital) for a patient with Ontario Drug Benefit (ODB) coverage. The ODB (funded by the Ontario Ministry of Health and Long Term Care) covers the cost of drugs and the pharmacy mark-up fees for Ontario residents over the age of 65.[57] The costs reported represent what is paid by the ODB to dispensing pharmacies.

Cost of treatment with fecal transplantation included a single fecal transplantation procedure. Cost data for fecal transplantation by enema was provided by the investigators of a UHN clinical trial of fecal transplantation for the treatment of recurrent CDI.[58] Cost information for fecal transplantation by NG tube was provided by the Toronto East General Hospital (TEGH) according to their protocol. Laboratory, personnel, supply, and space costs were included. Table 3 outlines the components in the transplantation protocol for both sites, including which tests are done on stool donors and recipients. Laboratory and supply costs were obtained in 2011 for the enema protocol, and 2013 for the NG protocol.

Personnel costs were obtained using hourly wage data for registered nurses from the Toronto region, as reported by Statistics Canada, with 13% added to account for benefits, as recommended by the Ontario Nursing Association.[59, 60] Physician fees were determined using the Ontario Schedule of Benefits.[57] Counselling and consent, which was performed by physicians, are included in these fees. Space costs were provided by the accounting department or department managers and include overhead (space, maintenance) costs.

The cost of a colonoscopy procedure (without physician fees) was obtained from a micro-costing study from the neighbouring province of Quebec, in Canada.[50] Physician fees for a full colonoscopy were added to this, according to the Ontario Schedule of Benefits.[57] Cost of nursing time post-procedure and processing of stool were added to this, based on the mean of these costs for the NG and enema protocols. The cost of laboratory testing with the fecal

Table 2. (Continued)

| Variable                                | Base Case | Range          | Range type | Distribution Type | Standard Error |
|-----------------------------------------|-----------|----------------|------------|-------------------|----------------|
| Hospitalization Cost[51]                | 16,800    | 8,266–65,512   | -50%-95% UCL | Gamma,            | 24,853         |
| Outpatient visits for patients treated with medications only | 297       | 148–445       | +/- 50%    | Gamma             | 76             |
| QALY Weights                            |           |                |            |                   |                |
| Clostridium difficile infection[52]     | 0.7       | 0.35–0.95     | Plausible range | Beta             | 0.15           |
| Community-dwelling 70–79 year old [53]  | 0.91      | 0.905–0.915   | 95% CI     | Beta              | 0.0026         |
| Community-dwelling 80+ year old [53]    | 0.88      | 0.87–0.89     | 95% CI     | Beta              | 0.004          |
| Dead                                    | 0         | -             |            |                   |                |
| Other                                   |           |                |            |                   |                |
| Number of patients eligible for fecal transplantation in institution-annual | 79        | 40–119        | +/- 50%    | Gamma             | 19.75          |
| Remaining life expectancy for a 70-year old (years)[45, 46] | 16.41     | 15.13–17.68   | Range      | Normal            | 0.65           |
| Remaining life expectancy for an 80-year old[45, 46] | 9.75      | 8.93–10.57    | Range      | Normal            | 0.42           |

NG = nasogastric tube, CDI = Clostridium difficile infection.

*Ranges for cost of outpatient visits in fecal transplantation by NG and enema strategies are +/- 50% of the mean of the two.

**Range is extremes of capital cost for NG and enema protocols.

doi:10.1371/journal.pone.0149521.t002
transplantation by colonoscopy strategy was similarly obtained from the mean of these costs in the NG and enema strategies.

Capital costs for equipment used to prepare stool were included in the fecal transplantation strategies, and are listed separately. In the enema protocol this was a Stomacher 400 Circulator (Seward, UK), whereas in the NG protocol this was a typical household blender. The capital cost for stool preparation equipment in fecal transplantation by colonoscopy was taken as the mid-point of these two figures. 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. The cost of a colonoscope was included in the per-procedure cost of colonoscopy, as reported by Sharara et al.[50]

The cost of two outpatient visits was included in each treatment strategy. In addition, the fecal transplantations strategies included an outpatient visit for the stool donor. Costs of visits for donors and recipients in fecal transplantation strategies were obtained from UHN and TEGH. The mean cost from these two sources was used to provide a cost for outpatient visits.

Table 3. Components of fecal transplantation protocols. Costing for fecal transplantation by colonoscopy was derived from cost of fecal transplantation by enema and NG protocols (see methods). For this reason, there is no listed protocol for fecal transplantation by colonoscopy.

