



Burden of *Clostridium (Clostridioides) difficile* infection during inpatient stays in the USA between 2012 and 2016

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SUMMARY

Background: The healthcare burden of *Clostridium (Clostridioides) difficile* infection (CDI) is high but not fully characterized.

Aim: To assess hospitalization costs, length of hospital stay (LOS) and in-hospital mortality attributable to CDI in the USA by analysing nationwide hospital discharge records over the 2012–2016 period.

Methods: A retrospective, observational study based on the Truven Health MarketScan Hospital Drug Database was conducted, in which 46,097 inpatient stays with a diagnosis of CDI were analysed. Costs, LOS and in-hospital mortality were studied for patients with either a principal or secondary (comorbidity) diagnosis of CDI, and for patients re-admitted because of CDI. If CDI was a comorbidity, its attributable burden was estimated by coarsened exact matching, comparing 17,273 CDI stays with 84,164 stays in a control group without a CDI diagnosis.

Findings: Inpatients for whom CDI was the main reason for hospitalization incurred mean costs of US\$10,528 and an average LOS of 5.9 days. For CDI as a comorbidity, the mean additional cost was US\$11,938 and the additional LOS was 4.4 days. CDI also increased the in-hospital mortality rate by 4.1%, on average.

Conclusion: This study is consistent with previous publications which demonstrated the high economic burden of CDI for healthcare settings and health insurance systems. When recorded as a comorbidity, CDI significantly increased hospital costs and LOS. These results highlight the need for innovative therapeutic approaches in the prevention and treatment of CDI.

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Introduction

Clostridium (Clostridioides) difficile is an opportunistic, anaerobic, Gram-positive, spore-forming, toxin-producing

bacterium of the intestinal microbiota. It can provoke potentially lethal *C. difficile* infection (CDI), with symptoms ranging from mild diarrhoea to pseudomembranous colitis [1]. *C. difficile* is acquired by ingesting spores transmitted from other patients or healthcare personnel, either through the hands or the environment [2,3]. CDI is responsible for 15–25% of nosocomial cases of antibiotic-associated diarrhoea [4,5]. It is the most commonly reported pathogen, responsible for 12.1% of healthcare-associated infections in the USA [6].

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Since the 2000s, an increase in the incidence of CDI, associated with poorer patient outcomes, has been observed. This increase is linked to the spread of a particular *C. difficile* strain (BI/NAP1/027), which is more virulent and notably resistant to fluoroquinolones [7–10]. From 2011 to 2015, the adjusted annual incidence rate of community-acquired CDI nearly doubled, while the incidence of healthcare-associated CDI increased from 0.62 to 0.88 cases per 1000 patient-days [11].

Risk factors for *C. difficile* include the use of antibiotics (especially broad-spectrum antibiotics that profoundly disrupt the gut microbiota), the severity of underlying diseases, advanced age, and length of hospital stay (LOS) [12].

In a recent study modelling the cost of CDI in the USA, the economic burden of CDI was estimated to reach US\$5.4 billion in 2014, including US\$4.7 billion (86.7%) in healthcare settings and US\$725 million (13.3%) in the community [13]. Given this high economic impact, there is a need to assess, in detail, the outcomes for patients with CDI, with a specific focus on mortality, LOS and costs borne by healthcare systems.

The objective of this study was to assess, from a third-party payer perspective, hospitalization costs, LOS and in-hospital mortality attributable to CDI in the USA by analysing nationwide hospital discharge records over the 2012–2016 period.

Methods

Data source

This study was a retrospective observational study, from a third-party payer (private and public insurances) perspective, using the Truven Health MarketScan Hospital Drug Database (HDD) of Truven Health Analytics, part of the IBM Watson Health business. HDD information is derived from the hospital billing systems of 593 hospitals across the USA, representing 10.7% of all hospitals [14]. It records demographic data, medical diagnoses, procedure codes, prescriptions, mortality, and all direct medical and non-medical costs associated with inpatient stays billed by hospitals. Using discharge dates from January 2012 to December 2016, 100,000 inpatient stays with a reported diagnosis of CDI were sampled at random from the database. In the Truven Health MarketScan HDD, detailed cost data were only available for a subset of hospitals. The sample was therefore reduced to the 46,097 inpatient stays for which detailed cost data were available (the study group). Table A (see online supplementary material) presents the characteristics of hospitals in the study group.

