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Original Article

Attributable costs and length of stay of hospital-acquired *Clostridioides difficile*: A population-based matched cohort study in Alberta, Canada

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Abstract

Objective: To determine the attributable cost and length of stay of hospital-acquired *Clostridioides difficile* infection (HA-CDI) from the healthcare payer perspective using linked clinical, administrative, and microcosting data.

Design: A retrospective, population-based, propensity-score–matched cohort study.

Setting: Acute-care facilities in Alberta, Canada.

Patients: Admitted adult (≥18 years) patients with incident HA-CDI and without CDI between April 1, 2012, and March 31, 2016.

Methods: Incident cases of HA-CDI were identified using a clinical surveillance definition. Cases were matched to noncases of CDI (those without a positive *C. difficile* test or without clinical CDI) on propensity score and exposure time. The outcomes were attributable costs and length of stay of the hospitalization where the CDI was identified. Costs were expressed in 2018 Canadian dollars.

Results: Of the 2,916 HA-CDI cases at facilities with microcosting data available, 98.4% were matched to 13,024 noncases of CDI. The total adjusted cost among HA-CDI cases was 27% greater than noncases of CDI (ratio, 1.27; 95% confidence interval [CI], 1.21–1.33). The mean attributable cost was $18,386 (CAD 2018; USD $14,190; 95% CI, $14,312–$22,460; USD $11,046-$17,334). The adjusted length of stay among HA-CDI cases was 13% greater than for noncases of CDI (ratio, 1.13; 95% CI, 1.07–1.19), which corresponds to an extra 5.6 days (95% CI, 3.10–8.06) in length of hospital stay per HA-CDI case.

Conclusions: In this population-based, propensity score matched analysis using microcosting data, HA-CDI was associated with substantial attributable cost.

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Clostridioides difficile is the primary bacterial cause of antibiotic-associated diarrhea and pseudomembranous colitis, with manifestations ranging from asymptomatic colonization to mild diarrheal illness to more severe disease, including toxic megacolon, sepsis, and death.[1,2] Hospital-onset (HO) or hospital-acquired CDI (HA-CDI) accounts for 24%–56% of all CDI cases presenting in the acute-care setting.[3–5] Although recent reports from the United States, Europe, and Canada have suggested that the rates of HA-CDI or HO-CDI have plateaued or have started to decline.[6–8] The rate of 30-day all-cause mortality continues to be significant at ~9.3%.[3,9]

Additionally, CDI places a significant economic burden on the healthcare system. A systematic review and meta-analysis modeling study estimated that the attributable cost of inpatient management for HA-CDI was $34,149 (USD 2015) with a mean attributable length of stay of 7.8 days.[10] One study in Canada evaluated the attributable cost of HA-CDI and found the 30-day cumulative costs to range from $12,350 to $20,905 (CAD 2014).[11] Although previous studies have estimated the attributable costs of CDI and particularly HA-CDI, many have been limited to individual hospitals, specific populations, small geographic areas; they employed variable methodologies, perspectives, and statistical analyses as well.[10,12,13] These factors make it uncertain whether the increased cost relates to the severity of underlying illness in patients who develop HA-CDI, or higher costs relating to a preventable complication. Because HA-CDI is largely preventable,[4,14]

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a better understanding of the cost savings that could be accrued by preventing HA-CDI is important to justify additional expenditures on infection prevention practices.[12,15]

In this study, we used a population-based dataset of >2 million patients and a rigorous propensity-score–based design and microcosting data to determine the attributable cost and length of stay of HA-CDI among adult inpatients in Alberta, Canada.

Methods

Setting

More than 70% of the population in Alberta, Canada, resides in 2 major geographic health zones: Calgary (2016 zone population: 1,622,391, 38.1% of provincial total) and Edmonton (2016 zone population: 1,363,653, 32.1% of provincial total). In fiscal year 2015–2016, there were 3,058,469 hospital patient days across Alberta (38.1% in the Edmonton zone and 32.8% in the Calgary zone). Of the 28 hospitals in the Calgary and Edmonton zones, 14 had microcosting data available, and these facilities provided 1,714,992 (79.0%) hospital patient days in these 2 zones in fiscal year 2015–2016.

Study population and design

In this multicenter retrospective, incidence-based, propensity-score–matched cohort study, we compared adult (≥18 years) inpatients with HA-CDI with adult inpatients who did not develop CDI at the 14 hospitals using microcosting data available between April 1, 2012, and March 31, 2016.

