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Evaluating the costs of *Escherichia coli* bloodstream infections: a population-based cohort study in a large metropolitan Canadian region

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Objectives: We evaluated the costs of susceptible and resistant *Escherichia coli* bloodstream infections (BSIs) in adults. Secondary outcomes were the impact of BSI on length of stay (LOS), readmissions and death.

Methods: We examined a population-based retrospective cohort of blood cultures from 2011 to 2018 in Calgary, Canada, linked to microcosting and gross costing data. Propensity score matching was completed, and costs were compared between no BSI and *E. coli* BSI over 90 days using linear regression.

Results: A total of 4581 BSIs in 89 673 adults experienced *E. coli* bacteraemia during the study period. The mean cost of an *E. coli* BSI at 90 days was $39 072 (SD: $95 747) in adults. Ceftriaxone-resistant (CRO-R) *E. coli*, resistant to fluoroquinolones (FQ) and trimethoprim/sulfamethoxazole, compared with susceptible *E. coli* BSI resulted in the greatest mean cost at $53 899 and the highest odds of readmission, increased LOS, and death.

Conclusions: *E. coli* BSI is associated with substantial costs. Total cost differences were highest in those with CRO-R *E. coli* with resistance to FQ and trimethoprim/sulfamethoxazole. Over the study period, bacteraemia secondary to these strains alone, added over $9 million to costs for healthcare in the Calgary Zone.

Introduction

Bloodstream infections (BSIs) are an important cause of morbidity and mortality in hospitalized patients, with a rising incidence.[1] *Escherichia coli*, a Gram-negative Enterobacterales and gut commensal, is the leading cause of BSI among adults in developed countries[2–4] and locally in the Calgary health region.[5] BSIs carry not only morbidity and mortality risks but a considerable cost to our healthcare systems.[5–10] In North America, the average cost associated with a single episode of bacteraemia is estimated between $6805 and $59 266 in US dollars (USD).[9,11,12] Limited population-level studies are available regarding the economic burden associated with BSI, and to our knowledge no studies have examined the healthcare costs of *E. coli* BSI in a Canadian health region. We aimed to determine the cost of susceptible and resistant *E. coli* BSI in adults in the Calgary health region. We hypothesized that the economic cost of a BSI would be higher than those without a BSI, with drug-resistant *E. coli* BSIs being the costliest.

Methods

Cohort

We conducted a population-based retrospective cohort study of adults (≥18 years of age) in the Calgary, Alberta, health region,[13] between 1 January 2011 and 30 December 2018 who had blood culture testing

done within the study period. All blood cultures were provided from a single centralized laboratory that services the entire population.

Groups within the cohort were compared:

1. Carbapenem resistant;
2. Ceftriaxone-resistant (CRO-R) (excluding carbapenem resistant) with fluoroquinolone (FQ) and trimethoprim/sulfamethoxazole resistance;
3. CRO-R (excluding carbapenem resistant) and FQ or trimethoprim/sulfamethoxazole susceptible;
4. Resistant to one or two antibiotics, excluding β-lactam antibiotics;
5. Susceptible (did not display resistance to any antibiotics).

Further details on these classifications and antibiotics considered can be found in the Supplemental Material Table S1 (available as Supplementary data at *JAC-AMR* Online). The stratification of antimicrobial resistance was based on clinical practice during the study period of using a third-generation cephalosporin or piperacillin/tazobactam upfront for Gram-negative bacteraemia with adjustment of therapy based on susceptibility results available approximately 24–48 h after initial results from blood cultures. All *E. coli* (including polymicrobial) BSIs were compared with patients with negative blood cultures during the study period. Resistance was determined at the time of standardized susceptibility testing based on CLSI susceptibility testing protocols,[14] where resistance was defined as an MIC above the established CLSI breakpoint for that antimicrobial.

