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Review

Economic burden and cost-effectiveness of therapies for *Clostridiodes difficile* infection: a narrative review

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***Abstract*:** *Clostridioides difficile* is the most common cause of healthcare-associated diarrhea. Disease complications as well as recurrent infections contribute significantly to morbidity and mortality. Over the past decades, there has been a rapid increase in the incidence of *C. difficile* infection (CDI), with a rise in the number of community-acquired cases. CDI has a profound economic impact on both the healthcare system and patients, secondary to recurrences, hospitalization, prolonged length of stay, cost of treatment, and indirect societal costs. With emergence of newer treatment options, the standard of care is shifting from metronidazole and vancomycin towards fidaxomicin and fecal microbiota transplantation (FMT), which despite being more expensive, are more efficacious in preventing recurrences and hence overall are more beneficial forms of therapy per cost-effectiveness analyses. Data regarding preferred route of FMT, timing of FMT, and non-conventional therapies such as bezlotoxumab is scant. There is a need for further studies to elucidate the true attributable costs of CDI as well as continued cost-effectiveness research to reduce the economic burden associated with the disease and improve clinical practice.

Keywords: *C. difficile*, cost-effectiveness, economic burden

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Introduction

Clostridiodes difficile is a Gram-positive, spore-forming, anaerobic bacillus which is widely distributed in the intestinal tract of humans and animals, and in the environment. Over the last two decades, *C. difficile* infection (CDI) has become among the most common hospital-acquired infections, accounting for substantial morbidity and mortality. Key risk factors for CDI include antibiotic exposure (penicillins, cephalosporins, clindamycin, fluoroquinolones), older age and hospitalization or stay in long-term care facilities.[1–4] Other risk factors include inflammatory bowel disease, gastrointestinal surgeries, immunological incompetence secondary to malignant neoplasms, organ transplantation, chronic kidney diseases, and other immunosuppressant use.[2,5] The clinical presentation of CDI is variable, ranging from an asymptomatic carrier state or mild diarrhea to fulminant life-threatening colitis.[6] Severe CDI can lead to toxic megacolon, colonic perforation, multiorgan failure, and even death.[7] Although classically thought to be a nosocomial infection, the incidence of community-acquired CDI is on the rise, accounting for up to one-fifth of CDI cases.[8] The first-line treatment for CDI is typically targeted antibiotics such as vancomycin, fidaxomicin, or metronidazole, with the latter increasingly out of favor due to lower efficacy. An important option that has emerged for the treatment of CDI, particularly in the setting of multiple recurrences, has been repopulation of the gut microbial diversity through fecal microbiota transplantation (FMT). In this review we will highlight the growing economic burden of CDI and discuss studies of the cost-effectiveness of the current treatment modalities.

Burden of *C. difficile*

C. difficile was first identified in 1935 and was initially thought to be a commensal. It was not until

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the 1970s that it was found to be linked to antibiotic-associated diarrhea.[9,10] CDI remained uncommon in the 1990s; however, since the early 2000s the incidence and severity of CDI has increased manifold to emerge as the most common nosocomial infection.[11–18] An important contributing factor was the emergence of the epidemic strain ribotype 027[13,19] as seen in Quebec, Canada where a deadly outbreak saw a four-fold increase in CDI incidence and 2.3-fold increase in recurrence over 13 years.[13,16,20,21] The introduction of more sensitive *C. difficile* assays over the past decade such as nucleic acid amplification tests probably contributed to higher case detection and disease burden.[22,23] Increasing incidence and outbreaks of CDI have also been reported from several countries worldwide.[24–34] In the US, the estimated number of hospitalizations associated with CDI doubled from 82,000 (or 31 per 100,000 of the general population) in 1996 to 178,000 (or 61 per 100,000 of the general population) in 2003.[14] While this upward trend continued in the early 2000s, there was a 4% annual decline in the adjusted estimate of national burden of hospitalizations owing to CDI from 2011 to 2017, likely secondary to the decrease in healthcare-associated CDI.[35]

