Research Article

Changes in bacterial epidemiology and antibiotic resistance among veterans with spinal cord injury/disorder over the past 9 years

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Objective: Patients with spinal cord injury and disorder (SCI/D) have an increased risk of infection with multidrug-resistant (MDR) bacteria. We described bacterial epidemiology and resistance in patients with SCI/D at Veterans Affairs Medical Centers (VAMCs) for the past 9 years.

Design: Retrospective cohort.

Setting: One hundred thirty VAMCs.

Participants: Veterans with SCI/D and bacterial cultures with antibiotic susceptibility testing performed between 1/1/2005–12/31/2013. Single cultures with contaminants and duplicate isolates within 30 days of initial isolates were excluded.

Interventions: None.

Outcomes: Trends in microbial epidemiology and antibiotic resistance.

Results: Included were 216,504 isolates from 19,421 patients. Urine was the most common source and Gram-negative bacteria (GNB) were isolated most often, with 36.1% of GNB being MDR. Logistic regression models clustered by patient and adjusted for location at an SCI/D center and geographic region showed increased odds over time of vancomycin resistance in *Enterococcus* [adjusted odds ratio (aOR) 1.67, 95% confidence interval (CI) 1.30–2.15], while methicillin resistance in *Staphylococcus aureus* remained unchanged (aOR 0.90, 95% CI 0.74–1.09). There were also increased odds of fluoroquinolone resistance (aOR 1.39, 95% CI 1.31–1.47) and multidrug resistance (aOR 1.46, 95% CI 1.38–1.55) in GNB, with variability in the odds of MDR bacteria by geographic region.

Conclusions: GNB are isolated frequently in Veterans with SCI/D and have demonstrated increasing resistance over the past 9 years. Priority should be given to controlling the spread of resistant bacteria in this population. Knowledge of local and regional epidemiologic trends in antibiotic resistance in patients with SCI/D may improve appropriate antibiotic prescribing.

Keywords: Spinal cord injury, Drug resistance, Bacterial, Epidemiology, Gram-negative bacteria, Gram-positive bacteria

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Introduction

Persons with spinal cord injury and disorders (SCI/D) are a growing population in the U.S., with an estimated annual incidence of traumatic SCI/D of 12,500 new cases each year.¹ Infections are common complications and leading causes of death in patients with SCI/D, often due to these patients' unique comorbidities, frequent healthcare contact and use of invasive medical devices such as indwelling urinary catheters.^{2–8} Patients with SCI/D often have repeated healthcare and antibiotic exposures that increase their risk for infection and colonization with multidrug-resistant organisms (MDROs).^{2,9–11} MDRO infection is associated with poor outcomes such as greater healthcare costs, longer hospital stays, and increased mortality.^{12–14} Furthermore, increasing resistance in Gram-negative bacteria (GNB) in particular poses a significant challenge due to an overall lack of antibiotics that are safe and effective for treatment of infections with these bacteria.

Prompt initiation of effective empirical antibiotic therapy is essential in patients with suspected MDRO infections. Decisions regarding empirical antibiotics should be supported by knowledge of local bacterial epidemiology and antibiotic susceptibility patterns. Because pathogen distribution and antibiotic resistance profiles may vary substantially for different patient populations,^{15,16} empirical antibiotic guidelines should be based on regular evaluations of microbial epidemiology within specific groups of high-risk patients. A framework for such an approach already exists for some infections, such as hospital-acquired and ventilator-associated pneumonia.¹⁷ Because patients with SCI/D have an increased risk of infection and colonization with MDROs, studies describing the prevalence, epidemiology, and antibiotic resistance of bacteria in general patient populations may not adequately reflect the SCI/D population. In addition, characterization of changes both nationally and at the facility level can help inform best practices for infection prevention, MDRO surveillance, and antibiotic guidelines for medical centers with large SCI/D populations. Despite this, large-scale studies of microbial epidemiology and antibiotic resistance across care settings in patients with SCI/D are lacking.