Data sources

Calgary Laboratory Services

Calgary Laboratory Services' (CLS) database was used to identify all patients who had blood cultures performed between 1 January 2011 and 30 December 2018 and then to identify those with a positive result for *E. coli*. If there were multiple positive blood cultures for one patient, only the first positive was used. We collected follow-up data for all patients for 90 days. The clinical sources of the bacteraemia and other positive cultures were not part of this study protocol. Susceptibility testing was done using the VITEK^{R} 2 system (bioMérieux Canada). Further testing for mechanisms of resistance (ESBL, ampC beta-lactamases, KPC, etc.) was not included in the analysis.

Alberta Health Services Analytics

Alberta Health Services (AHS) Analytics provided access to the Enterprise Data Warehouse (EDW), linked to the Discharge Abstract Database (DAD), National Ambulatory Care Reporting System (NACRS), Vital Statistics, and Alberta Health Registry, for Alberta residents with health insurance. Hospitalizations and length of stay (LOS) in hospital were identified in DAD, in-facility mortality from DAD and NACRS, and comorbidities, categorized by Elixhauser index,[15,16] were derived from both DAD and NACRS. Outpatient visits were identified from the NACRS. Average costs for outpatients were determined using gross costing data obtained from AHS Analytics, where costs were collected from the NACRS dataset using case mix group and resource intensity weight variables.

AHS corporate finance

Mean costs were determined using microcosting methods for inpatients, obtained from corporate data for the Calgary urban regional hospitals. Microcosting, the gold standard for costing data,[17] includes the costs of each resource component based on a derived unit cost, traced to individual patients. We included all costs incurred during an admission, including: drugs, medical supplies and equipment, procedures, diagnostic imaging, provision of services, direct physician costs (not billings), and administrative and overhead costs.

Outcomes

The primary outcome was the cost of the initial emergency department (ED) visit or hospitalization, and the full costs of all ED visits and admissions at 90 days, including cost differences between susceptible and resistant *E. coli* BSI, and no BSI. Secondary outcomes were the difference in LOS for susceptible and resistant *E. coli* BSI, the odds of readmission, and the odds of in-facility death between cohorts.

Statistical analyses

Patient demographics were summarized using frequencies and percentages for categorical variables, and mean and SD, or median and IQR, for continuous variables, by age group (0 to 17, and 18 and older) and presence of *E. coli* (no BSI, antibiotic-susceptible and antibiotic-resistant BSIs).

Linear regression estimated adjusted differences in total costs and LOS, whereas logistic regression estimated OR for death, comparing patients with no BSI, antibiotic-susceptible and antibiotic-resistant BSI. All models adjusted for confounding using 1:4 propensity score matching with replacement based on patient age, sex and Elixhauser comorbidity index based on hospitalizations within the 2 years prior to index date of blood culture. Variables that did not display optimal balance after matching were further adjusted by inclusion in the regression model.

All costs were inflated to 2019 Canadian dollars using the consumer price index. We used the public healthcare payer perspective: therefore, patient-borne costs were not included. All analyses were performed using R version 4.1.0. All tests of significance were two-tailed and evaluated at $\alpha = 0.05$.

This study was approved by the University of Calgary Research Ethics Board (Study number REB19-1183).

Results

Baseline characteristics

The baseline characteristics of the study cohort are summarized in Table 1. A total of 89 673 adults had blood cultures performed during the study period. Only three BSIs showed carbapenem resistance; these were excluded from analysis. Adults with susceptible or resistant *E. coli* BSI were on average older than those with negative blood cultures, with a mean (SD) age of 64.9 (18.4) compared with 55.8 (20.5) years, respectively. The median LOS admitted to hospital was longer for adults with CRO-R *E. coli* BSI resistant to FQ and trimethoprim/sulfamethoxazole (8 days, IQR 12) compared with susceptible (6 days, IQR 9) *E. coli* BSI.