Traditionally thought to be associated only with healthcare exposure, more recently there has been a rapid rise in the number of CDI cases in the community. The Centers for Disease Control and Prevention's Emerging Infections Program (EIP) has been conducting population-based surveillance of CDI in 10 US states (35 counties) since 2011 (California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon, and Tennessee).[36] A study using this EIP data estimated that *C. difficile* caused approximately 453,000 infections in the US in 2011.[37] More recent studies have suggested that the initial rise between 2000 and 2010 may have been blunted through various strategies including infection control and antibiotic stewardship. Another study[35] based on EIP data revealed that the number of cases of CDI in the 10 US sites was 15,461 in 2011 (10,177 healthcare-associated and 5284 community-associated cases) and remained stable at 15,512 in 2017 (7973 healthcare-associated and 7539 community-associated cases). The estimated national burden of CDI was extrapolated to be 462,100 cases in 2017. However, while the estimated burden of CDI among healthcare-associated infections declined, a similar pattern was not observed among community-acquired infections, which contributed to nearly 50% of the burden of CDI in 2017.[35] High rates of CDI are not only a problem in the US, but are a matter of global concern.[38]

CDI is associated with significant morbidity and mortality. In addition, the risk of recurrent infections adds to the overall burden of disease. Data from the Healthcare Cost and Utilization Project in the US between 1993 and 2008 revealed a steady increase in the number of hospitalizations associated with *C. difficile*, reaching 348,950 hospitalizations in 2008.[39] Similarly, the proportion of patients with complicated disease (defined as development of megacolon, perforation, need for colectomy, vasopressor support, or mortality) increased from 7.1% to 18.2%, while 30-day mortality rose from 4.7% to 13.8% during this period.[39] A recent large-scale study estimated the number of deaths within 30 days after diagnosis of CDI as 29,300 nationally with a 30-day crude case fatality rate of 9.3% among healthcare-associated infection.[37] In the intensive care unit (ICU) setting, mortality more than doubles (mortality rate directly owing to CDI 5%, mortality secondary to CDI complications 15–25%, overall mortality in ICU setting 34%).[40–42]

Recurrence rates for healthcare-associated CDI vary from 5% to 50%, with an average of 20%.[43–45] Using EIP data, there was at least one recurrence of CDI in approximately 21% of cases of healthcare-associated infections and 14% of cases of community-associated infection, leading to an estimated burden of 83,000 first recurrent infections.[37]

Cost and economic burden of CDI

CDI has a profound economic impact on both the healthcare system and patients. Contributing to the high economic burden are costs associated with hospitalization, treatment of secondary complications including surgical costs, prolonged length of stay, and ICU care. Compounding this burden is the impact of recurrent infections. Indirect patient and societal costs include impact on productivity loss because of either absenteeism (missed days of work) or presenteeism. In addition to costs incurred either directly or indirectly by the patient, episodes of CDI may also exert a negative economic cost through burden on the caregiver.

Table 1. Mean attributable costs of *Clostridiodes difficile* infection.

Study no.	Author	Country	Year of publication	Mean attributable CDI cost	Mean attributable CDI cost in US$ (2021)
1	Nanwa *et al.*[53]	US	2015	US$8911–30,049	US$8911–30,049
2	Zhang *et al.*[52]	US	2016	US$21,448	US$21,448
3	Nanwa *et al.*[55]	Canada	2016	Can$32,151 (for elective admissions) Can$21,909 (for non-elective admissions)	US$25,250 (for elective admissions) US$17,206 (for non-elective admissions)
4	Le Monnier *et al.*[56]	France	2015	€9575	US$11,544
5	Weigand *et al.*[57]	Germany	2012	€7147	US$8617
6	Grube *et al.*[58]	Germany	2015	€7654	US$9228
7	Magalini *et al.*[59]	Italy	2012	€13,958	US$16,829
8	Asensio *et al.*[60]	Italy	2015	€14,023	US$16,907
9	Asensio *et al.*[60]	Spain	2015	€4396	US$5300
10	Al-Eiden *et al.*[61]	Ireland	2000	£2860	US$3933
11	Wilcox *et al.*[49]	UK	1996	£4000	US$5500
12	Yasunaga *et al.*[62]	Japan	2012	US$6576–6724	US$6576–6724
13	Choi *et al.*[63]	Korea	2015	US$6554	US$6554
14	Jackson *et al.*[64]	Australia	2011	AUD$19,743	US$15,230

CDI, Clostridiodes difficile infection.

