Original Research Article

SAGE Open Medicine

SAGE Open Medicine
Volume 9: 1–8

DOI: 10.1177/2050312120986733
journals.sagepub.com/home/smo
SAGE

Clinical complications in patients with primary and recurrent *Clostridioides difficile* infection: A real-world data analysis

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Abstract

Objective: *Clostridioides difficile* infection and recurrent *C. difficile* infection result in substantial economic burden and healthcare resource use. Sepsis and bowel surgery are known to be serious complications of *C. difficile* infection. This study evaluated clinical complications in patients with *C. difficile* infection and recurrent *C. difficile* infection during a 12-month period following the primary *C. difficile* infection.

Methods: A retrospective analysis of commercial claims data from the IQVIA PharMetrics Plus™ database was conducted for patients aged 18–64 years with an index *C. difficile* infection episode requiring inpatient stay or an outpatient visit for *C. difficile* infection followed by a *C. difficile* infection treatment. Each *C. difficile* infection episode ended after a 14-day *C. difficile* infection-claim-free period was observed. Recurrent *C. difficile* infection was defined as a further *C. difficile* infection episode within an 8-week window following the claim-free period. Clinical complications were documented over 12 months of follow-up and stratified by the number of recurrent *C. difficile* infection episodes (0 rCDI, 1 rCDI, 2 rCDI, and 3+ rCDI).

Results: In total, 46,571 patients with index *C. difficile* infection episode were included. During the 6-month pre-index, the mean (standard deviation) baseline Charlson comorbidity index score, by increasing the recurrent *C. difficile* infection group, was 1.2 (1.9), 1.5 (2.2), 1.8 (2.3), and 2.3 (2.5). During the 12-month follow-up, sepsis occurred in 16.5%, 27.3%, 33.1%, and 43.3% of patients, and subtotal colectomy or diverting loop ileostomy was performed in 4.6%, 7.3%, 8.9%, and 10.5% of patients, respectively, by increasing the recurrent *C. difficile* infection group.

Conclusions: Reduction in recurrent *C. difficile* infection is an important step to reduce the burden of serious clinical complications, and new treatments are needed to reduce *C. difficile* infection recurrence.

Keywords

Clostridium difficile infection, *Clostridioides difficile* infection, recurrent *Clostridioides difficile* infection, sepsis, real-world analysis

Date received: 13 October 2020; accepted: 15 December 2020

Introduction

Clostridioides difficile infection (CDI) has a national burden of 462,100 cases in 2017 according to the latest estimate from the US Centers for Disease Control and Prevention (CDC).[1] The CDC also reported that the burden of recurrent CDI (rCDI) remained unchanged over the 7 years of observation, despite a decreasing trend in healthcare-associated CDI. The clinical burden of CDI has many facets, from prolonged hospital stay, increased risk of sepsis, and need for surgical intervention.[2] Previous research has shown that septic shock complicated CDI in 34.7% of patients being mechanically ventilated.[3] When managing severely ill patients with CDI, the need for colectomy may arise.[4] While bowel surgery can save the lives of patients with severe CDI, the procedure carries significant risk of mortality.[5] Taken together, the unmet needs of patients with CDI and rCDI remain high, but more precise information about the clinical burden is critically needed.

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Approximately 25% of patients with an initial CDI episode experience rCDI, and 40%–65% of patients with one recurrence will experience multiply-recurrent CDI (mrCDI; two or more recurrences).[6,7] While there is significant knowledge about the epidemiology and clinical manifestations of CDI, fewer clinical data exist from real-world analyses of CDI and rCDI complications of sepsis and bowel surgery, and the available data are not adequately generalizable to a broad US population.[7–10] Furthermore, there is limited knowledge of the clinical burden of the rapidly growing patient subgroup with mrCDI.[11,12]

The objective of this study was to quantify clinical complications of sepsis and bowel surgery in real-world patients who suffered CDI and rCDI. The study analyzed a large commercial healthcare claims database containing payment information for patients who received care in a variety of healthcare settings such as inpatient hospitals, outpatient hospitals, clinics, and pharmacies in the United States. Real-world analysis of cost and healthcare resource utilization in patients with CDI and rCDI was reported in a separate report.[13]

Methods

Study design

This longitudinal, retrospective study utilized real-world data from the PharMetrics Plus™ database (IQVIA; Durham, NC), which contains de-identified data from claims, enrollment, and demographic information for more than 140 million individuals with commercial insurance coverage throughout the United States, with data originating from over 90% of hospitals and over 90% of all US physicians.

