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Unique risks and clinical outcomes associated with extended-spectrum beta-lactamase *Enterobacteriaceae* in Veterans with spinal cord injury/disorder: a case-case-control study

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Abstract

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Objectives: To describe the burden of extended-spectrum beta-lactamase (ESBL) *Enterobacteriaceae* in Veterans with spinal cord injury/disorder (SCI/D), identify risk factors for ESBL acquisition, and assess impact on clinical outcomes.

Design: Retrospective case-case-control

Patients and setting: Veterans with SCI/D and utilization at a Veteran's Affairs medical center from January 1, 2012-December 31, 2013.

Methods: Cases had a positive culture for ESBL *Klebsiella pneumoniae*, *Escherichia coli*, or *Proteus mirabilis* and were matched to patients with non-ESBL organisms by organism, facility, and level of care and to uninfected controls by facility and level of care. Inpatients were also matched by time at risk. Univariable and multivariable matched models assessed for differences in risk factors and outcomes.

Results: 492 cases (62.6% outpatients) were matched 1:1 with both comparison groups. Recent prior use of 3rd/4th generation cephalosporins and fluoroquinolones were independently associated with ESBL compared to non-ESBL [adjusted odds ratio (aOR) 3.86, 95% confidence interval (CI) 2.06-7.25, p<0.001 and aOR 2.61, 95% CI 1.77-3.84, p<0.001, respectively] and control (aOR 3.31, 95% CI 1.56-7.06, p=0.002 and aOR 2.10, 95% CI 1.29-3.43, p=0.003, respectively) groups. Although there were no mortality differences, the ESBL group had longer post-culture length of stay (LOS) than the non-ESBL group (incidence rate ratio 1.36, 95% CI 1.13-1.63, p=0.001).

Conclusions: All SCI/D patients with ESBL were more likely to have recent exposure to fluoroquinolones and 3rd/4th generation cephalosporins and hospitalized patients were more likely to have increased post-culture LOS. Programs targeted toward reduced antibiotic use in SCI/D patients may prevent subsequent ESBL acquisition.

Introduction

The prevalence of infections caused by multidrug-resistant organisms (MDROs) has been steadily increasing in both healthcare and community settings.[1–3] In particular, *Enterobacteriaceae* that produce extended-spectrum β-lactamase (ESBL) enzymes have rapidly proliferated[4] and now account for 18.6% of gram-negative organisms isolated from patients in U.S. intensive care units (ICUs).[1] Infection with ESBL bacteria and the associated delay in effective antimicrobial therapy often leads to increased length of stay (LOS), higher healthcare costs, and increased mortality.[5,6]

Patients with spinal cord injury/disorder (SCI/D) have an increased risk of infection compared to the general patient population due to frequent healthcare contact, comorbidities, and use of invasive medical devices.[7–11] Furthermore, rehabilitation hospitals and long-term care facilities (LTCF) have become important reservoirs for MDROs.[12,13] Given the frequency with which SCI/D patients require admission to these types of facilities, the threat of infection with MDROs remains a significant burden in this population.

Studies describing the prevalence, risk factors for acquisition, and outcomes of MDRO infections in general acute care facilities may not adequately reflect the SCI/D population.[14] A few small studies have shown high rates of MDROs, including ESBL, in SCI/D patients in rehabilitation hospitals.[15–17] However, data are limited on the burden and outcomes of

infection or colonization with multidrug resistant gram-negative organisms (MDRGNO) among patients with chronic SCI/D, a population likely to have greater risk compared to those acutely injured due to repeated healthcare exposures. Likewise, little data exist on the prevalence of MDRGNOs among SCI/D patients across a range of healthcare settings.

In this study, we investigated the prevalence of ESBL-producing *Enterobacteriaceae*, identified risk factors for ESBL acquisition, and examined clinical outcomes in a large population of Veterans with SCI/D. We used a case-case-control design with three comparison groups: 1) ESBL cases; 2) patients with non-ESBL organisms; and, 3) uninfected controls. This allowed us to analyze predictors specific to acquisition of the ESBL resistant phenotype, rather than just acquisition of *Enterobacteriaceae*.