Several studies have examined the total and attributable cost of a CDI (Table 1). The burden of CDI is estimated to add 3–20 extra hospital days per patient with an additional cost of over US$1bn per year in the US.[16,46–49] In 2002, the annual cost of CDI in the US was estimated to be US$1.3bn,[47] which increased to US$3.4bn in 2009,[50] and to US$5.4bn[51] and US$6.3bn[52] in 2014 and 2016 respectively. A meta-analysis of 45 studies from 1998 to 2014 in the US reported the attributable mean CDI costs to range from US$8911 to US$30,049 for hospitalized patients,[53] which was similar to the findings of a second meta-analysis, reporting it to be US$21,448.[52] In a systematic review of studies performed between 1986 and 2013, CDI was among the top five most expensive healthcare-associated infections (HAIs) in the US, accounting for 15.4% of all HAIs.[54]

In 2012, the total societal cost owing to CDI in Canada was estimated at Can$281m; 92% was in-hospital costs, 4% was direct medical costs in the community, and 4% was owing to lost productivity. Management of CDI relapses alone accounted for Can$65.1m (23%).[65] One study found that an average hospital in Canada is likely to experience 10 readmissions per year for CDI manifesting itself after the patient has been discharged with the minimum cost of readmissions estimated to be Can$128,200.[66] Another population-based propensity-score matched study identified the attributable 1-year cost of CDI in Canada as Can$32,151 for elective admissions and Can$21,909 for non-elective admissions.[55]

In Europe, the direct cost associated with management of CDI was estimated to be €3bn in 2006;[3] however, the costs varied widely among

different countries. The mean CDI attributable cost was estimated to be €9575 per case in France,[56] €7147–7654 in Germany,[57,58] €13,958–14,023 in Italy,[59,60] €4396 in Spain,[60] £2860 in Ireland,[61] and £4000 in UK.[49]

Studies from Asia and rest of the world are sparse. The Korean Health Insurance Review and Assessment Service, for 2008–2011, estimated the overall economic burden of CDI in Korea to increase from US$2.4m in 2008 to US$7.6m, US$10.5m, and US$15.8m in 2009, 2010, and 2011, respectively.[63] In Japan, the CDI attributable cost was calculated to be between US$6576 and US$6724.[62] A study from Australia looking at additional costs due to hospital acquired conditions reported *C. difficile* enterocolitis to contribute an additional AUD$19,743 towards the total cost.[64]

A major limitation of most of these studies was that they mainly looked at hospitalization and drug costs and did not include indirect expenses, thereby underestimating the true attributable costs. Additional costs that need to be studied include cost of treatment of serious complications owing to CDI requiring surgery and postoperative care, post-discharge follow-up and outpatient care, need for environmental decontamination, isolation, and rigorous hygiene in wards, as well as societal costs. McGlone *et al.*[67] modeled different scenarios and found that the median cost of a case increased by 1.4–1.5 times when societal costs (e.g. productivity losses) were considered in addition to direct hospital costs, thus highlighting the overall economic burden of CDI. A second important limitation of the above studies is that most analyses of economic impact of CDI are based in Western countries. There is increasing recognition of *C. difficile* as an important pathogen in the low- and middle-income countries of South America, Africa, and Asia.[68] In a systematic review, Borren *et al.*[68] identified a similar frequency of occurrence of CDI in Asia as identified in studies from Europe and North America. Thus, there is an important unmet need in the literature to define the economic impact of CDI in these emerging economies. Finally, existing studies have also failed to adequately separate out the nuances in challenging clinical scenarios. This includes the potential differential cost between a true CDI episode compared with diarrhea from alternative causes in patients who were positive by polymerase chain reaction. In addition, sometimes refractory disease may be challenging to differentiate from early recurrence.

Management of *C. difficile*

Treatment should be started only in patients with CDI symptoms; presence of the *C. difficile* toxin without symptoms of the infection is not an indication for treatment. Treatment begins with discontinuation of the inciting antibiotic if possible. Traditionally, metronidazole and vancomycin were considered the cornerstones of treatment; however, more recently, guidelines from different societies are shifting away from metronidazole because of its lower efficacy and poor tolerance.

