Risk factors for community-associated multidrug resistant *Pseudomonas aeruginosa* in Veterans with spinal cord injury and disorder: a retrospective cohort study

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Abstract

Study Design—Retrospective cohort study

Objectives—To identify independent risk factors associated with community-associated multidrug resistant *P. aeruginosa* (MDRPA) in a population of Veterans with spinal cord injury and disorders (SCI/D).

Setting—127 Veterans Affairs healthcare facilities

Methods—Laboratory results from January 1, 2012 to December 31, 2013 were collected and MDRPA cultures were compared to non-MDRPA cultures.

Results—One thousand four hundred forty one cultures were collected from Veterans with SCI/D, including 227 cultures with MDRPA isolates. Characteristics associated with an increased

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odds of MDRPA include age 50-64 (aOR= 1.80, 95% CI= 1.13-2.87), MDRPA culture in the past 365 days (aOR= 9.12, 95% CI= 5.88-14.15), and carbapenem exposure in the past 90 days (aOR= 2.56, 95% CI= 1.35-4.87). In contrast, paraplegia was associated with a 53% decreased odds of MDRPA compared to those with tetraplegia (aOR= 0.47, 95% CI= 0.32-0.69).

Conclusions—Risk factors for community-associated MDRPA include prior history of MDRPA and exposure to carbapenems. Awareness of these factors is important for targeted prevention and treatment of MDRPA in patients with SCI/D.

Keywords

spinal cord injury; *P. aeruginosa*; multidrug resistance; community-associated; gram-negative bacteria

Introduction

Pseudomonas aeruginosa is a common gram-negative organism that was responsible for 8% of all healthcare-associated infections (HAIs) in 2013.[1] Antibiotic resistance in *P. aeruginosa* is an increasingly serious threat in multiple healthcare settings[2] as there are a decreasing number of effective drugs to combat the bacteria. Multidrug resistant strains account for 13-18.5% of healthcare-associated *P. aeruginosa* infections[1,3] and about 440 deaths per year in the US.[1] This growing level of drug resistance is a result of the spread of resistant strains from patient to patient as well as newly acquired resistance due to previous antibiotic exposure.[4]

Several studies have identified risk factors for acquiring multidrug resistant *P. aeruginosa* (MDRPA) in the general patient population. These include advanced age, severe injury (bedridden), use of invasive devices, admission from a chronic care facility, hospital unit, and treatment with inappropriate antibiotic therapy or a number of antibiotic classes.[3,5,6] In particular, hospital location and site of infection appear to substantially influence the risk for MDRPA. De Oliveria Costa et al. found that longer time to adequate antibiotic therapy was associated with greater risk of infection by MDR gram-negative bacteria among patients in the pediatric oncology intensive care unit (ICU).[3] According to the National Healthcare Safety Network, 16.8% of catheter-associated bloodstream infections are attributed to MDRPA in the ICU compared to 13.3% in non-ICU areas, whereas 12.6% of catheter-associated urinary tract infection occurs from MDRPA in the ICU, as opposed to the 15.6% found in non-ICU areas.[2]

Many studies of MDRPA have focused on HAIs; however, there is increasing antibiotic resistance observed in gram-negative bacteria isolated from patients in the community.[7] About 30% of all infections by *Pseudomonas* species are community-associated.[8] Most of the published literature regarding community-associated *P. aeruginosa* infections is comprised of case reports and case series. Though rare, these infections can occur in previously healthy individuals and can cause pneumonia that is rapidly progressive and fatal.[9-11]

Patients with spinal cord injury and disorders (SCI/D) are at particularly high risk of HAIs and infection with MDR pathogens due to functional impairments, comorbidities, frequent use of invasive devices, and frequent antibiotic and healthcare exposures.[12-14] Characteristics unique to SCI/D patients, such as completeness of injury, may influence certain infection rates.[15] *P. aeruginosa* is not an uncommon pathogen in SCI/D patients; in studies of SCI/D Veterans with HAIs, *P. aeruginosa* accounted for 11.3-12.2% of isolated organisms.[16,17] MDRPA infections in the general patient population are associated with poor clinical outcomes such as increased length of stay post-infection, invasive surgery, discharge to chronic care facilities and mortality.[5] However, risk factors for and clinical outcomes of MDRPA infections in patients with SCI/D have not been extensively studied. There are also limited data on community-associated *P. aeruginosa* infections in the SCI/D patient population. Therefore, the objective of this study was to identify independent risk factors associated with community-associated MDRPA in a population of Veterans with SCI/D by comparing cultures from patients with MDRPA to those of patients with antibiotic susceptible *P. aeruginosa*.