Methods

Study setting and design

This was a retrospective case-case-control study involving adult SCI/D patients treated at VA medical facilities between January 1, 2012 and December 31, 2013. Clinical data was collected retrospectively to January 1, 2011 for risk factor analysis. The cohort was drawn from a cumulative list of Veterans with SCI/D maintained by the VA Allocation Resource Center.[18] Veterans with multiple sclerosis, amyotrophic lateral sclerosis, and Guillain-Barre syndrome were excluded because the VA SCI/D system of care focuses on individuals with stable non-progressive spinal cord neurological deficits. National VA datasets were used to identify cases and controls and collect clinical data.

Cases had a positive culture for ESBL-producing *Escherichia coli*, *Klebsiella pneumoniae*, or *Proteus mirabilis*. These organisms were chosen because they are among the most common gram-negative bacteria isolated from SCI/D patients and frequently produce ESBLs.[19–21] Cases included patients with cultures performed in any healthcare setting (inpatient, outpatient, rehabilitation, LTCF) from any site except rectal screening cultures. Thus, both infected and silently colonized patients were included. Patients with cultures positive for > 1 organism were included if at least one organism was identified as *E. coli*, *K. pneumoniae*, or *P. mirabilis*. Only the first positive culture was included if patients had more than one ESBL isolate identified during the study period.

For all analyses, ESBL cases were matched in a 1:1 ratio with two comparison groups: 1.) SCI/D patients with non-ESBL *E. coli*, *K. pneumoniae*, and *P. mirabilis*; and 2.) uninfected SCI/D controls. Controls were identified by the absence of cultures positive for *Enterobacteriaceae* and the absence of an International Classification of Disease-Clinical Modification, 9th revision (ICD9-CM) code for an infection. All case patients were matched to group 1 (non-ESBL) by organism, facility, and level of care (outpatient vs. inpatient vs. LTCF), and to group 2 (control) by facility and level of care. Additionally, inpatients and residents of LTCFs were matched by time at risk, which was defined as the number of days from admission to the index positive culture date and was matched within ± 60 days. This flexibility in matching was required because SCI/D patients frequently have long inpatient, rehabilitation, and LTCF stays. The institutional review board at the Edward Hines, Jr. VA Hospital approved this study.

Clinical and microbiology data collection

Patient demographics, characteristics, and comorbid conditions were collected from national VA datasets, including the Veterans' Health Administration (VHA) Corporate Data Warehouse (CDW). These datasets were also used to gather information on healthcare and antibiotic exposures and clinical outcomes. The modified Charlson comorbidity index at the time of culture for ESBL and non-ESBL groups and at the index outpatient encounter or admission date for controls was also calculated.[22]

To determine ESBL cases, we obtained information from the CDW on all bacterial cultures for which antibiotic susceptibility testing was performed. Given that each local VA laboratory may have entered results of ESBL testing into the electronic medical record in slightly different places, we used both microbiology and general laboratory domains of the CDW to identify positive ESBL results. Medical charts were reviewed from a random subset of 100 patients in each group to validate the administrative data with regard to accurate assignment of patients into ESBL, non-ESBL, and control groups.

Statistical analysis

Paired t-tests and Wilcoxon sign-rank tests were used to compare continuous variables and univariable logistic regression was used for categorical variables to identify risk factors for ESBL and non-ESBL organisms. Bonferroni correction for multiple comparisons was applied, with $p < 0.017$ considered significant. Variables with a p-value < 0.05 or a 95% CI not including 1 were considered for inclusion in multivariable matched logistic regression analyses. Separate analyses were conducted comparing each group to the others. Variables were added with stepwise selection and the variance inflation factor was used to assess for multicollinearity. Multivariable adjusted logistic regression models were created to examine the association between ESBL and clinical outcomes with the exception of post-culture LOS, which was assessed with a multivariable adjusted negative binomial model. For all multivariable models, the individual clinical variables that make up the modified Charlson score were used to examine associations between individual comorbidities and outcomes. To avoid being overly conservative and increasing Type II error, correction for multiple comparisons was not applied to multivariable analyses, and $p < 0.05$ was considered statistically significant. Statistical analyses were carried out using SAS, version 9.4 (SAS Institute) and Stata, version 12.1 (Stata Corp LP).