|                          | Enema Protocol | NG Protocol |
|--------------------------|----------------|-------------|
| **Recipient baseline tests** |                |             |
| Stool culture for enteric pathogens | X             |             |
| Stool ova and parasites | X             |             |
| Stool *Helicobacter pylori* antigen assay | X             |             |
| Storage of blood samples for testing if seroconversion | X             |             |
| **Donor screening tests** |                |             |
| Stool culture for enteric pathogens | X             | X           |
| Stool for ova and parasites | X             | X           |
| Stool for *Clostridium difficile* toxin | X             | X           |
| Stool culture for methicillin-resistant *Staphylococcus aureus* | X             |             |
| Stool culture for vancomycin-resistant enterococci | X             |             |
| *Helicobacter pylori* stool antigen assay | X             |             |
| *Helicobacter pylori* serology assay | X             | X           |
| Hepatitis A, B and C serology | X             | X           |
| HTLV 1/2 serology | X             | X           |
| HIV test | X             | X           |
| Syphilis screen | X             | X           |
| **Donor fecal transplantation preparation** |                |             |
| Stool preparation | X             | X           |
| **Personnel** |                |             |
| Physician | X             | X           |
| Nurse | X             | X           |
| Lab technician | X             | X           |
| Radiology technician |              |             |
| **Clinic** |                |             |
| Medical day unit | X             |             |
| Outpatient clinic | X             | X           |
| **Capital investment** |                |             |
| Stomacher 400 Circulator (Seward, UK), Bag rack and Bags | X             |             |
| Blender | X             |             |

doi:10.1371/journal.pone.0149521.t003
in the fecal transplantation by colonoscopy strategy. In order to make an appropriate comparison with the fecal transplantation strategies, the cost of two outpatient visits was added to the medication-only treatment strategies. This was obtained from the mean cost of outpatient visits for fecal transplantation recipients in the fecal transplantation strategies.

Hospital Admission Costs, including the cost of in-hospital medications to treat CDI, were obtained from the Ontario Case Costing Initiative.[51] We extracted cost data for all patients over age 70 admitted in 2010–2011 with a most responsible diagnosis of A047 “Enterocolitis due to Clostridium difficile”.

Utilities and QALY weights. Utility measures for CDI have not been established through commonly accepted techniques. A previous cost-effectiveness analysis of CDI used utility measures for grade 3 and 4 chemotherapy-associated diarrhea to estimate the utility of CDI.[61] This value (0.3) is much lower than the utilities used for other gastrointestinal conditions, such as colitis (0.7) and irritable bowel syndrome (0.675).[52, 62] With the aim of being conservative, we used 0.7 as the utility for CDI; however we varied this utility widely in our sensitivity analysis.

We used a QALY weight for the well state obtained from a Health Utilities Index survey of community dwelling Canadians over age 70.[53] 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 of 5% was applied to QALYs over the patient’s remaining lifetime, consistent with recommendations from the Canadian Agency for Drugs and Technology in Health.[63]

Analysis

All analyses of cost-effectiveness were made using a willingness-to-pay of $50,000/QALY. Following analysis of the base-case, one-way sensitivity analysis was carried out on all variables within their ranges. In addition, we tested our model using a 0% discount rate for lifetime QALYs.

Variables found to have the greatest impact on base-case results were further analyzed in a two-way sensitivity analysis at a willingness-to-pay of $50,000/QALY. A probabilistic sensitivity analysis (PSA), using 10,000 Monte Carlo cohort-based simulations, was used to simultaneously assess the effect of uncertainty in all parameters on model conclusions.

We also conducted several scenario analyses, to examine how model conclusions were altered by patient age, fidaxomicin patent status, access to fecal transplantation procedures, and the number of recurrences. The cost of generic fidaxomicin is expected to be 25% of the per-unit cost of the brand-name drug.[64]

Results

Base-case analysis

Fecal transplantation by colonoscopy was dominant in the base case, as it was cost-saving and more effective than all other treatment options. This strategy led to $140 saved and 0.31 additional QALYs compared to treatment with metronidazole. Per 1,000 patients treated, fecal transplantation by colonoscopy resulted in 439 fewer recurrences, 76 avoided hospitalizations, and 31 lives saved, compared to metronidazole (see Table 4). Vancomycin, fidaxomicin, fecal transplantation by NG and fecal transplantation by enema were also more expensive and less effective than fecal transplantation by colonoscopy (see Table 5).

Sensitivity Analyses

Varying all parameters within their stated ranges did not change the preferred treatment strategy, with one exception. Fecal transplantation by enema became the preferred strategy when
the probability of recurrence following this strategy dropped below 8.7%. The effect of uncertainty in the probability of recurrence following fecal transplantation by colonoscopy and enema strategies is explored in Fig 2.

Varying costs within their stated ranges did not change the preferred strategy. The total treatment costs (capital and non-capital) for fecal transplantation by colonoscopy would have to exceed $8,062 per treatment before fecal transplantation by enema became the preferred strategy. Further, as long as the total per-treatment costs were below $1,446, fecal transplantation by colonoscopy was cost-saving compared to all alternative strategies. Removing the discount rate for future QALYs did not change model conclusions: fecal transplantation by colonoscopy remained dominant over all other options.

Probabilistic sensitivity analysis with 10,000 Monte Carlo trials demonstrated that fecal transplantation by colonoscopy was the most beneficial strategy in 87% of trials at a willingness-to-pay of $50,000/QALY. (Fig 3).

### Scenario Analyses

As a result of the higher rate of CDI recurrence and CDI-related mortality in older patients, fecal transplantation by colonoscopy was even more advantageous in this population ($288 saved and 0.33 additional QALYs compared to metronidazole). Fidaxomicin coming off-patent, while it would reduce the average cost of this strategy by 23%, did not change the preferred strategy, which remained fecal transplantation by colonoscopy (see Table 5).