The propensity matched scores are shown in Figure 1. The results of the propensity matching adjusted absolute standardized mean differences for covariates under the threshold of 0.1, except for Elixhauser index when comparing CRO-R, susceptible to FQ or trimethoprim/sulfamethoxazole compared to susceptible *E. coli* BSI (Figure 1d).

Cost outcomes

The results of the total costs are presented in Table 2. The cost differences for the initial visit and total cost at 90 days are presented in Table 3.The greatest total adjusted cost difference was seen with CRO-R, resistant to FQ and trimethoprim/sulfamethoxazole compared with susceptible *E. coli* BSI ($15 875; 95% CI: $1200 to $30 550; $P < 0.001$), followed by all resistant *E. coli* BSI compared with *E. coli*-negative cultures ($10 025; 95% CI: $5789 to $14 261; $P < 0.001$).

Table 1. Baseline characteristics of cohort ($N=89\,673$ adults)

	Negative blood cultures ($n=85\,092$)	Susceptible *E. coli* ($n=1888$)	Ceftriaxone-susceptible: resistant to FQ and/or SXT ($n=373$)	CRO-R, susceptible to FQ or SXT ($n=1684$)	CRO-R, resistant to FQ and SXT ($n=633$)
Age, y, mean (SD)	55.8 (20.5)	66.3 (17.9)	66.0 (16.2)	62.8 (19.5)	65.5 (17.6)
Female, *n* (%)	41 695 (49)	1071 (56.7)	185 (49.6)	1007 (59.8)	288 (45.5)
Male, *n* (%)	43 396 (51)	817 (43.3)	188 (50.4)	677 (40.2)	345 (54.5)
Other, *n* (%)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Elixhauser comorbidity index, *n* (%)					
Less than −10	26 (0)	0 (0)	0 (0)	0 (0)	0 (0)
−10 to −5	1304 (1.5)	7 (0.4)	0 (0)	15 (0.9)	1 (0.2)
−4 to 0	43 761 (51.4)	835 (44.2)	168 (45)	726 (43.1)	267 (42.2)
1 to 5	15 974 (18.8)	378 (20)	66 (17.7)	368 (21.9)	134 (21.2)
6 to 10	9268 (10.9)	238 (12.6)	46 (12.3)	221 (13.1)	112 (17.7)
11 to 15	8486 (10)	234 (12.4)	57 (15.3)	186 (11)	65 (10.3)
>15	6273 (7.4)	196 (10.4)	36 (9.7)	168 (10)	54 (8.5)
Length of stay					
Admitted to hospital, d, median (IQR, 90th quantile)	6 (10, 29)	6 (9, 31)	6 (10, 29.7)	6 (8, 25)	8 (12, 37.4)
In ED, h, median (IQR, 90th quantile)	4.8 (3.4, 9.4)	4.7 (3.1, 9.8)	4.9 (2.3, 10.0)	5.2 (3.1, 10.1)	5.2 (3.4, 10.5)
Admitted to hospital, *n* (%)					
ED only	26 975 (31.7)	298 (15.8)	59 (15.8)	257 (15.3)	86 (13.6)
Admitted to hospital	58 117 (68.3)	1590 (84.2)	314 (84.2)	1427 (84.7)	547 (86.4)
Required ED visit or hospital admission within 90 days, *n* (%)					
No	22 490 (26.4)	429 (22.7)	83 (22.3)	399 (23.7)	126 (19.9)
Yes	62 602 (73.6)	1459 (77.3)	290 (77.7)	1285 (76.3)	507 (80.1)
Admitted to hospital within 90 days, *n* (%)					
No	71 521 (84.1)	1497 (79.3)	281 (75.3)	1322 (78.5)	475 (75)
Yes	13 571 (15.9)	391 (20.7)	92 (24.7)	362 (21.5)	158 (25)
Died in facility at first ED visit or hospital admission, *n* (%)					
No	80 093 (94.1)	1723 (93.1)	349 (93.6)	1535 (91.1)	566 (89.4)
Yes	4999 (5.9)	165 (8.7)	24 (6.4)	150 (8.9)	67 (10.6)

CRO-R, ceftriaxone-resistant; ED, emergency department; FQ, fluoroquinolone; SXT, trimethoprim/sulfamethoxazole resistant.