Results

A total of 19,665 Veterans with SCI/D were eligible for inclusion, of which 13,862 (70.5%) had bacterial cultures performed during the study period. Among these, 7,067 (51.0%) had a positive culture for *E. coli*, *K. pneumoniae*, and/or *P. mirabilis* with 745 (10.5%) patients having ESBL-producing organisms. We successfully matched 492 of 745 (66.0%) ESBL cases to both comparison groups for a final cohort of 1,476 patients. Within this cohort, there were 924 (62.6%) outpatients, 528 (35.8%) inpatients, and 24 (1.6%) in rehabilitation units or LTCFs. Seventy-five percent (n=1,107) of visits or admissions were at a VA SCI specialty center. For the ESBL and non-ESBL groups, urine was the most common culture site (n=791, 80.4%) followed by blood (n=159, 16.2%), respiratory (n=6, 0.6%), and other

sites (n=28, 2.8%). Among ESBL cases, 245 (49.8%) had positive cultures for *E. coli*, 208 (42.3%) for *K. pneumoniae*, 17 (3.5%) for *P. mirabilis*, and 22 (4.5%) for > 1 organism.

Table 1 summarizes demographic and clinical characteristics and the results of the univariable analysis. Patients in the ESBL group had higher median Charlson comorbidity index scores. Prior healthcare exposures including hospital admission, surgery, ICU admission, and mechanical ventilation were associated with ESBL but not non-ESBL organisms. Fluoroquinolones were the most common prior antibiotic exposure for all three groups, and exposures to a number of antibiotics were associated with increased odds of ESBL (Table 1).

Matched multivariable analyses for acquisition of ESBL are displayed in Table 2. When compared with uninfected controls, the following variables were significant independent predictors of ESBL: diabetes, complete SCI, pressure ulcer, prior use of $3^{rd}/4^{th}$ generation cephalosporins, and prior use of fluoroquinolones. However, diabetes, complete SCI, and pressure ulcer were also associated with increased odds of non-ESBL organisms. Therefore, the only independent predictors of ESBL, but not non-ESBL, organisms were recent prior use of $3^{rd}/4^{th}$ generation cephalosporins and fluoroquinolones.

The univariable analysis of clinical outcomes stratified by comparison group is shown in Table 3. Patients in both the non-ESBL and ESBL groups had lower 30-day mortality and greater odds of hospital readmission within 90 days than controls but there was no difference between non-ESBL and ESBL groups. Inpatients with ESBL had longer post-culture LOS than the non-ESBL group. In adjusted multivariable models, ESBL was not an independent predictor of increased 30-day mortality (Table 4). Similarly, patients in the ESBL group did not have increased 1-year mortality compared with the control group [adjusted odds ratio (aOR) 0.45, 95% confidence interval (CI) 0.28-0.71] or the non-ESBL group (aOR 0.87, 95% CI 0.54-1.39). Inpatients with ESBL had greater odds of hospital readmission within 90 days as compared to the control group (aOR 3.73, 95% CI 2.20-6.32) and the non-ESBL group (aOR 1.56, 95% CI 0.99-2.47), although this did not reach statistical significance. Finally, ESBL was significantly associated with increased post-culture LOS among inpatients (Table 5).

Chart reviews were conducted on a random subset of 100 patients from each group to estimate the validity of the clinical and administrative data in assigning patients to comparison groups. No patients in the non-ESBL group actually had ESBL organisms but one patient in the ESBL group had a non-ESBL organism. Six out of 100 (6.0%) uninfected control patients were actually infected based on presence of signs and/or symptoms identified via chart review.

Discussion

This study represents a large and comprehensive evaluation of risks for and clinical outcomes of ESBL acquisition in SCI/D patients. This population deserves specific attention due to increased comorbidities and frequent use of healthcare services and indwelling devices--factors that broadly increase risk for many types of MDROs.[23] The VHA treats

more than 26,000 patients with SCI/D every year in multiple care settings[24], making VA data a robust resource for studying this population.