Study population

Individuals included in the study were aged between 18 and 64 years and had at least one inpatient visit with a diagnosis of CDI (Supplementary Table 1) or one outpatient visit with a CDI diagnosis code followed by an outpatient CDI treatment. The requirement of an observable CDI treatment for an outpatient CDI visit ensured that follow-up visits would not be counted as a recurrence. Treatment was defined as an outpatient prescription for vancomycin, fidaxomicin, metronidazole, rifaximin, or bezlotoxumab, or fecal microbiota transplant (FMT).

Index CDI episodes occurred between 1 January 2010 and 30 June 2017, the latest data cutoff available at the time of the study (Figure 1). Only patients who were continuously enrolled and observable 6 months before and 12 months after the first date of the index CDI episode were included. The pre-index period was used to quantify pre-CDI healthcare exposure and to minimize the likelihood that the first CDI diagnosis was a recurrent episode, while the post-index requirement allowed sufficient time for observing recurrences as well as ensured accurate quantification of post-index complications.

For this type of analysis, the beginning and end of CDI episodes must be clearly defined to capture the primary CDI event and the recurrences. A CDI episode started from the date of the index (first) CDI claim observed in the study time frame. Each CDI episode included consecutive medical claims with a CDI diagnosis and prescription medication fills that are common treatment for CDI. Medical claims included any inpatient and outpatient services with a CDI code. Each CDI episode would end after a 14-day CDI-claim-free period was observed (Figure 1). An episode of rCDI was defined as a second or subsequent CDI episode, using the same criteria as above for the index CDI episode, within an 8-week window following the end of the previous CDI episode. This 8 week window has been used by the CDC to define recurrences.[14] CDI events that occurred later than each 8-week window were not counted as recurrences and therefore were excluded in this analysis. mrCDI could occur after an index CDI event, up until 12 months following the index CDI date. The study population was stratified into mutually exclusive groups of patients with 0 rCDI (had primary CDI only), 1 rCDI, 2 rCDI, or 3+ rCDI.

Outcomes

Clinical complications were quantified for the 12-month period after an index CDI, for all study patients and by cohorts for number of rCDI episodes (0 rCDI, 1 rCDI, 2 rCDI, or 3+ rCDI). Sepsis, subtotal colectomy, and diverting loop ileostomy were identified by a medical claim with relevant codes (Supplementary Table 1). If there were multiple medical claims with sepsis diagnosis code, claims occurring with service dates within a 7-day period were grouped together as a single acute sepsis episode.

Data analysis

Patient characteristics and clinical complications for the cohorts were displayed using counts and percentages for categorical variables and measures of central tendency (mean (standard deviation—SD)) for continuous variables. Statistical analyses were conducted with SAS, version 9.3 (SAS Institute, Inc., Cary, NC, USA).

Results

Demographic and baseline characteristics

A total of 46,571 patients with an index CDI episode were included: 3129 (6.7%) experienced one recurrence, 472 (1.0%) had two recurrences, and 134 (0.3%) developed three or more recurrences (Table 1). The mean (SD) age was 47.4 (12.7) years, and 62.4% were female (Table 1). The mean (SD) baseline Charlson comorbidity index (CCI) score, by increasing the rCDI group, was 1.2 (1.9), 1.5 (2.2), 1.8 (2.3), and 2.3 (2.5). Autoimmune diseases (such as ulcerative colitis, Crohn's disease, type 1 diabetes, rheumatoid arthritis, or

Table 1. Demographic and baseline characteristics.

