ORIGINAL ARTICLE

A Comprehensive Study of Costs Associated With Recurrent *Clostridium difficile* Infection

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BACKGROUND. *Clostridium difficile* infection (CDI) is the most common healthcare-associated infection and is associated with considerable morbidity. Recurrent CDI is a key contributing factor to this morbidity. Despite an estimated 83,000 recurrences annually in the United States, there are few accurate estimates of costs associated with recurrent CDI.

OBJECTIVE. We performed this study (1) to identify the health consequences of recurrent CDI including need for repeat hospitalization, intensive care unit (ICU) stay, and surgery; (2) to determine costs associated with recurrent CDI and identify determinants of such costs; and (3) to compare the outcomes and costs of recurrent CDI to those who develop reinfection.

METHODS. We identified all patients with confirmed recurrent CDI between January to December 2013 at a single referral center. Healthcare burden associated with recurrence including diagnostic testing, pharmacologic treatment, and inpatient and outpatient healthcare visits were identified in the 12 months following the first recurrence. Total healthcare costs were calculated, and the predictors of high healthcare utilization were identified.

RESULTS. Our study population included 98 patients with recurrent CDI. The median interval between the initial infection and recurrence was 37 days. The mean age of the cohort was 67 years, two-thirds were women (62%), and the mean Charlson index was 8.6. During the year following the first recurrence of CDI, each patient underwent a mean of 4.4 stool *C. difficile* toxin tests and received a mean of 2.5 prescriptions for oral vancomycin (range, 0–6). Most patients (84%) with recurrence had a CDI-related hospitalization, and 6% underwent colectomy. The mean total CDI-associated cost was $34,104 per patient, with hospitalization costs accounting for 68%, surgery 20%, and drug treatment 8% of this cost, respectively. Extrapolating to the United States overall, we estimate an annual cost of $2.8 billion related to recurrent CDI.

CONCLUSION. Recurrent CDI is associated with considerable morbidity and cost.

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Clostridium difficile infection (CDI) is the most common healthcare-associated infection and is associated with considerable morbidity.[1–9] In 2011, there were an estimated 453,000 cases of CDI in the United States contributing to 29,000 deaths (6.4% of cases).[7] Consequently, CDI-related morbidity exerts a significant toll on patients and the healthcare system, with the costs attributable to CDI, with estimates ranging from $1.3 to 4.8 billion annually.[2,6,10,11] The consequences of CDI are compounded by the fact that an index episode, often occurring in a vulnerable population of older patients with significant comorbidity, is followed by a cascade of recurrences with progressive impairment of health status and poor outcomes.[3,12–15] Between 20% and 30% of patients with an index episode of CDI will develop at least 1 recurrence, and as many as 60% of those go on to develop subsequent recurrences.[3,12–15] In the past decade, an expansion in the therapeutic armamentarium for management of CDI has occurred (1) with the availability of antibiotics that cause less disruption to the microbiome such as fidaxomicin,[16] (2) with monoclonal antibodies targeting humoral anti-toxin immunity,[17] and (3) with the restoration of the microbial diversity through fecal microbiome transplantation (FMT).[18,19] While similar to vancomycin in effectiveness for treatment of the index episode, the newer treatment strategies demonstrate superior efficacy in achieving a sustained cure with fewer recurrences.[8,13,15,18,20,21] However, the newer strategies are also more expensive, restricting their widespread use.[22,23]

Decision models have attempted to inform cost-effectiveness of different strategies to treat recurrent CDI.[22,23] The key determinant of cost-effectiveness of each treatment and its position within the therapeutic algorithm is not only the ability to prevent recurrent CDI but also, importantly, the downstream cost associated with each recurrent episode. However, there are few accurate estimates of the costs associated with recurrent CDI.[24–28] The few prior studies have focused on hospitalized patients or inpatient costs alone.[27,28] Up to a quarter of patients with CDI are diagnosed in the ambulatory setting,[29]

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so these cost are likely underestimates of the actual burden of recurrent CDI.