In a setting with no access to colonoscopy, fecal transplantation by enema was cost-effective, with an ICER of $1,708/QALY gained compared to the metronidazole strategy. Meanwhile, if fecal transplantation in any form is not available, fidaxomicin became cost-effective, with an ICER of $25,968/QALY gained compared to metronidazole. Finally, running the model for only two cycles (one recurrence after the first) identifies fecal transplantation by colonoscopy as a cost-effective alternative to metronidazole (see Table 5).

### Discussion

In our cost-effectiveness analysis of treatments for recurrent CDI, fecal transplantation by colonoscopy was dominant in the base case, as it was both more effective and less costly than all other options. Our results were sensitive to uncertainty in the probability of recurrence with fecal transplantation by enema. Where the probability of CDI recurrence with fecal transplantation by enema was below 8.7%, it became the preferred strategy. After accounting for uncertainty in all parameters, there was an 87% probability that fecal transplantation by colonoscopy was the most beneficial strategy at our willingness-to-pay threshold. Where colonoscopy or

---

**Table 4. Health outcomes of each treatment strategy, per 1,000 patient cohort.**

| Strategy                      | Count of recurrences after the first | Count of hospitalisations | Count of CDI-related deaths* | Average life years |
|-------------------------------|--------------------------------------|--------------------------|------------------------------|--------------------|
| Vancomycin                    | 636                                  | 284                      | 119                          | 14.46              |
| Metronidazole                 | 593                                  | 275                      | 115                          | 14.78              |
| Fecal transplantation by NG   | 426                                  | 247                      | 108                          | 14.87              |
| Fidaxomicin                   | 458                                  | 253                      | 106                          | 14.90              |
| Fecal transplantation by enema| 340                                  | 233                      | 98                           | 15.04              |
| Fecal transplantation by colonoscopy | 144                              | 199                      | 84                           | 15.26              |

* includes deaths from treatment-related complications.

doi:10.1371/journal.pone.0149521.t004
Numerous observational studies, and one randomized controlled trial, have associated fecal transplantation for recurrent CDI with low rates of recurrence.\cite{9, 14} Until recently, access to fecal transplantation in Canada has been limited to study settings. With the relaxation of Health Canada regulations\cite{20}, the lack of facilities offering such treatments may now become the primary barrier to treatment. This could result from an absence of institutional support, leading to a lack of resources necessary for delivery. Our study provides evidence for hospital

| Treatment                                      | Cost (2014 Canadian dollars) | QALY  | ICER       |
|-----------------------------------------------|------------------------------|-------|------------|
| **Scenario 1: base case**                     |                              |       |            |
| Fecal transplantation by colonoscopy          | 5,246                        | 9.40  | Dominates  |
| Vancomycin                                    | 5,929                        | 9.03  | (Dominated)|
| Metronidazole                                 | 5,386                        | 9.09  | (Dominated)|
| Fecal transplantation by NG                   | 5,935                        | 9.15  | (Dominated)|
| Fidaxomicin                                   | 7,319                        | 9.16  | (Dominated)|
| Fecal transplantation by enema                | 5,667                        | 9.26  | (Dominated)|
| **Scenario 2: patient is ten years older**    |                              |       |            |
| Fecal transplantation by colonoscopy          | 5,310                        | 6.02  | Dominates  |
| Vancomycin                                    | 6,174                        | 5.63  | (Dominated)|
| Metronidazole                                 | 5,598                        | 5.69  | (Dominated)|
| Fecal transplantation by NG                   | 6,116                        | 5.77  | (Dominated)|
| Fidaxomicin                                   | 7,494                        | 5.77  | (Dominated)|
| Fecal transplantation by enema                | 5,815                        | 5.87  | (Dominated)|
| **Scenario 3: fidaxomicin is off-patent**     |                              |       |            |
| Fecal transplantation by colonoscopy          | 5,246                        | 9.40  | Dominates  |
| Vancomycin                                    | 5,929                        | 9.03  | (Dominated)|
| Metronidazole                                 | 5,386                        | 9.09  | (Dominated)|
| Fecal transplantation by NG                   | 5,935                        | 9.15  | (Dominated)|
| Fidaxomicin                                   | 5,521                        | 9.16  | (Dominated)|
| Fecal transplantation by enema                | 5,667                        | 9.26  | (Dominated)|
| **Scenario 4: no fecal transplantation option available** |                              |       |            |
| Metronidazole                                 | 5,386                        | 9.09  |            |
| Fidaxomicin                                   | 7,319                        | 9.16  | 25,968     |
| Vancomycin                                    | 5,929                        | 9.03  | (Dominated)|
| **Scenario 5: no colonoscopy available**      |                              |       |            |
| Metronidazole                                 | 5,386                        | 9.09  | 1,708      |
| Fecal transplantation by enema                | 5,667                        | 9.26  | (Dominated)|
| Vancomycin                                    | 5,929                        | 9.03  | (Dominated)|
| Fecal transplantation by NG                   | 5,935                        | 9.15  | (Dominated)|
| Fidaxomicin                                   | 7,319                        | 9.16  | (Dominated)|
| **Scenario 6: two cycles only (single recurrence after the first)** |                              |       |            |
| Metronidazole                                 | 4,793                        | 9.14  |            |
| Fecal transplantation by colonoscopy          | 4,918                        | 9.38  | 514        |
| Vancomycin                                    | 5,341                        | 9.07  | (Dominated)|
| Fidaxomicin                                   | 6,722                        | 9.21  | (Dominated)|
| Fecal transplantation by NG                   | 5,058                        | 9.24  | (Dominated)|
| Fecal transplantation by enema                | 4,954                        | 9.31  | (Dominated)|

doi:10.1371/journal.pone.0149521.t005
Fig 2. Two-way sensitivity analysis for the preferred strategy according to probability of recurrence following fecal transplantation by colonoscopy or enema. The colour indicates which strategy leads to the greatest number of QALYs at a willingness-to-pay of $50,000/QALY. The hatched white lines identify the values used in the base case. $CAN = Canadian dollars.