	No recurrence (n = 42,836)	1 recurrence (n = 3129)	2 recurrence (n = 472)	3+ recurrence (n = 134)
Age (years), mean (SD)	47.4 (12.7)	48.3 (12.8)	47.9 (13.0)	48.7 (11.5)
Female, n (%)	26,625 (62.2)	2036 (65.1)	319 (67.6)	82 (62.2)
Geographic region, n (%)				
Midwest	13,190 (30.8)	981 (31.4)	147 (31.1)	33.6 (45)
Northeast	9741 (22.7)	786 (25.1)	133 (28.2)	42 (31.3)
South	14,585 (34.1)	958 (30.6)	140 (29.7)	33 (24.6)
West	4663 (10.9)	360 (11.5)	51 (10.8)	12 (9.0)
Unknown	657 (1.5)	44 (1.4)	–[a]	–[a]
Type of benefit plan, n (%)				
PPO	32,990 (77.0)	2347 (75.0)	344 (72.9)	84 (62.7)
HMO	6103 (14.3)	519 (16.6)	87 (18.4)	36 (26.9)
CDHP	269 (0.6)	16 (0.5)	–[a]	–[a]
Other	3266 (7.6)	233 (7.5)	34 (7.2)	12 (9.0)
Unknown	208 (0.5)	14 (0.5)	–[a]	–[a]
CCI score, mean (SD)	1.15 (1.89)	1.54 (2.21)	1.83 (2.31)	2.29 (2.53)
Medications, n (%)				
Gastric acid–suppressing agents	11,943 (27.9)	1028 (32.9)	184 (39.0)	51 (38.1)
Antibiotics	33,411 (78.0)	2509 (80.2)	381 (80.7)	103 (76.9)
Immunosuppressant agents	1423 (3.3)	134 (4.3)	33 (7.0)	–[a]
Comorbid conditions, n (%)				
Autoimmune diseases	7745 (18.1)	723 (23.1)	116 (24.6)	53 (39.6)
Ulcerative colitis	2326 (5.4)	238 (7.6)	39 (8.3)	21 (15.7)
Crohn's disease	1782 (4.2)	175 (5.6)	22 (4.7)	11 (8.2)
Renal insufficiency	5618 (13.1)	571 (18.3)	105 (22.3)	36 (26.9)
Current or history of smoking	5729 (13.4)	533 (17.0)	89 (18.9)	30 (22.4)
Medical procedures and treatments, n (%)				
Transplant	1338 (3.1)	126 (4.0)	31 (6.6)	–[a]
GI surgery	8498 (19.8)	792 (25.3)	138 (29.2)	49 (36.6)
Enteral feeding	524 (1.2)	73 (2.3)	21 (4.5)	–[a]
Chemotherapy	8628 (20.1)	767 (24.5)	146 (30.9)	42 (31.3)
Healthcare exposure, n (%)				
Inpatient admission	13,938 (32.5)	1307 (41.8)	236 (50.0)	81 (60.5)
Inpatient admission with ICU stay	1258 (2.9)	132 (4.2)	21 (4.5)	13 (9.7)
Outpatient hospital visit	32,584 (76.1)	2576 (82.3)	404 (85.6)	116 (86.6)
ED visit	19,534 (45.6)	1581 (50.5)	268 (56.8)	77 (57.5)

CCI: Charlson comorbidity index; ED: emergency department; GI: gastrointestinal; ICU: intensive care unit; SD: standard deviation; PPO: preferred provider organization; HMO: health maintenance organization; CDHP: consumer-driven health plan.

[a]For patient privacy reasons and consistent with data reporting practices for the Centers for Medicare and Medicaid Services, data are not shown for cells in which the sample size was ⩽10.

multiple sclerosis) were present in 18.1%, 23.1%, 24.6%, and 39.6% of patients, by increasing the rCDI cohort.

Pre-index healthcare exposures

During the 6-month baseline period, antibiotics were prescribed for ⩾76% of patients in all groups (Table 1). Gastric acid–suppressing agents were prescribed, by increasing the rCDI cohort, for 27.9%, 32.9%, 39.0%, and 38.1% of patients. Gastrointestinal surgery or administration of chemotherapy was more frequently noted with higher rCDI cohorts during the baseline period. Baseline healthcare exposure was generally highest for those in the 3+ rCDI group, with 86.6% having an outpatient hospital visit, 60.5% having ⩾1 inpatient admission, and 57.5% having an ED visit within 6 months immediately preceding the index CDI episode (Table 1).

Treatment patterns

At the time of the study, standard of care for CDI treatment primarily involved the use of antibiotics, while FMT was used rarely. Across all index and rCDI episodes (n = 46,571), vancomycin was used to treat 16,215 (34.8%), metronidazole was used to treat 25,298 (54.3%), and fidaxomicin was used to treat 1738 (3.7%) of patients. For recurrences, vancomycin