Participants and Methods

Study setting and study design

A retrospective cohort study was performed in Veterans with SCI/D treated at any of 127 VA facilities from January 1, 2012 to December 31, 2013. The cohort included patients with a culture positive for *P. aeruginosa,* where MDRPA was defined as a *P. aeruginosa* isolate non-susceptible to a least one agent in three or more antimicrobial categories, as defined by Magiorakos, et al.[18] Non-MDRPA was defined as patients with SCI/D with positive cultures of antibiotic susceptible *P. aeruginosa*. Only patients with cultures containing *P. aeruginosa* from the community were included in the study. Community-associated *P. aeruginosa* was defined as any culture obtained from a patient who 1) was seen in the outpatient setting and had no hospital admission in the previous 28 days or 2) was admitted to the hospital in the previous 48 hours and had no previous admission in the past 28 days.

Data collection

Patient demographics, SCI/D characteristics, and comorbid conditions in the past 365 days were collected from national VA datasets, including the Veterans' Health Administration (VHA) Corporate Data Warehouse (CDW). The CDW is a relational database of national clinical and administrative data extracted from local electronic medical records for VA patients and is updated on a continual basis. These datasets were also used to gather information on healthcare and antibiotic exposures. Comorbid conditions were used to develop the Charlson Comorbidity Index, which was originally developed to measure mortality by weighting and summing the patient's comorbidities. A higher score indicates a greater likelihood of mortality.[19] The VA SCI/D system of care includes dedicated SCI/D specialty centers called 'hubs' across the nation that provide highly specialized SCI/D care. Each of these centers connects to a variable number of 'spoke' VA facilities that provide community-based primary care for SCI/D patients. All patients were either seen at a SCI/D hub center or at a spoke facility, where care may differ. Cultures were analyzed based on these VA facilities. Geographic regions where the cultures were collected are based on U.S.

Census regions defined by states. Locations outside of the continental U.S., such as San Juan, Puerto Rico, Manila, and Philippines were grouped into the "other" region category.

To determine whether *P. aeruginosa* isolates were MDR, we obtained information from the CDW on all positive bacterial cultures for which antibiotic susceptibility testing was performed. These records were then filtered to include only cultures positive for *P. aeruginosa*. Duplicate cultures within 30 days were excluded.

Statistical analysis

Chi-square and Fisher's exact tests were used to compare categorical variables and Wilcoxon rank sum tests to compare continuous variables. Unadjusted odds ratios and 95% confidence intervals are presented. Because some patients provided samples more than once during the study period, in both the inpatient and outpatient settings, they may have had multiple cultures positive for *P. aeruginosa*; therefore, the covariates are not entirely independent. To address this, a generalized estimating equation was used to create a multivariable logistic model that accounted for the multiple cultures taken from single patients.[20] This provided risk factors and their adjusted odds ratios and 95% confidence intervals. A p-value < 0.05 was considered statistically significant. Statistical analyses were conducted using SAS, version 9.3 (SAS Institute Inc., Cary, NC) and Stata, version 14.1 (StataCorp LP, College Station, TX).

Results

A total of 5,486 cultures positive for *P. aeruginosa* were collected from SCI/D patients seen at VA facilities during the study time period. Of these, 1441 (26.3%) cultures were collected from 1144 patients with *P. aeruginosa* in the community setting. Four hundred ninety six (34.4%) patients were seen as outpatients and 945 (65.6%) were admitted sometime in the 48 hours before culture collection. Nine hundred twenty-nine (64.5%) of the cultures were obtained from patients seen in SCI/D centers. The mean age of patients in this cohort was 61.3 years and 97.2% were male. Their median Charlson score was 2 (SD=1.6). The most common culture site was urine (81.3%), followed by other sites including respiratory, wound, skin and stool (17.8%), followed by blood (0.8%).Two hundred twenty-seven (15.6%) of the cultures collected grew MDRPA.

Table 1 summarizes the demographic and clinical characteristics of the patients from whom the cultures were collected and displays the results of the bivariate analysis. Paraplegia was associated with lower odds of MDRPA than tetraplegia. For all other comorbidities analyzed, there were no significant differences between the two groups; however, there was a significant difference in the distribution of Charlson scores (median (SD); MDR: 2 (1.5); Non-MDR: 2 (1.7)). Having had a previous culture positive for *P. aeruginosa,* and specifically MDR *P. aeruginosa,* in the past year was significantly associated with a positive MDRPA culture. In the 90 days prior to positive culture, admission to the hospital, admission to the ICU, mechanical ventilation and exposure to any antibiotic was associated with MDRPA. Exposure to a number of specific antibiotic classes was associated with increased odds of MDRPA (Table 1).