In this study, we analyzed data from a large cohort of Veterans with SCI/D to characterize changes in bacterial epidemiology and antibiotic resistance over the past 9 years. We paid particular attention to changes in GNB and defined multidrug-resistant GNB (MDRGNB) according to the international standards

proposed by the European Centre for Disease Prevention and Control and the Centers for Disease Control and Prevention.¹⁸ We focused on GNB because increasing prevalence of MDRGNB has become a global threat and infections with MDRGNB are commonly associated with limited antibiotic treatment options.^{16,19}

Methods

Study setting and design

This was a retrospective cohort study of adults with SCI/D treated at VA Medical Centers (VAMCs) between January 1, 2005 and December 31, 2013. The cohort was drawn from a cumulative list of Veterans with SCI/D maintained by the VA Allocation Resource Center.²⁰ 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 collect clinical and microbiologic data. This study was approved by the Institutional Review Board at the Edward Hines, Jr. VA Hospital.

Patients were included if they had ≥ 1 positive bacterial culture sent for antibiotic susceptibility testing during the study period. Because our objective was to assess global changes in microbial epidemiology, cultures performed in any healthcare setting and from any anatomic site were included, regardless of associated clinical signs and symptoms of infection. Although nares and rectal surveillance cultures for methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), and other MDROs were not specifically excluded, full susceptibility testing for surveillance cultures is not routinely performed or reported in the VA electronic medical record; thus, most of these cultures were excluded from the study by default. In addition, many VA facilities now perform MRSA surveillance with molecular testing (e.g. PCR) rather than culture.

Clinical and microbiology data collection

Patient demographics, characteristics, and facility locations were collected from national VA datasets, including the Veterans' Health Administration (VHA) Corporate Data Warehouse (CDW). Patient characteristics and comorbidities were identified using International Classification of Diseases 9th Revision (ICD-9) codes and were recorded for the year prior to and including the outpatient visit or hospitalization with the first positive culture. Data were included for

all 130 VAMCs. VAMCs are classified into three complexity levels determined in part by patient characteristics (Levels 1a-c, 2, and 3; with Level 1a being highest complexity). The national VA SCI/D system of care encompasses 24 Level 1a VAMCs with dedicated SCI/D centers called ‘hubs’ that provide highly specialized SCI/D care. Each of these centers connects to a variable number of ‘spoke’ facilities that provide community-based primary care for patients with SCI/D. Clinical and microbiologic data were analyzed from Level 1a vs. non-1a VAMCs and from hubs vs. spokes to capture facility-specific as well as aggregate national trends.

Bacterial species identification and antibiotic susceptibility testing was performed by each VAMC’s laboratory according to their protocol and entered into the electronic medical record, from which CDW datasets are compiled. Duplicate isolates, defined as a positive culture with the same organism and antibiotic susceptibility profile obtained within 30 days of an initial isolate, were excluded. Single positive cultures with common contaminants including coagulase-negative staphylococci, *Lactobacillus* spp., *Bacillus* spp., *Corynebacterium* spp. and other diphtheroids were excluded. If one of these organisms was present in two separate cultures isolated ≤ 48 hours apart from a single patient and the susceptibilities matched for all antibiotics tested against both isolates, then the first isolate was included.

Definitions of antibiotic resistance

Resistance in Gram-positive bacteria was assessed for *S. aureus*, *Enterococcus faecalis*, and *E. faecium* isolates. MRSA was defined as any *S. aureus* isolate with resistance to oxacillin, nafcillin, and/or methicillin; and VRE was defined as any *E. faecalis* or *E. faecium* isolate with resistance to vancomycin. Multidrug resistance in GNB was defined for *Enterobacteriaceae*, *Pseudomonas aeruginosa* and *Acinetobacter* spp. according to guidelines proposed by Magiorakos *et al.*¹⁸ These guidelines construct epidemiologically significant antimicrobial categories for each group of bacteria and define MDR as non-susceptibility to at least one agent in ≥ 3 antimicrobial categories. For GNB with susceptibility testing including at least one fluoroquinolone (FQ) antibiotic, FQ resistance was defined as resistance to ≥ 1 FQ antibiotic.