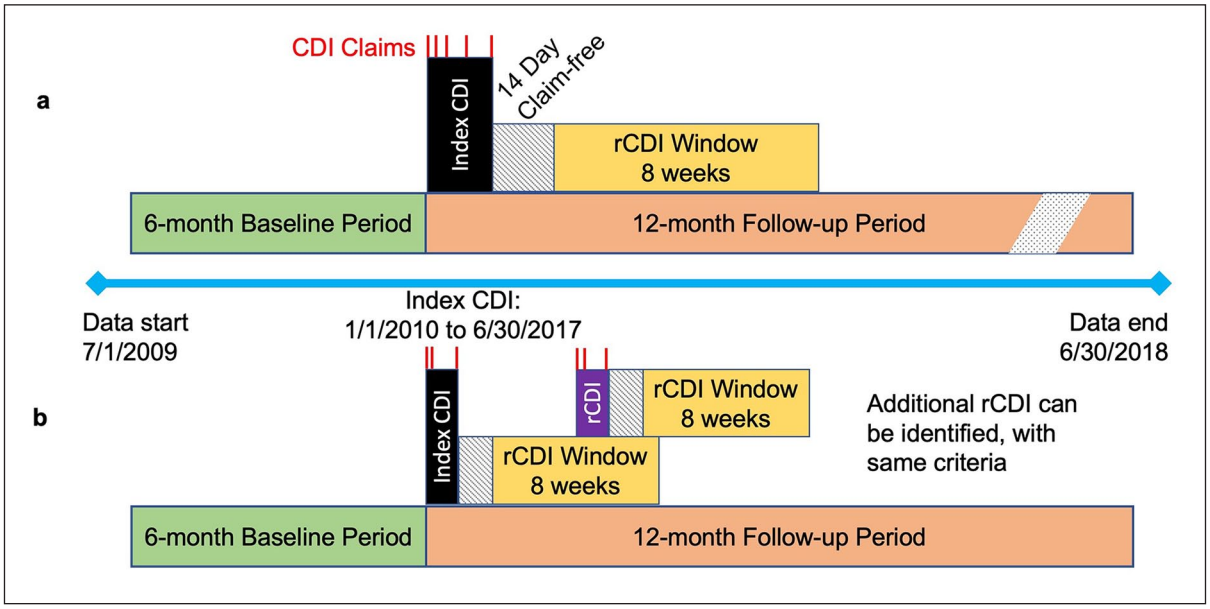

Figure 1. Study design: (a) the index CDI episode was followed by a 14-day claim-free period after last CDI claim and an 8-week period to identify rCDI and (b) the red star indicates a hypothetical point at which the first rCDI episode occurs during the 8-week window after the claim-free period. Following this first rCDI episode, a new 14-day claim-free period occurs plus a new window for a subsequent rCDI episode. Multiple rCDI could occur after an index CDI event in this manner, up until 12 months following the index CDI date.

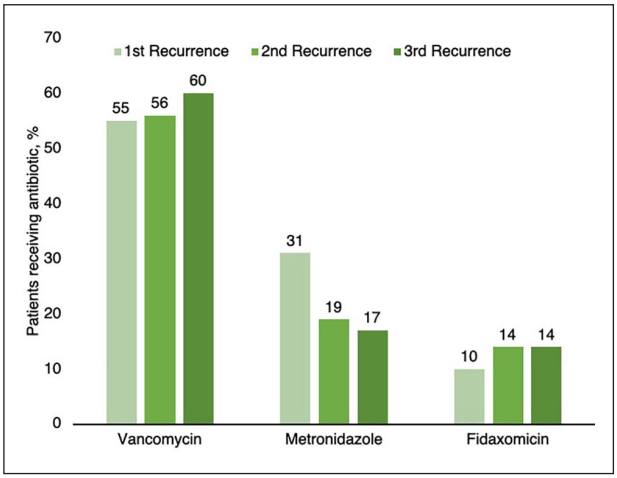

Figure 2. Vancomycin was the most commonly prescribed antibiotic to treat the first, second, and third rCDI episodes, followed by metronidazole and then fidaxomicin.

was the most commonly prescribed antibiotic used, with 55% receiving this with their first recurrence, 56% with their second recurrence, and 60% with the third recurrence (Figure 2). As expected, metronidazole treatment rates were lower for recurrences versus primary CDI, particularly in patients with second or third recurrences (19% and 17%, respectively). Fidaxomicin was used to treat a minority of patients at each recurrence episode.

Few study patients (333/46,571; 0.72%) had FMT procedures in the year after index episode. The proportion of patients who received FMT procedures was slightly higher during the later study years between 2014 and 2017 (0.89%) compared with 2010 and 2013 (0.54%). Among the 333 patients who had FMT, 364 procedures were conducted, with 27 patients having ⩾2 FMT procedures. More than half (55.6%) of the FMT procedures were performed in patients who had no recurrences (i.e. to treat the index CDI episode), corresponding to FMT being performed in 0.43% (185/42,836) of the cohort with no recurrence. The utilization of FMT increased with the number of recurrences experienced: 3.1% (97/3129) of patients with one recurrence, 8.1% (38/472) with two recurrences, and 9.7% (13/134) with three or more recurrences received FMT.