Thus, we performed this study (1) to identify the health consequences of recurrent CDI including need for repeat hospitalization, intensive care unit (ICU) stay, and surgery; (2) to determine costs associated with recurrent CDI and identify determinants of such costs; and (3) to compare the outcomes and costs of recurrent CDI to those who develop reinfection.

METHODS

Study Population

Our study population consisted of patients with recurrent CDI receiving care within the Partners Healthcare network in Boston. Patients with recurrent CDI were identified using a 2-step process described previously.[30] From among all patients with at least 2 *International Classification of Diseases, 9th edition* (ICD-9) codes for CDI (008.45) from January to December 2013 (n = 591), we applied a previously validated algorithm (≥3 ICD-9 codes for CDI and ≥2 prescriptions for vancomycin) with a negative predictive value of 90% in excluding recurrent CDI. Because the positive predictive value of this algorithm was poor, manual chart review was performed for each patient who passed this filter, and a confirmed diagnosis of recurrent CDI was established based on physician adjudication. This procedure yielded a final cohort of 185 patients with at least 2 distinct episodes of CDI during the study period. Among these, 98 patients were classified as having recurrent disease when the second infection occurred within 56 days after the end of treatment of the index infection.[8] The remaining 87 were deemed to have a re-infection (ie, a second episode occurring 56–365 days after the index episode).

Outcomes and Covariates

The primary outcome for our study was healthcare utilization associated with recurrent CDI measured by (1) the number of office visits and emergency room visits for diarrhea; (2) the number of recurrent CDI-related hospitalizations; (3) CDI-related diagnostic testing and pharmacologic costs; and (4) the cost of ICU stay and surgical treatment of CDI. The costs associated with recurrent CDI were noted over a 1-year period from the time of recurrent CDI.

Information on relevant covariates was obtained from the medical record including age at diagnosis of CDI, gender, race, comorbidity burden quantified using the Charlson comorbidity index,[31] and treatment used for the index CDI episode.

Estimation of Healthcare Costs

Because the actual direct healthcare costs for each patient was not available, we estimated costs based on previously published estimated costs (Supplemental Table 1).[15,22] Costs for stool testing for *C. difficile* by enzyme-linked immunosorbent assay (ELISA) and pharmacologic costs for each course of treatment were inferred from a published cost-effectiveness model.[22] The cost of FMT was also inferred from the decision model and included costs of donor testing as well as colonoscopic administration.[22] Costs for emergency room visits were obtained from the Medicare fee schedule (www.cms.gov; common procedure terminology [CPT] code 99284). The cost of inpatient stay was obtained from the Healthcare Cost Utilization Project (HCUP) Nationwide Inpatient Sample, the largest all-payer hospitalization database. The total cost of a hospitalization with a primary or secondary diagnosis of CDI ($9,845) was averaged across the mean length of stay for such hospitalizations (5.9 days), yielding a per day estimate of $1,669. All costs were updated to 2016 US dollars using the consumer price index adjustment.

Statistical Analysis

Continuous variables were summarized using means and standard deviations and were compared using the *t* test. Categorical variables were summarized using proportions and were compared using the χ^2 test with the Fisher's exact modification when appropriate. First, total costs associated with recurrent CDI were calculated and averaged to provide a per-patient estimate. We calculated the proportion of such costs that were attributable to diagnostic testing, treatment, outpatient care, hospitalization, and surgery. We performed a forward stepwise multivariate linear regression analysis to identify independent determinants of total per-patient healthcare costs, and we selected for inclusion those variables significant at $P < .05$ in univariate comparisons. Using the methods noted above, comparisons were performed between those with recurrent disease and reinfection. All statistical analyses were performed using Stata 14.0 (StataCorp, College Station, TX). The study was approved by the Institutional Review Board of Partners Healthcare.