The Infectious Disease Society of America (IDSA)[7] recommends either vancomycin (125 mg orally four times per day) or fidaxomicin (200 mg twice daily) for 10 days over metronidazole for an initial episode of CDI. In settings where access to vancomycin or fidaxomicin is limited, using metronidazole (500 mg orally three times per day for 10 days) is suggested for an initial episode of non-severe CDI only. For fulminant CDI (characterized by hypotension or shock, ileus, or megacolon), vancomycin (500 mg orally four times per day, or per rectum 500 mg in 100 ml normal saline every 6 h in case of ileus) is the regimen of choice. Intravenously administered metronidazole 500 mg every 8 h should be administered together with oral or rectal vancomycin, particularly if ileus is present. Antibiotic treatment options for patients with recurrence of CDI include oral vancomycin therapy using a tapered and pulsed regimen, a standard course of oral vancomycin followed by rifaximin, or fidaxomicin. FMT is recommended for patients with multiple recurrences of CDI who have failed appropriate antibiotic treatments.

The American College of Gastroenterology (ACG)[69] still recommends the use of metronidazole (500 mg orally three times per day for 10 days) for mild CDI, with switchover to vancomycin in the case of non-improvement of symptoms, whereas for severe disease oral vancomycin (±intravenous metronidazole) is preferred. Fidaxomicin, although equivalent to vancomycin, is more expensive. For recurrences of CDI, the ACG suggests the use of pulsed regimen of vancomycin and reports FMT to be the most effective treatment.

Per European Society of Clinical Microbiology and Infectious Disease guidelines,[70] the main

antibiotics that are recommended are metronidazole (500 mg orally three times per day for 10 days for mild/moderate CDI), vancomycin (125 mg or 500 mg orally four times per day for 10 days), and fidaxomicin (200 mg twice daily for 10 days). Fecal transplantation is strongly recommended for multiple recurrent CDI. In the case of perforation of the colon and/or systemic inflammation and deteriorating clinical condition despite antibiotic therapy, total abdominal colectomy or diverting loop ileostomy combined with colonic lavage is recommended.

Other emerging therapies include monoclonal antibodies against the *C. difficile* toxins. One such antibody, bezlotoxumab (a monoclonal antibody that binds to *C. difficile* toxin B), was approved by the FDA in 2016 for prevention of recurrent CDI in patients with high risk of CDI.[71] In two phase III clinical trials involving 2655 adults receiving standard of care antibiotics for primary or recurrent CDI, there was a significantly lower risk of recurrent CDI with bezlotoxumab compared with placebo (MODIFY 1: adjusted difference –10.1%, MODIFY 2: adjusted difference –9.9%).[72]

While considering only the direct treatment related costs, metronidazole is the least expensive option. A study from 1983 reported the cost of a 10-day course of metronidazole as only US$26.15, whereas the cost of vancomycin treatment ranged from US$855.74 to US$1148.41.[73] Another study from 2009 revealed metronidazole to be the much cheaper choice, with a 10-day course costing only US$20 as compared with US$300–600 for a similar course of vancomycin (US$45 for an orally administered generic intravenous formulation).[74] More recently, Rajasingham *et al.*[75] calculated the costs of the currently available therapies for CDI. The cost of oral metronidazole (10-day course) ranged from US$4.38 to US$13.14, intravenous metronidazole (14-day course) from US$19.56 to $58.68, vancomycin (10-day course) from US$7.04 to US$21.12, rifaximin (20-day course) from US$44.16 to US$132.48, and fidaxomicin (10-day course), being the most expensive option, ranged from US$883.60 to US$2650.80. It is difficult to predict the exact cost of FMT due to the multiple variables involved, including source of stool and route of administration. In general, one course of FMT is estimated to cost between US$500 and US$2000.[76]

Cost-effectiveness of therapies for *C. difficile*

Several studies have examined the cost-effectiveness of various treatments in the management of either the initial *C. difficile* infection or subsequent recurrences (Table 2). While some studies have examined individual treatments, other cost-effectiveness studies evaluated treated strategies and the appropriate positioning of interventions such as FMT. The cost-effectiveness of any strategy is informed not just by the direct costs of the specific treatment in question, but also its relative effectiveness in reducing subsequent disease related morbidity and mortality.