doi:10.1371/journal.pone.0149521.g002

Fig 3. Cost-effectiveness acceptability curve. *the most beneficial strategy is the one that leads to the greatest number of QALYs at each willingness-to-pay threshold. Vancomycin and fidaxomicin strategies are not included in this figure as the probability that either strategy was most beneficial was 0 at all included thresholds. $CAN = Canadian dollars. NG = nasogastric tube.

doi:10.1371/journal.pone.0149521.g003
leaders and healthcare funders that providing fecal transplantation is worthwhile. Where colonoscopy is not available, fecal transplantation by enema can be adopted with little up-front expense if a household-style blender is used for stool preparation, rather than a Stomacher.

Our conclusions are limited by the quality of our parameter estimates. Probabilities for recurrence following vancomycin taper-pulse and fecal transplantations were obtained almost entirely from observational studies, most of which were deemed to be of intermediate or low quality according to the National Institute for Health and Care Excellence checklist for quality of case series data.[14] The little randomized controlled trial evidence available came from a very small trial, with only 16 participants.[9] Data on fidaxomicin, although originating from trials, is limited by short follow-up periods (4 weeks), possibly underestimating recurrence in both fidaxomicin and oral vancomycin arms.[25] Estimates of relative cost-effectiveness will require revision if the results of future randomized controlled trials differ from existing estimates.

Costs of treatment with each modality will vary across jurisdictions, resulting in different conclusions and/or varying ICERs. For instance, costs of similar processes, used for fecal transplantation by NG or enema, varied between institutions within the same city. Capital costs for equipment used for stool preparation were particularly variable in our study. Further, the capital cost for fecal transplantation by colonoscopy did not include the cost of the colonoscope itself, since this was included in the per-procedure cost reported by Sharara et al.[50] Their estimates were obtained in a setting with a large volume of colonoscopies performed (greater than 4,000 colonoscopy procedures per year). In a lower-volume setting, the capital cost of acquiring a colonoscope for the purpose of treating a relatively small number of patients with recurrent CDI may be considered prohibitive. However, our results indicate that even at a high per-procedure cost, fecal transplantation by colonoscopy is cost-effective.

In our analysis we assumed that probability of recurrence remained fixed over time, yet in fact recurrence risk probably declines over time if a first recurrence has not occurred.[65] Conversely, risk of recurrence is thought to rise in relation to the number of recurrences already experienced.[12] As such, the data on vancomycin dose, duration and recurrence is likely confounded by the number of previous recurrences. In the absence of large prospective cohort or trial data for patients experiencing their first recurrence of CDI, generating probabilities specific to the number of recurrences would be challenging.

We did not model colectomy as a distinct state. Colectomy is rare, occurring in 1% or less of cases of CDI over the age of 65, and associated with a high mortality.[66–68] The inclusion of colectomy, a rare yet expensive complication, can be expected to increase the difference between groups, and make all treatments with improved efficacy appear more cost-effective, thus not altering the direction of our model conclusions.

We did not model adverse drug events because of the mild and transient nature of reported events. Both oral vancomycin and fidaxomicin have minimal systemic absorption, and reported adverse events were mild and transient, consisting of symptoms that could also be effects of CDI (most common: nausea, vomiting, fever, hypokalemia).[13] Our model accounted for the small mortality risk resulting from NG insertion and colonoscopy procedures, but did not include any variable for risk of exposure to fecal transplantation material itself. In a systematic review, only 3 of 11 studies of fecal transplantation reported any adverse events, for an event rate of three possible events for 273 treated patients; in these patients, described complications (upper gastrointestinal bleed, peritonitis and enteritis) may have related to the use of an NG tube rather than the stool material itself.[14]
Comparison with other work

A cost-effectiveness analysis of strategies for treatment of recurrent CDI using U.S. data concluded that fecal transplantation by colonoscopy was cost-effective with an ICER of $17,016 compared to vancomycin.[22] Unlike these authors, we adopted a lifetime perspective over which to model QALYs, as is recommended by the International Society of Pharmacoeconomics and Outcomes Research.[27] This approach accounts for the quality-adjusted years of life lost as a result of a CDI-related death. Cost data in our study was obtained using real hospital costs in a single payer publicly funded healthcare system with universal coverage, rather than reimbursements by Medicare, which insures only a portion of the population. In our study, fecal transplantation by colonoscopy was cost-saving, as a result of fewer hospitalisations occurring in this treatment group.[22] As the cost of hospitalisation used in our study was greater than that used by Konijeti et al, this could explain the difference in results.