Hospitalizations and mortality

No difference in hospital LOS was observed comparing all *E. coli* infections with negative cultures ($P=0.44$); however, all resistant *E. coli* BSIs resulted in longer initial hospitalizations than susceptible BSIs (1.30 days; 95% CI: 0.03 to 2.56; $P=0.04$). CRO-R, resistant to FQ and trimethoprim/sulfamethoxazole, compared with susceptible *E. coli* BSI had greater odds of readmission (OR: 1.48; 95% CI: 1.21 to 1.82; $P<0.001$), although CRO-R, susceptible to FQ or trimethoprim/sulfamethoxazole, compared with susceptible *E. coli* BSI, did not have greater odds of readmission (OR: 1.10; 95% CI 0.96 to 1.26; $P=0.16$) . The overall in-hospital mortality was 8.9% (406/4578). The odds of death in-facility were significantly increased by any resistance compared with susceptible *E. coli* BSI (OR: 1.18; 95% CI: 1.01 to 1.38; $P=0.04$). These results are displayed in the Supplemental Material Tables S2–S4.

Discussion

In our large, population-based cohort study of adults with *E. coli* BSI, the most costly event was a CRO-R, resistant to FQ and trimethoprim/sulfamethoxazole *E. coli* BSI, where the mean total cost at 90 days was $53 829 (SD = $184 335). The greatest cost difference was for a CRO-R, resistant to FQ and trimethoprim/sulfamethoxazole, compared with susceptible *E. coli* BSI, both for initial hospitalization or ED visit and at 90 days. Resistant BSIs led to longer hospitalizations compared with susceptible BSIs. The odds of readmission were highest among CRO-R, resistant to FQ and trimethoprim/sulfamethoxazole, compared with susceptible *E. coli* BSI. These findings accounted for differences in patient factors, including age, sex and comorbidities.

Our cost burden of an adult admission for an episode of bacteraemia was comparable to other studies. A 2016 study found the cost of Gram-negative BSI was $36 452 USD for susceptible infections and $59 266 USD for MDR BSIs in adults.[9] Multiple factors may explain the increased cost of resistant infections in adults, noted across other studies,[8,9,18] including initial inadequate antibiotic therapy and delays to appropriate therapy.[8,18] This delay can result in complications, such as the need for reserve antimicrobials, procedures or surgery, and critical care,[9] all of which are costly. The lag time for susceptibility results