Cost-effectiveness of treatment of the initial episode of CDI

Several studies have compared various strategies for treatment of the initial episode of CDI. A recent study[75] based on possible treatment algorithms from the 2018 IDSA/Society for Healthcare Epidemiology of America guidelines, using the Markov model, found the most cost-effective treatment strategy to be fidaxomicin for initial treatment for non-severe CDI and vancomycin for severe CDI, both followed by fidaxomicin for first recurrence and FMT for any subsequent recurrence. This strategy cost an additional US$478 for 0.009 quality-adjusted life-years (QALYs) gained per CDI patient, resulting in an incremental cost-effectiveness ratio (ICER) of US$31,751 per QALY, which was below the willingness-to-pay threshold of $100,000/QALY. Metronidazole use for non-severe CDI, while less expensive, was also less beneficial and not optimal at the commonly accepted willingness-to-pay thresholds in the US. When comparing fidaxomicin with vancomycin for initial episode of CDI, studies across the US, UK, and Europe have unanimously found fidaxomicin to be the more cost-effective option owing to its association with lower recurrence rates.[80–84] Watt *et al.*[83] compared vancomycin with fidaxomicin for the initial treatment of CDI. Overall, while the acquisition costs were higher for fidaxomicin, the lower rate of hospitalization, particularly for recurrent disease, was associated with cost savings, making fidaxomicin treatment the more cost-effective strategy for an initial episode of CDI. This is in contrast to data from a study conducted by Wagner *et al.*[79] in Canada which favored vancomycin over fidaxomicin, probably owing to the influence of a greater subpopulation of patients

Table 2. Studies of cost-effectiveness of therapies for *Clostridiodes difficile* infection.

Study no.	Author	Country	Year of publication	CDI episode	Treatment regimens compared	Most cost-effective treatment
Initial *C. difficile* infection						
1	Stranges *et al.*[77]	US	2013	Initial	Vancomycin *versus* fidaxomicin	Fidaxomicin for mild-moderate CDI Vancomycin for severe CDI
2	Varier *et al.*[78]	US	2014	Initial	Vancomycin *versus* metronidazole *versus* FMT	FMT
3	Wagner *et al.*[79]	Canada	2014	Initial	Vancomycin *versus* fidaxomicin	Vancomycin
4	Nathwani *et al.*[80]	UK	2014	Initial	Vancomycin *versus* fidaxomicin	Fidaxomicin
5	Marković *et al.*[81]	Serbia	2014	Initial	Vancomycin *versus* fidaxomicin	Fidaxomicin
6	Rubio-Terres *et al.*[82]	Spain	2015	Initial	Vancomycin *versus* extended-pulsed fidaxomicin	Extended-pulsed fidaxomicin
7	Watt *et al.*[83]	Germany	2016	Initial	Vancomycin *versus* fidaxomicin	Fidaxomicin
8	Watt *et al.*[84]	France	2017	Initial	Vancomycin *versus* fidaxomicin	Fidaxomicin
9	Rajasingham *et al.*[75]	US	2020	Initial	Vancomycin *versus* fidaxomicin *versus* metronidazole	Fidaxomicin for non-severe CDI Vancomycin for severe CDI
Recurrent *C. difficile* infection						
1	Konijeti *et al.*[85]	US	2014	Recurrent	Vancomycin *versus* fidaxomicin *versus* metronidazole *versus* FMT	FMT by colonoscopy
2	Zowall *et al.*[86]	Canada	2014	Recurrent	Standard antibiotic regimens *versus* FMT	FMT
3	Varier *et al.*[87]	US	2015	Recurrent	Tapered vancomycin *versus* FMT	FMT
4	Lapointe-Shaw *et al.*[88]	Canada	2016	Recurrent	Vancomycin *versus* fidaxomicin *versus* metronidazole *versus* FMT by enema *versus* FMT by colonoscopy *versus* FMT by NGT	FMT by colonoscopy
5	Merlo *et al.*[89]	Australia	2016	Recurrent	Vancomycin *versus* FMT	FMT