Conclusions

Recurrent CDI is associated with significant morbidity and mortality, however several treatment options are available. Our cost-effectiveness analysis revealed that fecal transplantation by colonoscopy is cost-effective for the treatment of recurrent CDI. In a setting where colonoscopy is not available, fecal transplantation by enema is a cost-effective alternative. Our conclusions are limited by the quality of data on the effectiveness of fecal transplantation and taper-pulse vancomycin. The availability of fecal transplantation is dependent on institutional support for the procedure. Healthcare leaders should note that although there may be upfront costs related to a fecal transplantation program, providing such a service for patients with recurrent CDI is likely worth the cost.

Supporting Information

S1 File. Treeage file used to model base case results.
(TREX)

Author Contributions

Conceived and designed the experiments: LLS KLT PCC RLHH JP SMP SH. Performed the experiments: LLS KLT. Analyzed the data: LLS KLT SH. Wrote the paper: LLS KLT PCC RLHH JP SMP SH.

References

1. Poutanen SM, Simor AE. Clostridium difficile-associated diarrhea in adults. CMAJ. 2004; 171(1):51–8. Epub 2004/07/09. PMID: 15238498; PubMed Central PMCID: PMCPMC437686.
2. McFarland LV. Epidemiology of infectious and iatrogenic nosocomial diarrhea in a cohort of general medicine patients. Am J Infect Control. 1995; 23(5):295–305. PMID: 8585641
3. Kelly CP, Pothoulakis C, LaMont JT. Clostridium difficile colitis. N Engl J Med. 1994; 330(4):257–62. Epub 1994/01/27. doi:10.1056/nejm199401273300406 PMID: 8043060.
4. Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, et al. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). Infect Control Hosp Epidemiol. 2010; 31(5):431–55. Epub 2010/03/24. doi: 10.1086/651706 PMID: 20307191.
5. McFarland LV, Surawicz CM, Greenberg RN, Fekety R, Elmer GW, Moyer KA, et al. A randomized placebo-controlled trial of Saccharomyces boulardii in combination with standard antibiotics for Clostridium difficile disease. JAMA. 1994; 271(24):1913–6. Epub 1994/06/22. PMID: 8201735.
6. Bartlett JG, Tedesco FJ, Shull S, Lowe B, Chang T. Symptomatic relapse after oral vancomycin therapy of antibiotic-associated pseudomembranous colitis. Gastroenterology. 1980; 78(3):431–4. Epub 1980/03/01. PMID: 7053190.

7. Wenisch C, Parschalk B, Hasenhundl M, Hirschl AM, Graninger W. Comparison of vancomycin, teicoplanin, metronidazole, and fusidic acid for the treatment of Clostridium difficile-associated diarrhea. Clin Infect Dis. 1996; 22(5):813–8. Epub 1996/05/01. PMID: 8729337.

8. McFarland LV, Surawicz CM, Rubin M, Fekety R, Elmer GW, Greenberg RN. Recurrent Clostridium difficile disease: epidemiology and clinical characteristics. Infect Control Hosp Epidemiol. 1999; 20(1):43–50. Epub 1999/02/02. doi: 10.1086/501553 PMID: 9927265.

9. van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, et al. Duodenal infusion of donor feces for recurrent Clostridium difficile. N Engl J Med. 2013; 368(5):407–15. Epub 2013/01/18. doi: 10.1056/NEJMoa1205037 PMID: 23323867.

10. McFarland LV, Elmer GW, Surawicz CM. Breaking the cycle: treatment strategies for 163 cases of recurrent Clostridium difficile disease. Am J Gastroenterol. 2002; 97(7):1769–75. Epub 2002/07/24. doi: 10.1111/j.1572-0241.2002.05839.x PMID: 12135033.

11. Crook DW, Walker AS, Kean Y, Weiss K, Cornely OA, Miller MA, et al. Fidaxomicin versus vancomycin for Clostridium difficile infection: meta-analysis of pivotal randomized controlled trials. Clin Infect Dis. 2012; 55 Suppl 2:S93–103. Epub 2012/09/05. doi: 10.1093/cid/cis499 PMID: 22752871; PubMed Central PMCID: PMCPMC3388031.

12. Cornely OA, Crook DW, Esposito R, Poirier A, Somero MS, Weiss K, et al. Fidaxomicin versus vancomycin for Clostridium difficile infection in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial. Lancet Infect Dis. 2012; 12(4):281–9. Epub 2012/02/11. doi: 10.1016/s1473-3099(11)70374-7 PMID: 22321770.

13. Louie TJ, Miller MA, Mullane KM, Weiss K, Lentnek A, Golan Y, et al. Fidaxomicin versus vancomycin for Clostridium difficile infection. N Engl J Med. 2011; 364(5):422–31. Epub 2011/02/04. doi: 10.1056/NEJMoia0910812 PMID: 21288078.

14. Kassam Z, Lee CH, Yuan Y, Hunt RH. Fecal microbiota transplantation for Clostridium difficile infection: systematic review and meta-analysis. Am J Gastroenterol. 2013; 108(4):500–8. Epub 2013/03/21. doi: 10.1038/ajg.2013.59 PMID: 23511459.

15. Ministry of Health and Long-term Care. Exceptional Access Program Reimbursement Criteria for Frequently Requested Drugs. Available from: http://www.health.gov.on.ca/en/pro/programs/drugs/pdf/frequently_requested_drugs.pdf.