The multivariable analysis demonstrated that the level of injury, a previous MDRPA culture in the past year and exposure to carbapenems in the previous 90 days were significantly associated with MDRPA. In addition, ages 50-64 were associated with MDRPA when compared to ages 18-49 and while adjusting for covariates. No other factors were independently associated with MDRPA (Table 2).

Discussion

The aim of this study was to identify factors associated with Veterans with SCI/D with multidrug resistant *P. aeruginosa* in a community setting. A quarter of this study population had community-associated *P. aeruginosa* positive cultures. Our analysis showed that patients age 50-64 years have 80% greater odds of having a positive culture with MDRPA compared to the younger age group, whereas patients 65 years had no significant association with MDRPA. These findings differ from other studies that found advanced age to be a risk for MDRPA and other infections.[6]

The study population of Veterans with SCI/D contained patients with different levels of injury. When adjusting for other factors, a patient with paraplegia had 53% lower odds of MDRPA compared to patients with tetraplegia. This is aligned with prior studies that found the level of injury influences the rate of infection. A patient with tetraplegia has greater functional impairments and thus a greater risk of infection.[21]

Previous MDRPA in the past year was a significant predictor of a positive MDRPA culture by more than nine times the odds of a non-MDRPA culture. Earlier studies have previously documented the recurrence of *P. aeruginosa.* A previous colonization or infection is associated with subsequent infections, with the pathogen commonly re-infecting the upper and lower respiratory tracts of patients.[22, 23] These existing strains are more often the cause of infection compared to exogenous sources.[24] Relapse of *P. aeruginosa* may be due to an inappropriate initial antibiotic choice and duration of therapy. It also provides information regarding length of treatment for the new occurrence.[23]

Along these lines, previous exposure to carbapenems increases the odds of MDRPA 2.56 times. Prior literature supports this association as a predictor for future resistant isolates. Exposure to these antibiotics can result in resistance through mechanisms including porin mutation, most commonly, and carbapenemase production.[25-27] Because of the likelihood of reinfection of an existing strain, these mechanisms of resistance are important to understanding the risk of a previous carbapenem exposure.

This study had the advantage of longitudinal data from the VHA, the largest integrated health care system in the U.S. and largest provider of care for patients with SCI/D in the country. Using this data, our report is the largest known study of community-associated *P. aeruginosa*. However, because the data are collected from VA facilities, this study does not account for Veterans who seek health care outside of the VA. This might introduce bias as there may be characteristics that are unique to that particular group of patients compared to this study population. Also, conclusions pertaining to Veterans with SCI/D may not be generalizable to other populations with SCI/D because some of the injuries of these Veterans

may be related to their military service, which are unique circumstances. These Veterans also all receive care from the same health care system.

Another limitation of this study was the lack of differentiation between colonization and true infection with *P. aeruginosa*. Although MDRPA may be present in a culture, the patient may or may not have had systemic infection, and, depending on this assessment, may or may not have been prescribed antibiotic treatment. Therefore, whether prior MDRPA or non-MDRPA cultures were indicative of true infection or colonization may have impacted the prior antibiotic use variables and, thus, may have affected some of the associations observed in this study. Also, as previously mentioned, an assessment of whether MDRPA infection or colonization is recurrent or persistent is particularly important when examining *P. aeruginosa* epidemiology. This information could have helped us determine whether recurrent or persistent *P. aeruginosa* cultures were due to non-treatment, inadequate treatment, or a newly acquired strain from an exogenous source. However, to determine recurrence or persistence, identification of bacterial strain type is required. Although an approximation of strain similarity can be inferred from antibiotic susceptibility testing, definitive determination of bacterial strain type requires molecular testing such as pulsed-field gel electrophoresis or other genetic sequencing techniques. Unfortunately, this information was not available in the administrative datasets used for this study. Future studies examining the relationship between strain type and recurrent or persistent *P. aeruginosa* colonization and infection in patients with SCI/D will be helpful.

This study of Veterans with SCI/D has identified that community-associated MDRPA colonization and infection are associated with age, level of injury, prior MDRPA isolation, and prior antibiotic exposure. Identification of these factors is important for the initiation of appropriate antibiotic therapy and the implementation of interventions to prevent the spread of MDRPA. As MDRPA is a serious threat per the Centers for Disease Control and Prevention, controlling its spread and acquisition in the community, as well as healthcare settings, is essential. These results should encourage research into effective prevention measures for community-associated multi-drug resistant infections to protect this special population.