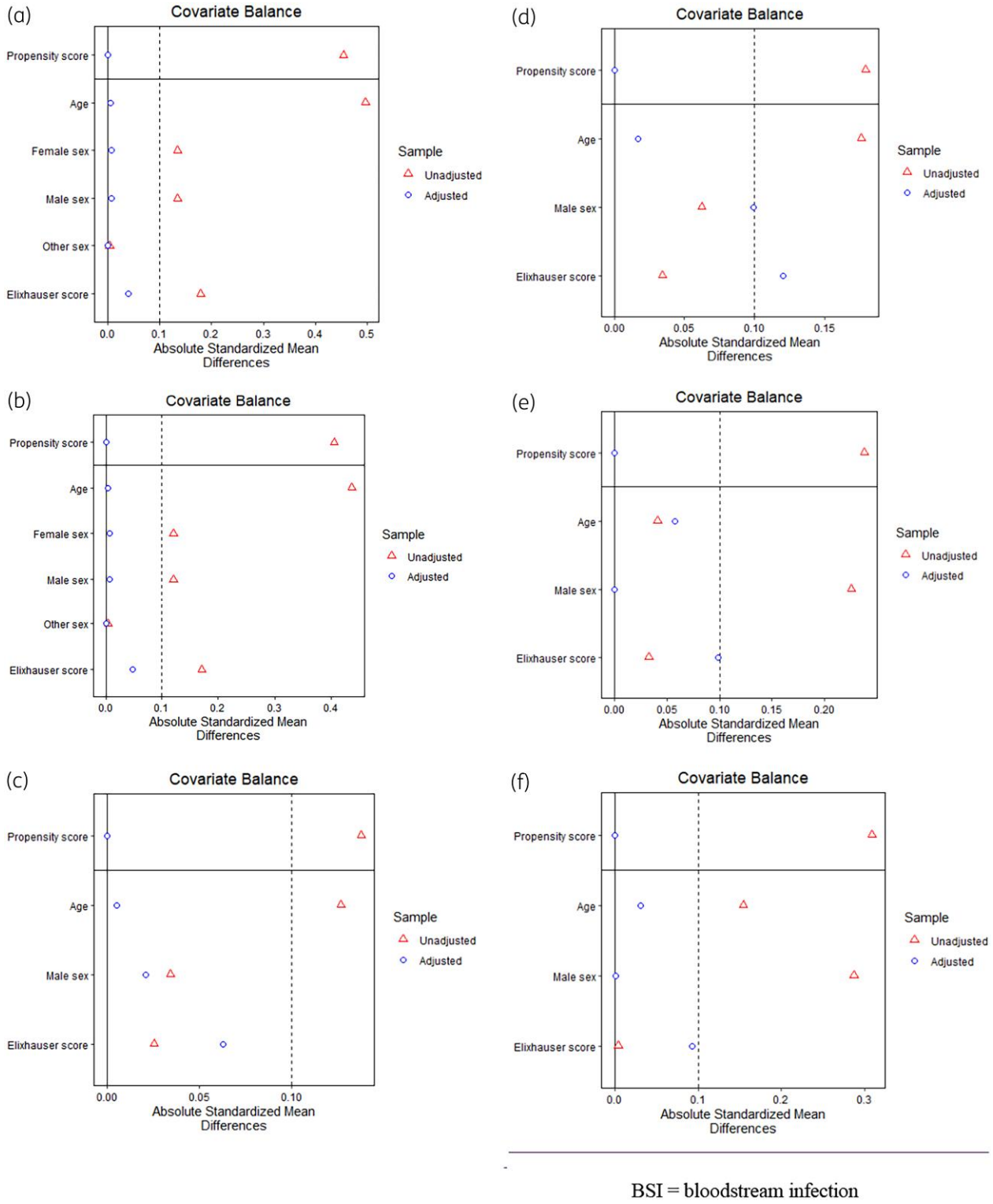

Figure 1. Absolute standardized mean differences of covariates unadjusted and adjusted by 1:4 propensity score matching among adults comparing (a) any *E. coli* BSI versus negative cultures; (b) all resistant *E. coli* BSI versus *E. coli*-negative cultures; (c) all resistant versus susceptible *E. coli* BSI; (d) ESBL, susceptible to FQ or SXT versus susceptible *E. coli* BSI; and (e) ESBL, resistant to FQ and SXT versus susceptible *E. coli* BSI; (f) ESBL, resistant to FQ and SXT compared to ESBL, susceptible to FQ or SXT. BSI, bloodstream infection; ESBL, extended-spectrum beta-lactamase; FQ, fluoroquinolones; SXT, trimethoprim/sulfamethoxazole.