From another sample from HDD, 500,000 inpatient stays with no CDI diagnosis but at least one antibiotic prescription were selected at random between January 2016 and December 2016. This sample was reduced to 214,660 inpatient stays for which cost data were available to serve as a control group for the matching analysis and to study costs attributable to CDI.

Identification of CDI

Diagnosis codes were coded using International Classification of Diseases-9 and -10 (ICD-9-CM and ICD-10-CM). Consequently, CDI was coded as either 008.45 (ICD-9-CM) or A04.7 (ICD-10-CM).

In the Health Truven MarketScan HDD, the final diagnosis that best explained why the patient was admitted to the

hospital was recorded as the principal diagnosis. Secondary diagnoses were defined as diagnoses other than the principal diagnosis. Therefore, in the present study, when a CDI diagnosis code was recorded as the principal diagnosis, the infection was considered to be the principal cause of hospital admission. When CDI was reported as a secondary diagnosis, it was considered as a comorbidity, the onset of which may have occurred before or after hospital admission.

Study groups

To study LOS, healthcare costs and in-hospital mortality, two subgroups were selected:

- hospital stays with a principal diagnosis of CDI (pCDI; i.e. a diagnosis of CDI that led to hospital admission); and
- hospital stays with CDI as a comorbidity (secondary diagnosis of CDI; sCDI).

To study the health-economic impact of CDI recurrence, a further subgroup of patients with recurrent CDI was identified in the dataset. Patients who were re-admitted to the same hospital were identified using a longitudinally conserved and encrypted medical record number (EMRN). For a given EMRN in a given hospital, patients with recurrent CDI were defined as patients hospitalized with a principal diagnosis of CDI <60 days after the end of a prior CDI hospital stay. Among stays of patients with recurrent CDI, two subgroups were selected:

- the first hospital stay recorded, defined as first CDI stay (fCDI); and
- subsequent hospital stays, defined as CDI re-admissions (rCDI).

Outcomes

Sex, age, LOS, mortality and costs were collected and analysed. Cost analyses, based on different categories of hospital settings, can be found in Tables B and C (see online supplementary material). The rCDI rate was computed as the proportion of stays that were considered to be re-admissions.

Patients admitted and discharged on the same date were assigned a LOS of one day. All costs were adjusted to 2016 US dollars using the consumer price index for all urban consumers of medical care services [15]. The non-age-adjusted, weighted Charlson comorbidity score was computed using both ICD-9-CM and ICD-10-CM diagnosis codes [16].

For sCDI stays, the principal diagnosis was analysed after conversion to ICD-9-CM coding. Each different diagnosis recorded in the database was considered as a different patient comorbidity. Three analyses were performed, as follows.

- For pCDI stays with CDI being the main reason for hospitalization, all costs, LOS and mortality recorded were attributed to CDI.
- For sCDI stays, a retrospective case–control analysis was performed to evaluate the impact of CDI on LOS, costs and mortality. Using coarsened exact matching (CEM), sCDI cases were matched with controls, defined as inpatient stays without a CDI diagnosis. CEM was selected, rather than propensity score matching (PSM), because this method made it easier to perform a one-to-many match.

Also, while PSM can aggravate an original imbalance [17], CEM is an appropriate alternative [18–20]. Each case was matched with as many controls as possible, based on sex (exact matching), principal diagnosis code in the ICD-9-CM classification (exact matching), Charlson comorbidity score (exact matching) and age (coarsened into three-year groups). CDI-associated costs, LOS and mortality were calculated as the differences between cases and controls.

- For rCDI stays, costs, LOS and mortality were compared with fCDI stays.