We estimated propensity scores using a logistic regression model that regressed exposure status (ie, HA-CDI vs noncases of CDI) using observed baseline characteristics. The propensity score for a patient was the probability of having HA-CDI conditional on the patient's observed baseline characteristics. This is a balancing score: when the propensity score is matched, the distribution of measured baseline covariates is similar between patients with and without HA-CDI.[16–18] The covariates included age category, gender, Elixhauser comorbidities, previous admissions, previous intensive care unit (ICU) visits, previous surgeries, admitting status, antibiotic exposure, serum creatinine, glucose, platelets, sodium, blood urea nitrogen, white blood cells, pH, fiscal year, hospital teaching status/type, and geographical location. Patients without CDI were matched 10:1 with HA-CDI cases, using a greedy matching approach. We used nearest-neighbor matching with replacement and within a caliper width of 0.2 of the standard deviation of the logit of the propensity score to increase precision and reduce bias.[16,19] Noncases of CDI were further matched to HA-CDI cases within their propensity-score–matched groups on exposure time, and controls were required to have an exposure time (defined below) at least as long as the matching case.

The Conjoint Health Research Ethics Board at the University of Calgary and the Alberta Health Services' Research, Innovation, and Analytics Department approved this study.

Cohorts and data sources

Cases of CDI were defined as a laboratory confirmation of *C. difficile* toxin in the stool plus diarrhea, or fever and abdominal pain and/or ileus if no diarrhea was present, or a diagnosis of pseudomembranes seen during endoscopy. Incident cases were those identified during hospitalization and with no CDI in the prior 56 days. Only the first incident case of CDI was included in this study. Hospital-acquired CDI was defined as an incident of CDI identified 3 days since admission to a hospital facility or CDI ≤3 days from admission if the patient had a previous discharge in the last 4 weeks and was not a long-term care resident or a dialysis patient. CDI cases were attributed to the hospital facilities where they likely acquired the CDI (ie, hospitalization of acquisition). Cases were provided by the provincial Infection Prevention and Control surveillance CDI program; all hospital facilities are required to participate in this program.

Patients without *C. difficile* were identified by excluding patients with clinical CDI or those with a positive laboratory result for *C. difficile* from any healthcare setting during the study period. Hospital discharges of patients without CDI were extracted from the Discharge Abstract Database (DAD). This database captures administrative, clinical, and demographic information on hospital discharges (including deaths, sign-outs, and transfers). The criteria for including hospital discharges for noncases of CDI included adult inpatients (≥18 years) without CDI, patients discharged (alive or dead) during the study period, and patients with a hospital length of stay ≥2 days to allow for controls being admitted for at least as long as HA-CDI cases. Each hospital visit was an index hospitalization.

Covariates and data sources

In-hospital exposure time of HA-CDI cases was defined as the number of days in hospital between the admission date of the facility where the CDI was acquired and the diagnosis date. For HA-CDI cases identified ≤3 days from admission with a discharge in the past 4 weeks, the exposure time included the entire length of stay of that previous hospitalization (during which they presumably developed CDI). The in-hospital exposure time for noncases of CDI was defined as the time between the admission and discharge dates of each hospitalization.

All data pertaining to potential predictors of HA-CDI, costs, and/or length of stay were collected using administrative and laboratory databases. Patient demographics, admitting status (ie, elective vs urgent), comorbidities, previous hospitalizations, previous ICU admission, previous surgeries, and length of stay were extracted from the DAD. Elixhauser comorbidities were identified in the DAD using *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada* (ICD-10-CA) discharge codes.[20,21] Previous hospitalizations had a discharge date within 1 year of the diagnosis date for the cases of HA-CDI and within 1 year of the admission date for noncases of CDI. Previous ICU visits and surgeries occurred between the admission and discharge date of the index hospitalization of noncases of CDI. HA-CDI cases could have occurred during either the hospitalization during which HA-CDI was identified or during the previous hospitalization of acquisition.

Laboratory measures (including serum albumin, serum creatinine, glucose, platelets, sodium, troponin, blood urea nitrogen, white blood cell count, and pH) were extracted from the Alberta provincial general laboratory repository.[22,23] This dataset included laboratory results from all hospital labs, community labs, and emergency rooms across Alberta. The first laboratory result of each measure taken within ±24 hours of the admission date of noncases and of the hospitalization during which the HA-CDI was acquired were included.

In-hospital antibiotic exposure was collected between the admission date and the HA-CDI diagnosis date or the discharge date for noncases of CDI and for the 90 days prior to admission date. In-hospital antibiotic exposure was defined as prescription