16. Ahmad A, Hugtenburg J, Welschen LM, Dekker JM, Nijpels G. Effect of medication review and cognitive behaviour treatment by community pharmacists of patients discharged from the hospital on drug related problems and compliance: design of a randomized controlled trial. BMC Public Health. 2010; 10:133. PMID: 20230611; PubMed Central PMCID: PMCPMC2850341. doi: 10.1186/1471-2458-10-133.

17. Bartsch SM, Umscheid CA, Fishman N, Lee BY. Is fidaxomicin worth the cost? An economic analysis. Clin Infect Dis. 2013; 57(4):555–61. Epub 2013/05/25. doi: 10.1093/cid/cit346 PMID: 23704121; PubMed Central PMCID: PMCPMC3719891.

18. Wagner M, Lavoie L, Goetghembeur M. Clinical and economic consequences of vancomycin and fidaxomycin for the treatment of Clostridium difficile infection in Canada. Can J Infect Dis Med Microbiol. 2014; 25(2):87–94. Epub 2014/04/25. PMID: 24855476; PubMed Central PMCID: PMCPmc4028674.

19. Allen-Vercoe E, Reid G, Viner N, Gloor GB, Hota S, Kim P, et al. A Canadian Working Group report on fecal microbiota transplantation for the treatment of Clostridium difficile infection: microbial ecosystems therapeutics. Can J Gastroenterol. 2012; 26(7):457–62. Epub 2012/07/18. PMID: 22803022; PubMed Central PMCID: PMCPMC3395448.

20. Health Canada. Fecal Microbiota Therapy Used in the Treatment of Clostridium difficile Infection Not Responsive to Conventional Therapies Ottawa, Canada2015.

21. Konijeti GG, Sauk J, Shrime MG, Gupta M, Ananthakrishnan AN. Cost-effectiveness of Competing Strategies for Management of Recurrent Clostridium difficile Infection: A Decision Analysis. Clin Infect Dis. 2014; 58(11):1507–14. Epub 2014/04/03. doi: 10.1093/cid/ciu128 PMID: 24692533; PubMed Central PMCID: PMCPmc4017891.

22. Gravel D, Miller M. Clostridium difficile Associated Diarrhea in Acute-Care Hospitals Participating in CNISP: November 1, 2004 to April 30, 2005. 2007.
24. Belmares J, Gerding DN, Parada JP, Miskevics S, Weaver F, Johnson S. Outcome of metronidazole therapy for Clostridium difficile disease and correlation with a scoring system. J Infect. 2007; 55(6):495–501. Epub 2007/11/07. doi: 10.1016/j.jinf.2007.09.015 PMID: 17983659.

25. Cornely OA, Miller MA, Louie TJ, Crook DW, Gorbach SL. Treatment of first recurrence of Clostridium difficile infection: fidaxomicin versus vancomycin. Clin Infect Dis. 2012; 55 Suppl 2:S154–61. Epub 2012/07/07. doi: 10.1093/cid/cis462 PMID: 22752865; PubMed Central PMCID: PMC3888030.

26. Naimark DM, Kabboul NN, Krahn MD. The half-cycle correction revisited: redemption of a kludge. Med Decis Making. 2013; 33(7):961–70. Epub 2013/09/21. doi: 10.1177/0272989x13501558 PMID: 24048350.

27. Roberts M, Russell LB, Palliel AD, Chambers M, McEwan P, Krahn M. Conceptualizing a model: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force—2. Value Health. 2012; 15(6):804–11. Epub 2012/09/25. doi: 10.1016/j.jval.2012.06.016 PMID: 22999129.

28. Pepin J, Routhier S, Gagnon S, Brazeau I. Management and outcomes of a first recurrence of Clostridium difficile-associated disease in Quebec, Canada. Clin Infect Dis. 2006; 42(6):758–64. Epub 2006/02/16. doi: 10.1086/501126 PMID: 16477549.

29. O’Brien JA, Lahue BJ, Caro JJ, Davidson DM. The emerging infectious challenge of clostridium difficile-associated disease in Massachusetts hospitals: clinical and economic consequences. Infect Control Hosp Epidemiol. 2007; 28(11):1219–27. Epub 2007/10/11. doi: 10.1086/522676 PMID: 17926270.

30. Debast SB, Bauer MP, Kuiper EJ, on behalf of the C. European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for Clostridium difficile infection. Clin Microbiol Infect. 2014; 20;1–26. doi: 10.1111/1469-0691.12418

31. Vardakas KZ, Polyzos KA, Patouni K, Rafailidis PI, Samonis G, Falagas ME. Treatment failure and recurrence of Clostridium difficile infection following treatment with vancomycin or metronidazole: a systematic review of the evidence. Int J Antimicrob Agents. 2012; 40(1):1–8. Epub 2012/03/09. doi: 10.1016/j.ijantimicag.2012.01.004 PMID: 22398198.

32. Kassam Z, Hundal R, Marshall JK, Lee CH. Fecal transplant via retention enema for refractory or recurrent Clostridium difficile infection. Arch Intern Med. 2012; 172(2):191–3. Epub 2012/01/25. doi: 10.1001/archinte.172.2.191 PMID: 22271132.