Acknowledgements

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Table 1

Bivariate analysis of risk factors for community-associated MDRPA and non-MDRPA

	Frequency (%)[a]		OR (95% CI)
	MDRPA N=227	Non-MDRPA N=1214	
Demographics			
Age			
18-49 years	34 (15.0)	221 (18.2)	Reference
50-64 years	104 (45.8)	469 (38.6)	1.44 (0.95-2.19)
65 years	89 (39.2)	524 (43.2)	1.10 (0.72-1.69)
Sex, female	7 (3.1)	34 (2.8)	1.11 (0.48-2.52)
Region			
Northeast	17 (7.5)	67 (5.5)	Reference
Midwest	38 (16.7)	229 (18.9)	0.65 (0.35-1.23)
South	130 (57.3)	636 (52.4)	0.81 (0.46-1.42)
West	130 (57.3)	262 (21.6)	0.54 (0.29-1.02)
Other[b]	6 (2.6)	20 (1.7)	1.18 (0.41-3.40)
SCI/D characteristics			
SCI/D level			
Tetraplegia	152 (67.0)	636 (52.4)	Reference
Paraplegia	49 (21.6)	503 (44.2)	**0.41 (0.29-0.57)**
Missing	26 (11.5)	75 (6.18)	1.45 (0.90-2.34)
SCI/D onset			
Non-traumatic	40 (17.6)	259 (21.3)	Reference
Traumatic	158 (69.6)	860 (70.8)	1.19 (0.82-1.73)
Missing	29 (12.8)	95 (7.8)	**1.98 (1.16-3.37)**
SCI/D extent			
Incomplete	88 (38.8)	480 (39.5))	Reference
Complete	94 (41.4)	606 (49.9)	0.85 (0.62-1.16)
Missing	45 (19.8)	128 (10.5)	**1.92 (1.27-2.89)**
Duration of injury			
0-10 yrs	67 (29.5)	409 (33.7)	Reference
11-20 yrs	42 (18.5)	195 (16.1)	1.31 (0.86-2.00)
21+ yrs	88 (38.8)	521 (42.9)	1.03 (0.73-1.45)
Missing	30 (13.2)	89 (7.3)	2.06 (1.26-3.35)
Patient seen at SCI/D center	135 (59.5)	794 (65.4)	0.78 (0.58-1.04)
Comorbidities			
Charlson comorbidity index, median (SD)	2 (1.5)	2 (1.7)	**p = 0.01** [*]

	Frequency (%)[a]		OR (95% CI)
	MDRPA N=227	**Non-MDRPA N=1214**	
Gastrostomy/jejunostomy	6 (2.6)	17 (1.4)	1.91 (0.75-4.90)
Renal disease	15 (6.6)	54 (4.5)	1.52 (0.84-2.74)
Liver disease	8 (3.5)	38 (3.1)	1.13 (0.52-2.46)
AIDS	1 (0.4)	4 (0.3)	1.34 (0.15-12.03)
Cancer/tumor	9 (4.0)	33 (2.7)	1.48 (0.70-3.13)
CHF	11 (4.9)	42 (3.5)	1.42 (0.72-2.80)
Diabetes	35 (15.4)	180 (14.8)	1.05 (0.71-1.55)
CVA	8 (3.5)	34 (2.8)	1.27 (0.58-2.78)
Arthritis	2 (0.9)	4 (0.3)	2.69 (0.49-14.77)
ASPVD	5 (2.2)	25 (2.1)	1.07 (0.41-2.83)
COPD	20 (8.8)	91 (7.5)	1.19 (0.72-1.98)
Myocardial infarction	1 (0.4)	8 (0.7)	0.67 (0.08-5.36)
Pressure ulcer	78 (34.4)	345 (28.4)	1.32 (0.98-1.78)
Specimen characteristics			
Specimen type			
Urine	188 (82.8)	984 (81.1)	Reference
Blood	1 (0.40)	11 (0.9)	0.48 (0.06-3.71)
Other[c]	38 (16.7)	219 (18.0)	0.91 (0.62-1.33)
Previous *P. aeruginosa* culture in past 365 days	106 (46.7)	380 (31.3)	**1.93 (1.44-2.56)**
Previous MDR *P. aeruginosa* culture in past 365 days	73 (32.2)	42 (3.5)	**13.23 (8.73-20.03)**
Healthcare exposures in past 90 days			
Hospital admission	55 (24.2)	211 (17.4)	**1.52 (1.08-2.13)**
Long-term care stay	3 (1.3)	8 (0.7)	2.02 (0.53-7.67)
Surgery	8 (3.5)	42 (3.5)	1.02 (0.47-2.20)
Genitourinary procedure[d]	10 (4.4)	27 (2.2)	2.03 (0.97-4.25)
Intensive care unit	13 (5.7)	30 (2.5)	**2.40 (1.23-4.57)**
Mechanical ventilation	16 (7.1)	28 (2.3)	**3.21 (1.71-6.04)**
Medication exposure in past 90 days			
Any antibiotics	166 (73.1)	777 (64.0)	**1.53 (1.12-2.10)**
Chronic steroids[e]	2 (0.9)	12 (1.0)	0.89 (0.20-4.01)
Pen-G/Pen-Amino	27 (11.9)	179 (14.7)	0.78 (0.51-1.20)
Antistaphylococcal penicillins	0 (0)	3 (0.25)	0.76 (0.04-14.79)
Extended Spectrum Penicillins	23 (10.1)	68 (5.6)	**1.90 (1.16-3.12)**
1st & 2nd Generation	23 (10.1)	97 (8.0)	1.30 (0.81-2.10)