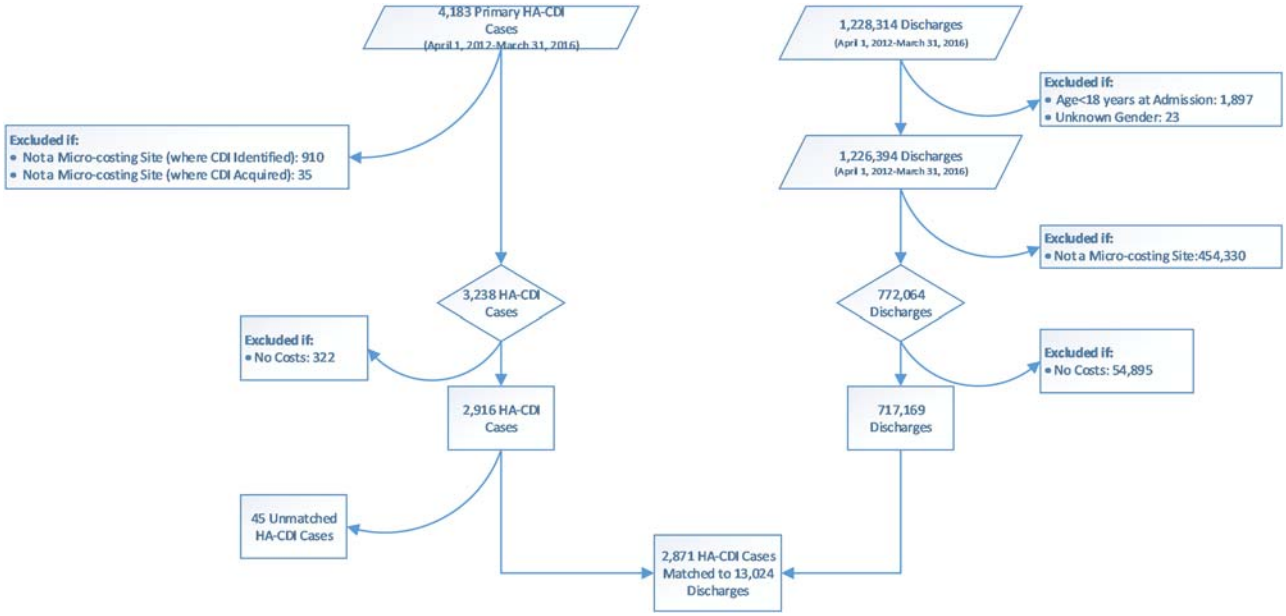

Fig. 1. Flow chart of study cohorts inclusion/exclusion criteria before and after matching. Note. HA-CDI, hospital-acquired *Clostridioides difficile* infection.

antibiotics dispensed from hospital pharmacies to admitted inpatients. These data were collated from all in-hospital pharmacy systems and were provided by Pharmacy Informatics and Technology Integration.

Facility-level characteristics of the index hospitalization of noncases of CDI and of the hospitalization of acquisition of HA-CDI cases included facility type, teaching status, and bed size.

Outcomes

The outcomes of this study were the cost and length of stay attributable to primary HA-CDI from the healthcare payer perspective. A microcosting approach was used as the cost-estimation method and included each hospitalization's inpatient costs (ie, direct and indirect costs for the provision of patient care). Patient-specific costs associated with respiratory and other therapies were included: intensive care unit stays, critical care unit stays, laboratory testing, diagnostic imaging, operating room time, nursing care, drug costs, medical/surgical supplies used, patient care administration, some medical staff compensation expenses such as physician interpretation fees for cardiovascular, pulmonary and electrodiagnosis exams and other services such as patient educators. Administration and support overhead costs were allocated to each clinical service used by the patient: site and regional administration, finance, laundry, patient food services, and building operating expenses. Costs associated with physician claims submitted for payment to Alberta Health were not included. Additionally, other related services (eg, community, ambulance, voluntary services), costs incurred by patients and their families, time lost from work and costs borne externally to health and welfare services were excluded because they were not available, or not consistent with the healthcare payer perspective. All costs were inflated to 2018 Canadian dollars using the healthcare component of the Canadian consumer price index.[24] Costs were converted to USD using the annual average exchange rate for 2018 (1 USD = 1.2957 CDN).[25] Length of stay was defined as the time from admission to discharge for the hospitalizations for cases and controls.

Statistical analysis

The unit of analysis was individual hospitalizations of the cases of HA-CDI and noncases of CDI. Descriptive statistics, such as frequencies and percentages for categorical variables and means with standard deviation (SD) for continuous variables, were used to describe the baseline characteristics of HA-CDI cases and noncases of CDI. Tests of proportions were used to compare differences between cases of HA-CDI across all hospitals in Alberta (n = 101) and HA-CDI cases at microcosting hospitals included for matching (n = 14). Univariate logistic regression was used to compare covariates between cases of HA-CDI and noncases of CDI. To account for many-to-one matching with replacement, controls were weighted inversely to the number that were matched to a particular control and inversely to the number of times a particular control was used. To assess balance in baseline characteristics, standardized differences in proportions between HA-CDI cases and noncases of CDI for each covariate were calculated before (unweighted) and after matching (weighted). A weighted standardized difference <10% indicated good balance and acceptable bias. In the matched data, we determined differences in cost and length of stay using generalized linear models with a γ distribution and log link, adjusting for any covariates that remained unbalanced after matching on propensity score and exposure time, and we assessed goodness of model fit.[26,27] Average marginal effects were calculated to determine the difference in costs and length of stay with 95% confidence intervals (CIs) between an HA-CDI case and a noncase of CDI, with average characteristics in the matched data. Statistical significance was observed at an α level of 0.05. All statistical analyses were performed using STATA/MP version 14.2 software (StataCorp, College Station, TX).