Statistical analysis

Descriptive statistics were used to summarize patient-level and isolate-level data. Random-effect logistic regression models with clustering by patient were

created to assess changes in the proportion of bacteria that were antibiotic resistant by year with adjustment for type of SCI/D facility (hub vs. spoke) and geographic region (based on U.S. Census Bureau regions²¹). Models also assessed the odds of antibiotic resistance in bacteria isolated at hub vs. spoke SCI/D facilities and from different geographic regions with adjustment for year of isolation. A P-value < 0.05 was considered statistically significant. Statistical analyses were carried out using SAS, version 9.4 (SAS Institute, Inc., Cary, NC, USA) and Stata, version 12.1 (Stata Corp LP, College Station, TX, USA).

Results

A total of 157,446 cultures with 216,504 bacterial isolates obtained from 19,421 Veterans with SCI/D were included in the study. Table 1 displays the patient and isolate characteristics. Over the study period, 65.7% of isolates were obtained from patients seen at an SCI/D hub center for inpatient or outpatient care, and this percentage did not vary substantially by year (data not shown). Just over half of all isolates were collected from inpatients. The majority of blood and respiratory isolates were collected from inpatients (92.7% of blood and 94.5% of respiratory isolates), while most urine isolates were collected from outpatients (50.3%). Isolates collected from hubs were more likely to be from inpatients than outpatients (62.7% vs. 37.3%), but the reverse was true for spokes (42.8% inpatient vs. 57.2% outpatient).

The total number of patients with bacterial cultures sent for susceptibility testing remained constant each year from 2005–2012 followed by a slight decrease in 2013 (Fig. 1, solid line). Among all isolates, 72.2% ($n = 156,330$) were Gram-negative and 27.8% ($n = 60,174$) were Gram-positive. The ratio of Gram-negative to Gram-positive bacteria significantly increased over time (Fig. 1, bar graph). *Enterobacteriaceae* were the most common GNB isolated, with *Escherichia coli* the most frequent species ($n = 42,562$; 27.7%) followed by *Klebsiella pneumoniae* ($n = 24,950$; 16.0%). Among non-*Enterobacteriaceae*, *Pseudomonas aeruginosa* ($n = 27,065$; 17.3%) and *Acinetobacter* spp. ($n = 4,497$; 2.9%) were most commonly isolated.

S. aureus, as a percentage of all Gram-positive isolates, remained constant from 41.6% in 2005 to 40.7% in 2013; however, the proportion of *S. aureus* isolates that were MRSA decreased (Fig. 2A). After adjustment in the regression model, the odds of methicillin resistance among *S. aureus* isolates remained unchanged (Fig. 3A). In contrast, the percentage of *E. faecalis* and *E. faecium* isolates that were vancomycin resistant

Table 1 Patient and isolate characteristics.

Variable	Value ^a
Demographics (n= 19,421 patients)	
Age, y, mean (SD) ^b	60 (14)
Sex, female	513 (2.6)
SCI characteristics	
SCI level (n= 15,598 patients)	
Tetraplegia	7946 (51.0)
Paraplegia	7652 (49.0)
SCI onset (n= 15,518 patients)	
Non-traumatic	4390 (28.3)
Traumatic	11128 (71.7)
SCI extent (n= 14,006 patients)	
Incomplete	7990 (57.1)
Complete	6016 (42.9)
SCI duration, y, mean (SD) (n= 14,117 patients)	16.2 (15.3)
Comorbidities recorded in the previous year (n= 19,421 patients)	
Chronic kidney disease	2179 (11.2)
Chronic liver disease	1531 (7.9)
AIDS	106 (0.6)
Malignancy or tumor	2485 (12.8)
CHF	2030 (10.5)
Diabetes	5470 (28.2)
Cerebrovascular disease	1831 (9.4)
Peripheral vascular disease	1904 (9.8)
COPD	3639 (18.7)
Pressure ulcer	8474 (43.6)
Bacterial isolate characteristics (n= 216,504 isolates)	
Source	
Blood	6,348 (2.9)
Urine	170,738 (78.9)
Respiratory	9,461 (4.4)
Other	29,957 (13.8)
Isolates from inpatients	120,881 (55.8)
Isolates from cultures performed at an SCI/D hub center	142,339 (65.7)

^aData are No. (%) unless otherwise specified.