Post-index clinical complications

During the 12-month follow-up, sepsis occurred in 16.5%, 27.3%, 33.1%, and 43.3% of patients by increasing the rCDI group. The proportion of patients who had two sepsis episodes during follow-up was highest for the 3+ rCDI cohort (Figure 3(a)). No patient had more than two sepsis episodes during the 12-month follow-up period. Likewise, subtotal colectomy or diverting loop ileostomy was performed in 4.6%, 7.3%, 8.9%, and 10.5% of patients, respectively, during the follow-up (Figure 3(b)).

Discussion

CDI and rCDI are associated with substantial patient and healthcare burden. Within our study, patients with mrCDI

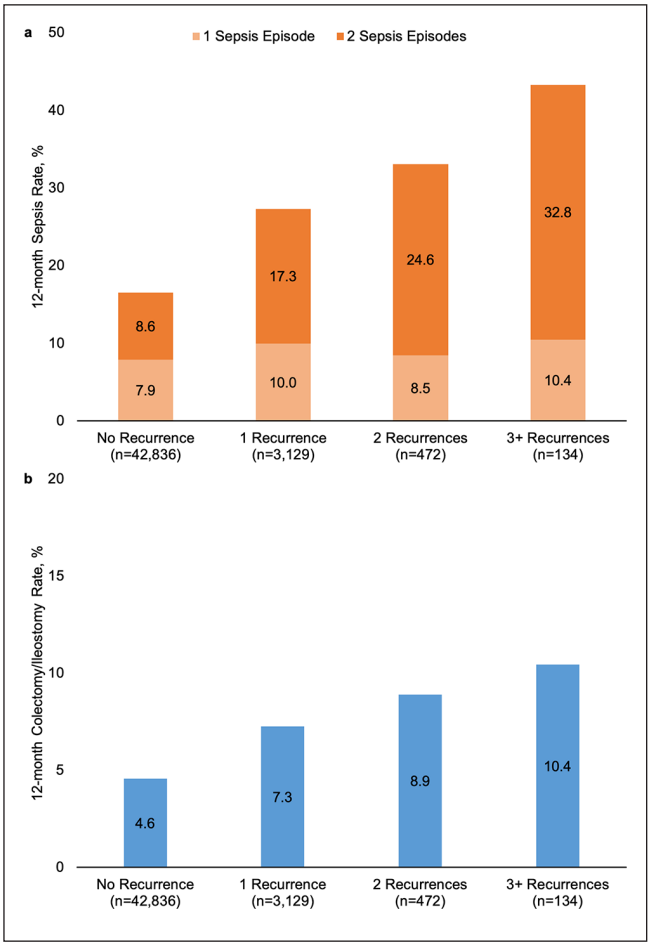

Figure 3. Rates of (a) sepsis and (b) subtotal colectomy or diverting loop ileostomy during the 12 months after index CDI, by recurrence cohort.

had high rates of all-cause sepsis and the need for surgical intervention via subtotal colectomy or diverting loop ileostomy. Mirroring the high clinical burden of mrCDI seen in this analysis, patients with three or more recurrences also had the highest healthcare resource utilization and total, all-cause, direct medical costs of all recurrence cohorts.[13]

During the 12-month follow-up, rates of sepsis were notable and highest for patients with three or more recurrences. Over 40% of patients with three or more recurrences went on to develop sepsis during the study period, and over 30% had two sepsis episodes. As there are few distinguishing factors for patients who suffer one versus multiple recurrences, the higher rate of sepsis in patients with more recurrences is likely due to this high-risk cohort having more opportunities to suffer such adverse outcomes.[13] In a retrospective study performed at two large institutions, Falcone et al.[15] demonstrated that 18.3% of patients with CDI developed a bloodstream infection (BSI) within 30 days following the CDI episode, most of whom were being treated for a CDI recurrence. Furthermore, the 30-day mortality rates for those with or without BSI were 38.9% versus 13.1% ($p < 0.001$), respectively.[15] Ianiro et al.,[16] reporting the results of a single-center study of patients with rCDI, found a 22% rate of BSI after rCDI treatment with antibiotics, and a 90-day mortality rate of 52.5% for those who developed a BSI. Sepsis carries a significant economic burden, with a mean cost of over US $16,000 per hospitalization in the United States; sepsis cases not diagnosed until after admission and those with higher severity had a higher economic burden than average.[17] Among patients readmitted with rCDI in the State Inpatient Databases, there is a significant gap in reimbursement of almost US $8000 to US $18,000 for patients who present with rCDI and septicemia on admission.[18] There are several theories regarding the pathophysiological basis for BSI in patients with CDI and rCDI. Most focus on disruption of the gut microbiota and/or a cellular inflammatory response, resulting from an impaired gut barrier function and immune response to CDI toxins.[19,20] Regardless of mechanism, our study, which had longer follow-up than other studies, revealed that in a broad population of patients with CDI, 16.5% of patients developed BSI and greater than 25% of those with one or more recurrence suffered this complication. We believe this indicates that the consequence of sepsis/BSI in patients with CDI might be more significant than previously thought when considered across a larger population.