Results

Study cohorts before matching

Microcosting facilities (n = 14) accounted for 69.7% (2,916 of 4,183) of the cases of HA-CDI and 58.4% (717,169 of 1,228,314) of the discharges of noncases of CDI (Fig. 1). Compared to the

initial cohort, microcosting facilities had more HA-CDI cases on broad-spectrum gram-negative antibiotic exposure (41.4% vs 35.9%), higher proportions of high serum creatinine (35.7% vs 30.2%) results, blood urea nitrogen (38.8% vs 32.3%) and white blood cell counts (WBC) (41.2% vs 33.3%), respectively and a greater proportion of cases in teaching (43.0% vs 34.0%), and large urban (49.2% vs 39.4%) hospitals (Supplementary Table 1 online). The mean length of stay was similar between the initial and microcosting cohorts (49.6 vs 48.9 days), and the median length of stay was 29.3 days for both cohorts. Nearly all covariates prior to matching were significantly different between cases of HA-CDI and noncases of CDI (Table 1).

The mean unadjusted costs of HA-CDI cases was $83,155 (USD $64,178) (SD± $137,677; ±USD $106,257) compared to $12,465 (USD $9,620) (SD± $24,465; USD $18,882) for noncases of CDI (Supplementary Table 2 online). The costs were primarily driven by length of stay, nursing, administration costs, and overhead costs for both cases and noncases. Cases of HA-CDI incurred more costs across all categories and had longer length of stay (Supplementary Table 2 online). The mean unadjusted total length of stay of HA-CDI cases was 48.9 days (SD ±65.6) compared to 7.6 days (SD ±17.5) for noncases of CDI.

Results from matching

After matching on propensity score and exposure time, 2,871 of the 2,916 (98.4%) HA-CDI cases at microcosting sites were matched to 13,024 noncases of CDI (Fig. 1). Matching on propensity score achieved substantial reductions in differences across all covariates between the cases of HA-CDI and noncases of CDI. Subsequent matching on exposure time within the propensity score matched cases and noncases introduced some imbalance in certain categories within the following covariates: previous ICU visits, previous surgeries, all antibiotic classes except for second- to fifth-generation cephalosporins, baseline creatinine, glucose, platelets, sodium, and WBC, AHS health zone, and facility type (Table 1). These covariates were adjusted in the subsequent regression analysis. All other covariates were similar between matched and nonmatched HA-CDI cases (Supplementary Table 3 online).

Attributable Cost of HA-CDI

Hospital-acquired CDI was associated with higher costs than noncases of CDI. The total adjusted cost among HA-CDI cases was 27% greater than noncases of CDI (ratio, 1.27; 95% CI, 1.21–1.33). The mean attributable cost of a typical HA-CDI case with average characteristics was $18,386 (USD $14,190) (95% CI $14,312–$22,460; USD $11,046–$17,334) (Table 2).

Attributable length of stay of HA-CDI

The adjusted length of stay among HA-CDI cases was 13% greater than noncases of CDI (ratio, 1.13; 95% CI, 1.07–1.19) corresponding to an extra 5.6 days (95% CI, 3.10–8.06) in the hospital for a typical HA-CDI case.

Provincial burden of HA-CDI

Extrapolating to the entire cohort of HA-CDI that occurred in Alberta during the study period, the burden to the healthcare system was substantial, resulting in an additional 5,856 hospitalized days/year and an excess of $19,227,379 per year (USD $14,839,376) on average.

Discussion

HA-CDI was associated with extended length of stay and increased hospitalization costs compared to noncases of CDI in this population-based study. Cases of HA-CDI incurred higher proportions of intensive care unit and total drug costs than noncases of CDI, and mean costs were higher across all categories among HA-CDI cases compared to noncases of CDI. Approximately 42% of the HA-CDI cases in the full cohort were severe CDI, possibly contributing to their prolonged LOS.[28] To our knowledge, this is only the second study in Canada to evaluate the attributable length of stay and costs of hospital-acquired CDI and the first to report the use of a microcosting approach for the estimation of costs.[11,12]

The results of this study are consistent with a systematic review of 45 other CDI cost-of-illness studies, each with varying study quality and limited ability to assess attributable cost, with attributable mean CDI costs ranging from $8,911 to $30,049 (USD 2014).[11] Among studies that evaluated the attributable mean cost of HA-CDI and used a propensity score matching design, this study was most similar in design to Campbell et al[29] and secondarily to Tabak et al.[30] Campbell et al found an adjusted mean attributable cost of $17,015 (USD 2013) when comparing the costs of hospital-onset CDI among 5 high-risk subpopulations while also adjusting for exposure time before CDI diagnosis.[29] However, Tabak et al accounted for the length of stay prior to onset of HO-CDI and found that HO-CDI added a mean of $6,117 (USD 2013) to hospitalization costs, much lower than other studies.[14,30]

The Canadian study by Nanwa et al[11] reported the index hospitalization attributable mean cost as $37,282 (CAD 2014) for elective admission cases of HA-CDI and $25,933 (CAD 2014) for nonelective admission cases of HA-CDI. They used ICD-10-CA discharge codes to identify CDI-infected subjects; they did not adjust for exposure time; and they used a top-down cost estimation approach.[11,31] The differences between this study and those previously reported using similar methods may be attributed to a different patient mix at the institutions studied, how cases were defined and identified, the variables adjusted for in the analysis, the approach to cost estimation, and whether time to HA-CDI onset was accounted for.