Statistical analysis

Percentages were used to describe categorical variables. Medians, ranges and means [with 95% confidence intervals (95% CI)] were used to describe continuous variables. Student's *t*-test was used to compare quantitative data. A *P*-value of 0.05 was the threshold for statistical significance. All analyses were performed using R Version 3.4.4 [21].

Findings

All inpatient stays with a diagnosis of CDI

The mean age of the CDI patients was 67.3 years (95% CI 67.1–67.5), and 59.7% of the sample were female. The most commonly reported health insurance plan was Medicare (68.8%). Medicare was billed 64.8% of total reported costs, and Medicaid was billed 13.4%.

Table II

Cost and length-of-stay information for patients with a principal diagnosis of *Clostridium difficile* infection

	Mean (95% CI)	Median	Range
Total costs (US\$)	10,528 (10,275–10,782)	7181	15–852,983
Length of stay (days)	5.9 (5.8–6.0)	5	1–142
Daily costs (US\$/day)	1849 (1828–1870)	1607	4–28,654

CI, confidence interval.

On average, 16.0 comorbidities were recorded for inpatient stays with CDI. Patient characteristics are presented in Table I.

Inpatient stays with pCDI

Among the 46,097 CDI stays, 15,552 were pCDI (33.7%). The mean age of pCDI patients was 66.5 years (95% CI 66.2–66.8), and 65.9% of the sample were women. On average, patients had 13.2 comorbidities (95% CI 13.0–13.3).

In total, 265 pCDI stays (1.7%) resulted in deaths in the hospital. On average, pCDI stays lasted for 5.9 days (95% CI 5.82–5.98) and cost US\$10,528 (95% CI 10,275–10,782), resulting in daily costs of US\$1849 (95% CI 1828–1870). Of the total costs for pCDI stays, 70.7% were billed to Medicare and 8.8% were billed to Medicaid. Table II presents information about costs and LOS for the pCDI group.

Table I

Characteristics of inpatient stays with *Clostridium difficile* infection (CDI)

	All inpatient stays with CDI	pCDI	sCDI	rCDI
Number of inpatient stays	46,097 (100%)	15,552 (33.7%)	30,545 (66.3%)	1017 (2.2%)
Age group (years), <i>N</i> (%)				
≤17	621 (1.4%)	296 (1.9%)	325 (1.1%)	12 (1.2%)
18–44	4621 (10.0%)	1836 (11.8%)	2785 (9.1%)	93 (9.1%)
45–64	12,153 (26.4%)	4015 (25.8%)	8138 (26.6%)	246 (24.2%)
≥65	28,702 (62.3%)	9405 (60.5%)	19,297 (63.2%)	666 (65.5%)
Sex, <i>N</i> (%)				
Female	27,499 (59.7%)	10,246 (65.9%)	17,253 (56.5%)	668 (65.7%)
Male	18,598 (40.4%)	5306 (34.1%)	13,292 (43.5%)	349 (34.3%)
Comorbidity				
Mean (95% CI)	16.0 (15.9–16.0)	13.2 (13.1–13.3)	19.4 (19.3–19.5)	13.8 (13.5–14.1)
Median	15	13	18	13
Range	0–48	0–45	1–48	1–45
Non-age-adjusted, weighted Charlson comorbidity score	2.71 (2.69–2.73)	2.02 (1.99–2.06)	3.06 (3.03–3.09)	2.3 (2.2–2.4)
Principal sources of payment, <i>N</i> (%)				
Medicare	31,691 (68.8%)	10,443 (67.2%)	13,434 (77.7%)	756 (75.4%)
Medicaid	4858 (10.5%)	1479 (9.5%)	1289 (7.5%)	101 (9.9%)
Other insurance companies	2896 (6.3%)	1016 (6.5%)	814 (4.7%)	35 (3.4%)
Blue Cross	2436 (5.3%)	1018 (6.6%)	604 (3.5%)	42 (4.1%)
HMO	1625 (3.5%)	686 (4.4%)	436 (2.5%)	33 (3.2%)
Self-pay	1428 (3.1%)	543 (3.5%)	321 (1.9%)	24 (2.4%)
Other	1068 (2.3%)	335 (2.2%)	336 (2.0%)	23 (2.3%)
No data	95 (0.2%)	32 (0.2%)	39 (0.2%)	40 (0.3%)

HMO, health maintenance organization; pCDI, patient hospitalized with primary diagnosis of CDI; sCDI, patients hospitalized with a secondary diagnosis of CDI; rCDI, patients re-admitted with CDI; CI, confidence interval.