Table 2. Costs of adults with *E. coli* BSI and no *E. coli* BSI

	Negative blood cultures ($n=85\,092$)	Susceptible *E. coli* ($n=1888$)	Ceftriaxone-susceptible: resistant to FQ and/or SXT ($n=373$)	CRO-R, susceptible to FQ or SXT ($n=1684$)	CRO-R, resistant to FQ and SXT ($n=633$)
Full cost of first admission or ED visit, $[a]					
Hospital admissions and ED visits, mean (SD)	14 846 (36 621)	18 883 (42 054)	17 844 (32 386)	18 646 (46 446)	28 381 (106 966)
Hospital admissions and ED visits, median (IQR)	4783 (12 599)	7112 (12 804)	6826 (12 413)	6795 (12 140)	8444 (14 174)
Hospital admissions, mean (SD)	21 497 (42 707)	22 311 (45 007)	21 089 (34 347)	21 907 (49 762)	32 758 (1 114 467)
Hospital admissions, median (IQR)	8772 (16 500)	8938 (14 146)	8367 (15 091)	8207 (13 509)	10 350 (15 673)
ED visits, mean (SD)	515 (369)	592 (377)	576 (394)	576 (394)	537 (370)
ED visits, median (IQR)	452 (468)	509 (439)	500 (286)	464 (383)	444 (392)
Full cost of total healthcare use ($[a]*), including first and subsequent admissions or ED visits within 90 days*					
Hospital admissions and ED visits, mean (SD)	27 410 (57 696)	36 566 (66 437)	34 061 (50 785)	37 444 (80 966)	53 829 (184 335)
Hospital admissions and ED visits, median (IQR)	9848 (25 808)	15 968 (31 032)	13 884 (31 331)	14 899 (30 747)	18 873 (37 067)
Hospital admissions, mean (SD)	37 038 (64 767)	40 502 (69 951)	38 013 (53 413)	41 093 (86 070)	58 486 (197 246)
Hospital admissions, median (IQR)	16 558 (31 569)	18 111 (32 697)	15 564 (37 980)	16 761 (31 644)	20 279 (37 379)
ED visits, mean (SD)	6666 (28 863)	15 567 (36 598)	13 026 (24 729)	17 182 (36 683)	24 202 (41 313)
ED visits, median (IQR)	1019 (1519)	1955 (6729)	1804 (10 837)	2028 (10 476)	3590 (27 124)

BSI, bloodstream infection; CRO-R, ceftriaxone-resistant; ED, emergency department; FQ, fluoroquinolone; SXT, trimethoprim/sulfamethoxazole resistant.
[a]Canadian dollars, inflated to 2019 values.

Table 3. First hospitalization or ED visit cost differences and 90 day total cost differences, comparing susceptible and resistant *E. coli* BSI with no BSI

	Estimated cost difference,[a,b] $ (95% CI)	*P* value
First hospitalization or ED visit		
Any *E. coli* BSI compared with negative blood cultures	3565 (1863 to 5266)	<0.001
All resistant *E. coli* BSI compared with *E. coli*-negative cultures	4129 (1671 to 6586)	<0.001
All resistant compared with susceptible *E. coli* BSI	3641 (891 to 6390)	0.009
CRO-R, susceptible to FQ or SXT compared with susceptible *E. coli* BSI	−153 (−2544 to 2238)	0.90
CRO-R, resistant to FQ and SXT compared with susceptible *E. coli* BSI	9135 (523 to 17 748)	0.04
CRO-R, resistant to FQ and SXT, compared with CRO-R, susceptible to FQ or SXT	9661 (1240 to 18 081)	0.02
Total cost at 90 days		
Any *E. coli* BSI compared with *E. coli*-negative cultures	7921 (5044 to 10 800)	<0.001
All resistant *E. coli* BSI compared with *E. coli*-negative cultures	10 025 (5789 to 14 261)	<0.001
All resistant compared with susceptible *E. coli* BSI	5485 (792 to 10 178)	0.02
CRO-R, susceptible to FQ or SXT, compared with susceptible *E. coli* BSI	1421 (−2662 to 5504)	0.50
CRO-R, resistant to FQ and SXT, compared with susceptible *E. coli* BSI	15 875 (1200 to 30 550)	0.03
CRO-R, resistant to FQ and SXT, compared with CRO-R, susceptible to FQ or SXT	14 374 (85 to 28 664)	0.049

BSI, bloodstream infection; CRO-R, ceftriaxone-resistant; ED, emergency department; FQ, fluoroquinolone; SXT, trimethoprim/sulfamethoxazole resistant.