RESULTS

Study Cohort

Our study population included 98 patients who developed recurrent CDI. Nearly two-thirds of the cohort were women (62%) and most were white (83%). The most frequent comorbidities were a history of malignancy (85%), diabetes (45%), and chronic kidney disease (53%) with a mean Charlson index of 8.6 (Table 1). The mean age of patients was 67 years (range, 21–100 years). The mean interval between date of diagnosis of initial infection and recurrent infection was 37 days (interquartile range [IQR], 23–57 days). The most common treatments for the index episode were vancomycin alone (32%) or metronidazole alone (32%) with one-quarter of patients (26%) receiving a combination of both antibiotics.

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TABLE 1. Characteristics of Patients With Recurrent *Clostridium difficile* Infection

Characteristic	No. (%) (n = 98)
Age, y mean (SD)	66.7 (16.5)
Female	61 (62)
Whites	81 (83)
Charlson comorbidity index, mean (SD)	8.6 (4.2)
Treatment of initial episode	
Metronidazole	31 (32)
Vancomycin	31 (32)
Metronidazole + Vancomycin	25 (26)
Other (rifaximin, fecal transplantation)	11 (11)
Interval between index episode and recurrence, d, mean (SD)	37 (18)

Healthcare Burden and Costs Due to Recurrent CDI

Information on healthcare utilization (at least 1 healthcare contact or prescription) was available for 95 patients with recurrent CDI. Table 2 presents the healthcare burden and costs in this population. A total of 95 patients accounted for 414 stool tests over the 1-year period, with a mean of 4.4 stool tests per patient (range, 1–25). Among these, a mean of 2.5 stool tests per patient were positive for *C difficile* toxin. A total of 233 distinct prescriptions for vancomycin were dispensed at a mean of 2.45 prescriptions per patient (range, 0–6). In addition, there were a mean of 1.1 prescriptions for metronidazole (range, 0–5) and 0.14 prescriptions for fidaxomicin. In total, 11 patients underwent a single FMT, and 3 patients each received 2 fecal transplants during the 1-year period following the recurrent CDI episode.

Reflecting the level of comorbidity in this population, there was a mean of 15.4 office visits per patient during the year following the episode of recurrent CDI (IQR, 6–18 visits), among which 2.2 were diarrhea related. An estimated 94% of patients required another hospitalization during the study period with 84% having at least 1 CDI-related hospitalization (147 CDI-related hospitalizations; mean, 1.6 per patient). The mean length of stay of CDI-related hospitalizations was 16 days (range, 1–75 days). Of these, 18 days were in the ICU (mean, 0.18 days per patient). In total, 6 patients (6%) underwent CDI-related surgery. Approximately 40% of patients were discharged to short-term rehabilitation facilities, and 13 patients (13%) died.

The healthcare cost estimates incurred per patient and in the entire population are presented in Table 2 and Figure 1. The mean total CDI-associated downstream healthcare cost per patient was $34,104 (range, $831–$146,353). Of these costs, those associated with hospitalization accounted for the major proportion ($30,122 per patient; 68% of total costs). Surgery-related costs accounted for the next-largest fraction (20%), with treatment costs (medication and FMT) accounting for 8% of total costs incurred. If this cost per patient were applied to the estimated 83,000 recurrences in the United States,[7] it would account for approximately $2.8 billion annually.

TABLE 2. Healthcare Burden Associated With Recurrent *Clostridium difficile*

Outcome Measure	Mean per Patient (Range)[a]
Diagnostic testing	
Stool test for *C. difficile*	4.4 (1–25)
Positive stool test	2.5 (1–7)
CT scans	0.5 (0–3)
Treatment	
Pharmacologic treatment	
Metronidazole	1.1 (0–5)
Oral vancomycin	2.5 (0–6)
Fidaxomicn	0.1 (0–3)
Rifaximin	0.03 (0–1)
Fecal microbial transplantation	0.2 (1–2)
Outpatient costs	
All office visits[b]	15.4 (0–79)
Diarrhea-related office visits	2.2 (0–11)
Diarrhea-related phone calls[b]	4.8 (0–36)
CDI-related emergency room visits	0.1 (0–2)
Inpatient costs	
All-cause hospitalization[b]	3.3 (0–13)
CDI-related hospitalization	1.6 (0–5)
Length of stay	15.8 (0–75)
ICU stay	0.2 (0–3)
Surgery, No. (%)	6 (6)
Died, No. (%)	13 (13)

NOTE. CT, computed tomography; CDI, *Clostridium difficile* infection; ICU, intensive care unit.
[a]Data could be obtained for 95 / 98 patients with recurrent CDI.
[b]Not included in calculation of healthcare costs.