Few studies have characterized MDRGNO epidemiology in SCI/D patients. Prior work by our group showed that hospital-acquired infections in SCI/D patients are frequently caused by methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus faecium*, and *Pseudomonas*, suggesting common risks for many MDROs in this population.[7] Other studies have been limited by small size,[17,25–27] inclusion of only urinary isolates,[16,21,25,27] and imprecise definitions of antimicrobial resistance.[17,26] Our study included all cultures collected from a large SCI/D population and identified laboratory-confirmed ESBL cases. We found that prior use of fluoroquinolones and 3rd/4th generation cephalosporins were significant independent predictors of ESBL but not non-ESBL organisms. Although prior antibiotic use is a well-recognized risk factor for ESBL,[2,12,28,29] some studies have had conflicting results. Many of these conflicting studies did not examine individual antibiotic classes and, thus, may have missed associations with specific antibiotics not reflected in overall antibiotic exposure.[30–32]

Frequency and type of antibiotic use in SCI/D patients is likely different from that observed in general patient populations. We have previously identified increased antibiotic prescribing for SCI/D patients in the Emergency Department, and higher prescribing for patients seen at non-SCI centers.[33] These patients' multiple comorbidities may create more opportunities for inappropriate antibiotic use, especially among providers less familiar with SCI/D. One circumstance may be treatment of asymptomatic catheter-associated bacteriuria, a practice not recommended due to lack of efficacy and emergence of resistance.[34] Waites et al. found that administration of ciprofloxacin for 10 days in men with SCI/D who performed intermittent urinary catheterization resulted in a subsequent increase in resistant staphylococci, enterococci, and *Acinetobacter* spp.[35] Clearly, these results, and those from our study, suggest that fluoroquinolone use strongly contribute to subsequent colonization and infection with MDROs in SCI/D patients.

In contrast to prior studies,[6] we did not identify increased mortality in our ESBL group compared with controls. Our chart reviews estimated that 6% of patients classified into the control group were actually infected. This estimate is consistent with prior literature evaluating the validity of observational administrative data[36,37], and suggests that our criteria for classifying patients performed well but not perfectly. Erroneously including enough infected patients in the control group may have contributed to a higher observed mortality than expected. Furthermore, our cohort included patients with ESBL isolated from any site and those who were colonized as well as infected, both factors that may have lowered the mortality observed in our ESBL group. Interestingly, we did observe increased post-culture hospital LOS for inpatients with ESBL, a finding previously reported in a small single-center study[5] but not validated in a larger population until now.

Our study has a number of important limitations. First, it was subject to selection bias, particularly from the exclusion of ESBL patients who could not be matched. Despite this, our final cohort included a diverse population with a range of SCI severity, who sought care from multiple different settings, and who visited both SCI specialty centers and non-SCI

centers. Second, we did not collect data on antibiotic treatment and, thus, could not analyze adequacy or timeliness of antibiotic therapy in regards to clinical outcomes. And finally, data were missing for some of the SCI characteristics such as level and extent of injury, which may have introduced bias into analyses including these variables.

In conclusion, we used a national cohort of Veterans to demonstrate that colonization and infection with ESBL organisms is common in SCI/D patients, particularly in the urine. Prior use of $3^{rd}/4^{th}$ generation cephalosporins and fluoroquinolones independently increases the odds of ESBL, but not non-ESBL organisms. Interventions that reduce inappropriate $3^{rd}/4^{th}$ generation cephalosporin and fluoroquinolone use will be particularly effective in decreasing ESBL acquisition in this population. Furthermore, given that ESBL was associated with longer post-culture hospital LOS, these same interventions are likely to have clinical and financial benefits on a broader, system-wide scale.

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Table 1.

Univariable analysis of risk factors for acquisition of non-ESBL and ESBL-producing *Enterobacteriaceae*.