^bAt the time of first culture.

AIDS, acquired immune deficiency syndrome; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease.

Figure 1. Proportion of Gram-negative vs. Gram-positive isolates (left y-axis) and total number of patients with bacterial cultures sent for susceptibility testing (right y-axis) by study year. Stars indicate years with significantly higher odds of any isolate being Gram-negative compared to the odds in 2005.

Figure 2 (A) Proportion of *S. aureus* isolates that were methicillin-resistant (MRSA), and (B) proportion of *E. faecalis* and *E. faecium* isolates that were vancomycin-resistant (VRE) by study year with accompanying trendlines.

increased over time (Fig. 2B), with greater odds of vancomycin resistance in *E. faecalis* and *E. faecium* in 2013 compared with 2005 [(aOR 1.67, 95% CI 1.30–2.15); Fig. 3B]. For Gram-negative isolates, 34.5% of GNB were MDR in 2005, and this increased to 36.3% in 2013 with a peak of 37.6% in 2010. In the adjusted regression models, multidrug resistance in GNB increased over the study (Fig. 4A), with greater odds of MDRGNB in 2013 compared with 2005 (aOR 1.46, 95% CI 1.38–1.55). Fluoroquinolone resistance similarly increased in GNB over the study period (Fig. 4B), with 1.39 times the odds of FQ resistance in GNB in 2013 compared to 2005 (95% CI 1.31–1.47).

With regard to type of VAMC, a greater proportion of all MDRGNB were isolated from patients who visited hubs (n=39,327 isolates; 69.5%) compared to patients who visited spokes (n=17,197 isolates; 30.5%) and from patients who visited Level 1a VAMCs (n=39,347; 69.7%) compared to patients who visited non-1a VAMCs (17,087 isolates; 30.3%). In the adjusted

logistic regression models, there were increased odds of methicillin resistance in *S. aureus* (aOR 1.42, 95% CI 1.27–1.58) and multidrug resistance in GNB (aOR 1.19, 95% CI 1.15–1.24) isolated from patients at hubs but no significant difference in the odds of FQ resistance in GNB or vancomycin resistance in *E. faecalis* and *E. faecium*. With regard to geographic region, the south contributed the greatest number of cultures with MDRGNB (n=27,773; 53.7%), followed by the midwest (n=8,142; 15.7%), west (n=7,874; 15.2%), northeast (n=5,915; 11.4%) and “other” (n=2,014; 3.9%) regions. After adjustment in the regression analyses, there was substantial variability in the odds of antibiotic resistant bacteria isolated from patients in different geographic regions (Table 2).

Discussion

The microbial epidemiology of bacterial infections exhibits important global, regional, and institutional trends and is often influenced by population-specific

Figure 3 Adjusted odds ($\pm$ 95% confidence intervals) of (A) methicillin resistance (MRSA) in *S. aureus* isolates, and (B) vancomycin resistance (VRE) in *E. faecalis* and *E. faecium* isolates for each study year compared to the odds in 2005. Stars indicate years with significantly higher odds compared to the odds in 2005 ($P < 0.01$).

Figure 4 Adjusted odds ($\pm$ 95% confidence intervals) of (A) multidrug resistance (MDR) in Gram-negative bacteria (GNB), and (B) fluoroquinolone resistance (FQR) in GNB for each study year compared to the odds in 2005. Stars indicate years with significantly higher odds compared to the odds in 2005 ($P < 0.01$).

risk factors, local antibiotic practices, and facility-level policies. Characterizing such trends for high-risk patient populations and care settings is essential for effective empirical antibiotic treatment guidelines and antimicrobial stewardship. In this large, comprehensive study of Veterans with SCI/D over a 9-year period, we analyzed all bacterial cultures sent for susceptibility testing to assess broad trends in bacterial epidemiology and antibiotic resistance.