(Continued)

Table 2. (Continued)

Study no.	Author	Country	Year of publication	CDI episode	Treatment regimens compared	Most cost-effective treatment
6	Waye *et al.*[90]	Canada	2016	Recurrent	Early FMT *versus* Delayed FMT	Early FMT
7	Baro *et al.*[91]	France	2017	Recurrent	Pulse-tapered vancomycin *versus* fidaxomicin *versus* FMT	FMT by enema
8	Prabhu *et al.*[92]	US, UK	2017	Recurrent	Bezlotuxumab *versus* placebo	Bezlotuxumab
9	Jiang *et al.*[93]	China	2018	Recurrent	Vancomycin *versus* ribotype-guided FMT	Ribotype-guided FMT
10	Abdali *et al.*[94]	UK	2020	Recurrent	Vancomycin *versus* fidaxomicin *versus* FMT	FMT by NGT
11	Rajasingham *et al.*[75]	US	2020	Recurrent	Vancomycin *versus* fidaxomicin *versus* metronidazole *versus* FMT	Fidaxomicin for first recurrence FMT for subsequent recurrences
12	You *et al.*[95]	China	2020	Recurrent CDI in IBD patients	Vancomycin *versus* fidaxomicin *versus* vancomycin plus bezlotuxumuab *versus* FMT	FMT

CDI, *Clostridiodes difficile* infection; FMT, fecal microbiota transplantation; IBD, inflammatory bowel disease; NGT, nasogastric tube.

infected with NAP1/B1/027 strains in Canada, where fidaxomicin did not effectively reduce recurrence rates in this subgroup analysis, leading to lower cost-effectiveness. Similarly, Stranges *et al.*[77] found that fidaxomicin dominated vancomycin in the case of mild–moderate CDI with an ICER of US$67,576 per QALY gained, which resulted in fidaxomicin having an 80.2% chance of being cost-effective at a willingness-to-pay threshold of US$100,000/QALY. However, it was less cost-effective than vancomycin in severe CDI (ICER US$352,994) and against the hypervirulent B1/027 strain infections.[77] Varier *et al.*[78] included FMT by colonoscopy in their analysis of initial CDI and showed that FMT ($1669, 0.242 QALYs) was less costly and more effective than vancomycin ($1890, 0.241 QALYs). It was also more costly but more effective than metronidazole ($1167, 0.238 QALYs), yielding an incremental cost-effectiveness ratio (ICER) of $124 964/QALY, which is higher than the usually accepted willingness-to-pay threshold of $50,000–$100,000.[78]

Cost-effectiveness of recurrent CDI

In contrast to the treatment of the initial episode, where there are few studies, several studies have examined the cost-effectiveness of treatment of recurrent CDI. Konijeti *et al.*,[85] using a decision-analytic model, compared the four treatment strategies (metronidazole, vancomycin, fidaxomicin, and FMT) and concluded that FMT by colonoscopy is the most cost-effective for management of recurrent CDI at a willingness-to-pay threshold of US$50,000 with an ICER of US$17,016 relative to vancomycin. Treatment of recurrent CDI by first-line fidaxomicin or metronidazole was both more expensive and less effective, thereby making vancomycin most cost-effective in clinical situations where FMT was not available. Alternative modes of FMT