Predictors of Healthcare Costs

Table 3 presents a multivariate regression model of predictors of recurrent CDI–associated healthcare costs. The strongest determinants of costs incurred in the year following recurrent CDI were the need for CDI-related surgery (+$48,366) and or hospitalization (+$26,290). A longer interval between initial episode and recurrence was associated with lower costs (−$513). Greater Charlson comorbidity but not older age was also associated with higher recurrent CDI–associated healthcare costs. The type of treatment used for the index or recurrent CDI episode did not predict healthcare costs or patient outcomes.

Comparison of Recurrent CDI and Reinfection

Supplemental Table 2 presents a comparison of patients with recurrent CDI to those who developed a reinfection diagnosed 56 days after the initial episode. Patients with recurrent CDI were older (67 years vs 60 years) but similar in distribution of gender and comorbidity. There were no differences in the initial treatments used in both populations. A comparison of the healthcare utilization between the 2 groups revealed greater

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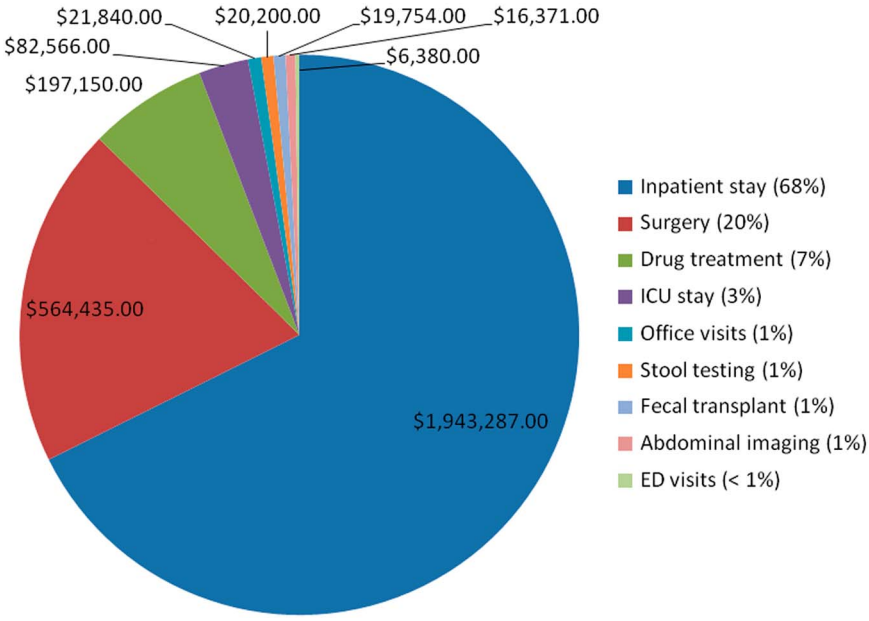


FIGURE 1. Relative contribution of different factors to recurrent *Clostridium difficile* infection (CDI)–associated costs. The total mean cost per patient was $34,103. All costs in United States dollars. All numbers represent percentages.