This study has several limitations. Firstly, although we adjusted for exposure time to infection onset, some time-dependent bias may still persist in our estimate of excess costs. With HA-CDI, the longer a person stays in hospital, the greater their risk of acquiring *C. difficile*.[32] If left unaccounted, length of stay and costs will be overestimated because the time from admission to the occurrence of HA-CDI is incorrectly assigned to patients with HA-CDI.[15,32,33] We were unable to identify those costs that occurred prior to the onset of HA-CDI and exclude them from the outcome; therefore, we may have overestimated attributable costs.[33] However, Nelson et al[15] studied the costs of HA methicillin-resistant *Staphylococcus aureus* and found that matching on exposure time resulted in an 11.8% overestimate of costs (vs 31.5% unmatched). We believe that any overestimate was similarly reduced in our study compared to studies that have not corrected for time-dependent bias.[15] Tabak et al[30] and Campbell et al[29] both matched on exposure time and found similar estimates of excess length of stay due to HA-CDI (2.3 days and 7.8 days, respectively).[29,30]

Second, this study only considered direct costs from the healthcare payer's perspective, which did not include physician costs, nonhealthcare resources, outpatient costs, long-term care costs, readmissions, or productivity losses. It is conceivable that the excess

Table 1. Characteristics of Patients With and Without *Clostridioides difficile* Infection Before and After Matching, Fiscal 2012–2016

Variable	Before Matching			After Matching		
	Cases (n = 2,916), No. (%)	Controls (n = 717,169), No. (%)	Unweighted Standardized Difference, %	Cases (n = 2,871), No. (%)	Weighted Controls (n = 2,871), No. (%)	Weighted Standardized Difference, %
Age categories						
18–44 y	290 (9.95)	281,921 (39.3)	−72.4	286 (9.96)	243.7 (8.5)	5.0
45–54 y	264 (9.05)	85,274 (11.9)	−9.3	256 (8.9)	257.0 (8.9)	−0.1
55–64 y	499 (17.1)	109,936 (15.3)	4.8	489 (17.0)	484.7 (16.9)	0.4
65–74 y	567 (19.4)	101,403 (14.1)	14.2	558 (19.4)	558.7 (19.5)	−0.1
75+ y	1,296 (44.4)	138,635 (19.3)	56	1,282 (44.6)	1,326.9 (46.2)	−3.1
Female sex	1,433 (49.1)	427,891 (59.7)	−21.2	1,415 (49.3)	1,410.3 (49.1)	0.3
Comorbidities						
Congestive heart failure	615 (21.1)	39,598 (5.5)	47.1	606 (21.1)	624.6 (21.7)	−1.6
Cardiac arrhythmias	720 (24.7)	55,195 (7.7)	47.4	710 (24.7)	724.8 (25.2)	−1.2
Valvular disease	201 (6.9)	14,279 (2.0)	24	200 (7.0)	203. (7.1)	−0.5
Pulmonary circulation disorders	200 (6.9)	14,082 (2.0)	24	195 (6.8)	204.9 (7.1)	−1.4
Peripheral vascular disorders	184 (6.3)	12,633 (1.8)	23.3	180 (6.3)	173.4 (6.0)	0.9
Hypertension, uncomplicated	1,203 (41.3)	115,410 (16.1)	57.9	1,186 (41.3)	1,174.5 (40.9)	0.8
Hypertension, complicated	36 (1.2)	2,131 (0.3)	10.8	35 (1.2)	30.4 (1.1)	1.5
Paralysis	91 (3.1)	7,556 (1.0)	14.5	90 (3.1)	123.6 (4.3)	−6.3
Other neurological disorders	232 (8.0)	22,312 (3.1)	21.3	230 (8.0)	259.1 (9.0)	−3.6
Chronic pulmonary disease	613 (21.0)	53,596 (7.5)	39.5	604 (21.0)	579.7 (20.2)	2.1
Diabetes, uncomplicated	255 (8.7)	29,910 (4.2)	18.7	249 (8.7)	282.0 (9.8)	−4.0
Diabetes, complicated	564 (19.3)	49,331 (6.9)	37.6	556 (19.4)	603.7 (21.0)	−4.1
Hypothyroidism	191 (6.5)	19,253 (2.7)	18.5	191 (6.6)	196.5 (6.8)	−0.8
Renal failure	304 (10.4)	18,628 (2.6)	32.1	296 (10.3)	273.8 (9.5)	2.5
Liver disease	193 (6.6)	16,139 (2.2)	21.3	187 (6.5)	184.2 (6.4)	0.4
Peptic ulcer disease excl. bleeding	74 (2.5)	3,828 (0.5)	16.3	72 (2.5)	66.7 (2.3)	1.2
AIDS/HIV	11 (0.4)	638 (0.09)	6	10 (0.3)	5.6 (0.2)	2.8
Lymphoma	105 (3.6)	4,110 (0.6)	21.3	104 (3.6)	95.0 (3.3)	1.7
Metastatic cancer	186 (6.4)	21,360 (3.0)	16.2	184 (6.4)	197.8 (6.9)	−1.9
Solid tumor without metastasis	336 (11.5)	38,377 (5.3)	22.3	329 (11.5)	314.8 (11.0)	1.5
Rheumatoid arthritis/collagen vascular diseases	104 (3.6)	7,550 (1.0)	16.8	104 (3.6)	100.6 (3.5)	0.6
Coagulopathy	159 (5.4)	11,731 (1.6)	20.8	153 (5.3)	153.6 (5.3)	−0.1
Obesity	140 (4.8)	16,712 (2.3)	13.4	137 (4.8)	133.7 (4.7)	0.5
Weight loss	259 (8.9)	12,117 (1.7)	32.6	254 (8.8)	294.6 (10.3)	−4.9
Fluid and electrolyte disorders	886 (30.4)	59,164 (8.2)	58.4	875 (30.5)	862 (30.0)	1.0
Blood loss anemia	70 (2.4)	4,658 (0.6)	14.3	69 (2.4)	58.2 (2.0)	2.5
Deficiency anemia	233 (8.0)	14,094 (2.0)	28	229 (8.0)	219.9 (7.7)	1.2
Alcohol abuse	225 (7.7)	29,021 (4.0)	15.6	219 (7.6)	228.8 (8.0)	−1.3
Drug Abuse	99 (3.4)	19,318 (2.7)	4.1	97 (3.4)	109.2 (3.8)	−2.3
Psychoses	51 (1.7)	11,107 (1.5)	1.6	50 (1.7)	68.7 (2.4)	−4.8
Depression	315 (10.8)	34,968 (4.9)	22.2	309 (10.8)	348.4 (12.1)	−4.3
Healthcare encounters						
No. of previous admissions in 1 year prior						
0	1,049 (36.0)	485,470 (67.7)	−66.9	1,027 (35.8)	1,051.7 (36.6)	−1.7