delivery (duodenal infusion or enema) did not meet cost-effectiveness thresholds owing to lower efficacy. Lapointe-Shaw *et al.*,[88] in their study in Canada, performed a more detailed evaluation, also including FMT by enema, FMT by NGT, and FMT by colonoscopy alongside antibiotic treatments in their analyses. They similarly identified FMT *via* colonoscopy to dominate all other base-case strategies. They identified an 87% probability that FMT *via* colonoscopy was the most beneficial strategy. In the absence of availability of colonoscopic FMT, FMT *via* enema was also cost-effective, with an ICER of $1708/QALY gained compared with metronidazole. In the absence of FMT, fidaxomicin was the most cost-effective strategy, with an ICER of $24,968 compared with metronidazole. A recent study from the UK in 2020 also revealed FMT to be the most cost-effective option compared with vancomycin and fidaxomicin for recurrent CDI. They showed FMT by nasogastric tube (NGT) to have a 78% probability to be cost-effective at a willingness-to-pay threshold of £20,000/QALY. While FMT by colonoscopy was slightly more effective compared with FMT by NGT (0.012 additional QALYs gained), it was more expensive, with an ICER of £242,514, thus making FMT by NGT the preferred route in terms of willingness-to-pay threshold.[94] However, another study showed that the difference between FMT routes of administration was not significant.[89] Irrespective of the mode of delivery, FMT stands out as the most cost-effective treatment compared with antimicrobials for patients with recurrent CDI per data from US, Canada, France, China, and Australia.[86,87,89,91,93] There is also evidence to support better results and lower costs associated with timely FMT (defined as FMT after two CDI recurrences) as compared with delayed FMT (FMT after ⩾3 CDI recurrences), as shown by a study from Canada where the mean difference in hospital length of stay and emergency room visits related to CDI was 13.8 days shorter and 1.3 visits fewer with timely FMT, associated with a mean cost saving of Can$29,842 per patient.[90] An economic modeling analysis from Ontario province in Canada suggested that implementation of FMT for treatment of recurrent CDI would result in a saving of Can$1.5m after the first year and up to Can$2.9m after 3 years.[96]

A few studies have also examined cost-effectiveness of less conventional therapeutic strategies. In a cost-effectiveness study from Spain,[97] extended-pulsed fidaxomicin regimen was associated with reduced costs when compared with vancomycin, resulting in a saving of €647 per patient treated, and achieving a more cost-effective treatment in the majority of simulations in individuals older than age 60 years. Prabhu *et al.*[92] used a Markov model to examine the cost-effectiveness of bezlotoxumab compared with placebo for recurrent CDI. Compared with placebo, bezlotoxumab was associated with a 0.12 QALY gained, and had an ICER of US$19,824/QALY gained, which was within the acceptable threshold of <US$50,000/QALY. Bezlotoxumab was also cost-effective in those >65 years of age (ICER US$15,298/QALY) and those with severe CDI (ICER US$21,430/QALY). You *et al.*[95] compared various strategies for the treatment of recurrent CDI in patients with IBD. Compared with vancomycin, fidaxomicin, or vancomycin plus bezlotoxumab, FMT was associated with reduced QALY loss and was less expensive. Compared with these above three strategies, FMT was cost saving by US$3765, US$3854, and US$6501 respectively. FMT saved more QALYs in nearly every model against each of these three strategies in 10,000 Monte Carlo simulations. Distinct from other studies on this topic, Shaffer *et al.*[98] examined the cost-effectiveness of an FMT unit and estimated the target catchment size needed to render this unit cost-effective. Using a Markov model, they estimated that the minimum number of patients with recurrent CDI required to treat to make an FMT unit cost-effective was 15 cases for colonoscopic delivery, 17 cases *via* capsule delivery, and 44 cases for FMT *via* enema compared with vancomycin with a modestly higher threshold (15–47) when compared with fidaxomicin. They estimated a minimum catchment area of 56,849 for a medical center for establishment of a cost-effective FMT unit.

Conclusion

CDI is a condition associated with high morbidity and mortality as well as a significant economic burden to the healthcare system and society alike, mainly attributable to its high rate of recurrence. There is still a gap in estimating the true attributable costs of CDI. There is need for more studies on the indirect costs associated with *C. difficile*, as well as on different settings such as long-term care facilities. The standard of care is gradually shifting from metronidazole and vancomycin towards novel treatment modalities like fidaxomicin and FMT, which have opened new avenues in CDI management. These therapies, though expensive, may be more cost-effective

owing to superior efficacy in preventing recurrence. There is an important need for continued cost-effectiveness research on this topic to inform clinical practice.

Author contributions

AG – review of literature and drafting of the manuscript; ANA – critical revision and approval of the final manuscript. Both authors approved the final manuscript.

Conflict of interest statement

ANA has served on scientific advisory boards for Abbvie, Takeda, Gilead, and Merck and has received research support from Pfizer. AG has no conflicts to declare.

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