TABLE 3. Predictors of Recurrent *Clostridium difficile* Infection (CDI)–Associated Healthcare Costs

Predictor	Adjusted Regression Coefficient[a]	95% Confidence Interval
CDI-related surgery	$48,366	$26,375–$70,417
CDI-related hospitalization	$26,290	$11,911–$40,668
Charlson index (per 1-point increase)	$2,819	$1,455–$4,182
Interval between index and recurrent episode (per 1 day)	−$513	−$802 to −$224

NOTE. All costs in United States dollars.
[a]Additionally adjusted for age, gender, and race/ethnicity.

numbers of stool tests performed (mean 4.4 vs 3.3 tests per patient per year; $P = .01$), positive stool tests (2.5 vs 1.8; $P = .0001$), and prescriptions of oral vancomycin (2.5 vs 2.0 prescriptions per patient; $P = .04$) in those with recurrent CDI compared to reinfection. Patients with recurrent CDI also incurred more ER visits but were similar in the number of inpatient or outpatient office visits. There were no differences in CDI related length of stay or duration of ICU stay, but patients with recurrent CDI were more likely to require surgery for their CDI (6% vs 0%; $P = .03$). In terms of healthcare expenditure, recurrent CDI was associated with higher mean testing and treatment costs per patient but a similar overall cost per patient.

DISCUSSION

Clostridium difficile infection is the most common healthcare-associated infection and accounts for significant morbidity and mortality;[1–9] its tendency to recur contributes to this prevalence.[3,13,14,26,32] Recurrence rates in the literature vary from 5% to 50%, with an estimated likelihood of 20%–30% after the index episode, and 45%–65% with subsequent recurrences.[14,15,20,21,26,33–35] Because most existing treatments, except for metronidazole, are similar in their effectiveness in treating the index episode,[16] cost-effectiveness and positioning of different strategies to manage CDI are determined by their ability to prevent recurrence and the cost of recurrent disease.[11,22] In a comprehensive study of healthcare costs associated with recurrent CDI, we estimate a 1-year downstream cost of $34,104 per patient with recurrent CDI. Extrapolating to the entire United States population, recurrent CDI may be associated with an annual cost of $2.8 billion.

Few studies have attempted to quantify the costs incurred by recurrent CDI, though several have examined the economic impact of CDI overall.[2,10,11,24,28,36–40] Initial estimates of the cost associated with each CDI episode used state hospitalization

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discharge databases[39] or linear regression and propensity score matching[2,10,37,38] and estimated the attributable cost for each case to be between $3,006 and $15,397.[2] Extrapolating the burden of CDI to the United States overall in 2008 resulted in total acute-care facility costs from CDI ranging between an estimated $1 billion[2,38] and $4.8 billion.[40] However, some limitations of the prior work included lack of differentiation between index and recurrent CDI and inclusion only of costs incurred during the initial acute care stay. Indeed, increasing the window of downstream costs to also include hospitalizations within 180 days after the index episode doubled the attributable cost per case.[38] Few studies have specifically estimated treatment costs associated with recurrent CDI. A systematic review by Ghantoji et al[24] estimated the costs per case of recurrent CDI to be $18,067. However, subsequent studies have suggested that the actual cost may be higher. Shah et al[28] quantified the inpatient treatment costs associated with CDI among hospitalized patients in a cohort of 540 patients with primary CDI, among whom 95 patients (18%) experienced recurrent episodes. The CDI-attributable median length of stay was 8 days greater for those with recurrent disease, resulting in a median cost of $28,218, which is twice that of primary infection.

The median cost of recurrent CDI in our study was higher than previously noted and is likely due to a few methodological differences. First, most previous studies of index or recurrent CDI focused almost entirely on acute-care facility costs.[2,10,11,24,28,37,38,40] Prior studies have suggested that between 50% and 85% of recurrent CDI episodes result in rehospitalization.[36,41] Our estimates fall within this range and suggest that two-thirds of the downstream costs of recurrence are attributable to hospitalization costs. The mean length of stay in our study of 16 days was similar to that by Shah et al,[28] but it was higher than that reported previously by McFarland.[26] When colectomy costs are included, the proportion of inpatient costs rose to 80%. Notably, however, a significant fraction of the estimated costs in our study were incurred in the outpatient setting or were related to diagnostic testing and treatment. Thus, studies exclusively focusing on inpatient costs may underestimate the economic burden of recurrent CDI. Second, prior studies have examined costs incurred during the hospitalization for recurrent episode alone but not other downstream costs incurred by the patient such as persistent diarrhea requiring outpatient evaluation, stool and radiologic testing, or pharmacologic treatment even in the absence of a confirmed episode of recurrence. In our estimate, these costs also compound the cost of recurrent CDI where, with 1 episode of confirmed recurrence, there may be persistent concern for future recurrence for both the patient and treating providers. This concern may lead to inappropriate testing such as a need to demonstrate 'a cure' by a negative stool test, or empiric treatment of persistent diarrhea with 1 or more courses of oral metronidazole, vancomycin, or fidaxomicin. Thus, we analyzed costs for up to 1 year after the recurrent episode (although the recurrence occurred within 8 weeks of the index episode) because we believe this method provides a more comprehensive and realistic estimate of the downstream burden of recurrent disease.