Table III
Principal diagnosis reported for patients with a secondary diagnosis of *Clostridium difficile* infection

Diagnosis	N (% of secondary diagnosis stays)
Unspecified septicaemia	6846 (22.4%)
Acute kidney failure, unspecified	973 (3.2%)
Sepsis due to anaerobes	748 (2.5%)
Pneumonia, unspecified organism	697 (2.3%)
Care involving other specified rehabilitation procedure	608 (2.0%)
Urinary tract infection, site not specified	543 (1.8%)
Septicaemia due to <i>Escherichia coli</i>	466 (1.5%)
Pneumonitis due to inhalation of food and vomit	435 (1.4%)
Acute respiratory failure	357 (1.2%)
Diverticulitis of the colon (without mention of haemorrhage)	326 (1.1%)

Inpatient stays with sCDI

Among 46,097 CDI stays, 30,545 were sCDI (66.2%). The mean age of sCDI patients was 67.7 years (95% CI 67.5–67.9), and 56.5% of the sample were female. On average, patients had 19.4 comorbidities (95% CI 19.3–19.5). Septicaemia was the most frequent primary diagnosis in patients with sCDI. Table III presents the principal diagnoses reported for sCDI inpatient stays.

It was possible to match 17,273 of the 30,545 cases with at least one control case. All cases were not matched because exact matching for multiple criteria was used, which is a very stringent procedure especially when matching exactly on the primary diagnosis. Matched cases were similar to all cases in terms of age, sex and Charlson comorbidity score. As presented in Table IV, the mean additional costs attributable to CDI were US\$11,938, and the additional LOS attributable to CDI was 4.4 days. Excess in-hospital mortality attributed to CDI was 4.1%.

Inpatient stays with re-admission for CDI

Out of the 46,173 stays, 1115 (2.4%) were CDI re-admissions. Patients with re-admissions had, on average, 1.1 CDI re-

admissions (range 1–3). On average, a re-admission stay occurred 24 days after the initial visit. As presented in Table II, the mean age of patients with re-admissions was 68.9 years (95% CI 67.8–70.1), and 65.7% were women.

A CDI re-admission did not result in significantly higher costs or LOS. Details on the total costs and LOS for initial stays with a primary diagnosis of CDI and re-admission stays are available in Table D (see online supplementary material).

Discussion

The present study analysed medico-administrative data of 46,097 inpatient stays in the USA with a diagnosis of CDI. It confirmed that CDI is a major burden for healthcare settings and health insurance systems. Inpatient stays with CDI as the main reason for hospitalization cost, on average, US\$10,528, with an average LOS of 5.9 days. The costs billed by hospitals for 17,273 inpatient stays with CDI as a comorbidity were further compared with a group of 84,164 stays without a diagnosis of CDI. This comparative analysis highlights excess costs of US\$11,938 per stay and excess in-hospital mortality of 4.1% attributable to CDI. As daily costs were similar for patients with and without CDI, the study results show that overall cost increases are primarily linked to prolonged LOS associated with CDI treatment. As expected, given the advanced age of the majority of patients with CDI, Medicaid and Medicare bear a sizeable share of all inpatient costs attributable to CDI (almost four-fifths of the total financial burden).