33. MacConnachie AA, Fox R, Kennedy DR, Seaton RA. Faecal transplant for recurrent Clostridium difficile-associated diarrhoea: a UK case series. QJM. 2009; 102(11):781–4. Epub 2009/09/04. doi: 10.1093/qjmed/hcp118 PMID: 19726581.

34. Garborg K, Waagsbo B, Stallemo A, Matre J, Sundøy A. Results of faecal donor instillation therapy for recurrent Clostridium difficile-associated diarrhoea. Scand J Infect Dis. 2010; 42(12):857–61. Epub 2010/07/29. doi: 10.3109/00365548.2010.499541 PMID: 20662620.

35. Aas J, Gessert CE, Bakken JS. Recurrent Clostridium difficile colitis: case series involving 18 patients treated with donor stool administered via a nasogastric tube. Clin Infect Dis. 2003; 36(5):580–5. Epub 2003/02/21. doi: 10.1086/376557 PMID: 12594658.

36. Mattila E, Uusitalo-Seppala R, Wuorela M, Lehtola L, Nurmi H, Ristikankare M, et al. Fecal transplantation, through colonoscopy, is effective therapy for recurrent Clostridium difficile infection. Gastroenterology. 2012; 142(3):490–6. Epub 2011/12/14. doi: 10.1053/j.gastro.2011.11.037 PMID: 22155369.

37. Rohlke F, Surawicz CM, Stollman N. Fecal flora reconstitution for recurrent Clostridium difficile infection: results and methodology. J Clin Gastroenterol. 2010; 44(8):567–70. Epub 2010/05/21. doi: 10.1097/MCG.0b013e3181dab16 PMID: 20485184.

38. Yoon SS, Brandt LJ. Treatment of refractory/recurrent C. difficile-associated disease by donated stool transplanted via colonoscopy: a case series of 12 patients. J Clin Gastroenterol. 2010; 44(8):562–6. Epub 2010/05/14. doi: 10.1097/MCG.0b013e3181e3181dad8dod PMID: 20463588.

39. Kelly CR, de Leon L, Jasutkar N. Fecal microbiota transplantation for relapsing Clostridium difficile infection in 26 patients: methodology and results. J Clin Gastroenterol. 2012; 46(2):145–9. Epub 2011/12/14. doi: 10.1097/MCG.0b013e318234570b PMID: 22157239.

40. Lund-Tonnesen S, Berstad A, Schreiner A, Midvedt T. [Clostridium difficile-associated diarrhoea treated with homologous feces]. Tidsskr Nor Laegeforen. 1998; 118(7):1027–30. Epub 1998/04/09. PMID: 9531822.

41. Patel NC, Griesbach CL, DiBaise JK, Orenstein R. Fecal microbiota transplant for recurrent Clostridium difficile infection: Mayo Clinic in Arizona experience. Mayo Clin Proc. 2013; 88(8):799–805. PMID: 23910407. doi: 10.1016/j.mayocp.2013.04.022

42. Brandt LJ, Aroniadis OC, Mellow M, Kanatzar A, Kelly C, Park T, et al. Long-term follow-up of colonoscopic fecal microbiota transplant for recurrent Clostridium difficile infection. Am J Gastroenterol. 2012; 107(7):1079–87. Epub 2012/03/28. doi: 10.1038/ajg.2012.60 PMID: 22450732.
43. Mellow MH, Kanatzar A. Colonoscopic fecal bacteriotherapy in the treatment of recurrent Clostridium difficile infection—results and follow-up. J Okla State Med Assoc. 2011; 104(3):89–91. Epub 2011/05/26. PMID: 21604850.

44. Eyre DW, Walker AS, Wyllie D, Dingle KE, Griffiths D, Finney J, et al. Predictors of first recurrence of Clostridium difficile infection: implications for initial management. Clin Infect Dis. 2012; 55 Suppl 2: S77–87. Epub 2012/09/05. doi: 10.1093/cid/cis356 PMID: 22752869; PubMed Central PMCID: PMCPmc3388024.

45. Statistics Canada. Table 7a Complete life table, males, Canada, 2009 to 2011: Minister of Industry, 2015 [cited 2015 October 22]. Available from: http://www.statcan.gc.ca/pub/84-537-x/2013005/tbl-eng.htm.

46. Statistics Canada. Table 7a Complete life table, females, Canada, 2009 to 2011: Ministry of Industry, 2015 [cited 2015 October 22].

47. Levin TR, Zhao W, Conell C, Seeff LC, Manninen DL, Shapiro JA, et al. Complications of Colonoscopy in an Integrated Health Care Delivery System. Ann Intern Med. 2006; 145(12):880–6. doi: 10.7326/0003-4819-145-12-200612190-00004 PMID: 17179057.

48. Rassias AJ, Ball PA, Corwin HL. A prospective study of tracheopulmonary complications associated with the placement of narrow-bore enteral feeding tubes. Crit Care. 1998; 2(1):25–8. Epub 2000/11/01. doi: 10.1186/cc120 PMID: 11056706; PubMed Central PMCID: PMCPmc28998.

49. Walker AS, Eyre DW, Wyllie DH, Dingle KE, Griffiths D, Shine B, et al. Relationship Between Bacterial Strain Type, Host Biomarkers, and Mortality in Clostridium difficile Infection. Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America. 2013; 56(11):1589–600. doi: 10.1093/cid/cit127 PMID: PMC3641870.