(*Continued*)

Table 1. (*Continued*)

Variable	Before Matching			After Matching		
	Cases (n = 2,916), No. (%)	Controls (n = 717,169), No. (%)	Unweighted Standardized Difference, %	Cases (n = 2,871), No. (%)	Weighted Controls (n = 2,871), No. (%)	Weighted Standardized Difference, %
1–2	1,329 (45.6)	183,030 (25.5)	42.8	1,315 (45.8)	1,298.7 (45.2)	1.1
3–5	452 (15.5)	40,767 (5.7)	32.3	444 (15.5)	439.5 (15.3)	0.4
≥6	86 (2.9)	7,902 (1.1)	13.1	85 (3.0)	81.1 (2.8)	0.8
No. of previous ICU admissions						
0	2,239 (76.8)	647,590 (90.3)	−37	2,211 (77.0)	2,084.8 (72.6)	10.1
1–2	633 (21.7)	66,903 (9.3)	34.7	619 (21.6)	705.1 (24.6)	−7.1
3–5	44 (1.5)	2,676 (0.4)	11.8	41 (1.4)	81.1 (2.8)	−10.1
No. of previous surgeries						
0	1,880 (64.5)	421,814 (58.8)	11.7	1,859 (64.7)	1,758.4 (61.2)	7.2
1–3	847 (29.0)	278,324 (38.8)	−20.7	831 (28.9)	823.8 (28.7)	0.6
4–6	139 (4.8)	14,678 (2.0)	15	132 (4.6)	184.7 (6.4)	−8.1
7 or more	50 (1.7)	2,353 (0.3)	13.8	49 (1.7)	104.1 (3.6)	−12.7
Antibiotic class[a]						
Broad-spectrum gram-negative agents	1,208 (41.4)	56,522 (7.9)	84.5	1,179 (41.1)	1,384.8 (48.2)	−14.5
Gram-positive antimicrobial resistant organism agents	817 (28.0)	32,812 (4.6)	66.9	794 (27.7)	1,001.0 (34.9)	−15.6
Narrow-spectrum agents	1,255 (43.0)	207,907 (29.0)	29.6	1,223 (42.6)	1,426.1 (49.7)	−14.2
Second- to fifth-generation cephalosporins	1,409 (48.3)	91,698 (12.8)	83.6	1,380 (48.1)	1,453.4 (50.6)	-–5.1
Other systemic antibacterial agents	2,170 (74.4)	195,191 (27.2)	107.1	2,128 (74.1)	2,297.7 (80.0)	−14.1
Severity on admission						
Admission category						
Urgent	2,383 (81.7)	433,668 (60.5)	48.2	2,344 (81.6)	2,392.0 (83.3)	−4.4
Elective	533 (18.3)	283,501 (39.5)	−48.1	527 (18.4)	479.0 (16.7)	
Serum creatinine[b]						
Low	131 (4.5)	18,189 (2.5)	10.6	129 (4.5)	145.5 (5.1)	−2.7
Normal	1,577 (54.1)	311,672 (43.5)	21.3	1,552 (54.1)	1,501.6 (52.3)	3.6
High	1,041 (35.7)	70,623 (9.8)	64.8	1,027 (35.8)	969.1 (33.7)	4.2
Missing	167 (5.7)	316,685 (44.2)	−99.1	163 (5.7)	254.7 (8.9)	−13.3
Glucose[c]						
Low	21 (0.7)	829 (0.1)	9.4	21 (0.7)	16.6 (0.6)	1.8
Normal	2,072 (71.1)	212,626 (29.6)	91.2	2,043 (71.2)	1,890.1 (65.8)	11.6
High	278 (9.5)	25,504 (3.6)	24.3	274 (9.5)	297.9 (10.4)	−2.8
Missing	545 (18.7)	478,210 (66.7)	−110.9	533 (18.6)	666.4 (23.2)	−11.7
Platelets[d]						
Low	481 (16.5)	68,014 (9.5)	21	473 (16.5)	480.9 (16.7)	−0.7
Normal	2,080 (71.3)	423,264 (59.0)	26	2,051 (71.4)	1,926.8 (67.1)	9.3
High	208 (7.1)	17,031 (2.4)	22.5	205 (7.1)	224.4 (7.8)	−2.6
Missing	147 (5.0)	208,860 (29.1)	−67.5	142 (4.9)	238.8 (8.3)	−14.5
Sodium[e]						
Low	445 (15.3)	37,886 (5.3)	33.3	437 (15.2)	445.7 (15.5)	-0.8
Normal	2,237 (76.7)	352,444 (49.1)	59.6	2,205 (76.8)	2,105.8 (73.3)	8.1
High	57 (1.9)	4,131 (0.6)	12.4	56 (1.9)	57.1 (2.0)	−0.3
Missing	177 (6.1)	322,708 (45.0)	−99.8	173 (6.0)	262.3 (9.1)	−12.6