The burden of colectomy was also apparent in the study population, with ~5% of those with no recurrences undergoing the surgery and >10% of those with three or more recurrences. Other studies estimated colectomy rates of 1.2%–8.7% in patients with CDI (initial and rCDI).[12,21–23] In the National Hospital Discharge Survey, 1.3% of patients with CDI required a colectomy.[24] Our colectomy data trended higher than previous reports, which may be related to the large cohort size, real-world nature of the data analyzed, the younger age of the population studied, a longer follow-up period, and/or a broader group of healthcare settings. Colectomies create a significant burden for the patient and the healthcare system. Colectomy to treat CDI is associated with a lengthy hospital stay, with a mean (SD) stay of 33 (28) days for those who survived to discharge.[25] Colectomy is also a significant predictor of mortality following CDI (odds ratio: 3.14).[24] The in-hospital mortality rate following colectomy for CDI varies widely but is substantial, ranging from 36% to 80%.[25] Over 75% of those who have a colectomy for CDI suffer colectomy-related morbidity within 30 days, with 65% of patients suffering serious complications.[26] These post-operative complications underscore the patient's burden of CDI, especially those with mrCDI. The cost of a colectomy to treat rCDI is estimated at US $39,000 (2016 dollars]).[23] In patients readmitted for rCDI after a major operating room procedure, there is average reimbursement gap of US $20,000.[18]

Despite being a new therapeutic paradigm for rCDI, FMT use was observable during the study period. The use of FMT

for rCDI has gained momentum in recent years, with the enforcement discretion by the FDA and the advent of stool banks.[27] FMT remained a rare observation in this claims data set, which may be attributable to FMT being considered a novel and relatively unknown management option during the study period, a lack of coverage for the procedure by health plans, cash payment for the procedure (which would not be captured by the database), or underreporting/miscoding of FMT procedures. A small number of patients (0.7% of the entire cohort) received FMT, with a slight increase in FMT rates with more recurrent episodes. Interestingly, the timing of FMT procedures was largely not in accordance with current or prior guidelines, with most of our observed FMT procedures performed after the index CDI.[4,28] An analysis from the Indiana University Hospital reported data from patients with severe and fulminant CDI who received FMT.[29] The median number of prior CDI was 0, meaning that at least half of the 225 patients received FMT after their primary infection. Our data may reflect similar use pattern; however, this practice would be considered experimental and did not align well with available guideline recommendations at the time or currently.[28,30] Additional research on the practice patterns of FMT is needed to evaluate appropriateness of use.

The recurrence rates seen in our study are somewhat lower than those reported in the literature.[6,31] These lower rates are likely due to our study including a younger cohort (aged 18–64 years) than other studies, which are predominantly a population aged 65 years or older, the data source being solely an employer-covered population (which tends to be healthier on average than the entire adult population), in addition to the stringent criteria we used to identify rCDI cases, as detailed by literture[13,31–33] To address the key objective of quantifying the occurrence of clinical complications, our study included patients who had a minimum of 18 months of continuous enrollment (6-month look back plus 12-month follow-up). This criterion excluded patients who disenrolled before 12-month follow-up, including patients who died or those who lost or changed health insurance for any reason, the reason for which the database does not disclose to protect patient's privacy. Importantly, exclusion of patients who died during the study period after index CDI ensured that the study cohorts were sufficiently homogeneous, as the level and type of medical care provided to dying patients would have been distinctly different, potentially skewing the data and rendering it less valuable. The impact of these inclusion criteria is that, given the potential mortality consequence of CDI complications reported in the literature, this analysis may have underestimated the proportion of patients who developed sepsis or required colectomy. Claims data can be limited by the misclassification of medical conditions or by missing events/diagnoses. In this study, CDI was identified by diagnosis codes and CDI-related treatments and not by diagnostic test results, which may have resulted in random misclassifications. In addition, claims-related bias may have resulted in an underreporting of sepsis event counts (i.e. sepsis occurred during a hospitalization but was not coded). As this was a descriptive study and was not designed for hypothesis testing, we did not perform a sample size calculation a priori; the sample from the commercial claims database resulting from the inclusion criteria was used for the analyses. Despite the potential limitations and underestimations, we believe that our study provides a good cross-sectional view of a broad population in the United States who experienced CDI and rCDI and resulted in a large population (~46,000) of individuals with CDI to describe. In addition, the incidence of CDI-related surgeries and sepsis was further detailed in cohorts stratified by rCDI group. The results may be generalized to adult populations younger than 65 years who remained with a healthcare system for at least 1 year after the primary CDI episode. Specifically, healthcare decision makers may use our findings to estimate the lower bound of the clinical burden of rCDI.