50. Sharara N, Adam V, Crott R, Barkun AN. The costs of colonoscopy in a Canadian hospital using a microcosting approach. Can J Gastroenterol. 2008; 22(6):565–70. PMID: PMC2660815.

51. Ontario Ministry of Health and Long-Term Care. Ontario Case Costing Initiative 2013 [December 15, 2013]. Available from: http://www.occp.com/mainPage.htm.

52. Gold MR, Franks P, McCoy KI, Fryback DG. Toward consistency in cost-utility analyses: using national measures to create condition-specific values. Med Care. 1998; 36(6):778–92. Epub 1998/06/18. PMID: 9630120.

53. Mittmann N, Trakas K, Risebrough N, Liu BA. Utility scores for chronic conditions in a community-dwelling population. Pharmacoconomics. 1999; 15(4):369–76. PMID: 10537955.

54. Kassam Z, Lee CH, Yuan Y, Hunt RH. Fecal microbiota transplantation for Clostridium difficile infection: systematic review and meta-analysis. Am J Gastroenterol. 2013; 108(4):500–8. PMID: 23511459. doi: 10.1038/ajg.2013.59.

55. Statistics Canada. Consumer Price Index, health and personal care, by province (Canada) 2015 [12 November, 2015]. Available from: http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/econ161a-eng.htm.

56. Monthly Average Exchange Rates: 10-Year Lookup [Internet]. 2013 [cited 12 November, 2015]. Available from: http://www.bankofcanada.ca/rates/exchange/monthly-average-lookup/.

57. Ministry of Health and Long Term Care. Schedule of Benefits. Toronto, Ontario: Province of Ontario; 2013.

58. U.S. National Institutes of Health. Oral Vancomycin Followed by Fecal Transplant Versus Tapering Oral Vancomycin NCT01226992: ClinicalTrials.gov; 2013 [cited 2014 June 16]. Available from: http://clinicaltrials.gov/ct2/show/NCT01226992.

59. Ontario Nurses’ Association. Unions and the Ontario Nurses’ Association 2014 [cited 2014 March 30]. Available from: http://www.ona.org/faqs.html#f15.

60. Government of Canada. Explore Careers- Wage Report http://www.workingincanada.gc.ca/. Government of Canada; 2013 [updated 2013; cited 2014 February 4]. Available from: http://www.workingincanada.gc.ca/LMI_report_area.do?reportOption=wage&PROVINCE_ID=35&GEOAREA_CD=9219&selectLocation=Continue.

61. Stranges PM, Hutton DW, Collins CD. Cost-effectiveness analysis evaluating fidaxomicin versus oral vancomycin for the treatment of Clostridium difficile infection in the United States. Value Health. 2013; 16(2):297–304. Epub 2013/03/30. doi: 10.1016/j.jval.2012.11.004 PMID: 23538181.

62. Mohseninejad L, Feenstra T, van der Horst HE, Woutersen-Koch H, Buskens E. Targeted screening for Coeliac Disease among irritable bowel syndrome patients: analysis of cost-effectiveness and value of information. The European journal of health economics: HEPAC: health economics in prevention and care. 2013; 14(6):947–57. Epub 2012/11/28. doi: 10.1007/s10198-012-0441-4 PMID: 23179163.

63. Canadian Agency for Drugs and Technologies in Health. Guidelines for the Economic Evaluation of Health Technologies: Canada. Ottawa: 2006.
64. Law MR. Money Left on the Table: Generic Drug Prices in Canada. Healthcare Policy. 2013; 8(3):17–25. PMID: 23968624

65. Lynne V. McFarland P, Surawicz CMMD, Rubin MMD, Fekety RMD, Elmer GWP, Greenberg RNMD. Recurrent Clostridium difficile Disease: Epidemiology and Clinical Characteristics • Infect Control Hosp Epidemiol. 1999; 20(1):43–50. doi: 10.1086/501553 PMID: 9927265

66. Halabi WJ, Nguyen VQ, Carmichael JC, Pigazzi A, Stamos MJ, Mills S. Clostridium difficile colitis in the United States: a decade of trends, outcomes, risk factors for colectomy, and mortality after colectomy. J Am Coll Surg. 2013; 217(5):802–12. Epub 2013/09/10. doi: 10.1016/j.jamcollsurg.2013.05.028 PMID: 24011436.

67. Gravel D, Miller M, Simor A, Taylor G, Gardam M, McGeer A, et al. Health care-associated Clostridium difficile infection in adults admitted to acute care hospitals in Canada: a Canadian Nosocomial Infection Surveillance Program Study. Clin Infect Dis. 2009; 48(5):568–76. Epub 2009/02/05. doi: 10.1086/596703 PMID: 19191641.

68. Collins CE, Ayturk MD, Flahive JM, Emhoff TA, Anderson FA Jr, Santry HP. Epidemiology and Outcomes of Community-Acquired Clostridium difficile Infections in Medicare Beneficiaries. J Am Coll Surg. 2014; 218(6):1141–7.e1. Epub 2014/04/24. doi: 10.1016/j.jamcollsurg.2014.01.053 PMID: 24755188.