	No. (%)[a]			Matched OR (95%CI) *P* value[*]		
Variable	**Control**	**Non-ESBL**	**ESBL**	**Non-ESBL vs. Control**	**ESBL vs. Control**	**ESBL vs. Non-ESBL**
Demographics						
Age, years, mean (SD)	61.2 (13.7)	60.9 (13.5)	61.5 (14.4)	p=0.80	p=0.71	p=0.53.
Sex, female	19 (3.9)	13 (2.6)	10 (2.0)	0.67 (0.33-1.38) p=0.28	0.50 (0.22-1.11) p=0.09	0.77 (0.34-1.75) p=0.53
Comorbidities						
SCI level[b]						
Tetraplegia	199 (40.4)	228 (46.3)	233 (47.4)	Reference	Reference	Reference
Paraplegia	154 (31.3)	229 (46.5)	217 (44.1)	1.30 (0.97-1.74) p=0.07	1.22 (0.91-1.63) p=0.19	0.92 (0.71-1.20) p=0.55
SCI onset[b]						
Non-traumatic	135 (26.9)	119 (23.8)	136 (27.1)	Reference	Reference	Reference
Traumatic	228 (46.3)	325 (66.1)	311 (63.2)	**1.70 (1.23-2.35) p=0.001**	1.32 (0.96-1.81) p=0.09	0.83 (0.61-1.13) p=0.23
SCI extent[b]						
Incomplete	265 (52.9)	269 (53.7)	215 (42.9)	Reference	Reference	Reference
Complete	69 (14)	183 (37.2)	225 (45.7)	**2.78 (1.94-3.99) p<0.001**	**4.31 (2.94-6.31) p<0.001**	**1.50 (1.16-1.96) p=0.002**
SCI duration[b]						
0-10 years	174 (35.4)	182 (37.0)	201 (40.9)	Reference	Reference	Reference
11-20 years	51 (10.4)	77 (15.7)	80 (16.3)	1.39 (0.89-2.17) p=0.15	1.36 (0.89-2.06) p=0.15	0.94 (0.65-1.36) p=0.74
>20 years	118 (24.0)	184 (37.4)	156 (31.7)	1.49 (1.07-2.06) p=0.02	1.09 (0.79-1.50) p=0.61	0.77 (0.58-1.03) p=0.08
Charlson comorbidity index, median (range)	2 (0-20)	2 (0-12)	3 (0-14)	p=0.06	**p<0.001**	**p<0.001**
Gastrostomy or jejunostomy	7 (1.4)	8 (1.6)	18 (3.7)	1.14 (0.41-3.15) p=0.80	2.57 (1.07-6.16) p=0.03	2.43 (1.01-5.86) p=0.05
Chronic kidney disease	46 (9.3)	38 (7.7)	60 (12.2)	0.81 (0.52-1.27) p=0.36	1.34 (0.9-2.01) p=0.16	1.65 (1.08-2.52) p=0.02
Chronic liver disease	39 (7.9)	23 (4.7)	37 (7.5)	0.58 (0.34-0.98) p=0.04	0.94 (0.59-1.52) p=0.81	1.64 (0.96-2.78) p=0.07
AIDS	9 (1.8)	1 (0.2)	5 (1.0)	0.11 (0.01-0.88) p=0.04	0.56 (0.19-1.66) p=0.29	5.00 (0.58-42.80) p=0.14
Malignancy or tumor	57 (11.6)	44 (8.9)	49 (10)	0.74 (0.48-1.13) p=0.17	0.84 (0.56-1.27) p=0.41	1.12 (0.74-1.71) p=0.59
CHF	36 (7.3)	32 (6.5)	37 (7.5)	0.88 (0.53-1.45) p=0.61	1.03 (0.65-1.64) p=0.91	1.18 (0.71-1.95) p=0.52