This study is consistent with previous publications which demonstrated significant increases in hospital costs and LOS attributable to CDI [22,23]. Recently, Zhang *et al.* evaluated the attributable costs for patients with primary CDI (either pCDI or sCDI) in the USA [22]. They found healthcare costs attributable to primary CDI reaching US\$24,205 (i.e. more than twice that found in the present analysis). This difference is explained by the different scope of studies; while the present study focused solely on the costs billed by hospitals, Zhang *et al.* considered all costs billed to the patient's insurance within the 6-month period following the first CDI diagnosis, thus including health expenditures from inpatient and outpatient settings. Interestingly, they found an average inpatient cost for patients with CDI of US\$28,014, close to the average inpatient cost of sCDI patients in the present analysis (US\$27,122). These

Table IV
Costs and length of stay attributable to *Clostridium difficile* infection (CDI)

	Secondary diagnosis CDI stays (N=17,273)	Control group (N=84,164)	Attributable to CDI	P-value
Total costs (US\$)				
Mean (95% CI)	27,122 (26,470–27,773)	15,183 (15,056–15,310)	11,938	<0.001
Median	15,711	9656	-	-
Range	10.1–2,151,408	6–696,790	-	-
Length of stay (days)				
Mean (95% CI)	11.1 (10.9–11.4)	6.7 (6.7–6.8)	4.4	<0.001
Median	8	5	-	-
Range	1–999	1–289	-	-
Daily costs (US\$/day)				
Mean (95% CI)	2439 (2412–2467)	2426 (2415–2438)	26	0.09
Median	2058	2011	-	-
Range	8–95,427	2–65,904	-	-

CI, confidence interval.

results illustrate the strong economic impact of CDI during hospitalization, but also in the months following hospital discharge (which are not captured in the present study).

Several studies have also studied the costs of CDI in Europe. The majority, either prospective or retrospective, used a costing methodology similar to that used in the present study (with case–control matching). They found similar excess costs attributable to CDI: between €8295 and €11,251 in France [24,25], £8207 in the UK [26] and €7993 in Germany [27]. The higher costs seen in the USA compared with Europe are consistent with generally higher medical costs in the USA [28]. Of note, the reported LOS is much higher in the French studies, which is reflected in the usual practice of shorter hospital stays in the USA (visible in international comparisons by the Organisation for Economic Co-operation and Development) [29].

It is interesting to note that, among the 10 leading reasons for hospitalization with CDI as a comorbidity, five are related to bacterial infections, for which patients presumably received antibiotics which are known to strongly increase the risk of CDI. Further causality cannot be explored because the medico-administrative dataset used did not permit diagnoses and health interventions to be related in time.

The present study was not designed to evaluate the total economic burden of CDI in the USA, but it helps to understand the substantial CDI economic burden for third-party payers. It highlights the need for better treatments and prevention of CDI to tame the substantial costs of the disease.

One interesting approach of the present study is the use of CEM with a particularly large sample of inpatient stays, which confirms the authors' estimate of extra CDI costs. As many studies focus on the costs of CDI as a principal diagnosis, data regarding the impact of CDI as a comorbidity are scarce.

This study has some limitations which relate to the limits of the data source. Although sampled at random, the subset of 100,000 CDI stays may not be representative of all CDI stays in the USA. Also, as only 2016 non-CDI stay cost information was used, the costs of CDI stays for 2012–2015 were inflation-normalized to 2016. This may have introduced bias into the evolution of complex healthcare costs. Costs may also have been distorted by the lack of data for New England hospitals. Finally, the database does not account well for 'medical nomadism' (patients being hospitalized in different hospitals over time), which may have underestimated re-admission rates for patients with CDI.

In conclusion, the cost burden associated with CDI is substantial, and better prevention and treatment options for CDI are needed in the USA and elsewhere.

Conflict of interest statement

P.-A. Bandinelli, L. Lurienne and S. Mollard were employees of Da Volterra, France at the time of the study. S.M. Heimmann has received research and travel grants from Astellas and Merck; research grants from Basilea, Gilead, and 3M; travel grants from Pfizer; lecture honoraria from Astellas and Merck; and is a consultant to Basilea, Gilead and Merck.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhin.2019.01.020>.

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