Table 1. (*Continued*)

Variable	Before Matching			After Matching		
	Cases (n = 2,916), No. (%)	Controls (n = 717,169), No. (%)	Unweighted Standardized Difference, %	Cases (n = 2,871), No. (%)	Weighted Controls (n = 2,871), No. (%)	Weighted Standardized Difference, %
Blood urea[f]						
Low	88 (3.0)	20,634 (2.9)	0.8	85 (3.0)	87.2 (3.0)	−0.4
Normal	1,233 (42.3)	198,195 (27.6)	31.2	1,215 (42.3)	1,159.2 (40.4)	3.8
High	1,132 (38.8)	69,846 (9.7)	72.1	1,115 (38.8)	1,083.5 (37.7)	2.2
Missing	463 (15.9)	428,494 (59.7)	−101.4	456 (15.9)	541.0 (18.8)	−8.0
White blood cell counts[g]						
Low	155 (5.3)	14,105 (2.0)	17.9	151 (5.3)	151.6 (5.3)	−0.1
Normal	1,417 (48.6)	308,684 (43.0)	11.2	1,402 (48.8)	1,418.3 (49.4)	−1.2
High	1,202 (41.2)	186,332 (26.0)	32.7	1,181 (41.1)	1,060.8 (36.9)	8.5
Missing	142 (4.9)	208,048 (29.0)	−68	137 (4.8)	240.2 (8.4)	−15.6
pH[h]						
low	306 (10.5)	25,363 (3.5)	27.5	298 (10.4)	309.8 (10.8)	−1.3
normal	327 (11.2)	27,353 (3.8)	28.4	323 (11.2)	308.0 (10.7)	1.6
high	106 (3.6)	7,551 (1.0)	17.1	104 (3.6)	113.1 (3.9)	−1.7
missing	2,177 (74.7)	656,902 (91.6)	−46.4	2,146 (74.7)	2,140 (74.5)	0.5
Admission or HA-CDI characteristics						
Fiscal year						
2012	665 (22.8)	172,419 (24.0)	−2.8	658 (22.9)	611.9 (21.3)	3.9
2013	808 (27.7)	170,609 (23.8)	9	798 (27.8)	785.4 (27.4)	1.0
2014	729 (25.0)	183,066 (25.5)	−1.2	713 (24.8)	732.2 (25.5)	−1.5
2015	714 (24.5)	191,075 (26.6)	−4.9	702 (24.4)	741.6 (25.8)	−3.2
Zone						
Calgary	1,189 (40.8)	338,666 (47.2)	−12.9	1,171 (40.8)	1,322.5 (46.1)	−10.7
Edmonton	1,726 (59.2)	377,423 (52.6)	13.2	1,699 (59.2)	1,547.4 (53.9)	10.7
North	1 (0.03)	1,080 (0.1)	−3.8	1 (0.03)	1.02 (0.04)	−0.1
Facility type						
Teaching facility	1,253 (43.0)	227,934 (31.8)	23.3	1,228 (42.8)	1,243.6 (43.3)	−1.0
Large urban	1,436 (49.2)	438,443 (61.1)	−24.1	1,420 (49.5)	1,362.4 (47.4)	4.0
Specialty	51 (1.7)	5,991 (0.8)	8.1	50 (1.7)	128.7 (4.5)	−16.6
Suburban/Rural	176 (6.0)	44,801 (6.2)	−0.9	173 (6.0)	136.3 (4.7)	5.6