	Frequency (%)[a]		OR (95% CI)
	MDRPA N=227	**Non-MDRPA N=1214**	
Cephalosporins			
3rd Generation Cephalosporins	26 (11.5)	80 (6.6)	**1.83 (1.15-2.93)**
4th Generation Cephalosporins	12 (5.3)	29 (2.4)	**2.28 (1.15-4.54)**
Carbapenems	19 (8.4)	32 (2.6)	**3.38 (1.88-6.07)**
Macrolides	5 (2.2)	37 (3.1)	0.71 (0.28-1.84)
Tetracyclines	14 (6.2)	81 (6.7)	0.92 (0.51-1.65)
Aminoglycosides	21 (9.3)	63 (5.2)	**1.86 (1.11-3.12)**
Lincomycins/Clindamycin	9 (4.0)	24 (2.0)	**2.05 (0.94-4.47)**
Quinolones	83 (36.6)	305 (25.1)	**1.72 (1.27-2.32)**
Nitrofurantoins	28 (12.3)	156 (12.8)	0.96 (0.62-1.47)
Sulfonamides	30 (13.2)	135 (11.1)	1.22 (0.80-1.86)
Colistimethate	6 (2.6)	2 (0.2)	**16.47 (3.30-82.11)**
Daptomycin	4 (1.8)	11 (0.9)	1.96 (0.62-6.22)
Fosfomycin	1 (0.4)	2 (0.2)	2.68 (0.24-29.72)
Linezolid	8 (3.5)	22 (1.8)	1.98 (0.87-4.51)
Metronidazole	15 (6.6)	43 (3.5)	**1.93 (1.05-3.53)**
Vancomycin	35 (15.4)	101 (8.3)	**2.01 (1.33-3.04)**

MDRPA, multidrug resistant *P. aeruginosa*; OR, odds ratio; CI, confidence interval; SCI/D, spinal cord injury and disorders; SD, standard deviation; AIDS, acquired immune deficiency syndrome; CHF, congestive heart failure; CVA, cerebrovascular accident; ASPVD, atherosclerotic peripheral vascular disease; COPD, chronic obstructive pulmonary disease; MDR, multidrug resistant

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

[b]Includes San Juan, Puerto Rico, Manila, and Philippines

[c]Includes respiratory, wound, skin, and stool

[d]Minimally invasive or non-invasive genitourinary procedures

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

[*]Wilcoxon rank sum test was used for Charlson score

Table 2

Multivariable GEE logistic regression analysis of risk factors for community-associated MDRPA

	MDRPA vs. Non MDRPA aOR (95% CI)
Age (ref: 18-49 years) 50-64 65 years	**1.80 (1.13-2.87)** 1.41 (0.87-2.27)
SCI/D level (ref: Tetraplegia) Paraplegia Missing	**0.47 (0.32-0.69)** 1.54 (0.90-2.65)
Previous MDR *P. aeruginosa* culture in past 365 days	**9.12 (5.88-14.15)**
Carbapenems	**2.56 (1.35-4.87)**

GEE, generalized estimating equation; MDRPA, multidrug resistant *P. aeruginosa*; aOR, adjusted odds ratio; CI, confidence interval; MDR, multidrug resistant