We initially analyzed trends in Gram-positive bacteria and observed that the odds of methicillin resistance in *S. aureus* remained unchanged over the study period. Between 2007–2008, the VA implemented a bundled MRSA Prevention Initiative that was associated with reduced rates of MRSA transmission and healthcare-associated MRSA infection.^{22,23} An analysis of VAMC SCI/D centers between 2007 and 2011 found a decrease in MRSA healthcare-associated infections but no difference in MRSA transmission rates or admission prevalence ($38.6\% \pm 19.1\%$), which remained higher than in VAMC acute care hospitals.²⁴ Our results are consistent with this analysis and demonstrate that, although MRSA remains a significant burden in patients with SCI/D, the trend of increasing methicillin resistance in

S. aureus observed among studies in the early 2000s may be abating as a result of VA national prevention efforts. In contrast to MRSA, the odds of vancomycin resistance in *E. faecium* and *E. faecalis* increased significantly during the study. A 2007 study of hospitalized patients with SCI/D at the Cleveland VA Medical Center found that 55% of patients were asymptomatic carriers of VRE²⁵ and suggested a high baseline burden of VRE colonization in this population. Further studies are needed to clarify factors underlying the increases in VRE observed in our study; however, possible explanations might be increased colonization with enterococci, increased antibiotic exposures, and increased healthcare exposures.

The proportion of all isolates that were Gram-negative increased over time, which suggests a growing burden of colonization and infection with GNB in the SCI/D population. Shifts in bacterial epidemiology have been observed in other patient populations with frequent antibiotic exposures and high risk for MDR bacteria, such as neutropenic patients and transplant recipients.^{26,27} The trend from Gram-positive to Gram-negative in our study is an important finding given the increased severity of illness observed with

Table 2 Adjusted odds of antibiotic resistance by geographic region.

Region	aOR ^a (95%CI) of antibiotic resistant bacteria			
	Methicillin resistance in <i>S. aureus</i> Ref	Vancomycin resistance in <i>Enterococcus</i> Ref	FQ resistance in Gram-negative isolates Ref	Multidrug resistance in Gram-negative isolates Ref
Northeast				
Midwest	1.51 (1.19–1.90)	1.05 (0.81–1.38)	0.65 (0.59–0.72)	0.67 (0.61–0.74)
South	1.99 (1.62–2.44)	0.66 (0.52–0.85)	1.03 (0.94–1.12)	0.86 (0.79–0.93)
West	0.97 (0.78–1.22)	0.47 (0.35–0.63)	0.63 (0.57–0.70)	0.59 (0.54–0.64)
Other ^b	1.73 (0.99–3.03)	2.02 (1.13–3.62)	2.24 (1.83–2.74)	2.17 (1.81–2.60)

^aModels adjusted for year of isolation and presence at an SCI/D hub center.

^bIncludes San Juan, Puerto Rico (n=4,497 isolates) and Manila, Philippines (n=9 isolates).

GNB infections.²⁸ Compared with Gram-positive bacteria, GNB are more commonly isolated from ICU patients²⁹ and are the most common causes of ventilator-associated pneumonia and catheter-associated urinary tract infection.³⁰ Although prior small studies that examined microbial epidemiology in patients with SCI/D identified *staphylococci* as the most common bacteria overall,^{2,7,31–34} GNB may be more commonly isolated from patients with severe infections, such as bacteremias.^{33,35,36} Careful attention to minimizing the spread of GNB in healthcare settings is necessary to effectively decrease infection rates in this population.

We further identified important trends in antibiotic resistance in GNB. Currently used FQ antibiotics were introduced in the late 1980s and are preferred first line agents for community-acquired pneumonia and genitourinary tract infections. Over 40% of all GNB in this study were FQ-resistant, which is consistent with rates reported in recent studies of urine isolates from patients with SCI/D in Korea and Thailand.^{37,38} This is in contrast to an earlier U.S. study from the mid-1990s where FQ resistance in urine *Enterobacteriaceae* isolates from patients with SCI/D was only 9%.³⁹ The increase in resistance reported in these prior studies supports the trend we observed of increasing odds of FQ resistance in GNB. The change in FQ resistance in GNB in our cohort represents an example of this study's applicability in guiding selection of adequate empiric antibiotics for common infections in patients with SCI/D. Although FQs have long been preferred antibiotics to treat urinary tract infection, our findings support choosing an alternate antibiotic class for empiric treatment given the high levels of resistance and the recent Food and Drug Administration warning regarding safety concerns.⁴⁰ Efforts to study the utility of SCI/D-specific antibiograms to address such issues and provide alternate recommendations for empiric prescribing in this population are ongoing.⁴¹