Note. AIDS/HIV, human immunodeficiency virus infection and acquired immune deficiency syndrome; ICU, intensive care unit; HA-CDI, hospital-acquired *Clostridioides difficile* infection.
[a]Broad-spectrum gram-negative agents: ertapenem, meropenem, piperacillin/tazobactam; gram-positive antimicrobial-resistant organism active agents: linezolid, vancomycin; narrow-spectrum agents: amoxicillin, ampicillin, cefazolin, cephalexin, cloxacillin, gentamicin, penicillin G sodium, penicillin V potassium, tobramycin. Second- to fifth-generation cephalosporins: cefepime, cefixime, cefotaxime, cefprozil, ceftazidime, ceftriaxone, cefuroxime. Other systemic antibacterials: amoxicillin/clavulanate, ciprofloxacin, clarithromycin, clindamycin, colistin erythromycin, levofloxacin, metronidazole, nitrofurantoin, piperacillin, sulfamethoxazole/trimethoprim, tetracycline, trimethoprim.
[b]Serum creatinine reference: 35–125 µmol/L.
[c]Glucose reference: 2.2–11.0 mmol/L.
[d]Platelet reference: 140–450 $\times 10^9$ /L.
[e]Sodium reference: 133–148 mmol/L.
[f]Blood urea reference: 2.0–9.0 mmol/L.
[g]White blood cell count reference: 4.0–11.0 $\times 10^9$/L.
[h]pH reference: 7.35–7.45.

Table 2. Adjusted Outcomes after Matching

Outcome	Adjusted Ratio (Case:Control)	95% CI	Marginal Estimatefor Cases[a]	Marginal Estimate for Controls[a]	Difference[a]	95% CI
Total cost[b]	1.27	1.21–1.33	$87,142.50 (USD $67,255)	$68,756.29 (USD $53,065)	$18,386.21 (USD $14,190)	$14,312.36–$22,460.06 (USD $11,046–$17,334)
Total length of stay, d	1.13	1.07–1.19	49.45	43.87	5.58	3.10–8.06

Note. CI, confidence interval; USD, US dollars.
[a]Marginal effects show how the adjusted predictions for cases of HA-CDI differ from the adjusted prediction for noncases of CDI. With average marginal effects (AME) the observed values of the variables are used instead of their means, and a predicted cost for each individual is computed, assuming they are all a case (ie, case=1). This is then repeated assuming each individual is a control (ie, case=0). The difference in predicted costs for each individual is calculated and averaged.
[b]Costs shown in 2018 Canadian dollars and in US dollars.

costs of HA-CDI would be significantly greater had these costs been included,[34,35] though studies suggest that >70% of attributable costs relate to hospitalization costs and decreases over time.[11,36] Third, the conditioning of the propensity score does not balance unmeasured covariates; thus, the estimates may include some bias due to unmeasured confounding.[16]

However, our study had many strengths. It was a population-based study of all HA-CDI cases in Alberta, spanning multiple years and multiple acute-care facilities. Although outcomes were measured at facilities with microcosting data available, we found minimal differences between the initial and microcosting cohorts. A microcosting approach for the cost estimation is more accurate and precise than gross costing methods because it allocates costs to individual healthcare services based on the actual use of the specific resources and incorporates costs related to hospital administration and other services that support patient care, which is a significant portion of total costs of inpatient care (eg, institutional overhead costs, labor costs).[37,38] We also used a clinical surveillance definition of HA-CDI. Most studies evaluating excess costs and length of stay due to HA-CDI use ICD-10 codes for case identification using national hospital discharge databases. Although these data are readily available, coding practices vary, and the timing of HA-CDI onset is not captured.[39] The use of a clinical surveillance definition for HA-CDI is more robust in identifying true episodes of HA-CDI; it allows accurate assessment of location of acquisition and the ability to determine timing of onset. Additionally, these surveillance data are used by researchers and decision makers to evaluate the burden of HA-CDI both provincially and nationally and to evaluate the impact of interventions on HA-CDI trends.

In summary, using rigorous propensity-matched design and analysis, this study has demonstrated that HA-CDI is associated with significant attributable costs. Our estimates will assist decision makers, healthcare providers, and patients in understanding the healthcare system burden of disease, justifying expenditures on intervention efforts and policies related to infection prevention and control, evaluating program effectiveness, determining allocation of research funding, and assessing the potential cost savings or bed days saved due to prevented infections.[15,40]

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2019.178

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