Conclusion

Our findings indicate that, among patients with more rCDI, there was a parallel trend for higher rates of colectomy and sepsis. These complications have been documented in previous studies to be associated with poor outcomes. Reduction in rCDI may be an important step to reduce the burden of serious clinical complications.

Acknowledgements

Medical writing and editorial support was provided by Agnella Izzo Matic, PhD, CMPP (AIM Biomedical, LLC) and was funded by Ferring Pharmaceuticals, Inc. Portions of the data contained in this article appeared in abstract/poster form at ACG Annual Scientific Meeting, 25–30 October 2019.

Author contributions

L.S., D.N.D., N.S., K.L., and W.W.N. designed and conducted the study. All authors analyzed and interpreted the data, drafted and critically revised the article for important intellectual content, and approved the article for publication.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: M.B., L.S., W.W.N., and D.N.D. are employees of Ferring Pharmaceuticals, Inc. P.F. has served as a consultant to and on the speaker's bureau for Merck and Co and has served as a consultant for Ferring Pharmaceuticals, Inc. and Roche Pharmaceuticals. N.C.S. and K.L. are employees of Precision Health Economics and Outcomes Research and provided consulting services to Ferring Pharmaceuticals, Inc.

Ethical approval

This study was exempt from institutional review board approval, as it did not involve any interventional biomedical research with human subjects. Ethical approval was not sought for this study because the

data used were de-identified medical and pharmacy claims data, and they were obtained by HIPAA-compliant methods.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded by Ferring Pharmaceuticals, Inc. (Parsippany, NJ).

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Supplemental material

Supplemental material for this article is available online.