The overall cost of an episode of reinfection was similar to that of recurrence, suggesting that all patients with a prior history of CDI may be considered as a group at risk for incurring high healthcare costs. The more frequent utilization of stool testing, pharmacologic treatment, and CDI related surgery, arguably more disease specific than total healthcare costs, suggesting that recurrent CDI may be associated with a greater adverse impact on patient outcomes than reinfection. This finding is consistent with those reported when results are compared to an index episode of CDI. Importantly, recurrent CDI offers a more defined window for intervention aiming at prevention and may be a more suitable target for controlling CDI-related costs.

There are several implications to our findings. Interest in the economic burden of CDI is driven by the prevalent nature of this infection and resultant prolongation of hospitalization stay and associated high healthcare costs.[2,11,24] Up to a one-third of patients with an index episode of CDI and nearly two-thirds of those with 1 or more recurrences will have an episode of recurrent disease;[3,8,14,26,42] therefore, the downstream costs incurred are of significant importance to the patient and the healthcare system. Positioning of the various existing and emerging treatments for prevention of recurrent CDI is complicated by the fact that differences in the upfront cost of a course of treatment may influence provider and institutional preferences such that more effective but also more expensive options are restricted for use later in the course of CDI for multiply recurrent disease. However, doing so may result in accrual of significant economic costs by the initial episode of recurrence. Initial decision models for management of CDI have been limited by lack of accurate data to inform burden of recurrent disease.[22,43] With emerging data, including ours, accurately quantifying the full downstream costs of recurrent CDI, and with the availability of newer therapeutic options, such decision models can be updated to accurately inform our practice regarding to the most effective and cost-effective method to treat this disease.

We readily acknowledge several limitations to our study. It was a single-center study based at a referral center. Consequently, the severity of our patient population (and consequently the associated costs) of our patient population may be higher than in a population-based setting. Second, we were not able to account for indirect costs, which include those associated with a rehabilitation facility stay or lost economic productivity. It will be important for future studies to examine the indirect cost of CDI as well. Third, we may have underestimated the costs incurred by patients who sought care outside of our healthcare system. Fourth, we did not specifically examine the costs associated with multiply recurrent episodes of CDI; rather, we quantified all costs incurred during the 12 months after the first recurrence. We believe that such cost estimates may be a more realistic estimate of the burden of recurrence because even without

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microbiologic confirmation of a second recurrence, patients may be placed on empiric treatment for CDI or incur costs related to persistent diarrhea. Because none of the patients in our study had other underlying diarrheal diseases including inflammatory bowel disease, we believe our estimates can be considered attributable to recurrent CDI.

In conclusion, we have demonstrated a significant healthcare burden associated with recurrent CDI, estimated at $34,104 over 1 year after the recurrence, which translates to $2.8 billion nationally. There is an important need for tools to predict those at risk for recurrent disease as well as therapies that reduce rates of recurrence, and thereby decrease associated morbidity. Accurate estimates of the comprehensive cost and quality of life impairment by *C. difficile* are essential to optimally position various strategies for management of this common healthcare-associated infection to improve patient outcomes.

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SUPPLEMENTARY MATERIAL

For supplementary material/s referred to in this article, please visit http://dx.doi.org/doi:10.1017/ice.2016.246.

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