	No. (%)[a]			Matched OR (95%CI) *P* value[*]		
Variable	**Control**	**Non-ESBL**	**ESBL**	**Non-ESBL vs. Control**	**ESBL vs. Control**	**ESBL vs. Non-ESBL**
Diabetes	117 (23.8)	138 (28.0)	180 (36.6)	1.24 (0.94-1.65) p=0.13	**1.89 (1.42-2.52) p<0.001**	**1.54 (1.16-2.05) p=0.003**
Cerebrovascular disease	39 (7.9)	51 (10.4)	41 (8.3)	1.32 (0.86-2.01) p=0.20	1.06 (0.66-1.69) p=0.81	0.78 (0.51-1.21) p=0.27
Peripheral vascular disease	39 (7.9)	38 (7.7)	75 (15.2)	0.97 (0.61-1.55) p=0.91	**2.16 (1.41-3.31) p<0.001**	**2.28 (1.47-3.52) p<0.001**
COPD	101 (20.5)	69 (14.0)	96 (19.5)	**0.64 (0.46-0.89) p=0.01**	0.93 (0.67-1.29) p=0.68	1.51 (1.07-2.14) p=0.02
Pressure ulcer	71 (14.4)	162 (32.9)	268 (54.5)	**2.82 (2.04-3.89) p<0.001**	**6.79 (4.74-9.74) p<0.001**	**2.47 (1.88-3.25) p<0.001**
Healthcare exposures in past 90 days						
Hospital admission	108 (22.0)	96 (19.5)	170 (34.6)	0.85 (0.61-1.17) p=0.32	**1.87 (1.4-2.5) p<0.001**	**2.42 (1.75-3.35) p<0.001**
LTCF or rehabilitation stay	15 (3.0)	7 (1.4)	16 (3.3)	0.38 (0.14-1.08) p=0.07	1.07 (0.53-2.16) p=0.86	2.5 (0.97-6.44) p=0.06
Surgery	34 (6.9)	25 (5.1)	55 (11.2)	0.69 (0.39-1.22) p=0.20	**1.75 (1.1-2.78) p=0.02**	**2.76 (1.59-4.81) p<0.001**
GU procedure[c]	17 (3.5)	22 (4.5)	29 (5.9)	1.31 (0.68-2.52) p=0.41	1.80 (0.96-3.38) p=0.07	1.41 (0.76-2.63) p=0.28
ICU admission	23 (4.7)	20 (4.1)	44 (8.9)	0.85 (0.45-1.62) p=0.62	**2.11 (1.22-3.63) p=0.008**	**2.50 (1.40-4.46) p=0.002**
Mechanical ventilation	10 (2.0)	5 (1.0)	22 (4.5)	0.50 (0.17-1.46) p=0.21	2.33 (1.07-5.09) p=0.03	**5.25 (1.8-15.29) p=0.002**
Medication exposures in past 90 days						
Any antibiotic	148 (30.1)	185 (37.6)	287 (58.3)	**1.40 (1.07-1.82) p=0.01**	**3.21 (2.42-4.25) p<0.001**	**2.44 (1.85-3.21) p<0.001**
Chronic steroids[d]	6 (1.2)	2 (0.4)	6 (1.2)	0.33 (0.07-1.65) p=0.18	1.00 (0.32-3.10) p=1.00	3.00 (0.61-14.86) p=0.18
Penicillins	24 (4.9)	36 (7.3)	57 (11.6)	1.55 (0.90-2.64) p=0.11	**2.57 (1.55-4.26) p<0.001**	1.72 (1.09-2.72) p=0.02
Extended-spectrum penicillins	23 (4.7)	26 (5.3)	56 (11.4)	1.14 (0.64-2.02) p=0.66	**2.65 (1.58-4.43) p<0.001**	**2.50 (1.49-4.20) p=0.001**
1st/2nd gen cephalosporins	27 (5.5)	35 (7.1)	36 (7.3)	1.35 (0.79-2.31) p=0.28	1.35 (0.81-2.24) p=0.25	1.03 (0.64-1.66) p=0.90
3rd/4th gen cephalosporins	19 (3.8)	17 (3.4)	80 (16)	0.89 (0.47-1.72) p=0.73	**5.07 (2.91-8.81) p<0.001**	**5.50 (3.11-9.72) P<0.001**