References

1. Guh AY, Mu Y, Winston LG, et al. Trends in U.S. burden of *Clostridioides difficile* infection and outcomes. *N Engl J Med* 2020; 382: 1320–1330.
2. Kwon JH, Olsen MA and Dubberke ER. The morbidity, mortality, and costs associated with *Clostridium difficile* infection. *Infect Dis Clin North Am* 2015; 29(1): 123–134.
3. Micek ST, Schramm G, Morrow L, et al. *Clostridium difficile* infection: a multicenter study of epidemiology and outcomes in mechanically ventilated patients. *Crit Care Med* 2013; 41: 1968–1975.
4. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis* 2018; 66: e1–e48.
5. Luciano JA and Zuckerbraun BS. *Clostridium difficile* infection: prevention, treatment, and surgical management. *Surg Clin North Am* 2014; 94(6): 1335–1349.
6. Smits WK, Lyras D, Lacy DB, et al. *Clostridium difficile* infection. *Nat Rev Dis Prim* 2016; 2: 16020.
7. Leffler DA and Lamont JT. *Clostridium difficile* infection. *N Engl J Med* 2015; 372: 1539–1548.
8. DePestel DD and Aronoff DM. Epidemiology of *Clostridium difficile* infection. *J Pharm Pr* 2013; 26: 464–475.
9. Feher C, Munez Rubio E, Merino Amador P, et al. The efficacy of fidaxomicin in the treatment of *Clostridium difficile* infection in a real-world clinical setting: a Spanish multi-centre retrospective cohort. *Eur J Clin Microbiol Infect Dis* 2017; 36(2): 295–303.
10. Dubberke ER and Olsen MA. Burden of *Clostridium difficile* on the healthcare system. *Clin Infect Dis* 2012; 55(Suppl. 2): S88–S92.
11. McFarland LV, Surawicz CM, Rubin M, et al. Recurrent *Clostridium difficile* disease: epidemiology and clinical characteristics. *Infect Control Hosp Epidemiol* 1999; 20(1): 43–50.
12. Sheitoyan-Pesant C, Abou Chakra CN, Pépin J, et al. Clinical and healthcare burden of multiple recurrences of *Clostridium difficile* infection. *Clin Infect Dis* 2015; 62: 574–580.
13. Feuerstadt P, Stong L, Dahdal DN, et al. Healthcare resource utilization and direct medical costs associated with index and recurrent *Clostridioides difficile* infection: a real-world data analysis. *J Med Econ* 2020; 23: 603–609.
14. Centers for Disease Control Prevention. *Clostridioides difficile* infection (CDI) tracking, https://www.cdc.gov/hai/eip/cdiff-tracking.html (accessed 15 January 2020).
15. Falcone M, Russo A, Iraci F, et al. Risk factors and outcomes for bloodstream infections secondary to *Clostridium difficile* infection. *Antimicrob Agents Chemother* 2016; 60(1): 252–257.
16. Ianiro G, Murri R, Sciumè GD, et al. Incidence of bloodstream infections, length of hospital stay and survival in patients with recurrent *Clostridioides difficile* infection treated with fecal microbiota transplantation or antibiotics: a prospective cohort study. *Ann Intern Med* 2019; 171: 695–702.
17. Paoli CJ, Reynolds MA, Sinha M, et al. Epidemioogy and costs of sepsis in the United States—an analysis based on timing of diagnosis and severity level. *Crit Care Med* 2018; 46: 1889–1897.
18. Zilberberg MD, Nathanson BH, Marcella S, et al. Hospital readmission with *Clostridium difficile* infection as a secondary diagnosis is associated with worsened outcomes and greater revenue loss relative to principal diagnosis: a retrospective cohort study. *Medicine* 2018; 97(36): e12212.
19. Chatila W and Manthous CA. Clostridium difficile causing sepsis and an acute abdomen in critically ill patients. *Crit Care Med* 1995; 23(6): 1146–1150.
20. Baggs J, Jernigan JA, Halpin AL, et al. Risk of subsequent sepsis within 90 days after a hospital stay by type of antibiotic exposure. *Clin Infect Dis* 2019; 66: 1004–1012.
21. Kasper AM, Nyazee HA, Yokoe DS, et al. A multicenter study of *Clostridium difficile* infection-related colectomy, 2000–2006. *Infect Control Hosp Epidemiol* 2012; 33(5): 470–476.
22. Loo VG, Poirer L, Miller MA, et al. A predominantly clonal multi-institutional outbreak of *Clostridium difficile*-associated diarrhea with high morbidity and mortality. *N Engl J Med* 2005; 353: 2442–2449.
23. Rodrigues R, Barber GE and Ananthakrishnan AN. A comprehensive study of costs associated with recurrent *Clostridium difficile* infection. *Infect Control Hosp Epidemiol* 2017; 38(2): 196–202.
24. Khanna S, Gupta A, Baddour LM, et al. Epidemiology, outcomes, and predictors of mortality in hospitalized adults with *Clostridium difficile* infection. *Intern Emerg Med* 2016; 11(5): 657–665.
25. Hall JF and Berger D. Outcome of colectomy for *Clostridium difficile* colitis: a plea for early surgical management. *Am J Surg* 2008; 196(3): 384–388.
26. Venkat R, Pandit V, Telemi E, et al. Frailty predicts morbidity and mortality after colectomy for *Clostridium difficile* colitis. *Am Surg* 2018; 84: 628–632.
27. US Food and Drug Administration. Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat Clostridium difficile Infection Not Responsive to Standard Therapies, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enforcement-policy-regarding-investigational-new-drug-requirements-use-fecal-microbiota-0 (accessed 15 January 2020).
28. Surawicz C, Brandt LJ, Binion DG, et al. Guidelines for diagnosis, treatment, and prevention of *Clostridium difficile* infections. *Am J Gastroenterol* 2013; 108(4): 478–498; quiz499.
29. Cheng Y-W, Phelps E, Nemes S, et al. Fecal microbiota transplant decreases mortality in patients with refractory severe or fulminant *Clostridioides difficile* infection. *Clin Gastroenterol Hepatol* 2020; 18: 2234–2243.

30. Cohen SH, Gerding DN, Johnson S, 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): 431–455.
31. Lessa FC, Mu Y, Bamberg WM, et al. Burden of *Clostridium difficile* infection in the United States. *N Engl J Med* 2015; 372: 825–834.
32. Pechal A, Lin K, Allen S, et al. National age group trends in *Clostridium difficile* infection incidence and health outcomes in United States community hospitals. *BMC Infect Dis* 2016; 16: 682.
33. Desai K, Gupta SB, Dubberke ER, et al. Epidemiological and economic burden of *Clostridium difficile* in the United States: estimates from a modeling approach. *BMC Infect Dis* 2016; 16: 303.