[a]Based on linear regression model of first hospitalization or total costs at 90 days of blood culture using propensity score matching based on age, sex, Elixhauser comorbidity index, and facility, further adjusted for Elixhauser comorbidity score.

[b]Canadian dollars, inflated to 2019 values.

disproportionately impacts those with resistant infections. Implementation and evaluation of rapid diagnostic susceptibility practices in laboratories is required.

Previous studies have demonstrated excess mortality among BSIs compared with no BSI for all pathogens.[1,3,4,19] Mortality is further increased for resistant organisms, particularly ESBL-producing organisms, in the case of *E. coli*.[3,5,8,18,20] However, in our study, the odds of death were increased comparing any resistant compared with susceptible *E. coli* BSI. In the 2008 Calgary cohort *E. coli* bacteraemia demonstrated a case-fatality rate of 11% (230/2041), whereas our case in-facility fatality rate at first ED visit or hospital admission was 8.9% (406/4578). These are different measures of mortality, and thus we are unable to draw conclusions regarding trends in *E. coli* BSI mortality within the region between time periods.

Our study has several strengths. We included the entire population of patients in a large Canadian health region, making it the largest cohort analysis of *E. coli* BSI costs in Canada to date. We used high-quality microcosting data for our analysis where available, making our results more accurate and generalizable. Further, we adjusted for confounding through propensity score matching. We included both outpatient and inpatient *E. coli* BSI, creating a more accurate representation of costs to the healthcare system.

Our study is subject to limitations. The costs did not include physician claims, which could underestimate costs, though this likely did not greatly impact our results as physician claims are small compared with hospitalization costs.[21] We did not have data at the level of community-acquired, healthcare-associated, or hospital-acquired BSI, which some literature has suggested may be a factor in cost difference and LOS.[5,9] This attribution would not likely impact the overall cost burden results, although it may have allowed us to further explain differences between groups.

Conclusion

We have described the costs of *E. coli* BSI in a large metropolitan Canadian health region for both susceptible and resistant *E. coli* BSIs. In this cohort, costs increase substantially in conjunction with the amount of resistance. *E. coli* CRO-R BSIs with resistance to FQ and trimethoprim/sulfamethoxazole accounted for over a $9 million increase in expenditure over the study period relative to other *E. coli* BSIs. In addition, in-facility mortality was increased among patients with any resistant compared with susceptible *E. coli* BSIs, and was higher when combined with CRO-R, FQ and trimethoprim/sulfamethoxazole susceptible compared with susceptible *E. coli* BSI, and even higher when combined with CRO-R, and FQ and trimethoprim/sulfamethoxazole resistance.

Our work adds a large cohort study to the evidence for increased economic cost and mortality associated with emergence of CRO-R-positive *E. coli* bacteraemia. These findings support the need for improved ways to control antimicrobial resistance at the community level, to both reduce the economic burden and improve patient outcomes.

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Transparency declarations

None to declare.

Author contributions

T.K.: Writing, original draft; Writing—review and editing; Visualization; Project administration. E.R.-M.: Methodology; Writing—review and editing;

Validation. R.S.: Methodology; Writing—review and editing; Validation. J.L.: Methodology; Writing—review and editing. J.E.B.: Software; Data curation; Formal analysis; Writing—review and editing. J.M.C.: Conceptualization. D.G.: Conceptualization; Writing—review and editing, Redrafting and resubmission.

Supplementary data

Tables S1 to S4 are available as Supplementary data at *JAC-AMR* Online.

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