	No. (%)[a]			Matched OR (95%CI) *P* value*		
Variable	**Control**	**Non-ESBL**	**ESBL**	**Non-ESBL vs. Control**	**ESBL vs. Control**	**ESBL vs. Non-ESBL**
Carbapenems	7 (1.4)	6 (1.2)	28 (5.7)	0.86 (0.29-2.55) p=0.78	**4.50 (1.86-10.9) p=0.001**	**6.50 (2.27-18.62) p<0.001**
Macrolides	13 (2.6)	13 (2.6)	13 (2.6)	1.00 (0.46-2.16) p=1.00	1.00 (0.46-2.16) p=1.00	1.00 (0.46-2.16) p=1.00
Tetracyclines	9 (1.8)	5 (1)	18 (3.6)	0.56 (0.19-1.66) p=0.29	2.00 (0.90-4.45) p=0.09	**3.60 (1.34-9.70) p=0.01**
Aminoglycosides	7 (1.4)	8 (1.6)	14 (2.8)	1.14 (0.41-3.15) p=0.80	2.00 (0.75-5.33) p=0.17	1.77 (0.74-4.27) p=0.20
Fluoroquinolones	59 (12.0)	52 (10.6)	142 (28.9)	0.87 (0.58-1.29) p=0.48	**3.18 (2.21-4.58) p<0.001**	**3.31 (2.31-4.73) p<0.001**
Vancomycin	38 (7.7)	28 (5.7)	78 (15.9)	0.70 (0.41-1.19) p=0.18	**2.38 (1.54-3.67) p<0.001**	**3.94 (2.31-6.71) p<0.001**
Clindamycin	6 (1.2)	8 (1.6)	8 (1.6)	1.33 (0.46-3.84) p=0.59	1.33 (0.46-3.84) p=0.59	1.00 (0.35-2.85) p=1.00
Nitrofurans	16 (3.3)	22 (4.5)	43 (8.7)	1.38 (0.72-2.62) p=0.33	**2.80 (1.55-5.05) p=0.001**	**2.31 (1.29-4.16) p=0.005**
Sulfonamides	30 (6.1)	35 (7.1)	56 (11.4)	1.20 (0.71-2.04) p=0.50	**2.04 (1.26-3.29) p=0.003**	1.66 (1.07-2.57) p=0.02
Metronidazole	6 (1.2)	14 (2.8)	36 (7.3)	2.33 (0.90-6.07) p=0.08	**7.00 (2.74-17.87) p<0.001**	**2.70 (1.43-5.06) p=0.002**
Methenamine	4 (0.8)	26 (5.3)	18 (3.7)	**6.50 (2.27-18.62) p<0.001**	**4.50 (1.52-13.30) p=0.007**	0.67 (0.35-1.25) p=0.21
Rifamycin	4 (0.8)	2 (0.4)	2 (0.4)	0.50 (0.09-2.73) p=0.42	0.50 (0.09-2.73) p=0.42	1.00 (0.14-7.10) p=1.00

ESBL, extended-spectrum beta-lactamase; OR, odds ratio; CI, confidence interval; SD, standard deviation; SCI, spinal cord injury; AIDS, acquired immune deficiency syndrome; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; LTCF, long term care facility; GU, genitourinary; ICU, intensive care unit; gen, generation;

[a] All data displayed are number (%) unless otherwise indicated

[b] Some data missing for this variable

[c] Minimally invasive or non-invasive GU procedures

[d] Defined as ≥ 85 days of use in the prior 90 days

* Paired t-test was used for age and Wilcoxon sign-rank test was used for Charlson score

Table 2.

Multivariable conditional logistic regression analysis of risk factors for acquisition of non-ESBL and ESBL-producing *Enterobacteriaceae*.