The results from this current study build upon results from prior studies. Our group recently reported increased rates of MDR bacteria in patients with SCI/D compared to with patients without SCI/D from 2012–2013 at one VA medical center.¹¹ Other surveillance studies of bacterial cultures from patients with SCI/D have shown similarly high rates of MDRGNB.^{10,37–39} Older studies of urine cultures from outpatients with SCI/D in Germany and the U.S. showed an increase in resistant GNB in the 1990s and early 2000s, particularly for *E. coli* and *Klebsiella* spp.^{39,42} Unfortunately, these earlier studies focused on small, single-center SCI/D populations, did not include non-urinary isolates, and did not apply

uniform definitions of antibiotic resistance. Because we included all isolates from any anatomic site from a large cohort of Veterans and applied standard international definitions for MDRGNB,¹⁸ we believe that our study better captures the current burden of MDR bacteria in the SCI/D population.

Finally, we observed noteworthy trends in antibiotic resistance at specific types of VAMCs and in different geographic regions. SCI/D hubs had greater odds of methicillin resistance in *S. aureus* and multidrug resistance in GNB compared to spokes. This is likely related to a higher acuity of care provided at hubs (which are all located at Level 1a VAMCs) to more medically complex patients who are also at greater risk for MDR bacteria. Furthermore, the “other” region had significantly increased odds of antibiotic-resistant bacteria, with the exception of MRSA. This is consistent with global GNB surveillance studies that have demonstrated higher resistance rates in the Asia/Pacific and Latin American regions compared with the mainland U.S.^{43–45} It is important to note that the overwhelming majority of isolates in our study from the “other” region were from the SCI/D hub center in San Juan. A broad analysis of antibiotic resistance trends in Puerto Rico between 1996–2003 demonstrated higher rates of GNB resistance compared with the continental U.S.,⁴⁶ consistent with our data. This suggests that regional geographic variation in antibiotic resistance should be assessed when developing targeted antibiograms and antimicrobial stewardship interventions for patients with SCI/D.

Our study has several limitations. First, any study conducted exclusively at VAMCs may have limited generalizability, in part due to the predominantly male population. Approximately 80% of SCI/D occurs in men, so these limitations are likely to be less significant for our study than many others. Second, the VA has an integrated network of multidisciplinary SCI/D specialty centers and other care settings that may not accurately reflect less coordinated care provided to patients with SCI/D at many private and community hospitals. Third, due to the retrospective study design and use of administrative datasets, we did not collect patient-level data regarding clinical findings, risk factors for MDR bacteria such as use of invasive medical devices and antibiotic exposures, the presence of infection, and patient outcomes. As a result, we did not assess the impact that changes in any of these variables may have had on the trends reported here. Also, although we ensured that we had culture data for each VAMC, there may have been changes over time in the capture and reporting of bacterial susceptibilities that we did

not identify, therefore underestimating antibiotic resistance. Finally, our exclusion of cultures without antibiotic susceptibility testing may have inappropriately excluded some clinically relevant isolates.

Conclusions

In this large cohort study of Veterans with SCI/D, we identified a critical shift in bacterial epidemiology toward GNB with a high overall prevalence of MDRGNB and trends of increasing multidrug resistance in GNB and vancomycin resistance in *E. faecalis* and *E. faecium*. We also observed greater odds of multidrug resistance in GNB isolated from patients seen at higher complexity VAMCs with associated SCI/D hub centers and in specific regional areas such as Puerto Rico and the northeast. This study highlights the importance of targeted antimicrobial stewardship interventions to encourage judicious antibiotic use in patients with SCI/D, particularly for agents such as FQ antibiotics. Furthermore, this study can also inform the development of up-to-date and accurate local and regional empirical antibiotic treatment guidelines for the SCI/D population.

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Ethics approval None.

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