	Non-ESBL vs. Control		ESBL vs. Control		ESBL vs. Non-ESBL	
	aOR (95% CI)	***P***	**aOR (95% CI)**	***P***	**aOR (95% CI)**	***P***
Variable						
Diabetes	1.35 (0.95-1.90)	0.09	1.63 (1.10-2.42)	0.02	1.26 (0.91-1.74)	0.17
Complete SCI	2.69 (1.83-3.94)	<0.001	3.15 (2.02-4.91)	<0.001	1.34 (0.99-1.82)	0.06
Pressure ulcer	2.52 (1.72-3.70)	<0.001	4.15 (2.77-6.21)	<0.001	2.07 (1.53-2.80)	<0.001
Exposures in the prior 90 days						
Mechanical ventilation	0.12 (0.03-0.47)	0.003	1.81 (0.59-5.60)	0.30	3.46 (0.97-12.35)	0.06
$3^{rd}/4^{th}$ gen cephalosporins	0.65 (0.29-1.45)	0.29	3.31 (1.56-7.06)	0.002	3.86 (2.06-7.25)	<0.001
Fluoroquinolones	0.75 (0.46-1.23)	0.26	2.10 (1.29-3.43)	0.003	2.61 (1.77-3.84)	<0.001

ESBL, extended-spectrum beta-lactamase; aOR, adjusted odds ratio; CI, confidence interval; SCI, spinal cord injury

Table 3.

Clinical outcomes stratified by comparison group.

	No. (%)			OR (95% CI) *P* value		
Outcome	**Control**	**Non-ESBL**	**ESBL**	**Non-ESBL vs. Control**	**ESBL vs. Control**	**ESBL vs. Non-ESBL**
30-day mortality	27 (5.5)	11 (2.2)	11 (2.2)	0.36 (0.17-0.77) p=0.009	0.41 (0.20-0.82) p=0.01	1.00 (0.42-2.40) p=1.00
1-year mortality	72 (14.6)	46 (9.3)	56 (11.4)	0.58 (0.39-0.88) p=0.009	0.74 (0.50-1.08) p=0.12	1.26 (0.83-1.93) p=0.28
Post-culture LOS, days, median (range)[a]	--	11 (0-419)	22 (0-985)	--	--	p=0.001
90-day hospital readmission[a]	28 (5.7)	50 (10.2)	66 (13.4)	2.00 (1.20-3.34) p=0.008	3.38 (1.93-5.90) p<0.001	1.44 (0.94-2.21) p=0.09

OR, odds ratio; CI, confidence interval; ESBL, extended-spectrum beta-lactamase; LOS, length of stay

[a]For inpatients only

Table 4.

Multivariable logistic regression analysis of variables associated with 30-day mortality.

Variable	aOR (95% CI)	*P* value
ESBL (ref: control group)	0.14 (0.05-0.40)	<0.001
ESBL (ref: non-ESBL group)	0.42 (0.14-1.23)	0.11
Patient location (ref: outpatient)		
Inpatient	2.82 (1.20-6.59)	0.02
LTCF	3.10 (0.43-22.22)	0.26
Culture source (ref: urine)		
Blood	4.63 (1.88-11.42)	<0.001
Other	2.50 (0.92-6.82)	0.07
Traumatic SCI	0.28 (0.11-0.70)	0.006
Malignancy or tumor	7.22 (3.40-15.34)	<0.001
Renal disease	2.44 (1.09-5.47)	0.03
Pressure ulcer	3.30 (1.49-7.31)	0.003
Exposures in prior 90 days		
Mechanical ventilation	9.68 (2.89-32.35)	<0.001
Sulfonamides	0.06 (0.01-0.39)	0.004
Vancomycin	3.50 (1.42-8.65)	0.007

aOR, adjusted odds ratio; CI, confidence interval; ESBL, extended-spectrum beta-lactamase; LTCF, long-term care facility; SCI, spinal cord injury

Table 5.

Multivariable negative binomial regression analysis of variables associated with increased post-culture hospital length of stay for inpatients.

Variable	IRR (95% CI)	*P* value
ESBL (ref: non-ESBL)	1.36 (1.13-1.63)	0.001
Patient seen at SCI center	1.60 (1.19-2.13)	0.002
Exposures in prior 90 days		
Mechanical ventilation	1.86 (1.26-2.73)	0.002
Vancomycin	1.29 (0.99-1.68)	0.06
Macrolides	0.49 (0.27-0.86)	0.01

IRR, incidence rate ratio; CI, confidence interval; ESBL, extended-spectrum beta-lactamase; SCI, spinal cord injury